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Series Editors:
MICHAEL J. AMINOFF, FRANÇOIS BOLLER,
DICK F. SWAAB

130

3rd Series

NEUROLOGY OF SEXUAL AND BLADDER DISORDERS

Edited by:
DAVID B. VODUŠEK
FRANÇOIS BOLLER

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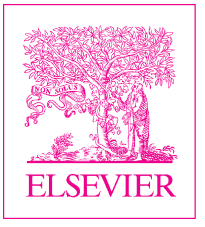

EDINBURGH LONDON NEW YORK OXFORD PHILADELPHIA
ST LOUIS SYDNEY TORONTO 2015

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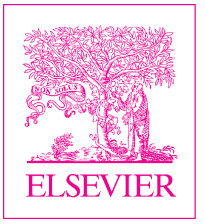

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ELSEVIER B.V.
Radarweg 29, PO Box 211, 1000 AE Amsterdam, Netherlands
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, UK
225 Wyman Street, Waltham, MA 02451, USA

ISBN: 9780444632470

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging in Publication Data
A catalog record for this book is available from the Library of Congress

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Foreword

Sexuality (and the reproduction to which it leads) are not only crucial functions for the survival of our species, but, for many people, an important component of a fulfilled life. Despite the great importance of sexuality, however, discussion about sexual disorders remains extremely difficult for both patients and physicians. When one of us (DFS) was in medical school, his professor did not accept the abbreviation NA, which stood for "no abnormalities," in the paragraph on the reproductive tract in the patient's file; he claimed, rightly, that NA really meant that possible issues had not been discussed with the patient in a professional way. "NA means 'no attention'," he would shout. The same reluctant attitude crops up when lower urinary tract dysfunctions are concerned, in spite of the fact that, like sexuality, they are so vital for quality of life. Disorders of these functions are common in patients with peripheral, somatic, autonomic, or central nervous system disorders. Doctors and patients alike feel inhibited when it comes to talking about such dysfunctions, with some interesting exceptions, which are discussed briefly in the history part of the first chapter in this volume.

This volume of the *Handbook of Clinical Neurology* pays specific attention to the best way to approach patients with sexual or urinary tract dysfunction. The volume starts with chapters on the anatomy and physiology of the genital organs and urinary tract, including data obtained with functional imaging. Disorders due to lesions at all levels of the nervous system and in relation to the major neurologic disorders are systematically described. Finally, detailed attention is paid to the management and rehabilitation of neurologic patients with sexual and bladder dysfunction.

We have been fortunate to have as volume editors Professors David B. Vodušek and François Boller, who have assembled a truly international group of authors with acknowledged expertise in this particular area to contribute to an excellent synthesis of the literature. We are grateful to them and to all the contributors.

We have read and commented on each of the chapters in our capacity as series editors and believe that both clinicians and basic scientists will find much to appeal to them in this volume. Not only is there plenty of room for clinical improvement in this field, but the more fundamental aspects of the subject require increased attention from basic scientists. The electronic availability of this volume on Elsevier's Science Direct site should ensure its ready accessibility and facilitate searches for specific information.

As always, it is a pleasure to thank Elsevier, our publishers – and in particular Mica Haley, Michael Parkinson, and Kristi Anderson – for their assistance in the development and production of this volume.

Michael J. Aminoff
Dick F. Swaab

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Preface

Sexual and lower urinary tract (LUT) dysfunction are not uncommon in the general population, but they are much more common in patients with neurologic disorders. Both may occur as the presenting symptom in an otherwise "neurologically normal" subject with a developing and as yet unrevealed neurologic disease, as an isolated phenomenon after local nerve injury, or as a consequence of the complex issues accompanying a chronic neurologic disorder. Whereas the link between nervous system involvement and the ensuing dysfunction is, at least in principle, rather straightforward in the case of a peripheral nerve lesion, the correlation gets increasingly complex when ascending the central nervous system. Indeed, even the normal neural control of both organs, which include the somatic and the autonomic nervous system as significant players, is not completely clear. But researchers in neuroscience have become increasingly interested in these issues, and we are proud to present in this volume the reviews of some of the most pre-eminent workers in the field.

In the realm of clinical work, research in neurogenic LUT and sexual dysfunction has not kept pace with the mainstream of modern evidence-based medicine, and this has hampered progress and is frustrating in practice. Yet, knowledge of sexual and LUT dysfunction is clinically pertinent for several reasons, not least because sexuality and bladder control are major determinants of quality of life in patients with neurologic disease. Both sexual and LUT dysfunction are common in neurologic disorders, but patients often fail to mention them spontaneously – at least, to the neurologist. Among other reasons, there is the belief of patients that the neurologist would "not be the right specialist" to address such problems, and is "not interested." More often than not, this conviction of patients may, unfortunately, still be correct. It is the aim of this volume of the *Handbook* to try to reverse this attitude and convince neurologists that sexual and LUT function should be addressed in their patients, for reasons of correct diagnosis, possible therapeutic consequences and gaining their trust. More research in sexual and LUT dysfunction in neurologic patients is needed, but will only become possible if neurologists fully embrace the need to address these issues in their patients. We have managed to convince the comparatively few practitioners in the field to share their expertise in this *Handbook*, and we hope to provide in the respective clinical chapters not only an overview of the epidemiology, pathophysiology, and clinical presentations, but also some guidance for patient management.

It should be mentioned that for this volume in the *Handbook* series, we may not have – in the opinion of some – included everything that comes to mind, or indeed is relevant to the topic; for example, we have intentionally omitted the neurology of the bowel, although it is highly relevant in many populations of neurologic patients. We nevertheless feel that a comprehensive *Handbook* on neurogenic bowel disorders is much needed and that, eventually, an integrated work on neuroscientific and neurologic issues related to sexuality, fertility, and pregnancy; the urinary tract; bowel disorders; and pelvic and perineal chronic pain syndromes should be attempted, to provide a comprehensive overview of the normal somato-autonomic integrated neural control of these interlaced functions, and the neurogenic derangements thereof.

We express our gratitude to the authors who valiantly collaborated in our endeavor. We thank Dr. Ellen Frank for her suggestions during the preparatory phases of this volume. We also thank the editorial staff of Elsevier, particularly Michael Parkinson, for his help in the production of this book.

David B. Vodušek, Ljubljana, Slovenia
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Introduction

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 1

Introduction

DAVID B. VODUŠEK[1]* AND FRANÇOIS BOLLER[2]

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This volume deals with neurologic disorders of sex and bladder. Sexuality is for the large majority of humans a component of a fulfilled life, and most would agree with the World Health Organization (WHO) that sexuality is, indeed, a central aspect of life and a fundamental right of the individual (WHO, 2006). While sexual dysfunction (SD) is not "vital" in the usual sense of the word, i.e., is not strictly indispensable for individual survival, dysfunctions of the lower urinary tract (LUT) are, as they may lead to chronic infection, dilatation of the upper urinary tract, renal insufficiency, and death. Thanks to appropriate management of neurogenic LUT dysfunction (LUTD), mortality after spinal cord injury has dropped dramatically. Treatment of complications such as renal failure and/or urosepsis has reduced from a mortality of up to 75% in 1969 (Whiteneck et al., 1992) to only 2.3% in 1992 (Devivo et al., 1993).

Dysfunction of both sexual activity and of the LUT is of major importance for quality of life, and is often considered by patients to be more important than motor impairment such as paraplegia (Anderson, 2004). Unfortunately, even in the absence of trauma and motor symptoms, SD is far from uncommon in the general population, both in men and in women. It is therefore surprising that most physicians are ill prepared to discuss SD with their patients, let alone diagnose and treat them. One of the chapters in this volume quotes a patient expressing the opinion that "[Physicians] haven't been educated enough about being open. They might be a little inhibited themselves." Contemporary medical curricula are attempting to remedy this, but it is slow in coming. It is just as surprising that mention of these disorders was slow in appearing in the literature.

HISTORY OF SEX AND LUT DYSFUNCTION

An early specific mention of a "sexual" disorder is found in the work of François de la Peyronie (1668–1747). He was surgeon to King Louis XV of France, when he described the condition that bears his name, also known as induratio penis plastica, a sclerosis of the corpora cavernosa which deforms the penis, usually in erection, and may prevent sexual intercourse, mainly because it is often accompanied by pain.

In Europe and around the world, in the 19th century, sexual subjects were considered taboo and repression was the main position toward them (Schultheiss and Glina, 2010). Contrary to that trend, Paolo Mantegazza (1831–1910) can be considered the founder of modern sexual medicine. Borne in Monza near Milan, Italy, he graduated in Pavia in 1854. He then embarked on a world tour and came back to Italy in 1858 after having practiced medicine in various countries, including India, Argentina, and Uruguay. He was given the position of Professor of General Pathology at the University of Pavia and in 1870 he became Professor of Anthropology at the University of Florence.

Mantegazza pioneered the development of experimental work and formulated new sexual theories, founding a new science which he called "science of embrace." As pointed out by Schultheiss and Glina (2010):

> *Curiously, Mantegazza referred to love [*amore*] when he was talking of sexual relation. He never used the term sexual. Besides his interest on physiology of "nervous" states (the beginning of neurophysiology) and the action of drugs*

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(e.g. cocaine), Mantegazza wrote about female sexuality, sexuality in children, masturbation, erectile dysfunction, vaginism, and male and female infertility. He had tried gonad transplantations in frogs and he had measured the blood flow and temperature increase during penile erection (p. 2033).

But again, Mantegazza was an exception. Nineteenth-century clinicians had no qualms about publishing pictures of or even filming their patients, men and women, without any clothes on. Yet one does not find a clear mention of disorders of bladder control or impaired sexual function in Charcot's description of multiple sclerosis or Parkinson disease. That does not mean that Charcot and his contemporaries ignored problems related, or thought to be related, to SD. Charcot, for instance, had "a special reputation for ailments related to sexuality" (Goetz et al., 1995, p. 255). This, however, for the most part involved the role of "*la chose génitale*" in neuroses or even in the "treatment" of homosexuality.

Richard Freiherr von Krafft-Ebing (1840–1902) was an Austrian–German psychiatrist. His main work was *Psychopathia Sexualis* (1886), one of the first monographs to study sexual topics such as clitoral orgasm and female sexual pleasure, consideration of the mental states of sexual offenders, and homosexuality. As pointed out by Schultheiss and Glina (2010), in contrast to popular and scientific belief at that time, Krafft-Ebing was one of the first authors to point out that homosexuals did not suffer from mental illness or perversion.

It may have been the influence of Charcot which led to the "sexualization of hysteria," Freud's belief in the sexual origin of all hysteric symptoms (Bogousslavsky and Dieguez, 2014). Apart from these psychopathologies, one finds at least one mention of a potentially organic problem. Impotency was one of the ailments which was "treated" by Charcot and his acolytes with the use of suspension. This approach consisted of having these unfortunate patients hang for several minutes from a contraption fitted under their armpits and around their neck. This had been introduced by a Ukrainian physician for a patient with tabes dorsalis and it is rightly included among the cruelest treatment of neurologic diseases in the 19th century (Walusinski, 2013).

Another noticeable 19th-century attempt to deal with SD took place not far from the Salpêtrière, at the Collège de France in 1889. That is when Edouard Brown-Séquard, then aged 72, made his most famous presentation about a series of rejuvenation experiments. He claimed that daily injections of testicular blood, seminal fluid, and testicular extract from guinea pigs and dogs made him feel 30 years younger. Following that presentation, Brown-Séquard received a considerable amount of publicity, not all of it favorable. He was attacked as a quack and a charlatan. The antivivisection movement, very strong, especially in the UK, also threw its anger at him. We are not aware of double-blind experimental research aimed at proving or disproving Brown-Séquard's theory. Yet he is considered by many as the father of modern neuroendocrinology for having pioneered the idea that parenterally administred substances could have an action on the hormonal system (Aminoff, 2010; Boller et al., 2015). Actual testicular implants were proposed in subsequent years, particularly in France by the Russian-born Serge Voronoff (1856–1951) and in the USA, where a certain John Brinkley (known as Dr. Goat Gland Brinkley, 1885–1942) is said to have given "new joy" to many thousands of people, men and women, before he was tried for fraudulent practice of medicine, convicted, and forbidden from practicing.

Perhaps because of its more prominent impact on everyday life, diagnosis and even some treatments of LUT, particularly of urinary incontinence, are dealt with in the literature. In his *History of Urinary Incontinence and its Treatment*, Schultheiss (2000) shows that ancient Egyptian sources mentioned devices to collect urine and pessaries for women and even provided advice on how to deal with overflow incontinence ("remove the urine which runs too often"). In subsequent years, reports mainly address cases of extraurethral incontinence, for instance fistulas acquired after childbirth or, in males, overflow incontinence following spinal cord injury. Ambroise Paré (1510–1590), the famous surgeon of the Renaissance, was very interested in the urinary tract and proposed a device that could be used as a urinal by incontinent men.

One had to wait until the 19th century to see the appearance of work aimed at understanding and treating LUT. Here again we have a pioneer: Ludwig Robert Müller (1870–1962), from Augsburg, Bavaria. He performed essential research on the autonomic nervous system which included work elucidating the mechanism of the neurogenic bladder (Müller, 1901; Neundoerfer and Hilz, 1998). An early treatment attempt proposed to use ectrotherapy (alternating current applied to the bladder or rectum). This was introduced by Robert Ulzmann (1842–1889) for the treatment of various conditions, including enuresis in children.

Almost all the diagnostic and therapeutic measures for LUT as described in Chapter 9 and 26 only appeared well into the 20th century.

CLINICAL ASPECTS OF SEX DYSFUNCTION

What is the cause of SD in the population at large? As for other functions, there may be some decline with aging, but in essence, age is not a valid response to the question

of causation. We know about statistical correlations of SD in the population and several so-called "risk factors," among them neurologic disease, and neurologic diseases are, indeed, more common with advanced age.

There is great variability insexual functioning in the population, and particularly so in the elderly. Overall, the frequency of intercourse in the healthy elderly decreases. Men need more time and stimuli to achieve erection and orgasm, and have a decreased sensation of impending ejaculation and a decreased ejaculatory volume. Their refractory period after orgasm is prolonged (Rowland et al., 1993). Hormonal changes in women after menopause lead to decreased desire, decreased sexual thoughts, decreased frequency of intercourse, and thinning of the vaginal wall with decreased elasticity and lubrication (Gracia et al., 2007). Despite this, 26% of the 75–85-year-old age group reports sexual activity during the past 12 months (Lindau et al., 2007).

The neurologist's clinical interest is necessarily focused more on the physiologic aspects of sexuality. To the neurologist, sexual function involves a series of neurally controlled phenomena occurring in a hormonally defined milieu. Therefore, to the neurologist a cauda equina lesion is a clear-cut "cause" of neurologic deficits (among which SD is prominent), not a risk factor, as it is categorized in an epidemiologic study. But, indeed, not every patient with cauda equina complains of SD (Podnar et al., 2002); thus, cauda equina lesion in the terminology of risk factors is defined as a "high-risk factor"! Sexuality depends not only on intact nervous system function but on many other physiologic systems, and also on psychosocial factors. Both somatic and psychosocial factors may be compromised by neurologic disease. The perspective of partnership and social issues should never be forgotten.

In a neurologic practice, SD may be reported in a patient (referred from a urologist) as an early or even presenting symptom of a developing and as yet undiagnosed neurologic disease (e.g., erectile dysfunction in multisystem atrophy), as an isolated phenomenon after local nerve injury (e.g., erectile dysfunction after prostate surgery), or as a consequence of the complex issues accompanying a chronic neurologic disorder. It is helpful to conceptualize SD in neurologic disease as Foley and Iverson (1992) did for multiple sclerosis: there are primary effects stemming from physiologic or pharmacologic factors; secondary problems related to sensorimotor, bladder, and bowel disturbances and higher brain dysfunction; and tertiary issues related to psychosocial and cultural changes resulting from the disease.

The focus of this volume of the *Handbook of Clinical Neurology* is not only on the "physiologic/neurologic" but also on the "sexologic" dimensions of sexuality, and therefore eminent sexologists have been invited to contribute. The common denominator of almost all contributions is that research in neurogenic SD is only in its early stage and particularly so in the domain of female sexuality.

The relationship of the neural lesion (as far as it can be precisely determined) and sexual (dys)function is not straightforward and becomes more and more elusive as we "ascend" the nervous system from the periphery to the frontal lobes. Also, how sexual function is defined in the first place will influence both the way we think about brain–function interaction and the research that is done in the field. Prior to 2013, the *Diagnostic and Statistical Manual,* fourth edition (DSM-IV: American Psychiatric Association, 1994) described SD as disturbances in sexual desire and/or in the sexual response cycle, occurring in any of the four phases of the human sexual response cycle, including libido (desire), arousal, orgasm/climax, and resolution (Gregorian et al., 2002). In accordance with this conceptualization, among other issues, questionnaires about sexual function have been constructed and used. The new DSM-5, released in 2013 (American Psychiatric Association, 2013), creates a paradigm shift, suggesting that sexuality may be experienced differently according to gender and as such should be classified and managed differently (Sungur and Gunduz, 2014; see Chapter 2). We are thus in a period where we are still trying to understand the physiology of sexuality, and still far from completely integrating the information of the neural (particularly brain) control of sexual function (see Chapter 6).

CLINICAL ASPECTS OF LUT DYSFUNCTION

SD and LUTD are common occurrences in neurologic patients. (Note that the term LUT is used by specialists who are primarily interested in this organ system; it is the preferred term, although neurologists tend to use "bladder" or, possibly even worse, "sphincter" as a jargon term to denote LUTD.)

Similarly to SD, LUTD is not uncommon in the general population, and a large proportion of those dysfunctions are thought of as "idiopathic." Indeed, the comorbidity of SD and LUTD is not uncommon, as discussed in Chapter 10. Thus, urologists, urogynecologists, and sexologists are dealing with a large population of non-neurologic patients who suffer from LUTD or SD, or both. These patients with uncertain etiology often demonstrate clinically similar manifestations of SD and LUTD to those encountered in neurologic patients. This also needs to be appreciated by neurologists, who might suppose that all LUTDs and SDs without obvious other cause are neurogenic.

LUTD may also occur as the presenting symptom in a "neurologically normal" subject with a developing and as yet unrevealed neurologic disease (e.g., urinary incontinence in multisystem atrophy), as an isolated phenomenon after local nerve injury (e.g., urinary retention after a cauda equina lesion), or as a consequence of the complex issues accompanying a chronic neurologic disorder (wetting due to difficulties in gait, and not being able to get to the toilet in time; wetting due to cognitive deficits). Again, research into neurogenic LUTD has not kept pace with the mainstream of modern evidence-based medicine, and this has hampered progress and is frustrating in practice. However, in comparison to our understanding of brain control of sexual function, we have a much better-defined model of neural control of LUT (see Chapters 5 and 7).

While sexual dysfunction and LUTD are common in neurologic disorders, they are most often not spontaneously mentioned by the patient – at least not to the neurologist. Among other reasons there is the conviction of patients that the neurologist would "not be the right specialist" to address such problems, and "not interested." Most often than not this conviction may, unfortunately, still be correct at the present time. It is the aim of this volume of the *Handbook* to try to reverse this attitude and convince neurologists that sexual and LUT function in fact need to be addressed in their patients, for reasons of correct diagnosis, possible therapeutic consequences, and gaining overall trust from the patient. The approach to the patient is not too sophisticated as it is primarily clinical (see Chapters 8 and 9); it only needs understanding, motivation, and time. The need for further assessment is logical in the patient with LUTD, and minimal in the patient with SD. The first line of management is also straightforward (see Chapters 24–26): the necessary and potential therapies need at least to be understood by the neurologist, even though the patient may be referred to a urologist, gynecologist, rehabilitation specialist, or sexologist. Indeed, the need to tend to the overall needs of the patient in neurology departments taking care of large populations of patients with multiple sclerosis, movement disorders, or stroke should lead to the organization of multidisciplinary teams akin to spinal cord injury centers, where it is established that evaluation and treatment of LUT and SD are carried out by dedicated personnel.

As is often the case, it is the patients' organizations which have taken the lead in disseminating information on SD and LUTD in particular patient groups, and producing clinical guides (documented information), websites, and internet videos, providing useful information for patients and caregivers.

In conclusion, it should be no surprise that sexuality and LUT function are major determinants of quality of life, and therefore of major importance to the well-being of all of us, and possibly even more to those who have lost other abilities. More research into sexual and LUTD in neurologic patients is very much needed, but will only become possible if neurologists fully embrace the need to address these issues in their patients.

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Section 2

Neural substrate

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 2

Human sexual response

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CURRENT CONCEPTUALIZATION OF HUMAN SEXUAL RESPONSE

Introduction

Human sexual response is conceptualized as a motivation/incentive-based cycle comprising phases of physiologic response and subjective experience (Basson, 2000, 2001a; Janssen et al., 2000; Balercia et al., 2007; Basson and Weijmar Schultz, 2007; Laan et al., 2008). The phases of the circle overlap and their order is variable (El-Sakka, 2007; Porst et al., 2007). As depicted in Figure 2.1, sexual "desire"/"urge"/"hunger" may or may not be sensed initially: desire can be triggered by the sexual excitement, i.e., the subjective sexual arousal in response to sexual stimuli (Basson, 2001a; Basson and Weijmar Schultz, 2007; Vannier and O'Sullivan, 2010; Goldhammer and McCabe, 2011; Hayes, 2011). Some researchers perceive all arousal and desire to be responses to sexually relevant stimuli: any internal thoughts or fantasies also stem from something external (Both et al., 2007). This overlap of phases is in keeping with neuroimaging data of sexual arousal which have led to the concept that motivation is one facet of sexual arousal and desire is one component of motivation (Stoléru et al., 2012).

Many factors, psychologic and biologic, influence the brain's appraisal and processing of the sexual stimuli to allow or disallow subsequent arousal. The sexual and non-sexual outcomes influence future sexual motivation. The cycle may be partially or completely repeated a number of times during any given sexual encounter. Variability is marked both between individuals and within a person's own sexual life, influenced by multiple factors, including stage of life cycle, age, and relationship duration, and robustly linked to mental health and relationship happiness (Mitchell et al., 2013).

A former understanding of sexual physiology emanated from the work of Masters, Johnson, and Kaplan in the 1960s and 1970s. Sexual desire, as in a sexual "drive," was considered to be the initiator of any sexual response. Similar to the physiologic urge to breathe, to eat, and to sleep, it was implied that to become sexually aroused and experience orgasm was necessary to avoid some kind of discomfort or non-physiologic state. However this conceptualization is not evidence-based. So, rather than a built-in mechanism to maintain homeostasis, human sexual response is understood to be linked to the rewards associated with sex, these being both sexual and non-sexual in nature.

Thematic analysis of the interview transcripts in a recent qualitative study investigating the meaning and experience of sexual desire in partnered women indicated that the experience of desire was primarily responsive rather than an autonomous experience (Goldhammer and McCabe, 2011). This is in keeping with similar research in men and women confirming that an awareness of desire may not be present at the outset of sexual activity (Vannier and O'Sullivan, 2010). Both men and women find it difficult to distinguish desire from arousal, reporting that sexual stimuli trigger both desire and arousal simultaneously (Janssen et al., 2008; Sidi et al., 2008; Brotto et al., 2009). Researchers using functional brain imaging of sexual arousal from erotic visual stimuli speak of psychologic manifestations of sexual arousal, including sexual desire, and physiologic manifestations, including genital responses (Stoléru et al., 2012). Women's sexual dysfunction typically involves lessened arousal and desire and infrequency of orgasm, as is now reflected in the recently named sexual interest arousal disorder in the American Psychiatric Association (2013) *Diagnostic and Statistical Manual,* fifth edition (DSM-5). Although

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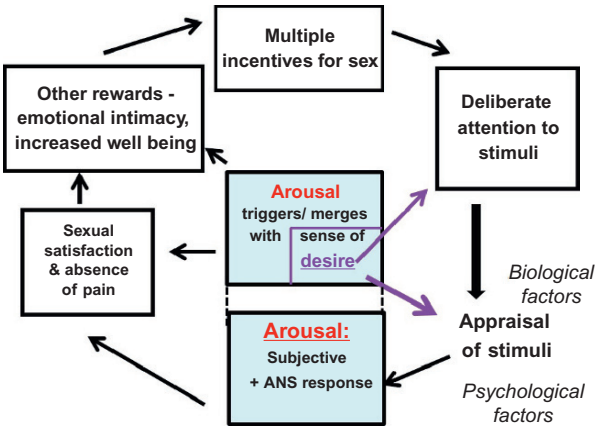

Fig. 2.1. Human sexual response is depicted as a motivation/incentive-based cycle of overlapping phases of variable order. A sense of desire may or may not be present initially: it can be triggered alongside the sexual arousal resulting from attending to sexual stimuli. Sexual arousal comprises subjective (pleasure/excitement/wanting more of the same) and physical (genital and non-genital responses). Psychologic and biologic factors influence the brain's appraisal of the sexual stimuli. The sexual and non-sexual outcomes influence present and future sexual motivation. ANS, autonomic nervous system. (Adapted from Basson, 2001b.)

the focus in men has typically been on erectile dysfunction (ED) or premature ejaculation, they too may experience a more generalized "sexual distress disorder," affecting desire, erectile function, and ease of orgasm (Carvalho et al., 2011).

Sexual motivation

Recent empiric research indicates that motivation for partnered sexual activity may be distinct from "solitary sexual desire," as evidenced by sexual thoughts and fantasies, and that motivation for partnered sex is far more relevant to sexual well-being. Of 65 men and 65 women complaining of markedly reduced or absent interest in partnered sexual activity, some 75% continued to report sexual thoughts, on average multiple times per week for men and three-plus times per month for women (McCabe and Goldhammer, 2013). This and other research has identified marked discrepancy between the person's own self-diagnosis and clinicians' diagnosis of low desire, the latter focusing on traditional markers of sexual thoughts and fantasies (King et al., 2007).

The majority of factors underlying and influencing sexual motivation reflect pleasure and emotional intimacy. Some 1500 (mostly young) men and women identified 237 distinct reasons why they engaged in sex: factor analysis produced four overall factors – emotional, physical, goal attainment, and insecurity (Meston and Buss, 2007). Emotional factors included love and commitment and the expression of the same. Physical reasons included pleasure and experience seeking, as well as reduction of stress. Goal attainment reasons included social status, resources, and even revenge. The insecurity factors included a wish to boost self-esteem, to fulfill a sense of duty, and to "mate guard."

This research supported the clinical observation that men and women have multiple sexual and non-sexual reasons for initiating or agreeing to partnered sex: a sense of sexual desire/urge/drive is just one potential underlying reason instead of being the prime mover of sexual initiation, as in the former model of human sexual response. The chief initiating reasons for men were physical: for women, emotional reasons predominated.

Further study focusing on 327 women aged 18–66 years found that, for all women, 72% of their top 25 reasons pertained to either sexual pleasure or love and commitment to the partner (Meston et al., 2009). Consistent with their first study, emotional factors slightly predominated over physical pleasure; reasons to do with insecurity and goal attainment were infrequent. It is readily apparent that neurologic disease interfering with sexual pleasure and/or causing partnership difficulties will severely compromise sexual motivation in both men and women.

Studies point to depression as a major cause of reduced sexual motivation in otherwise healthy persons. This appears to be true also for patients with neurologic disease: increased sexual dysfunction was noted in women with multiple sclerosis compared to controls only when there was comorbid depression (Zivadinov et al., 1999). Even when clinical depression is excluded, low or absent sexual interest is associated with having more depressed and more anxious thoughts, and lower sexual self-image than controls (Hartmann et al., 2004). Neurologic illness can markedly lessen sexual self-image from the associated altered appearances, mobility and cognition changes, ability to provide self-care and be continent, and ability to be gainfully employed. Research confirms individual differences in the effect of mood on sexuality: heterosexual men sometimes sense increased desire for solitary sex, i.e., masturbation, when depressed, but this is rarely reported by women or homosexual men (Janssen et al., 2013).

Empiric data on inhibitory and excitatory factors modulating the brain's appraisal of sexual stimuli has suggested a "dual-control model" which posits that sexual arousal is influenced by both excitatory and inhibitory mechanisms. These determine a person's tendency to experience sexual excitation/inhibition (trait), and operate during any given sexual situation (state). Factor analysis of questionnaires developed to explore how men and women would respond to sexual situations with and

without problematic aspects indicated some differences between genders, notably the importance of "arousal contingency factors" for women. Such factors reflect the potential for emerging sexual arousal to fade or fail "unless things are just right." In general, women show higher inhibition, and men higher excitation (Bancroft et al., 2009). Exploring "dual control," in men, two inhibition factors emerged: fear of performance failure and threat of performance consequences. A separate questionnaire was developed for women. For them, inhibitory factors included concerns about relationship importance, sexual function, and arousal contingency.

Investigating factors inhibiting sexual arousal is clearly relevant for neurologic patients, for whom there are yet further arousal contingency factors, e.g., for neurologic symptoms to be optimally controlled, and specific factors affecting the relationship, such as when the partner is the caregiver as well as the sexual delegate. Impaired erection or delayed orgasm from autonomic damage typically leads to fears about performance. Feared untoward outcomes include worsening of neurologic symptoms after orgasm, e.g., the rigidity of Parkinson's disease or neuropathic pain involving genital areas.

Sexual arousal can be heightened to problematic levels in persons with neurologic disease, such as those receiving dopaminergic agonist treatment for Parkinson's disease (see Chapter 17), or patients suffering severe injury to prefrontal lobes or to both amygdalae, as in the Klüver–Bucy syndrome (see Chapter 6).

Sexual stimuli and sexual context

Adequate sexual stimulation and an appropriate sexual context are essential components of human sexual response. The sexual stimuli may include erotic talking, sexual memories, as well as visual and physical stimulation. The latter includes non-genital as well as genital, and non-penetrative as well as penetrative genital modalities. Choices of stimulation may be curtailed by neurologic disease: touches may not be felt or may cause dysesthesiae; excessive salivation may hinder kissing; and immobility limit the giving of pleasure to the partner. Clinical experience confirms the importance of contextual factors, including the need for privacy from children and from caregivers; of pain relief; and of freedom from undue fatigue. The interpersonal context is critical for many: a longitudinal 8-year study of women transitioning through menopause suggested that feelings for the partner along with mood were the two most important factors determining sexual motivation (Dennerstein et al., 2002).

Relationship difficulties were a major factor associated with low sexual function in the recently published third National Survey of Sexual Attitudes and Lifestyles (Natsal-3), involving 4913 men and 6777 women, the adjusted odds ratio for relationship difficulties being 2.89 and 4.10 respectively (Mitchell et al., 2013). Adjustment between couples is strongly linked to sexual desire in a detailed questionnaire completed by 205 men and 237 women from the general population (Carvalho and Nobre, 2010). Emphasized in qualitative study is, especially for women, the importance of partner characteristics (Bancroft et al., 2009). There is preliminary evidence that, in monozygotic twin women, relationship factors play a key role in the development of sexual dysfunction (Burri et al., 2013). Stress originating within the couple, e.g., worry about the partner's well-being, rather than external stressors, has been shown to have an incremental effect upon sexual problems after adjusting for relationship quality and psychologic factors (Bodenmann et al., 2006). Whereas neurologic illness can greatly intrude into the interpersonal relationship, sometimes the illness can bring partners closer together emotionally.

Appraisal of sexual stimuli: "information processing"

Even with sufficient sexual motivation and the presence of adequate stimuli in a context satisfactory to the person, arousal and pleasure may not occur if attention is not focused on the present moment, on the sexual stimuli, and on the intimacy of the situation. Review of the literature on sexual arousal in 2009 confirmed a central role for attentional processes in facilitating the subjective but also the physiologic components of sexual arousal (DeJong, 2009). Sexual information is processed in the mind both automatically and consciously. The sexual nature of the stimuli is processed by the limbic system, allowing genital congestion (observed to be quick and "automatic" in women and slower but still involuntary in men). Interestingly, the objective measurement of automatic genital response in sexually healthy women is comparable to the response in women complaining of lack of sexual arousal (Laan and Both, 2008). Conscious appraisal of the sexual stimuli and the contextual cues can lead to subjective arousal. The latter may be further increased by awareness of the genital congestion of arousal, which is more accurately registered and more relevant to men's experience than to women's (Basson, 2001a). The subjective arousal will also be cognitively appraised – for instance, is this pleasurable and safe or is this shameful or likely to have a negative consequence? Cognitions such as these continually modify both physiologic and subjective responses (Nobre and Pinto-Gouveia, 2008).

Focusing on non-erotic thoughts during sexual stimulation, generated possibly by anxiety as first suggested

by Barlow (1986), is associated with having sexual problems. A recent study of 253 men and women in long-term relationships found that women tended to report non-erotic thoughts about their body image and the external consequences of sexual activity whereas men were more likely to report non-erotic thoughts about problematic sexual performance (Nelson and Purdon, 2011). Both men and women had some non-erotic thoughts about the emotional consequences of the sexual activity. Regardless of content, the more frequent the non-erotic thoughts, the more sexual dysfunction. Importantly, the more difficult it was to refocus back on an erotic thought uniquely predicted the intensity of sexual problems. This research is clearly relevant to patients with neurologic disease which frequently has a negative impact upon sexual self-image and/or sexual functioning.

Previous research studying 490 men and women with and without sexual problems highlighted a number of significant correlations between automatic biased thoughts, emotions, and sexual arousal. For both men and women, sadness and disillusion were positively related to negative cognitions and negatively associated with sexual arousal (Nobre and Pinto-Gouveia, 2008). Neurologic disease adds further sources of maladaptive thinking as well as sadness and disillusion.

Divergence of subjective and genital responses

Investigators have found that, in sexually healthy women, a highly variable correlation exists between objective measurement of genital congestion (as measured with the vaginal plethysmograph), subjective arousal (Laan et al., 2008; Chivers et al., 2010; Graham, 2010), and brain activation patterns, as recorded from functional magnetic imaging (Arnow et al., 2009). To examine arousal, women viewed a neutral film followed by an erotic film, and the percentage of increase in vaginal pulse amplitude was noted along with their ratings of subjective arousal. Women with sexual arousal disorder typically showed increases in vaginal pulse amplitude in response to visual erotica similar to those of sexually healthy women (Laan et al., 2008; Graham, 2010), but reported minimal or absent sexual arousal during the erotic films, and they may report negative emotions. Similarly, their awareness of genital sensations was minimal, correlating poorly with objective measurement of congestion in response to erotic stimuli.

In addition, the degree of congestion of clitoral structures and vaginal circulation is not accurately perceived by women in general; it is clear that women's arousal (physical/genital or subjective) cannot be measured by their estimation of genital swelling and vaginal lubrication. DSM-5 criteria for sexual disorder merge components of arousal (subjective and genital) with sexual interest/motivation into one diagnosis – sexual interest arousal disorder. This contrasts with the previous DSM-IV (American Psychiatric Association, 1994) focus on a desire disorder due to lack of fantasies and desire, and an arousal disorder due to women's report of lack of lubrication and swelling.

In contrast to women, men without neurologic (or vascular) disease generally have high correlations between penile erection and subjective sexual arousal (Chivers et al., 2010); however, there are many exceptions. For instance, sleep-related erections are mostly dissociated from erotic dreams or from subjective sexual arousal. Psychophysiologic studies have found that men can get erections in response to films of assault or rape while experiencing no subjective arousal (Janssen et al., 2002). In contrast, a psychophysiologic study identified some 25% of men in a community sample with minimal penile response to an erotic video while their subjective arousal was similar to the remaining 75% of men with recorded penile congestion (Janssen et al., 2009).

So, in both men and women it is suggested that unconscious processes underlie the automaticity of the genital response while subjective feelings of sexual arousal are modulated by higher-level conscious cognitive processes. Support for this theory includes experiments where subliminal presentations of sexual stimuli trigger sexual responses in both men and women. However subliminal stimuli, in contrast to supraliminal ones, do not trigger subjective sexual arousal (Janssen et al., 2000; Ponseti and Bosinski, 2010). In women but not in men the automatic genital response can be elicited in response to a stimulus that is deemed simply sexual in a biologic sense and not erotic or potentially arousing, e.g., viewing a video of primates engaged in mating (Chivers et al., 2010).

This complex physiology of variable linkage between genital congestion and subjective arousal (itself hardly distinguishable from desire) must be kept in mind during the assessment and management of autonomic neuropathy disrupting erections and clitoral engorgement and vaginal lubrication. For example, disruption of the sacral segments of the spinal cord from multiple sclerosis may be irrelevant to a woman's lack of sexual arousal. Inattention to sexual stimuli due to lowered self-image, fears of incontinence, and fatigue may prevent her subjective arousal: augmenting genital congestion pharmacologically would not be of benefit. In contrast, a man with similar pathology will likely be distressed by both his ED and his lack of subjective arousal from sensing genital engorgement: phosphodiesterase type 5 inhibitors may restore objective engorgement and subjective arousal.

Sexual outcome

A rewarding experience and outcome, emotionally and physically, will enhance present and subsequent sexual motivation. Sexual satisfaction has received less study than sexual function/dysfunction, but would appear to be a more relevant entity. New questionnaires, notably Natsal-SF (Mitchell et al., 2012), now reflect the importance of sexual satisfaction, in contrast to many previous instruments modeled on DSM-IV (American Psychiatric Association, 1994), in turn modeled on a linear sexual response depicting desire/urge which triggered erection/lubrication, leading to orgasm/ejaculation and then "resolution" of genital effects.

There can be satisfaction despite dysfunction. Dissatisfaction may occur in the context of a functional response. Nevertheless, particularly in men, concerns about sexual outcome in terms of sexual performance and consequences of sexual activity are common (Bancroft et al., 2009). Women's satisfaction may or may not include orgasm(s) (Graham, 2010) but usually requires freedom from any pain and freedom from partner dysfunction (Heiman et al., 2008), and a positive emotional conclusion. Men's satisfaction is thought to more frequently require orgasm and ejaculation. Recent study confirms strong links between sexual satisfaction and sexual motives (Stephenson et al., 2011). When the motivation is focused on a specific sexual outcome, e.g., erection or orgasm or the act of intercourse, and this is precluded by the neurologic condition, dissatisfaction may be so profound as to quickly limit further activity.

Figure 2.2 illustrates how all points of the circular sexual response cycle are vulnerable to neurologic disease and its consequences to patients and their sexual relationship.

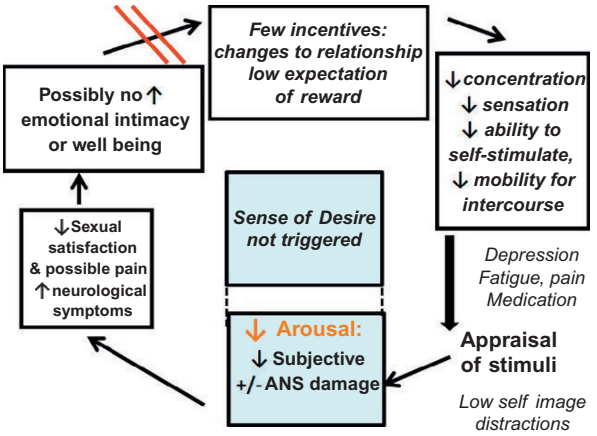

Fig. 2.2. The sexual response cycle may be weakened at all stages by neurologic disease. Incentives lessen as intimacy between partners is altered and expectation of reward fades. Reduced sensation and mobility limit the effectiveness of stimulation. Attention to stimuli is interrupted by distractions about illness or sexual outcome or by difficulties in concentration. Appraisal of stimuli is negatively affected by depression, medication, or pain, thereby precluding subjective arousal. A sense of desire may not be triggered. Autonomic involvement limits physical arousal and orgasm. The outcome is unsatisfactory and lessens any future motivation. ANS, autonomic nervous system. (Adapted from Basson, 2001b.)

Functional brain imaging

Functional neuroimaging techniques have become one of the key approaches to understanding the neural correlates of sexual response. A detailed review of some 73 published studies, mostly on healthy male heterosexual volunteers, has led to a model that includes multiple facets of sexual arousal (Stoléru et al., 2012). Brain regions related to the different components of sexual arousal are being delineated. This research also identifies inhibitory processes. Brain imaging during mostly visual sexual stimulation (a minority of studies employed tactile stimulation) engages complex circuitry, with lessening of inhibition combined with sexual excitation.

In keeping with the current circular model of sexual response (depicting sexual incentives or motivations, information processing, overlap of arousal and desire, emphasis on subjective as well as physiologic arousal, plus importance of reward), the model of sexual arousal emanating from the neuroimaging data comprises cognitive, motivational, emotional, and autonomic components (Fig. 2.3). The cognitive component includes appraisal of potentially sexual stimuli, focused attention

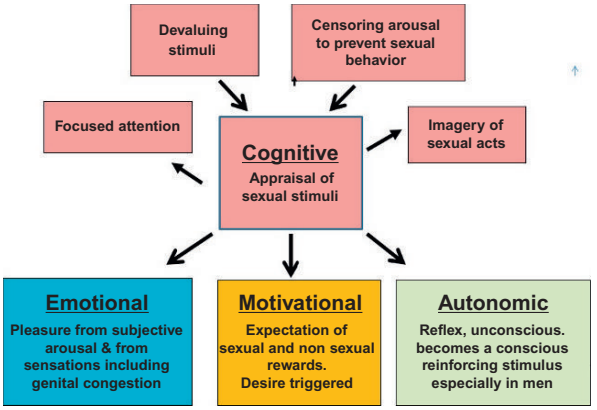

Fig. 2.3. Brain areas activated during sexual arousal to allow: (1) continued focus on sexual stimuli, imaging of sexual behavior, evaluation/censorship, and limitation or prevention of actual behavior despite arousal (all constituting a cognitive component of arousal); (2) sexual feelings (an emotional component); (3) anticipation of reward (a motivational component); and (4) an autonomic/ neuroendocrine response of physical sexual arousal. (Adapted from Basson and Weijmar Schultz, 2007.)

on those deemed erotic, and motor imagery in relation to sexual behavior. The activations of the right lateral orbitofrontal cortex, of the right and the left inferior temporal cortices, of the superior parietal lobules, and of areas belonging to the neural network mediating motor imagery (inferior parietal lobules, left ventral premotor area, right and left supplementary motor areas, cerebellum) are considered to be the neural correlates of the cognitive component. The motivational component comprises the processes that direct behavior to a sexual goal, including the perceived urge to express overt sexual behavior. Thus, the motivational component is conceptualized as including the experience of sexual desire. Neural correlates are thought to be the anterior cingulate cortex, claustrum, posterior parietal cortex, hypothalamus, substantia nigra, and ventral striatum. The emotional component is the brain activity underlying the pleasure from the mental excitement and the perceiving of bodily changes, especially those of the genital response. This pleasure comprises "liking" and "wanting" (Berridge, 1996). The left primary and secondary somatosensory cortices, the amygdalae, and the right posterior insula are conceived as neural correlates of this emotional component. The autonomic and neuroendocrine component includes various responses (e.g., genital, cardiovascular, respiratory, changes in hormonal plasma levels), leading subjects to a state of physiologic readiness for sexual behavior: activations in the anterior cingulate cortex, anterior insulae, putamens and hypothalamus contribute to this component.

From studying the deactivations with sexual arousal, three components of inhibition are envisioned:

1. inhibition mediated by regions in the temporal lobes and the gyrus rectus of the orbitofrontal cortex in the resting state. Patients with lesions in the gyrus rectus are noted to have excessive appetite for sexual and other pleasurable activities (Miller et al., 1986). Temporal-lobe involvement is consistent with the marked hypersexuality of Klüver–Bucy syndrome (Devinsky et al., 2010). The deactivated temporal regions are distinct from those activated in response to visual sexual stimuli
2. inhibition of arousal once it has begun, e.g., to limit its expression, is mediated in the caudate nucleus and putamen. This is consistent with reports of hypersexuality associated with lesions in the head of the caudate nuclei (Richfield et al., 1987)
3. cognitions related to undermining of sexual stimuli, mediated by failure of the left orbitofrontal cortex to deactivate.

It is of interest that those regions thought to mediate inhibition of sexual arousal have been found to be activated during tasks that require moral judgments and those that involve guilt and embarrassment (Takahashi et al., 2004).

SEXUAL DYSFUNCTIONS

A circular sexual response cycle of overlapping phases of variable order reflects the well-documented typical comorbidity of dysfunctions in women (Lewis et al., 2010). Recent study suggests similar comorbidity is also frequent in men. Low desire in 1350 men, unassociated with psychopathology, hypogonadism, or hyperprolactinemia, was comorbid with ED, premature ejaculation, and delayed ejaculation in 38%, 28%, and 50% respectively (Corona et al., 2013). Using structural equation modeling, in a different study of 406 men with sexual problems, a model emerged linking low desire, ED, and orgasm delay (Carvalho et al., 2011). This is in keeping with clinical experience of a global sexual disorder in men, especially men with chronic disease. Unfortunately, many physicians view ED as synonymous with male sexual dysfunction (Carvalho et al., 2011). Similarly, ED has been the major focus of research and clinical attention. The most frequently used validated questionnaires are the International Index of Erectile Function and Female Sexual Function Index. However, these questionnaires reflect a non-evidence-based conceptualization of sexual response simplified as a linear entity of discrete sequential phases, beginning with desire at the outset of sexual activity, arousal that is focused on genital events rather than subjective excitement, followed by orgasm and resolution: dysfunctions are considered phase-specific. Thus there is uncertainty as to the true prevalence of sexual disorders, as currently understood in both health and in neurologic disease (Althof et al., 2005).

CONCLUSION

This current conceptualization of human sexual response guides the assessment and management of sexual dysfunction associated with neurologic illness. Assessment of the various stages of the circular incentives or motivations-based response cycle allows the clinician to create the patient's own cycle (Fig. 2.2). The various areas of vulnerability or weakness are clarified: patients sees the logic to their situation. This in itself is therapeutic. The role of the neurologic condition and its treatment is explained: interruption of sexual neurophysiology may have reduced genital sensation and caused orgasmic, erectile, or lubrication dysfunction, or sexual pain. Thus the outcome is no longer rewarding and motivation fades. One aspect of sexual rehabilitation will be the treatment of these dysfunctions. The consequences of living with the condition also disrupts the sex response cycle and can be addressed:

attention can be directed at changes within the relationship and the need for more potent sexual stimuli and optimal sexual environment. Impairment of the brain's appraisal of sexual stimuli from distractions, depression, and lowered self-image is explained and further guides treatment.

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 3

Anatomy and physiology of genital organs – men

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INTRODUCTION

Amongst all physiologic functions, those related to reproduction are probably uniquely essential for the survival of the living species without being vital for the individual. The goal of sexual functions is to allow and optimize reproduction, with the exception of humans and some primate species that can seek sexual relationships only for the pleasure they provide. The human male sexual response consists of desire, excitation (erection), orgasm (ejaculation), and resolution (Levin, 2000). In the absence of a pathologic state, the production of fertilizing gametes in the human male begins at puberty and extends over the entire lifespan. Erection and ejaculation allow optimal insemination of the female partner and are controlled by a complex and coordinated interplay of multiple systems involving the brain, spinal cord, and relevant peripheral organs.

A description of the anatomic organization and innervation of the genitosexual organs and anatomic structures participating in male sexual response is provided in this chapter. In addition, the physiologic mechanisms underlying sexual response and its control by the central nervous system are addressed.

ANATOMY OF GENITOSEXUAL ORGANS

Penis

The main component of the penis is constituted of three cylindrical spongy bodies containing erectile tissue: the paired corpora cavernosa on the dorsal side and the corpus spongiosum surrounding the distal segment of the urethra (penile urethra) on the ventral side of the penis (Fig. 3.1). Proximally, the corpora cavernosa divide bilaterally to form the roots of the penis (penile crura) which attach to the perineum via the ischiopubic ramus. Distally, the corpus spongiosum expands and covers the distal part of the corpora cavernosa to form the penile glans. Corpora cavernosa and corpus spongiosum share common histologic features which consist of sinuses (trabeculae) lined by endothelium and separated by connective tissue septa deriving from the tunica albuginea. This organization explains the spongy appearance of erectile tissue. A multilayered structure of inner circular and outer longitudinal layers of connective tissue, namely the tunica albuginea, envelops the corpora cavernosa.

The tunica albuginea with unique biomechanic properties is composed of fibrillar collagen interlaced with elastin fibers and affords great flexibility, rigidity when stretched, and tissue strength to the penis. The inner coat contains the cavernosal erectile tissue and supports it by radiating throughout the cavernosum bodies. The outer coat extends from the penile glans to the proximal crura and provides strength to the tunica albuginea. Deep (Buck's) and superficial fasciae envelop the tunica albuginea and enclose penile blood vessels and nerves. The penile skin is continuous with that of the abdominal wall and covers the glans of the penis as the prepuce to reattach at the coronal sulcus. The skin of the penile shaft has no hair follicle, eccrine sweat or sebaceous glands, except at the base of the glans corona, where smegma is produced.

Vascularization of the penis is of particular importance in erectile function (Fig. 3.1), with cardiovascular diseases being major causes of erectile dysfunction. The internal iliac artery gives rise to the internal pudendal artery which provides the main blood supply to the

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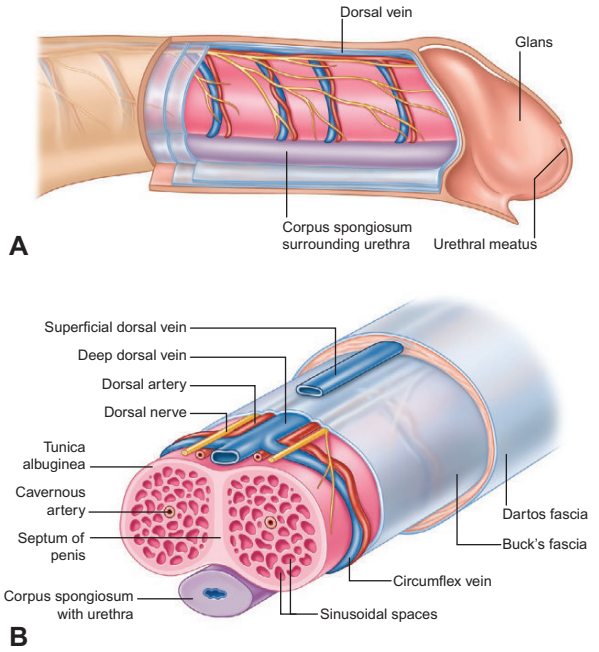

Fig. 3.1. (**A, B**) Transverse section of the penis illustrating the anatomy, vascularization, and innervation of the organ. (Reproduced from Standring, 2009).

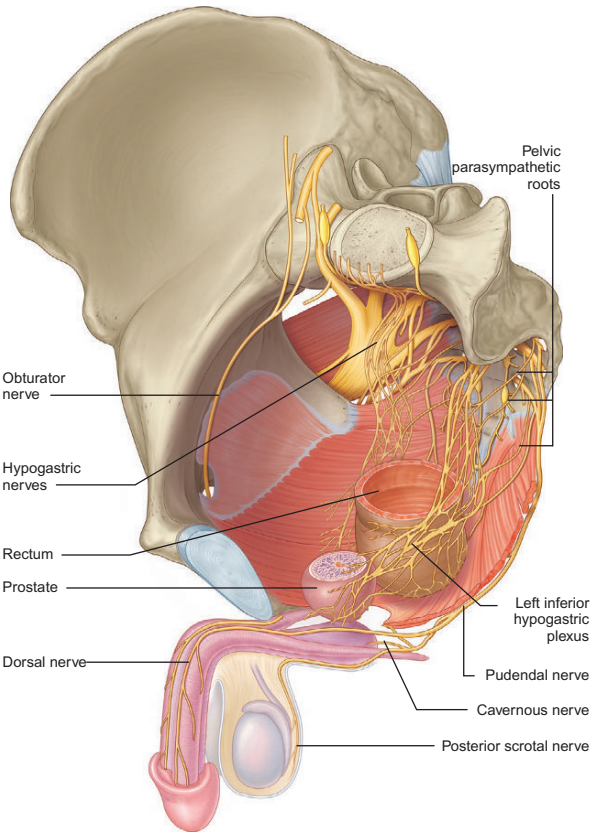

Fig. 3.2. Innervation of genitalia. (Reproduced from Standring, 2009.)

penis. Alternatively, arterial blood can be provided to the erectile tissue by accessory internal pudendal arteries. The internal pudendal artery continues in Alcock's canal to become the common penile artery and then terminates in three branches: the bulbourethral, cavernosal, and dorsal penile arteries. The bulbourethral artery vascularizes urethra, corpus spongiosum, and glans. The cavernosal arteries, which run in the corpora cavernosa, furnish the erectile tissue with blood with terminal branches, helicine arteries, providing arterial supply to every trabecula. The dorsal penile artery runs on the dorsal aspect of the penis to supply superficial penile components. Note that penile arteries show high interindividual variability in branching, courses, and anastomoses (Bare et al., 1994).

The venous drainage system of the penis occurs at three levels (Fig. 3.1). Superficially, on the dorsal aspect of the penis, the superficial dorsal vein drains the skin into the external pudendal veins. The intermediate system consists of the deep dorsal and circumflex penile veins. The deep dorsal vein receives blood from emissary veins, which arise from subtunical venules draining trabeculae and passing through the tunica albuginea and circumflex veins. In the infrapubic region, the deep dorsal vein drains into the pelvic preprostatic venous (Santorini's) plexus or the internal pudendal veins. The deep drainage system includes the crural and cavernosal veins that drain the deeper cavernous tissue and empty into the internal pudendal veins.

Autonomic innervation of smooth-muscle cells of the erectile tissue is provided by the cavernous nerve which runs close to the prostate at its dorsolateral aspect and can be damaged during radical prostatectomy, leading to erectile dysfunction (Fig. 3.2). Sensory innervation of the penis is derived from the pudendal nerves and their terminal branches, i.e., the dorsal nerves of the penis (Fig. 3.2). The dorsal nerve of the penis carries sensory impulses to the upper sacral segments (S2–4) of the spinal cord from sensory receptors harbored in the penile skin, prepuce, and glans. Encapsulated receptors (Krause–Finger corpuscles) have been found in the glans but the majority of afferent terminals are represented by free nerve endings (Halata and Munger, 1986).

Testes

The testes are suspended and maintained in position within the scrotal cavity by the various structures constituting the spermatic cord. The testicular parenchyma is enclosed in a tough capsule made up of three layers. Multiple septa from the capsule radiate into the parenchyma to form several hundred cone-shaped lobules, each of which contains one or more tortuous seminiferous tubules (Fig. 3.3). These tubules converge at the

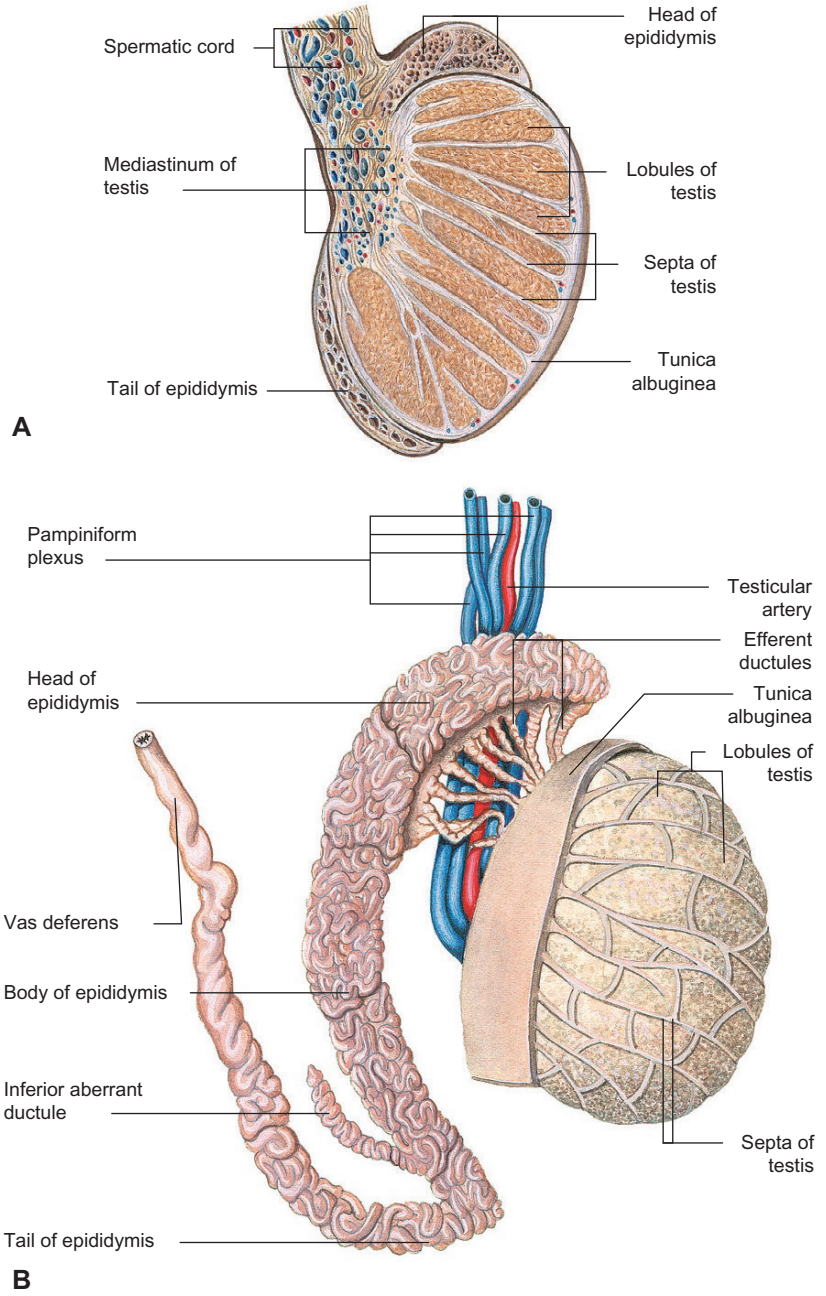

Fig. 3.3. (**A, B**) Sagittal representation of the testis illustrating the organization of the tubules transporting spermatozoa. (Reproduced from Standring, 2009.)

hilar region of the testis (mediastinum testis) where they become straight and anastomose to form the rete testis. The tubules of the rete testis empty into the efferent ducts through which spermatozoa migrate to the epididymis. Seminiferous tubules are lined with a basement membrane which supports the germinal epithelium and the sustentacular Sertoli cells. The intertubular connective tissue contains the androgens-producing Leydig cells.

Two spermatic nerves (superior and inferior) innervate male gonads. The superior spermatic nerve, the major contributor of testicular innervation, originates in the renal and aortic plexi and runs caudally with the gonadal vessels. The parasympathetic component of the nerve originates from the vagus nerve. The inferior spermatic nerve, which contains testicular afferents and efferents, arises from the pelvic plexus, travels in association with the vas deferens to reach the testis at

its lower pole. It is generally accepted that autonomic nerves of the gonads play a physiologic role in vasomotor control, secretion of exocrine glands, and in the contraction of tubular smooth muscles. In addition, testicular function is under the control of the hypothalamic–pituitary axis.

Epididymis

Anatomically, the epididymis, located at the superior pole of the testes, is divided into three segments: the caput proximal to the testis, the corpus, and the cauda. The epididymal tubule (3–4 meters in length; Turner et al., 1978) is coiled and encapsulated within the tunica vaginalis to form the ductus epididymis. Contractile smooth-muscle cells surround epididymal duct and exhibit rhythmic contractions spontaneously and upon neural stimulation. Distally, the ductus epididymis gradually assumes the features of the ductus deferens. Innervation of the epididymis is mainly provided by the inferior spermatic nerve carrying sympathetic fibers. Non-adrenergic, non-cholinergic (NANC) fibers containing the neurotransmitters vasoactive intestinal peptide, neuropeptide Y (NPY), calcitonin gene-related peptide (CGRP), substance P (SP), and nitric oxide (NO) are present in the epididymis (Owman and Stjernquist, 1988). The functions of the epididymis are to allow migration of the spermatozoa from the testicular efferent ducts to the ductus deferens and to sustain the biologic process during which spermatozoa acquire motility and fertility maturity.

Ductus deferens

The ductus (or vas) deferens is a tubular structure with a narrow lumen (approximately 5 mm in diameter) surrounded by a thick muscular coat that is made up of circular and longitudinal muscle layers. Dual adrenergic and cholinergic innervations arising from the pelvic plexus have been reported (Alm, 1982). The sympathetic system contributes the highest density of fibers reaching the ductus deferens; the adrenergic innervation forms an extensive plexus throughout the muscle layers (Carvalho et al., 1986). Most of the cholinergic fibers are concentrated close to the epithelium (Yamauchi and Burnstock, 1969). NANC innervation, including VIP, NPY, and NO, is present in the ductus deferens (Owman and Stjernquist, 1988). Immediately before the emission phase of ejaculation, rapid and effective transport of spermatozoa occurs from the distal cauda of epididymis to the proximal ductus deferens due to sympathetic innervation stimulation. In addition, sympathetic tone controls peristaltic contractions throughout the ductus deferens that drive spermatozoa to the ampulla deferentia of the ductus deferens, which acts as a reservoir. The ampulla deferentia, located proximal to the prostate and adjacent to the seminal vesicles, fuses with the central ducts of the seminal vesicles to form the ejaculatory ducts.

Seminal vesicles

Seminal vesicles, measuring 2–4 cm in length and 1–2 cm in diameter (Kim et al., 2002), are paired and lie behind the posterior wall of the bladder and consist of epithelial tubular alveoli (goblet cells) separated by thin layers of elastic fibrils and smooth-muscle cells. The seminal vesicles produce a fluid enriched in fructose which contributes 50–80% of the entire ejaculatory volume (King et al., 1991). Sympathetic and parasympathetic fibers coming from the pelvic plexus terminate in the seminal vesicles. The adrenergic innervation to the seminal vesicles is distributed throughout the smooth-muscle layers. In contrast, the cholinergic nerve endings are located at the level of the rich glandular epithelium of the seminal vesicles. NANC fibers (VIP, NPY, SP, and NO) provide additional innervation to the seminal vesicles (Owman and Stjernquist, 1988). Emitted seminal fluid can be stored within the lumen of the seminal vesicles until the emission phase of ejaculation occurs. At that time, the fluid is injected into the ejaculatory ducts via strong contractions of smooth-muscle cells. The ejaculatory ducts traverse the prostate and open into the prostatic urethra in a prominent structure called verumontanum (Fig. 3.4).

Prostate

The size of the prostate gland varies with age. It is divided into five lobes (anterior, posterior, median, and two laterals) that surround the proximal urethra (prostatic urethra) from the bladder neck to the urogenital diaphragm (Fig. 3.4). The prostatic tissue is composed of alveoli lined with columnar glandular epithelium embedded in the relatively thick fibromuscular stroma. A capsule constituting collagen, elastin, and smooth-muscle cells in high density encloses the prostatic epithelium and stroma. The prostate receives sympathetic and parasympathetic fibers traveling through the cavernous nerves from the pelvic plexus. Parasympathetic nerve endings are found in the glandular acini and promote excretion of prostatic fluid. The sympathetic fibers terminate in the vicinity of the prostatic smooth-muscle cells in the stroma and capsule of the prostate. Radioautographic investigations carried out in human prostates indicate that α_1-adrenoreceptors are predominant (Chapple et al., 1989). In addition, the prostate receives NANC (VIP, NPY, and NO) fibers (Owman and Stjernquist, 1988). During the emission phase of ejaculation, smooth-muscle cells contract to express

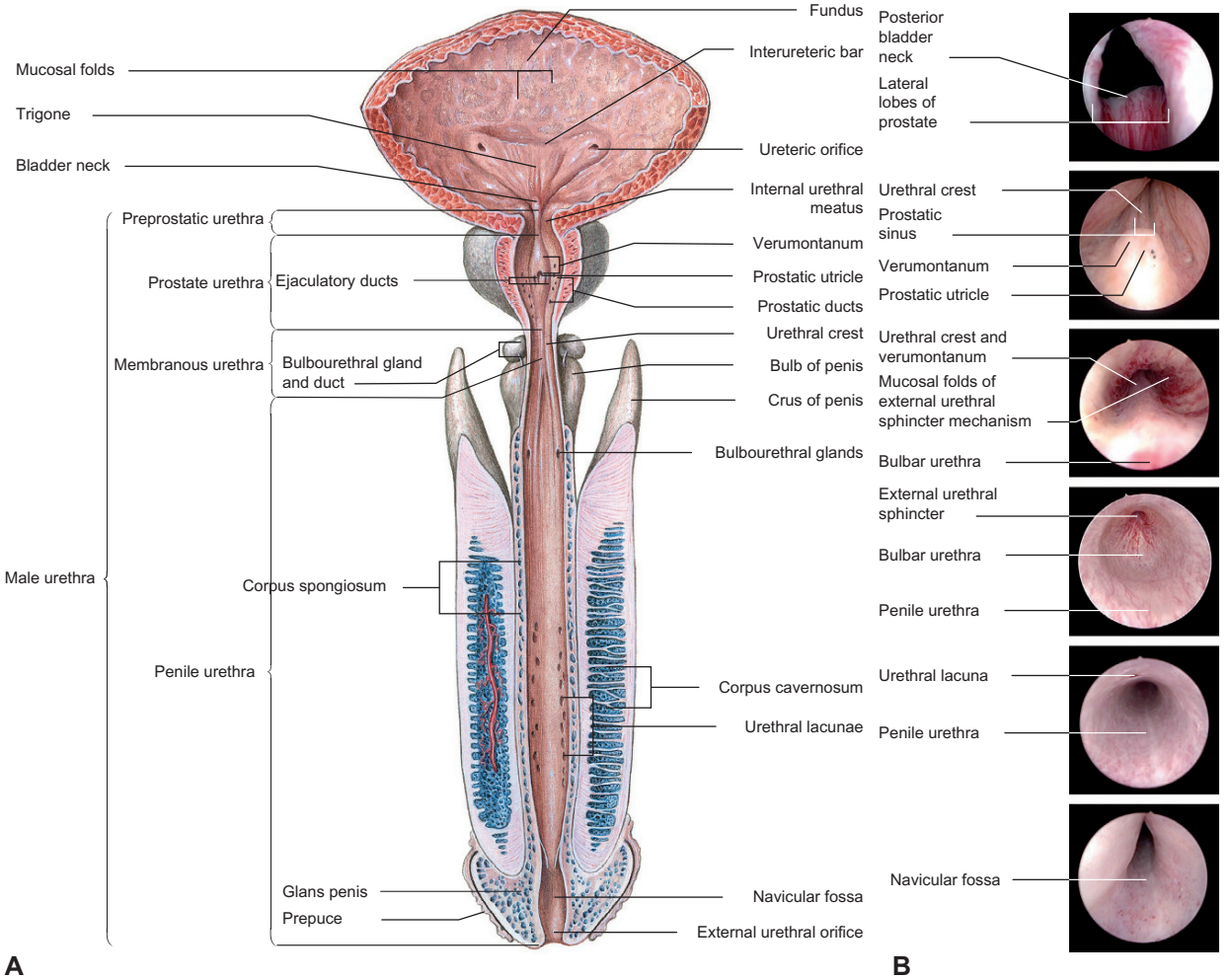

Fig. 3.4. (**A, B**) Longitudinal section of the penis illustrating male urethra and ejaculatory ducts. (Reproduced from Standring, 2009.)

prostatic secretion into the urethra via several orifices in the verumontanum. There, prostatic fluid, which is slightly alkaline and rich in sugars and zinc, is mixed with spermatozoa, providing them with higher motility and longevity.

Urethra

The male urethra can be divided into three main segments that are, from the bladder neck to the urethral meatus: prostatic, membranous, and anterior or (penile) urethra. The urethral epithelium is surrounded by smooth-muscle fibers. Noradrenergic, cholinergic, and NANC (VIP and NO) neural fibers conveyed by the cavernous nerve terminate into the urethral wall. At the junction between bladder and urethra, three smooth-muscle fiber layers are distinguished with longitudinal (inner and outer layers) and circular (intermediate layer) orientations. This tissue organization forms the bladder neck (or internal urethral sphincter; Fig. 3.4) that contributes to urinary continence but also plays a key role in ejaculation. Strong contraction of the bladder neck occurring during the expulsion phase of ejaculation prevents sperm flowing backwards into the bladder and thereby causing retrograde ejaculation.

The bladder neck is richly innervated by the sympathetic nervous system, via hypogastric and pelvic nerves, and expresses preferentially α_1-adrenoreceptors (Michel and Vrydag, 2006). Surgical damage to these nerves or impairment of their function (e.g., in diabetic patients) may be responsible for insufficient bladder neck contraction, resulting in retrograde ejaculation. At the level of the membranous urethral segment, a layer of striated muscle (external urethral sphincter) circles the urethra. At the time of the expulsion phase of ejaculation, the external urethral sphincter exhibits intense rhythmic contractions interrupted by periods of silence, allowing sperm passage to the distal urethral segment and further

to the urethral meatus. The external urethral sphincter is under the control of motoneurons and axons travel in the pudendal nerve.

Embedded in the urogenital diaphragm, between the fascia and the external urethral sphincter, are the bulbourethral (Cowper's) glands (Fig. 3.4). This pair of pea-sized glands opens into the membranous urethra at the base of the penis, where they pour cleaning and lubricating excretion during sexual arousal to facilitate sperm flow. The epithelium of the penile urethra contains small tubular glands (Littré's glands) that produce mucus, protecting the epithelium from urine.

Perineal striated muscles

Two perineal striated muscles (ischiocavernosus and bulbospongiosus (BS) muscles) have an important role in the male sexual response (Fig. 3.5). The paired fusiform ischiocavernosus muscles attach to the ischial tuberosities and ischiopubic rami of the pubic bone and partially cover the penile crurae. The main function of the ischiocavernosus muscles is to provide extra rigidity of the erected penis by compressing the penile crus during the rigid phase of erection.

The BS muscle arises from the central point of the perineum and from the median raphe. It envelopes the bulb of the corpus cavernosum, encircles corpora cavernosa and corpus spongiosum, and attaches to the perineal membrane and dorsum of the penis. The major function of the BS muscle is to act as a pump that forcefully propels sperm out of the body from the prostatic urethra to the urethral meatus during the expulsion phase of ejaculation. Rhythmic intense contractions of the BS muscle are concomitant with orgasmic feeling accompanying ejaculation. Somatic motor system contributes the innervation of perineal striated muscles via motoneuron axons conveyed by the pudendal nerves.

Innervation of the genitalia

The innervation of the genitosexual tract consists of autonomic (sympathetic, parasympathetic, and NANC) and somatic (motor and sensory) innervations. Most of the organs and anatomic structures participating in the peripheral male sexual responses are under autonomic influences. The predominant tone results from the balance between sympathetic and parasympathetic

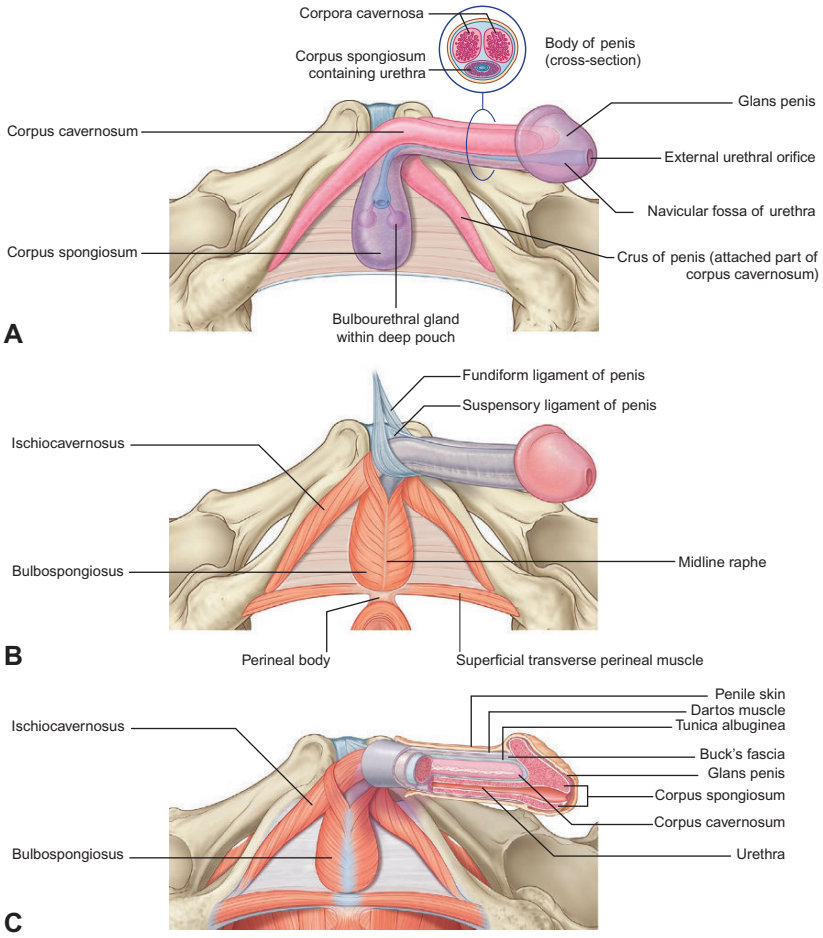

Fig. 3.5. (**A–C**) Major perineal striated muscles. (Reproduced from Standring, 2009.)

systems while the NANC system exerts a modulatory role. However, the action of NANC transmission can be major (e.g., NO release in erectile tissue during erection).

Cell bodies of sympathetic preganglionic neurons are located in the 12th thoracic to the second lumbar spinal cord segments (T12–L2; Fig. 3.6). The sympathetic preganglionic fibers run in the thoracic paravertebral sympathetic chain and then, via the lumbar splanchnic nerves, reach the inferior mesenteric and superior hypogastric plexi. These plexi compose the prevertebral ganglia where preganglionic neurons synapse with their postganglionic counterparts. Sympathetic postganglionic fibers travel via the hypogastric nerves to the pelvic plexus (Figs 3.2 and 3.6). In addition, sympathetic preganglionic axons synapse with postganglionic neurons in the caudal lumbar and sacral ganglia of the paravertebral sympathetic chain and then, postganglionic fibers reach the pelvic plexus via the pelvic nerves (Fig. 3.6).

The parasympathetic preganglionic fibers originate in neurons lying in the intermediolateral cell column of the second to the fourth sacral spinal cord segments (S2–4). The parasympathetic preganglionic fibers traveling via the pelvic nerve synapse with postganglionic neurons in the pelvic plexus (Figs 3.2 and 3.6). From the pelvic plexus, which actually results from the junction between hypogastric and pelvic nerves, arise various nerves (e.g., cavernous nerves) providing innervation to the different organs and anatomic structures involved in erection and ejaculation.

Axons of somatic motoneurons, whose cell bodies are found at the sacral (S2–4) spinal level in Onuf's nucleus, exit the ventral horn of the medulla and proceed via the motor branch of the pudendal nerve to the pelvic floor striated muscles (Figs 3.2 and 3.6), including BS and ischiocavernosus muscles as well as the external urethral sphincter.

The genitalia are abundantly supplied with sensory nerve endings of different types but their exact physiologic role is not always clear. Some sensory receptors are located around blood vessels while others are concentrated in skin or parenchyma. The major sensory pathway involved in the male sexual response consists of projections traveling in the pudendal nerve from primary sensory neurons whose cell bodies are located in sacral (S2–4) dorsal root ganglia (Fig. 3.6). A second afferent pathway is constituted by fibers traveling along the hypogastric nerve and, after passing through the paravertebral lumbosacral sympathetic chain, enters the spinal cord via thoracolumbar (T12–L2) dorsal roots (Fig. 3.6). Central projections of primary sensory neurons innervating genitalia terminate in the dorsal horn and intermediate area in the corresponding spinal segments.

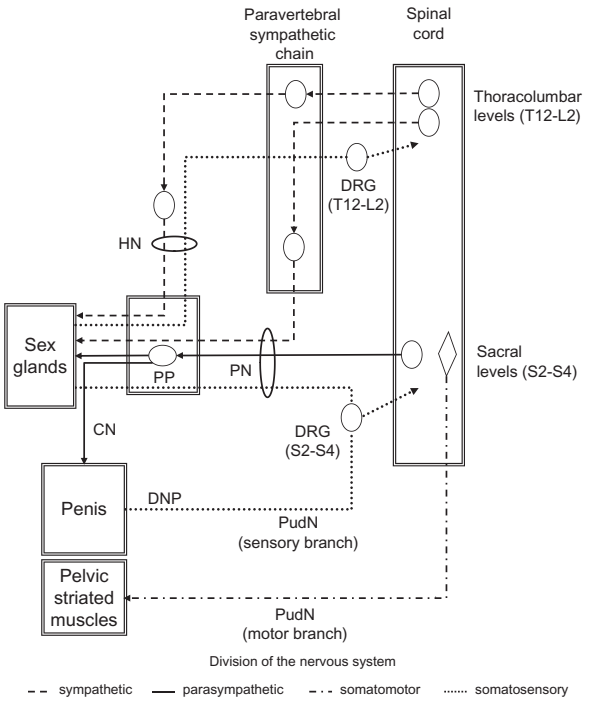

Fig. 3.6. Schematic view of the autonomic and somatic innervation of genitalia. Neural pathways involved in erection and ejaculation are indicated. CN, cavernous nerve; DNP, dorsal nerve of the penis; DRG, dorsal root ganglia; HN, hypogastric nerve; PN, pelvic nerve; PP, pelvic plexus; PudN, pudendal nerve.

PHYSIOLOGY OF MALE SEXUAL RESPONSE

The use of experimental models in the field of sexual medicine is critical. Indepth investigations into the physiology, cell biology, biochemistry, and pharmacology of male sexual responses are rarely feasible in humans. Therefore, much of our understanding of the mechanisms of male sexual function comes from animal studies.

Testicular functions

The testes are part of the reproductive (exocrine) and endocrine systems as they produce spermatozoa and androgenic hormones. Both testicular functions are under complex, finely regulated control of the hypothalamic–pituitary axis.

Hypothalamic–pituitary–testicular axis (Fig. 3.7)

The hypothalamus, especially the preoptic area and arcuate nucleus, secretes gonadotropin-releasing hormone (GnRH) in the hypophyseal portal blood stream in the median eminence that connects the hypothalamus and pituitary gland. Then, GnRH reaches the anterior lobe of the pituitary gland (adenohypophysis) where it stimulates synthesis and release in the blood circulation of

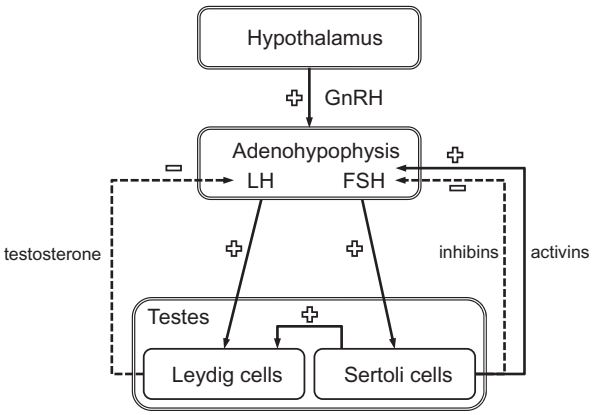

Fig. 3.7. Hypothalamic–pituitary–testicular axis. Leydig cells produce testosterone and Sertoli cells contribute to spermatogenesis. FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by endocrine cells (gonadotropic cells). LH acts on specific receptors expressed on Leydig cells to activate the production and secretion of sex hormones, notably testosterone, dihydrotestosterone (DHT), and, in smaller amounts, estradiol. FSH binds to its receptors located on Sertoli cells to promote spermatogenesis. In addition, FSH enhances testosterone synthesis by Leydig cells through paracrine mechanisms involving Sertoli cells.

Both LH and FSH are released by adenohypophysis gonadotropic cells in a pulsatile manner due to pulsatile secretion of GnRH by neurons of the hypothalamic nuclei. Activity of GnRH-producing neurons is regulated by central catecholamines and neuropeptides (Hrabovszky and Liposits, 2013). Prolonged activation of GnRH receptors on adenohypophysis gonadotropic cells leads to receptor desensitization and loss of responsivity to GnRH. Analogs of GnRH which cause receptor downregulation are used in the palliative treatment of androgen-dependent prostate cancers. Testosterone, 95% of which is produced by Leydig cells, exerts a negative feedback on LH release by decreasing the frequency of peaks in GnRH release and lowering gonadotropic cell sensitivity to GnRH. Secretion of FSH is regulated by inhibitory and activatory gonadal peptides (inhibins and activins, respectively) produced by FSH-stimulated Sertoli cells (Halvorson and DeCherney, 1996). These peptides regulate FSH signaling specifically but also act as paracrine factors modulating spermatogenesis (Ying et al., 1997).

Actions of androgens

In most androgen-sensitive tissues, free plasma testosterone, which passively diffuses into cell cytoplasm, is converted into DHT by the enzyme 5α-reductase and estradiol by the aromatase CYP19. These hormones mediate most of the biologic actions of androgens. Testosterone and DHT bind to the intranuclear androgen receptor to form the androgen receptor complex, which interacts with specific gene-regulatory elements, modulating the expression of various genes. Androgen receptor affinity is higher for DHT than for testosterone. In addition, androgen receptors are capable of binding adrenal androgens (e.g., dihydroepiandrosterone and androstenedione) and non-androgen steroids (e.g., progesterone and estradiol), although with a relatively low affinity.

Androgen receptors are expressed in a wide variety of tissues, explaining the large range of action of androgens. Differential effects of testosterone and DHT have been identified. The testosterone receptor complex downregulates LH secretion, stimulates spermatogenesis (paracrine action), and is responsible for the virilization of the wolffian ducts during embryogenesis, which develop into seminal vesicles, epididymis, and vas deferens. The DHT receptor complex has a primary role in the formation of male external genitalia during embryogenesis and is the molecular substratum for most of the actions of androgens during sexual maturation and adult sexual life. Decreasing DHT levels by administering inhibitors of 5α-reductase is a therapeutic strategy for the treatment of symptomatic benign prostate hyperplasia.

There is evidence for a role of testosterone in sexual response in men, although its exact role is incompletely understood (Randeva et al., 1999). Castration causes a marked decline in sexual interest and desire (libido) and, in most men, alteration (but not suppression) of erectile function. On the other hand, some men reported sexual intercourse for up to 20 years after castration (Heim and Hursch, 1979) and no clear correlations have been found between plasma levels of testosterone and erectile function (Mills and Lewis, 1999). Hypogonadal men have impaired sexual functions, some of which can be improved after testosterone supplementation, and this usually leads to increased frequency of masturbation or intercourse (Buris et al., 1992). The most consistently recovered sexual response after testosterone replacement is libido, whereas erectile response is partially ameliorated: nocturnal penile tumescence is significantly improved but not erection in response to erotic movies (Carani et al., 1995).

Administration of antiandrogens or GnRH agonists impairs the different aspects of the male sexual responses. From these observations a cerebral site of action for testosterone is suggested. This view is supported by neurohistologic data in humans, reporting androgen receptor expression in various brain structures

involved in the control of sexual response and sexual dimorphism regarding density of these receptors (Fernandez-Guasti et al., 2000). In the male rat, androgen receptors have been detected in the same brain structures and were found to be activated in relation to sexual activity (Gréco et al., 1996). In the central nervous system, androgens interfere with dopamine, serotonin, oxytocin, and NO systems (Du and Hull, 1999; Fink et al., 1999) involved in the neurochemical control of sexual responses. Modulation of neurotransmission in brain and spinal cord areas belonging to the network controlling sexual responses represents a mechanism of action of androgens (more particularly testosterone) in male sexuality.

Spermatogenesis

In the adult man, $200–300 \times 10^6$ spermatozoa are produced each day in the testes and it takes 70–75 days for a primordial germ cell to divide and differentiate into spermatozoa. The process of spermatogenesis is divided into five stages, each characterized by a particular cell type. The first stage corresponds to spermatogonia – diploid cells located in the basal area of the seminiferous tubule. Spermatogonia divide (mitosis) into diploid primary spermatocytes (stage 2) which migrate toward the lumen of the seminiferous tubule. Primary spermatocytes undergo meiosis to give haploid secondary spermatocytes (stage 3), which in turn are subject to a second meiotic division forming haploid spermatids (stage 4). Then spermiogenesis takes place, corresponding to the maturation of spermatids leading to spermatozoa (stage 5). Spermatozoa are released in the lumen of the seminiferous tubule and are transported in secretions of Sertoli cells to the epididymis where they undergo final maturation (acquisition of motility and fertility).

Both androgens mainly produced by Leydig cells and FSH released from adenohypophysis stimulate spermatogenesis. Androgens, and notably testosterone, have an essential role in spermatogenesis. High concentrations of androgens must be reached locally in order for spermatogenesis to be initiated and maintained. Androgen-binding protein synthesized by Sertoli cells allows androgens to reach such a high concentration in seminiferous tubules. The gonadotropin FSH is not essential for spermatogenesis although, through stimulation of Sertoli cells, it increases the number of spermatozoa and promotes their maturation. Spermatogenesis is also regulated by multiple factors (paracrine and autocrine), including cytokines, growth factor, and temperature. In humans, the optimal temperature for spermatogenesis is 2 °C below body temperature and this is achieved through regulation of testicular blood flow and the positioning of the testes outside the body.

Penile erection

Two types of erection (reflexogenic and psychogenic) can be distinguished depending on the level where it is initiated. Reflexogenic erection is due to genital (mainly penile) stimulation, whereas psychogenic erection is due to sexual signals/cues (visual, auditory, olfactory, or fantasy) processed or generated in the brain. Reflexogenic and psychogenic erections have in common the spinal and peripheral executive mechanisms involved in penile erection. The pudendal nerves conveying genital stimuli to sacral (S2–4 segments) spinal cord and the cavernous nerves containing parasympathetic fibers en route to the penis constitute the afferent and efferent branches, respectively, of the penile reflex. This reflex is under brain influence but persists in spinal cord-injured men with complete lesion, provided sacral segments are not damaged. Psychogenic erection occurs in the absence of genital stimuli and is elicited when brain excitatory outputs generated in specific brain regions activate the sacral neurons involved in erection. During sexual intercourse or masturbation reflexogenic and psychogenic erection mechanisms act in synergy.

Changes in the penis status during the male sexual response are characterized by five successive phases:

1. Flaccid phase: in the absence of erotic and genital stimuli, blood flow to the penis is low and trabecular content in the blood is small due to contraction of trabecular smooth-muscle fibers of the erectile tissue.
2. Tumescence phase: blood flow to the penis increases due to dilatation of penile arteries and blood accumulates in trabeculae due to relaxation of trabecular smooth-muscle fibers. Expanding trabeculae prevent venous drainage by compressing the emissary veins, thus trapping blood in erectile bodies and leading to full erection; this is the passive veno-occlusive mechanism.
3. Full erection phase: the volume of blood accumulated in the penis is high and intracavernosal pressure reaches the systolic blood pressure. In the absence of genital stimulation (e.g., psychogenic erection) penile rigidity shows no further increase.
4. Rigid erection phase: at full erection, genital stimulation induces a further increase in penile rigidity due to contraction of ischiocavernosus muscles (bulbocavernosal reflex). Blood inflow and outflow of the penis is completely shut down and intracavernosal pressure can exceed systolic pressure.
5. Detumescence phase: when sexual stimulation stops or after sexual climax (ejaculation), penile arterial blood flow diminishes and venous drainage

augments, leading to progressive evacuation of blood from trabeculae. At the end of the detumescence phase, the penis reverts to its flaccid state.

Peripheral control

Penile erection is engorgement of the penis with blood due to increased arterial supply and decreased venous drainage of trabeculae. Dilation of the penile arteries is responsible for increased blood flow into the trabeculae. Mechanical compression of emissary veins, which drain trabeculae, against the tunica albuginea and relaxation of trabeculae smooth cells reduce blood evacuation. Arterial vasodilation and distension of trabeculae rely upon a change in the tone of the arterial wall and trabecular smooth-muscle fibers, respectively. Smooth-muscle tone is regulated by a variety of chemical messengers that are released by autonomic nerve terminals and endothelial cells (Table 3.1). Chemical messengers interact either with specific receptors expressed at the surface of the smooth-muscle cells or with intracellular targets after diffusing through cell membranes.

Contracting factors

Tonic sympathetic input maintains the penile smooth-muscle cells contracted. Sympathetic nerve terminals release NA and NPY, which enhances NA action. NA, through activation of α-adrenoceptors (mainly α_1) expressed by cavernosal as well as penile artery smooth-muscle cells, plays a major role in flaccidity and detumescence (Traish et al., 1995). Endothelin-1, prostaglandin $F_{2\alpha}$, and angiotensin II are synthesized and released by local vascular endothelium and, through stimulation of the respective protein G-coupled receptors located on cavernosal smooth-muscle cells, participate in maintaining the penis in a flaccid state (Holmquist et al., 1990; Becker et al., 2001; Angulo et al., 2002).

Table 3.1

Main factors involved in the peripheral control of penile smooth-muscle tone. Erection occurs when the balance between contracting and relaxing factors (both neuronal and local) goes in favor of the latter

Source	Contracting factors	Relaxing factors
Nerve terminals	Noradrenaline Neuropeptide Y	Nitric oxide Acetylcholine Vasoactive intestinal peptide Calcitonin gene-related peptide
Endothelium	Endothelin-1 Prostaglandin $F_{2\alpha}$ Angiotensin II	Nitric oxide Prostaglandin E_1

Relaxing factors

Smooth-muscle relaxation in erectile tissue bodies depends on activation of the parasympathetic system, in which the most important neurotransmitters are acetylcholine and NO. The relaxing action of acetylcholine is indirect since cavernosal smooth-muscle cells are not equipped with cholinergic receptors. Acetylcholine has a dual action: stimulation of NO production from vascular endothelial cells and inhibition of NA release, i.e., reduction of sympathetic tone (Saenz de Tejada et al., 1988). NO is probably the most potent relaxing factor in the penis. It freely diffuses across cell membranes from the site of production (catalyzed by NO synthase) to the molecular targets in or at the surface of cavernosal smooth-muscle cells. NO is produced in parasympathetic nerve endings (neuronal NO synthase) and in the endothelium of blood vessels and trabeculae (endothelial NO synthase). VIP and CGRP, co-released with acetylcholine, are additional factors contributing to cavernosal smooth-muscle cell relaxation (Hedlund and Andersson, 1985). In addition to NO, endothelial cells produce prostanoids, such as prostaglandin E_1, which interact with their receptors located on cavernosal smooth-muscle cells, causing relaxation (Angulo et al., 2002).

Intracellular mechanisms

It is the amount of free calcium in the cytoplasm that controls the tone of smooth-muscle fibers. Higher concentration of cytoplasmic calcium, via its release from intracellular stores (sarcoplasmic reticulum) and its entry from the extracellular milieu (opening of L-type membrane calcium channels), causes smooth-muscle cell contraction. Conversely, activation of calcium ATPase in the membrane of sarcoplasmic reticulum, which pumps cytoplasmic calcium back into the intracellular store, and closure of L-type calcium channels result in decreased cytoplasmic calcium levels.

The cyclic nucleotides guanosine monophosphate (cGMP) and adenosine monophosphate (cAMP) have a key role in erection as intracellular second messengers (Fig. 3.8). They initiate a cascade of intracellular events, eventually leading to a decrease in cytoplasmic calcium concentration (i.e., smooth-muscle relaxation). Synthesis of cGMP and cAMP is catalyzed by guanylate and adenylate cyclases respectively and their degradation is achieved by phosphodiesterases. Selective inhibitors of

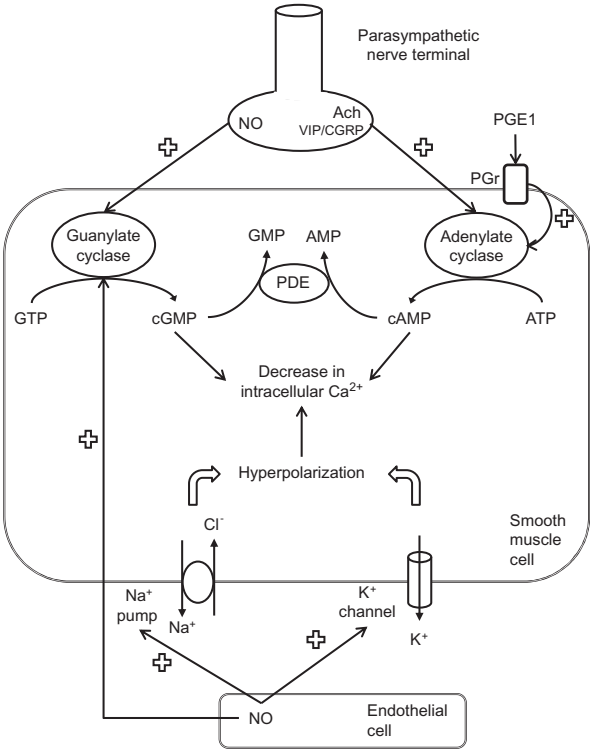

Fig. 3.8. Schematic representation of the processes leading to relaxation of penile smooth-muscle cells. Ach, acetylcholine; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; CGRP, calcitonin gene-related peptide; GTP, guanosine triphosphate; NO, nitric oxide; PDE, phosphodiesterase; PGE1, prostaglandin E_1; PGr, prostaglandin receptor; VIP, vasoactive intestinal peptide.

type 5 phosphodiesterase (sildenafil, tadalafil, vardenafil, and avanafil), which is preferentially distributed in the penis, enhance cavernosal smooth-muscle cell relaxation when impaired and have proven effective in the treatment of erectile dysfunction. Guanylate cyclase is activated by direct action of NO (Hobbs, 1997). Adenylate cyclase is activated by Gs protein, liberated after interaction between VIP or prostanoids and the corresponding protein G-coupled receptor (Andersson, 2001). Another mechanism responsible for smooth-muscle cell relaxation is hyperpolarization. It causes closure of voltage-dependent calcium channels, resulting in decreased calcium entry from the extracellular milieu and lower cytoplasmic calcium levels (Fig. 3.8). In cavernosal smooth-muscle cells, hyperpolarization occurs through opening of potassium channels and sodium/potassium ATPase (sodium pump). Regulation of potassium channel opening is dependent on cyclic nucleotides (both cGMP and cAMP), whereas activity of the sodium pump can be modulated by direct action of NO (Christ et al., 1993; Gupta et al., 1995).

Activation of the phospholipase C intracellular signaling pathway (including inositol triphosphate and protein kinase C as second messengers) induces calcium release from sarcoplasmic reticulum, opening of L-type calcium channels, and closure of potassium channels (depolarization), leading to smooth-muscle cell contraction. Binding of NA, endothelin-1, prostaglandin $F_{2\alpha}$, or angiotensin II with respective receptors, which are coupled with phospholipase C, activates this pathway (Andersson, 2001).

Because smooth-muscle fibers of the penile erectile tissues are connected with gap junctions, it is not required for chemical messengers to reach all of the cells to elicit a global effect. Indeed, gap junctions allow for a rapid spread of electric current and intercellular diffusion of second messengers and ions (Christ, 2000).

Spinal control

The spinal cord contains the three groups of neurons (thoracolumbar sympathetic, sacral parasympathetic, and sacral somatic) that are neurally connected with the penis and functionally involved in erection (reflexogenic and psychogenic). Most sympathetic preganglionic cell bodies whose axons run in the paravertebral sympathetic chain are located in the intermediolateral cell column of T12–L2 spinal segments. Other sympathetic preganglionic neurons, whose axons travel in the hypogastric nerve, originate in the dorsal gray column (Hancock and Peveto, 1979). The cell bodies of the preganglionic parasympathetic neurons are located in the intermediolateral cell column of the S2–4 segments of the spinal cord in an area referred to as the sacral parasympathetic nucleus. The sacral motoneurons are located in the ventral cord of the S2–4 spinal segments in Onuf's nucleus. Synchronized activity of the different components of the spinal circuit involved in the control of erection through reciprocal connections is essential for erection (Schroder, 1980).

Cerebral control

In humans and animals, penile erection occurs in several contexts, some of which have no sexual content (*in utero* or during paradoxic sleep). It is thought that several different cerebral regions participate in erection in different contexts (Sachs, 2000). Each context may reflect the contribution of a unique combination of several brain nuclei, and one brain nucleus may participate in the occurrence of erection in several contexts. The participation of each brain nucleus in erection depends on the amount of excitatory and inhibitory information it receives from the periphery and from other central nuclei, and to a lesser extent to its hormonal environment.

Several brain nuclei in the rat have been found to contain neurons projecting directly on to sacral parasympathetic and somatic neurons innervating the penis and the ischiocavernosus muscles (Marson et al., 1993). Those nuclei include areas of the medulla oblongata (raphe nuclei, paragigantocellular nucleus (PGi), locus coeruleus, and Barrington's nucleus), pons (A5 noradrenergic cell group and periaqueductal gray), and hypothalamic (paraventricular nucleus (PVN)). Investigation of the immediate early gene c-fos pattern of expression, which reflects neuronal activity at a given time, led to the identification of neurons in forebrain regions (medial preoptic area (MPOA), bed nucleus of the stria terminalis (BNST), and medial amygdala) that are activated following sexual behavior in the rat (Coolen et al., 1997; Hamson and Watson, 2004). Further investigations on the role of these brain structures in the control of erection have evidenced the MPOA as a key structure (Stefanick and Davidson, 1987; Giuliano et al., 1996).

There are no direct projections from the MPOA to the spinal cord. However, MPOA integrates/processes sensory and hormonal signals and contacts other brain nuclei that in turn project on the spinal centers of erection. One of these brain nuclei that is of particular importance is the PVN, more particularly the parvocellular part. From this site, oxytocinergic and vasopressinergic neurons produce excitatory outputs to the spinal circuit of erection (Monaghan et al., 1993; Liu et al., 1997). In addition, serotonergic neurons lying in the PGi have been found to exert an inhibitory tone on spinal erection reflex (Marson et al., 1992; Monaghan et al., 1993).

Central neurochemistry

A brief overview of the major endogenous compounds participating in the central control of erection is provided in this section; for more detail, readers may refer to exhaustive reviews (Argiolas, 1999; Andersson, 2011).

The role of serotonin (5-HT) in erection is dual, either excitatory or inhibitory, depending on the site of action and the 5-HT receptor subtypes involved. In the rat, activation of spinal 5-HT_{1A} receptors inhibits reflex erection (Lee et al., 1990), whereas stimulation of spinal 5-HT_{2C} receptors enhances erectile activity (Millan et al., 1997). Nevertheless, the predominant action of central 5-HT in both laboratory animals and humans is inhibition of the spinal erectile reflex with a possible implication in the modulation of penile sensory information (Andersson, 2011). Dopamine is strongly implicated in the central control of erection. Erection can be induced in the rat by stimulation of dopamine D_1 or D_4 receptors in the PVN (Melis et al., 1987, 2005) and D_1 or $D_{2/3}$ receptors in spinal cord (Giuliano et al., 2001a). The non-selective dopamine receptor agonist apomorphine has been registered in Europe for the treatment of erectile dysfunction, although its use is limited because of frequent side-effects as well as limited efficacy (Heaton et al., 1995).

Another classic neurotransmitter that contributes to the central control of erection is NA. It exerts an antierectile activity that appears to be mediated by brain α_2-adrenoreceptors in the rat (Bitran and Hull, 1987). Several neuropeptides have also been demonstrated to be involved in the central modulation of the erectile response. Oxytocin can trigger erection in rats when injected into the PVN and hippocampus (Melis et al., 1986), as well as by acting on oxytocin receptors located in the lumbosacral spinal cord (Giuliano et al., 2001b).

Opiates have long been associated with erectile dysfunction in men. Stimulation of μ-opioid receptor subtypes in the PVN inhibits non-contact (i.e., psychogenic) penile erections in the rat (Melis et al., 2005). In addition to its primary role in the relaxation of cavernosal smooth muscles, NO has an important proerectile activity in the central nervous system, and especially within the PVN in the rat (Melis and Argiolas, 1997). The role of cerebral NO seems pivotal since dopamine and oxytocin induce NO release in the PVN and NO synthase inhibitors delivered within the PVN reverse the proerectile effect of dopamine and oxytocin (Argiolas and Melis, 2004). Adrenocorticotropic hormone (ACTH) and α-melanocyte-stimulating hormone (α-MSH) are peptides derived from pro-opiomelanocortin that act in the central nervous system as neurotransmission modulators. Both ACTH and α-MSH can trigger penile erection when injected into the cerebral ventricle of the rat by acting on melanocortin receptors (Serra et al., 1987; Vergoni et al., 1998). The agonist of the melanocortin 3/4 receptor subtypes bremelanotide has proven effective in the treatment of erectile dysfunction (Diamond et al., 2004).

Ejaculation

Ejaculation consists of two successive phases: emission and expulsion. Emission corresponds to the secretion of the different components of sperm into the urethra. Sperm is composed of spermatozoa transported from the epididymis and secretions of the bulbourethral glands, prostate, and seminal vesicles. In humans, the fluid is released from the glands in a specific sequence during ejaculation. The first portion of the ejaculate consists of a small amount of fluid from the bulbourethral glands. This is followed by a low-viscosity opalescent fluid from the prostate containing a few spermatozoa. Then the principal portion of the ejaculate is secreted; this contains the highest concentration of spermatozoa, along with secretions from the epididymis, and vas

deferens, as well as prostatic and seminal vesicle fluids. The last fraction of the ejaculate consists of seminal vesicle secretions. In sexually mature men, the volume of sperm varies between 0.1 and 10 mL and contains an average of 30×10^6 spermatozoa/mL. Sperm volume depends on multiple factors and on the time elapsed from the previous ejaculation. Once the emission phase ends, expulsion occurs, and this corresponds to intense rhythmic contractions of pelviperineal striated muscles. Concomitantly, smooth-muscle fibers of the bladder neck strongly contract to prevent sperm from being propelled into the bladder.

Peripheral control

Autonomic and somatic nervous systems act in synergy to produce a complete ejaculatory response, i.e., forceful expulsion of sperm through the urethra meatus. In addition, NANC innervation participates in the control of ejaculation through modulation of sexual glands.

Autonomic system

Neuroanatomic data suggest that, in the male accessory sex glands and seminal tract, parasympathetic tone controls epithelial secretion whereas sympathetic tone controls smooth-muscle cell contraction. For the latter, the functional role is documented by experimental studies carried out in different animal species. It has been demonstrated that activation of the sympathetic nervous system, whether by stimulating sympathetic nerves (e.g., hypogastric nerve) or using sympathomimetic agents, elicits a strong contractile response in the ducti deferens (Kolbeck and Steers, 1992), seminal vesicles (Terasaki, 1989), prostate (Watanabe et al., 1988), and urethra (Kontani and Shiraoya, 2002). Blockade of α_1-adrenoceptors partially inhibits ductus deferens and seminal vesicle smooth-muscle contractions induced by sympathetic stimulation (Kolbeck and Steers, 1992).

The exact functional role of the parasympathetic system in the emission phase of ejaculation is still not clarified. A cholinergic excitatory mechanism involving muscarinic receptors has been described in the sexual tract (Lepor and Kuhar, 1984; Moss et al., 1987; Terasaki, 1989). However, electric stimulation of the pelvic nerve (containing sympathetic and parasympathetic fibers en route to the urogenital region) elicits contractions (Watanabe et al., 1988; Kolbeck and Steers, 1992) but no appreciable emission of seminal fluid (Watanabe et al., 1988). These observations led to the suggestion, in contrast to the conventional view of the organization of pelvic autonomic pathways, that sympathetic innervation to the prostate includes both adrenergic and cholinergic components. In addition to adrenergic and cholinergic commands, peptidergic (VIP and NPY) and purinergic (ATP) regulation of NA action on the genital tract has been demonstrated in laboratory animals (Stjernquist et al., 1983; Allcorn et al., 1986; Ventura et al., 2003).

In humans, disruption of sympathetic pathways supplying the bladder neck, ductus deferens, and prostate is widely accepted to be the cause of postoperative anejaculation or retrograde ejaculation. Accordingly, surgical strategies that spare sympathetic efferents reduce the incidence of ejaculatory dysfunction, as in patients who have undergone retroperitoneal lymphadenectomy for testicular cancer or resection for rectal cancer (Sugihara et al., 1996; Pocard et al., 2002). In paraplegic men, whose ability to ejaculate is frequently impaired, sperm can be obtained upon electric stimulation of the hypogastric plexus (Brindley et al., 1989).

Somatic motor system

Pulsating ejection of semen out of the urethra via the glans meatus is caused by synchronized rhythmic contractions of perineal muscles and sphincter of the urethra, with a primary role for the BS muscle. The pattern of BS contractions is characterized by bursts of activity, varying in number from one individual to another (11–33 bursts); a proportion of these bursts of activity are not accompanied by expulsion of sperm out of the body (Gerstenberg et al., 1990). Lesion of the pudendal nerves, as may occur after trauma or neuropathy related to diabetes, can be responsible for retrograde and/or dribbling ejaculation (Grossiord et al., 1978; Vinik et al., 2003).

Somatic sensory system

Stimulation of sensory afferents can be sufficient to trigger expulsion reflex or even complete ejaculatory response. In humans, contractions of BS muscle, as evidenced by electromyogram measurement, can be provoked by electric stimulation of the dorsal nerve of the penis, mechanical distension of the posterior urethra, and magnetic stimulation of the sacral root (Nordling et al., 1979; Opsomer et al., 1989; Shafik and El Sibai, 2000). These procedures are currently routinely used to evaluate the integrity of neural pathways controlling ejaculation and have also served as the basis for developing a method that produces ejaculation in patients with neurogenic anejaculation. This method, namely penile vibratory stimulation, consists of placing a vibration-delivering device on the glans of the penis, either the dorsum or frenulum, and applying 2.5-mm amplitude vibrations for 5–15 minutes in 1–3 series (Sonksen et al., 1994; Brackett et al., 1998). Penile vibratory stimulation allows sperm to be collected in more than 50% of men with spinal cord injury (Brackett et al., 1998).

Spinal control

The spinal circuit commanding the peripheral events leading to ejaculation comprises autonomic and somatic nuclei, whose organization is very similar to that of the erectile spinal circuit (Fig. 3.9). The intermediolateral cell column and the dorsal gray column of thoracolumbar (T12–L2) spinal segments contain the somae of preganglionic sympathetic neurons. Cell bodies of preganglionic parasympathetic neurons are found in the intermediolateral cell column of sacral segments (S2–4). The ventral horn of S2–4 segments also contains somatic motoneurons (Onuf's nucleus). The autonomic and somatic spinal nuclei integrate peripheral and central signals and send coordinated outputs to ejaculatory tissues. Synchronized activation of the spinal ejaculatory nuclei is essential for ejaculation to occur.

Synchronization is carried out by a group of spinal neurons, namely the spinal generator for ejaculation (SGE), that have been characterized in the male rat (Fig. 3.9). A key element of the SGE is composed of neurons (lumbar spinothalamic neurons: LSt) that reside around the central canal in laminae X and VII (medial part) of the L3–4 spinal segments (Truitt and Coolen, 2002). Lumbar spinothalamic neurons project to sympathetic and parasympathetic preganglionic neurons innervating the prostate and seminal vesicles (Xu et al., 2005; Sun et al., 2009). Moreover, connections between LSt and motoneurons innervating the BS muscle have been reported (Xu et al., 2005). Interestingly, most of the LSt neurons are probably in direct connection with both autonomic (sympathetic and/or parasympathetic) and somatic neurons (Xu et al., 2006).

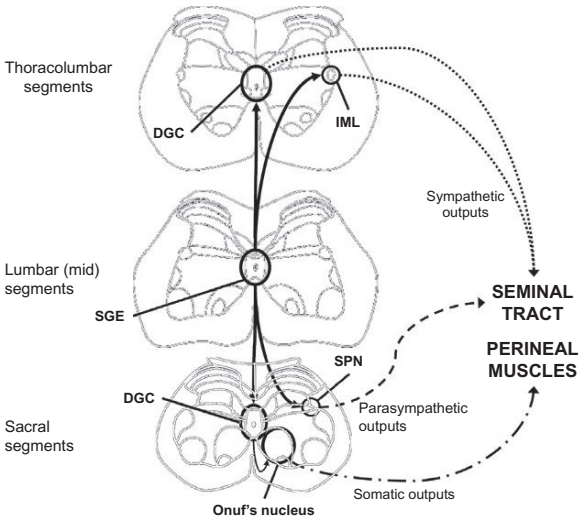

Fig. 3.9. Schematic view of the spinal network of ejaculation. The spinal generator of ejaculation (SGE) projects to: (1) thoracolumbar sympathetic centers, including dorsal gray column (DGC) and intermediolateral nucleus (IML); (2) lumbosacral parasympathetic centers, including sacral parasympathetic nucleus (SPN); and (3) lumbosacral somatic centers, including Onuf's nucleus. Those autonomic and somatic spinal centers control seminal tract and perineal striated muscles.

Immunohistochemical investigations have shown that LSt neurons contain galanin, cholecystokinin, enkephalin, and gastrin-releasing peptide (Young et al., 2009). They also express receptors for SP, glutamate, and androgens. Spinal projections of sensory fibers of the pudendal nerve have been reported to terminate close to LSt (McKenna and Nadelhaft, 1986), although a direct connection has not been proved yet. Functional investigations have been undertaken in order to support the crucial role of LSt neurons in ejaculation. Their selective chemotoxic lesion in male rats free to copulate resulted in abolition of ejaculation ability, whereas the other components of sexual behavior (e.g., sexual motivation, erection) were not impacted (Truitt and Coolen, 2002). In addition, electric microstimulation applied in the spinal area where LSt neurons are located elicits ejaculation in anesthetized male rats with motile spermatozoa detected in expelled sperm (Borgdorff et al., 2008).

The current understanding of LSt neuron function is that peripheral and brain stimulatory and inhibitory outputs are summated in the LSt neurons and, once an excitatory threshold is reached, a programmed sequence is generated and activates autonomic and somatic spinal nuclei commanding ejaculation. Integrity of LSt and spinal autonomic and somatic centers is necessary and sufficient for the expression of ejaculation, as demonstrated in rats with spinal cord transection at the thoracic level (Borgdorff et al., 2008). In humans, the existence of an SGE in L3–5 spinal segments is supported by clinical observations in spinal cord-injured patients (Chéhensse et al., 2013).

Cerebral control

A brain network dedicated to the control of ejaculation has been delineated in the rat (for review, see Giuliano and Clément, 2012). This network comprises several interconnected groups of neurons distributed in all divisions of the brain in sensory/integrative, excitatory, and inhibitory areas.

Activated neurons in relation to ejaculation have been detected in small regions of the posteromedial BNST, the posterodorsal medial amygdala, the posterodorsal preoptic nucleus, and the parvicellular part of the subparafascicular thalamus (Baum and Everitt, 1992; Coolen et al., 1997). These brain areas are known to process information of various origins, including sexual cues and peripheral somatosensory stimuli. Notably, the

subparafascicular thalamus receives projection from LSt neurons (Ju et al., 1987).

An MPOA–PVN–spinal cord pathway, similar to that described for erection, forms a major axis in the control of ejaculation. Experimental investigations have demonstrated the excitatory function of MPOA (Marson and McKenna, 1994; Hull and Dominguez, 2006; Kitrey et al., 2007). In the parvocellular division of the PVN, activity of oxytocin neurons that project on to spinal ejaculatory autonomic nuclei but not on to LSt neurons has been reported, correlated with ejaculatory performance (Pattij et al., 2005). In the lateral hypothalamus in the rat reside neurons that directly contact LSt neurons (Facchinetti et al., 2014) and whose function in ejaculation appears to be excitatory (Kippin et al., 2004).

Gigantocellular nuclei and raphe nuclei (pallidus, magnus, and obscurus) in the ventral medulla directly project on to the different components of the spinal ejaculatory circuit, including LSt neurons (Marson and McKenna, 1992, 1996; Facchinetti et al., 2014). In addition, neuroanatomic data suggest that ventral medulla neurons are under the influence of MPOA. Functional studies in the rat have evidenced the inhibitory role of serotonergic neurons located in the gigantocellular nuclei on ejaculation (Marson and McKenna, 1992; Gravitt and Marson, 2007).

Central neurochemistry

A number of factors participate in the central control of ejaculation (for review, see Giuliano and Clément, 2012). Several lines of experimental evidence support the involvement of dopamine in ejaculation. The primary role of MPOA D_2/D_3 receptors in mediating the proejaculatory action of dopamine has been reported in the rat (Hull et al., 1989; Clément et al., 2007). It has been suggested that dopamine release in the MPOA progressively increases during copulation, eventually triggering ejaculation (Hull et al., 1995). The delaying action on ejaculation of the antipsychotic levosulpiride, which blocks D2/D3 receptors, has been reported in a clinical trial in premature ejaculation patients (Greco et al., 2002), although the incidence of side-effects limits its use on a wider scale.

A great body of evidence supports the inhibitory role of cerebral 5-HT on ejaculation. The stimulation of somatodendritic 5-HT_{1A} autoreceptors, which mediate the inhibitory feedback of 5-HT on its own release, has been found to reduce the time to ejaculate in the rat (Hillegaart and Ahlenius, 1998). However, 5-HT_{1A} receptors at different locations (brain, raphe nuclei, and spinal cord) may modulate ejaculation in opposing ways (Rehman et al., 1999). Postsynaptic 5-HT_{2C} receptors have also been found to be involved in mediating the inhibitory activity of 5-HT on ejaculation (Foreman et al., 1989). In humans as well, 5-HT tone is a major factor in the control of ejaculation with, globally, an inhibitory action.

Prolonged ejaculation latency is a frequent side-effect of the selective serotonin reuptake inhibitors, which increase 5-HT bioavailability within the central nervous system (Giuliano and Clément, 2006). On the basis of these clinical observations, the use of the selective serotonin reuptake inhibitor dapoxetine for the treatment of premature ejaculation was developed, eventually leading to the registration of the first medicine for this condition.

Among the other neurotransmitters that are implicated in the central control of ejaculation, acetylcholine and NO in MPOA, as well as oxytocin in PVN and spinal cord, exert an excitatory action (Hull et al., 1988; Argiolas and Melis, 2004; Hull and Dominguez, 2006; Clément et al., 2013). Conversely, endogenous opioids have an inhibitory action which is mediated, at least in part, by μ receptors in the MPOA (Coolen et al., 2004). In men complaining of premature ejaculation the centrally acting opioid analgesic tramadol has proven effective in delaying ejaculation (Giuliano, 2007). It is to be noticed that tramadol also acts as a blocker of 5-HT transporters and its effect on ejaculation could be explained by combined central nervous system μ-opioid receptor stimulation and increased brain 5-HT tone.

CONCLUSION

The neurobiologic approach developed in the last 20 years in sexual medicine has led to tremendous advances in the description of the neurophysiology of the male sexual responses. However some key issues remain to be elucidated and further research is needed to complete the current view. Animal models have proven valuable in improving our understanding of male sexual functions. However there are differences between animals and humans, more particularly regarding the cerebral control of sexual responses, and investigations in humans appear to be indispensable. In this sense, the recent and continuing progress in medical imaging techniques (see Chapter 7) opens up exciting perspectives.

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 4

Anatomy and physiology of genital organs – women

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INTRODUCTION

"Anatomy is destiny" (Wallace, 1983; Freud, 1895): Sigmund Freud's intense consideration has a rich symbolic and clinical meaning. It does not simply refer to the gender issues, which is the more frequent reading of his sentence. It can be appropriately applied to the importance that human anatomy has in predetermining functions, dysfunctions, and related vulnerabilities, particularly in the elusive domain of women's sexuality. Freud, a skilled physician and neurologist himself, knew and stressed the importance of basic anatomy and physiology for perceiving the full meaning of what clinicians see and may read from human's behavior. Son of his time, and with the scientific limits of his historic period, he was nevertheless trying to bridge the anatomy of the brain with complex mental functions, emotions, and dreams.

The quote is pertinent as a reminder that women's sexuality is deeply rooted in the anatomy and physiology of their whole bodies, with a specific focus here on their genital organs – a sexuality whose biologic anatomic and functional basis is then modulated and reshaped throughout life by personal, relational, and context-dependent events and affective dynamics (Graziottin et al., 2009; Lukasiewicz and Graziottin, 2014).

The goal of this chapter is to offer an updated view of women's genital anatomy and physiology, with a clinically oriented perspective.

EMBRYOLOGY OF WOMEN'S GENITAL ORGANS

The female genital organs differentiate in the feminine phenotype during the embryonic period without particular hormonal influences. Indeed, the "female" is the "default" program, that can be differentiated into the "male" only in the presence of androgens at male physiologic levels for the gestational age. The genital organs are comprised of gonads, reproductive ducts, and external genitalia (Standring, 2008). The process of sexual differentiation is central for sexuality and reproduction. In sex development, it encompasses first the processes of sex determination, that is, the developmental decision that directs the undifferentiated embryo into a sexually dimorphic individual. Sex determination equals gonadal development, in human beings as in all mammals. The second process, known as sex differentiation, takes place once the sex determination decision has been made through factors produced by the gonads that determine the development of the phenotypic sex. Generally, factors influencing sex determination are transcriptional regulators, whereas factors important for sex differentiation are secreted hormones and their receptors (Biason-Lauber, 2010).

Anatomically and morphologically, fetal sex development consists of three sequential stages:

1. the undifferentiated stage, when identical primitive structures develop in the XY and XX embryos
2. gonadal differentiation into testes or ovaries (key for sex determination)
3. the sexual differentiation of internal and external genitalia, which depends on the action of testicular hormones.

Disorders of sex development, of the highest importance for their sexual consequences, may result from defects in any of these stages (Rey and Grinspon, 2011).

The gonads

The gonads develop from primitive germ cells, the mesothelium of the posterior abdominal wall and

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mesenchyme during the fifth fetal week, counting from the first day of the last period (Netter, 2010). There are three key directors of male gonad differentiation:

1. the sex-determining region Y (SRY) protein, also known as testis-determining factor (Harley et al., 2003). It is a protein that in humans is encoded by the SRY gene, located in the Y chromosome. Its expression causes the development of primary sex cords, which later develop into seminiferous tubules. These cords form in the central part of the as yet undifferentiated gonad, turning it into a testis. The now induced Leydig cells of the testis then start secreting testosterone, while the Sertoli cells produce anti-müllerian hormone (AMH)
2. androgens, secreted by Leydig cells, further "force" the basic program into the progressively male fenotype
3. AMH, produced by Sertoli cells in men and by granulosa cells of the ovary in women.

In summary, the gonadal differentiation takes place in the second month of fetal life: the female phenotype depends therefore on the absence of sexual SRY protein, androgens, and AMH, leading to gonads composed of an inner medulla (ovarian stroma) and an outer cortex (parenchyma) (Standring, 2008).

Internal genital organs: tubes, uterus, and upper vagina

In male mammals, AMH blocks the female "default" program, as it prevents the development of the müllerian ducts (MD) into the uterus and other müllerian structures (Matuszczak et al., 2013). The effect is ipsilateral, that is, each testis suppresses müllerian development only on its own side. In humans, this action takes place during the first 8 weeks of gestation. If the process is only ipsilateral, the co-presence of mixed internal genitalia may result (AlJurayyan, 2013). If no AMH is produced from the gonads, as normally happens in female subjects, or as happens in Turner syndrome (45,X0), the MD develop (Sajjad, 2010). Meanwhile the wolffian ducts, which are responsible for male reproductive ducts, are progressively reabsorbed, occasionally leaving only small cystic remnants (usually 1 cm in diameter or less) without any clinical meaning, that can be palpated/visualized with the ecographic probe or magnetic resonance imaging in the vaginal lateral wall, on either side.

The fallopian tubes, the uterus, and the upper part (two-thirds) of the vagina originate from the mesodermal paramesonephric ducts (of Müller). This process is referred to as müllerian organogenesis: the paired paramesonephric ducts (MD) fuse to form a confluence; the cranial end of the fused ducts yields the future uterus which contains mesoderm that will form the uterine endometrium and myometrium. The unfused cranial ends assume a funnel-shaped configuration (the fimbrial portions of the fallopian tubes) and remain open to the future peritoneal cavity. The caudal end of the fused ducts gives origin to the upper two-thirds of the vagina (Healey, 2012). The lower part of the vagina, urethra, vaginal vestibule, and glands (urethral, paraurethral and vestibular) arises from the urogenital sinus (endoderm).

During development, the MDs undergo a dynamic morphogenetic transformation from simple tubes consisting of homogeneous epithelium and surrounding mesenchyme into several distinct organs – the oviduct, uterus, cervix, and vagina. Following the formation of anatomically distinctive organs, the uniform MD epithelium (MDE) differentiates into diverse epithelial cell types with unique morphology and functions in each organ. Classic tissue recombination studies, in which the epithelium and mesenchyme isolated from the newborn mouse were recombined, have established that the organ-specific epithelial cell fate of MDE is dictated by the underlying mesenchyme (Kurita, 2011). Tissue recombination studies have also demonstrated that there is a narrow developmental window for determination of the epithelial cell fate in MD-derived organs. If the signaling that controls epithelial differentiation is disrupted at the critical developmental stage, the cell fate of MD-derived epithelial tissues will be permanently altered and can result in epithelial lesions in adult life. Cervical/vaginal adenoses and uterine squamous epithelium are examples of such incidences (Kurita, 2011).

Adenomyosis, i.e., the presence of endometrium, the inner mucosal layer of the uterus, within the myometrium, could be the result of a disrupted epithelial differentiation, with serious clinical consequences, in terms of incapacitating dysmenorrhea, deep dyspareunia, and chronic pelvic pain (Graziottin et al., 2013).

The external genitalia

The external genitalia remain sexually undifferentiated until the seventh fetal week and then begin to develop from the urogenital sinus, genital tubercle, and labioscrotal swellings. The corpora cavernosa of the clitoris and the glands are formed from the genital tubercle; the vestibule of the vagina, the labia minora, the vestibular bulbs, and the female corpus spongiosum are formed by the urogenital sinus and from the urogenital folds which do not fuse together (O'Connell and De Lancey, 2005). The labioscrotal swelling does not fuse either and forms the labia majora.

A knowledge of the embryonic differentiation of sexual apparatus is important to understand congenital malformations, so-called müllerian anomalies. They have a prevalence of 4–7% (Chan et al., 2011) and result from an altered fusion of the MD, leading to different abnormalities of the uterus and upper vagina (Lin et al., 2002). From the same embryologic origin, congenital genital/sexual malformations are often associated with renal abnormalities: comorbidity may be as high as 40%. The common associated anomalies are unilateral agenesis, ectopia, renal hypoplasia, multicystic dysplastic kidney, and hydronephrosis (Morcel et al., 2007). Therefore, the urologic system should always be evaluated when müllerian anomalies are documented (Jaramillo et al., 1990).

According to the gravity of failure of fusion of the two paramesonephric ducts, it is possible to identify different anomalies such as the Mayer–Rokitansky–Kuster–Hauser syndrome (characterized by congenital vaginal agenesis and an absent or rudimentary uterus in genotypic females), uterus bicornis, either unicollis or bicollis, uterus septus and vaginal septum (Epelman et al., 2013). The septum can be longitudinal, when it derives from an incomplete fusion of the caudal end of the two MDs. In its extreme form, it may lead to two distinct parallel vaginas, two cervices and two uteri.

The vaginal septum can be transverse, complete or incomplete, single or multiple, when it results from incomplete cavitation of the vagina that initially is a solid organ. The hymen is generated when the still solid vagina connects with the cloacal tissue which leads to the external genitalia: it is just an embryonic remnant of the former fusion line, incompletely separating the lower end of the vagina with the vulvar vestibule. It is a circunferential skin structure composed of non-hair-bearing skin (O'Connell et al., 2008). It may have different shapes (e.g., annular, cribrous, septate) and thickness: it may be very elastic and/or subtle ("complacent") or so fibrotic and thick as to constitute an anatomic, mechanical barrier to penetration, causing introital dyspareunia (Graziottin and Murina, 2011). In the most severe cases a tight fibrotic hymen may require surgical incision with topical analgesia, to allow painless penetration. Due to its strategic position at the entrance of the vagina, it had (and still has, in some cultures) an enormous symbolic meaning (proof of virginity) that far outweighs its otherwise irrelevant function as a simple embryonic remnant. The vestibule and the outer part of the basis of the hymen are densely innervated (Bohm-Starke et al., 1999; Bornstein et al., 2004): they are among the critical sites of coital pain ("introital dyspareunia") and of genital pain ("provoked vestibulodynia") in premenopausal women.

THE ADULT GENITAL ORGANS

The external genitalia

The external genitalia consist of the mons pubis, labia majora, labia minora, clitoris, and the vestibule of the vagina; they are supported by superficial and deep muscles of the perineum and their fasciae (Yavagal et al., 2011).

The mons pubis

The mons pubis is an inverted triangular area of fatty tissue, covered by hair-bearing skin lying on top of the pubic bone; it extends from the pubic hairline (the base of the triangle) to the glands of clitoris inferiorly (Standring, 2008). The labia majora are two prominent longitudinal cutaneous folds situated between the mons pubis and the perineum. They fuse together forming the anterior labial commissure; posteriorly, they are not really joint, but fuse with the surrounding tissue into the posterior labial commissure. Each labium has two surfaces: an outer one, covered with pigmented skin and pubic hair; and an inner surface, which is smooth and has sebaceous follicles (Williams and Bannister, 2008).

The labia minora

The labia minora are two small cutaneous folds 3–4 cm long, situated between the labia majora and extending from the clitoris anteriorly to the fourchette posteriorly (Putz and Pabst, 2008). Anteriorly each labium is divided into two portions: the upper division passes above the glans of the clitoris to fuse with the opposite part and forms the preputium clitoridis; the lower division passes under the clitoris, forming the frenulum of the clitoris with its contralateral part. The labia minora are rich in sebaceous glands, connective tissue, and vascular erectile tissue, with a considerable number of sensory nerve endings and receptors (Netter, 2010).

The clitoris

The clitoris is an erectile structure, homolog to the male penis, formed by two corpora cavernosa and the glans, covered by the prepuce. Only a fifth (or less) is visible (glans) while the rest is hidden under the skin (O'Connell and De Lancey, 2005). The corpora cavernosa are made of cavernous erectile tissue and diverge and follow the pubic rami on each side, forming the crura. It represents the hidden part of the clitoris which is covered by the ischiocavernosus muscle: it may reach 7 cm or more in length. The glans of the clitoris is the free extreme of it: it is 4–7 mm long and covers the distal part of the corpora cavernosa, from which it is not dependent

(Williams and Bannister, 2008). It represents the most innervated part of the clitoris, full of free nerve endings, Krause-finger corpuscles, corpuscles of Pacini and Meissner (Yang et al., 2006).

The clitoris is connected to the mons pubis and pubic symphysis by the suspensory ligament which influences the stability of the clitoris during sexual intercourse (Rees et al., 2000). The urethra lies surrounded by this complex with the body directly anterior to it, flanked superficially by the bulbs and deeply by the crura. In anatomy texts the bulbs are referred to as the bulbs of the vestibule and appear as if they form an erectile structure of the labia minora (Standring, 2008; Netter, 2010). However, according to most studies, the bulbs relate most closely to the clitoris and urethra (O'Connell et al., 1998), so that they should be renamed the bulbs of the clitoris (O'Connell and De Lancey, 2005).

The G spot

The G spot represents the most controversial area of the female genitalia (Jannini and Whipple, 2010), caused above all by lack of knowledge of the anatomy and innervation of this area (Foldes and Buisson, 2009). The G spot name is given in recognition of the researcher who found its existence and relationship to female ejaculation (Grafenberg's spot) (Grafenberg, 1950). Considered to be a prostate remnant, it may have consistent dimensional variations in different women: from being almost non-existent in some women, to covering an area that can be dynamically visualized through a vaginal ecographic probe in others (Hines, 2001). According to some authors, physical anatomic differences in G-spot size should be taken into account as a source of physiologic variability in female sexual response.

An interesting sonographic finding correlates with the presence of a thicker urethra vaginal space in women who have vaginal orgasms (Gravina et al., 2008). The close contact between the internal roots of the clitoris and the anterior vaginal wall during vaginal penetration could explain the special sensitivity of the lower anterior vaginal wall (Foldes and Buisson, 2009). O'Connell refers to the clitoral complex, composed of the distal vagina, urethra, and clitoris, as "the" location of female sexual activity (O'Connell et al., 2008). Another study supplies the evidence for the idea that the so-called G spot is a complex anatomic area encompassing the anterior vaginal wall and the embedded structures, so that it would be better to use the term clitoral–urethral–vaginal complex (Jannini and d'Amati, 2006). Different innervation has recently been demonstrated in the clitoral–urethral complex. Increased density of small nerves in the glans suggests that this is the location of the highest sensation. Opposite to that, the area closer to the urethra is characterized by a reduced number of nerves so that it can be hypothesized that this zone is less important for sexual sensation (Oakley et al., 2013).

The vestibule of the vagina

The vestibule of the vagina extends from the glans clitoridis to the posterior fourchette between the labia minora, up to their internal border. It contains the vaginal orifice, external urethral meatus, vestibular bulbs, and the openings of the greater vestibular glands (also known as Bartholin's glands). The vaginal orifice is below the opening of the urethra and is characterized by the presence of the hymen (a circumferential hairless skin with variable shape) (Standring, 2008). The urethral orifice (lower third of the urethra) is surrounded by erectile tissue of the clitoral bulbs, partly considered the equivalent of the male urethral corpus spongiosum (O'Connell et al., 1998; O'Connell and De Lancey, 2005). It has both a sexual and protective function. It becomes very congested during physiologic sexual arousal, contributing to genital congestion and the formation of the so-called "orgasmic platform" (Masters et al., 1986). Meanwhile, it constitutes a kind of physiologic air bag, protecting the urethra from the "mechanic" trauma of repeated sexual thrusting at intercourse. When women suffer from vaginal dryness and/or inadequate genital arousal due to different etiologies, including low desire, poor foreplay, and/or vestibular pain with dyspareunia, and/or hyperactive pelvic floor mechanically narrowing the vaginal entrance, the lack of this protective cuff increases urethral and bladder vulnerability to the "mechanic" trauma of intercourse, contributing to recurrent cystitis. Sixty percent of recurrent urinary tract infections are reported 24–72 hours after intercourse and are referred to as "postcoital cystitis," a powerful contributor to chronic bladder pain syndrome (Graziottin, 2014).

Recent data from an observational study on recurrent urinary tract infections indicate that comorbidity with vulvar vestibulity/provoked vestibulodynia/introital dyspareunia is as high as 60% (Salonia et al., 2013). During sexual arousal urethral secretions derive through distal urethral glands (Skene's).

Vestibular bulbs

The vestibular bulbs (recently renamed "bulbs of the clitoris": O'Connell and De Lancey, 2005) are two erectile organs situated laterally to the vaginal orifice directly beneath the skin of the labia minora and joined together (pars intermedia) and extended to the base of the glans. They are in contact with the greater vestibular glands posteriorly and covered by the bulbocavernosus muscles

superficially. The greater vestibular glans (Bartolini's) are two small glands situated one on either side of the vaginal orifice, and through a 2-cm-long duct opening between the hymen and the labia minora (Standring, 2008).

The internal genitalia

The internal genital organs consist of the vagina, uterus and cervix, fallopian tubes, and ovaries.

The vagina

The vagina is a fibromuscolar tubular structure (length range 6–12 cm) extended between the vulva and the cervix. It represents a potential space, with anterior and posterior walls collapsed so that in a transverse section it results in an "H" shape, while in the longitudinal axis it is like a greatly stretched "S" (Netter, 2010). The entrance of the vagina is partially hidden by the labia minora and its back ends in a cul-de-sac penetrated by the uterine cervix. The recess formed by the presence of the cervix is called the fornix: anterior, posterior and lateral, left and right (Standring, 2008). The vagina is related anteriorly to the base of urinary bladder and urethra, so closely that some anatomists recently wrote that "the urethra is embedded in the vaginal wall" (O'Connell and De Lancey, 2005; Furness et al., 2011). Laterally the vagina is connected to the levator ani muscle and endopelvic fascia, and posteriorly to the perineal body and anal canal. The vaginal wall consists of three layers: (1) the inner mucosal layer (tunica mucosa) is a non-keratinized stratified squamous epithelium based on an extremely richly vascular network embedded in connective tissue called lamina propria (Fig. 4.1); (2) a middle muscolar layer (tunica muscularis), divided into an external longitudinal and an internal circular layer of smooth muscle; and (3) an outer adventitial layer of collagen and elastin (Standring, 2008; Yavagal et al., 2011).

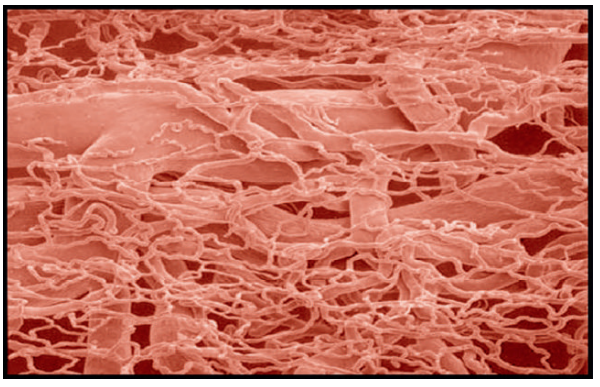

Fig. 4.1. Female sexual function *in vitro* studies of vaginal microvascular architecture. To become congested and give lubrication, the vessels need estrogens and testosterone. (Reproduced from Shabsigh et al., 1999.)

The vagina is surrounded by different striated pelvic muscles, forming two main parallel layers: the most superficial is composed of three muscles, laid out in two triangles: bulbocavernosus, ischiocavernous, and superficial transverse perineal muscles (Standring, 2008). In particular the bulbocavernosus, which is laterally closer to the vaginal entrance, was defined as "constrictor cunni" by old anatomists, as it was considered to modulate the anatomic entrance door of the vagina, but it is too small and weak to play such a role. This role is more appropriately pertinent to the much stronger pubococcygeus part of the levator ani, just deeper to the bulbocavernous (Netter, 2010).

The normal vaginal ecosystem or microbiota (the microorganisms living in a specific organ or tissue) defends the host against pathogen invasion, more so in the fertile age, when the specialized population of lactobacilli maintains the ecosystem (Graziottin and Murina, 2011). The first anatomic element important for vaginal microbiota is the vaginal epithelium, which proliferates and thickens in response to estrogens. Also vaginal transudation is controlled by estrogen levels and is composed of water, salts, mucins, carbohydrates, immunoglobulins, lysozyme, and other substances (Boris and Barne, 2000). The normal vaginal microbiota consists of a pool of anaerobic and aerobic microorganisms (Mehta and Talwalkar, 1995). Lactobacilli, Gram-positive bacilli, and so-called Döderlein's bacilli, represent the most prevalent microorganism (up to 90%) in the normal vaginal ecosystem and they present two mechanisms to interfere with pathogens: (1) adherence to the mucus, forming a barrier which prevents colonization by pathogens; and (2) the production of antimicrobial compounds such as lactic acid, hydrogen peroxide, and bacteriocin-like substances (Boris and Barne, 2000).

The vaginal acid system is facilitated by lactobacilli, which metabolize glycogen into lactic acid, lowering vaginal pH to a normal value of 4.2. In physiologic conditions, lactobacilli include 90% of the vaginal ecosystem during the fertile age; the remaining 10% is composed of different commensal germs. The ecosystem is important for limiting the growth of pathogenic bacteria (Stumpf et al., 2013). The concept of "pathogenic biofilms" currently refers to structured germ communities living inside a self-produced polysaccharide network adhering to the vaginal mucosa and/or to inert medical devices. They can contribute to recurrent vaginitis and cystitis with their associated sexual comorbidities, such as introital dyspareunia and postcoital cystitis.

The uterus

The uterus is a muscular organ situated in the pelvis between the bladder and the rectum; its cavity communicates with the vagina inferiorly and with the fallopian tubes with its upper part. It consists of two portions separated by the isthmus, an upper fibromuscular body and a lower cervix (Netter, 2010). The cervix (neck) is the lower part of the uterus which projects through the anterior wall of the vagina. It can be distinguished in a supravaginal and an intravaginal portion. The cavity of the cervix communicates with that of the vagina through a circular aperture, the external orifice of the uterus. The form, size, anatomic and functional characteristics of the uterus vary in different periods of life and circumstances (prepubertal, menstruation, pregnancy, menopause). Levels of estrogens, progesterone, and testosterone in different life phases modulate its anatomic and functional changes (see Chapter 10).

The body uterus wall is composed of three layers: an external or serous, a middle muscular and an internal or mucous (Standring, 2008). The serous coat derives from the peritoneum which invests the fundus, all of the posterior surface, and the anterior surface only as far as the junction of the body and cervix. The muscular layer is the most representative coat of the uterus and consists of a longitudinal external, a middle (whose fibers do not present in a regular direction), and circular internal layer. The mucous membrane in the body of the uterus is lined by columnar ciliated epithelium. It differs from that of the cervix, which is rich in deep glandular follicles, producing an alkaline mucus under hormonal estrogenic stimulation. The mucosal layer of the vagina is pluristratified, with a clear pink soft color; the columnar monolayer epithelium of the inner cervix has a bright red/purple color (Kurita, 2011). The cells that give origin to both types of epithelium are called "metaplastic" and are the most vulnerable from an oncogenic point of view, specifically to the oncogenic strains of papillomaviruses.

The cervical squamocolumnar (SC) junction is the site of a recently discovered "embryonic" cell population that was proposed as the cell of origin for cervical cancer and its precursors. Early in life, embryonic cervical epithelial cells were seen throughout the cervix and subsequently diminished in number to become concentrated at the SC junction in the adult. Cuboidal embryonic/SC junction cells give rise to subjacent metaplastic basal/reserve cells with a switch from the SC junction positive to negative immunophenotype (Herfs and Vargas, 2013).

The salpinges

The salpinges (fallopian tubes) are tubular structures about 10 cm long situated from the upper lateral end of the uterus to the ovary. They are divided into four parts: interstitial, isthmic, ampullary, and infundibulum with the fimbria (Standring, 2008). Sperm and egg meet at the external third of the salpinges, where fertilization occurs. The salpinges wall is made up of three coats: a serous peritoneal, a middle muscular, and an internal mucous coat, with a columnar and ciliated epithelium (Kurita, 2011). The cilia of the mucous coat, like moving fingers, are responsible for the transport of the fertilized egg, together with the waveform movements of the salpinges muscular layer.

Transport from the outer third of the salpinges to the uterine cavity requires on average 3 days. If the ciliary epithelium has been damaged by inflammatory processes, usually as a consequence of sexually transmitted disease or endometriosis, the fertilized egg will not be transported within the proper time window. It will then start early placental differentiation in the salpinges, resulting in an ectopic pregnancy.

The ovaries

The ovaries are two oval organs situated in the ovarian fossa on the lateral wall of the pelvis, connected to the uterus by the utero-ovarian ligament and to the pelvic side wall by the infundibulum pelvic ligament. Each ovary consists of an inner medulla and an outer cortex with follicles and stroma. The surface of the ovary is covered by the germinal epithelium of Waldeyer, a layer of columnar cells, and just immediately beneath it lies the stroma, with a large number of follicles in earliest condition (cortex). Going deep inside the ovary to the center of the organ (medulla), other large and mature follicles are found surrounded by a great amount of vessels. The follicular cells are responsible for the production of estradiol; after ovulation, the corpus luteum (the residual part of the follicle after the oocyte was delivered) produces progesterone for up to 14 days, unless a new pregnancy has started. Deep in the ovary (hilum ovarii) are located the Leydig cells, responsible for the ovarian production of testosterone, androstenedione, and dehydroepiandrosterone in women (Standring, 2008).

Recent findings in stem cell biology have presented new perspectives and opportunities for the understanding and treatment of reproductive diseases. In a departure from the long-held dogma of embryologically fixed numbers of oocytes, current literature suggests that human ovaries contain stem cells which form new oocytes even in adulthood and that these stem cells can be cultured *in vitro* to develop into mature oocytes. These findings have provided new hope and broader options for fertility preservation (Duke and Taylor, 2013).

The implications that fertility preservation may have for women's sexual identity, sexual function, and sexual relationships are countless, thanks to ovarian stem cell discovery and therapeutic use.

On a more general functional note, the high level of plasticity recently demonstrated in human stem cells challenges the old dogma of fixed and rigid evolution of tissues of genital organs. Evidence of endometrial regeneration by bone marrow stem cells in endometrial tissue of women who received bone marrow transplant highlights the potential for the novel treatments of uterine disorders and supports new theories for the etiology of endometriosis as an ectopic transdifferentiation of stem cells (Duke and Taylor, 2013).

Further, endometrial-derived stem cells have been demonstrated to be useful in the treatment of several chronic and often debilitating diseases, including Parkinson's disease and diabetes. Other cells that may present future therapeutic benefits for a myriad of disease states include placental and fetal cells which enter maternal circulation during pregnancy and can later promote parenchymal regeneration in maternal tissue. These findings highlight novel functions of the uterus and ovaries. They demonstrate that the uterus is a dynamic organ permeable to fetal stem cells that are capable of transdifferentiation as well as a renewable source of multipotent stem cells (Duke and Taylor, 2013). While we still have much to understand about stem cells, their potential applications in reproductive biology and women's sexuality are consistent.

The bony pelvis

The pelvis is a ring composed of the two innominate or hip bones which are joined anteriorly at the symphysis pubis and posteriorly to the sacrum and coccyx (Fig. 4.2: Standring, 2008). The pubic symphysis is a unique joint consisting of a fibrocartilaginous disc sandwiched between the articular surfaces of the pubic bones. It resists tensile, shearing, and compressive forces and is capable of a small amount of movement under physiologic conditions in most adults (up to 2 mm shift and 1° rotation). During pregnancy, circulating hormones such as relaxin induce resorption of the symphyseal margins and structural changes in the fibrocartilaginous disc, increasing symphyseal width and mobility (Becker et al., 2010).

Each innominate bone is formed by the fusion of ilium, ischium, and pubis, and on its lateral surface there is an acetabulum, which articulates with the femoral head. In front and below it, ischium and pubis form the obturator foramen covered by the obturator membrane and pertinent muscles. The pelvis is divided into the greater and lesser pelvis by an oblique plane that passes through the prominence of the sacrum, the arcuate and pectineal lines, and the upper margin of the symphysis pubis (Netter, 2010). The circumference of this plane is named the linea terminalis or pelvic brim. The greater pelvis (pelvis major) is situated above the pelvic brim, and bounded on either side by the ilium, while in front it is incomplete. The lesser pelvis (pelvis minor), situated below and behind the pelvic brim, is divided into an inlet and outlet part. The superior aperture or inlet is formed laterally by the pectineal and arcuate lines, in front by the crests of the pubis, and behind by the anterior margin of the base of the sacrum and sacrovertebral angle. It has three diameters: anteroposterior (from the sacrovertebral angle to the symphysis pubis), transverse (connecting the middle of the brim on each side), and oblique (from the iliopectineal eminence of one side to the sacroiliac articulation of the opposite side) (Standring, 2008). The cavity of the lesser pelvis is a short, curved canal deeper on its posterior than on its anterior wall. The inferior aperture or outlet is bounded by the point of the coccyx and laterally by the ischial tuberosities. It has two diameters, an anteroposterior (from the tip of the coccyx to the lower part of the pubic symphysis) and a transverse one (between the ischial tuberosities). The pelvis allows transfer of weight-bearing forces between the trunk and lower limbs, protects the pelvic organs, gives insertion for muscles, fascia, and ligaments and plays an important role during sex and labor (Standring, 2008).

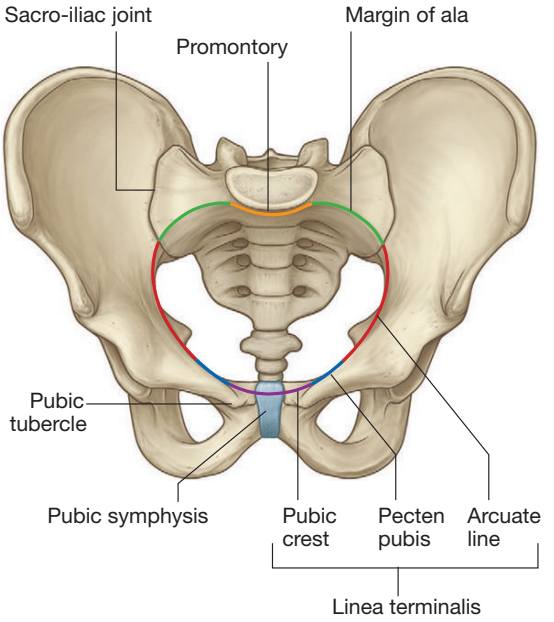

Fig. 4.2. The pelvis. (Reproduced from Standring, 2008.)

The sacrum is a triangular bone, situated in the lower part of the vertebral column and at the upper and back part of the pelvic cavity, inserted between the two hip bones. Inferiorly it articulates with the coccyx in a movable articulation (Standring, 2008). Physiologic mobility of the coccyx is important for sexual and reproductive reasons, as it allows higher mobility and elasticity of the levator ani, partially inserted to the coccyx. When rigid or lesioned, it may contribute to chronic pelvic pain and dyspareunia. Physiologic retropulsion of the coccyx increases the diameter of the lower pelvic and gives more room to permit the passage of the fetus during labor (Edmonds, 2012).

The pelvic floor muscles

"There is no considerable muscle in the body whose form and function are more difficult to understand than those of the levator ani, and about which such nebulous impressions prevail" (Dickinson, 1889). Despite over a century of medical progress since Dickinson offered this observation, the details of levator ani muscle anatomy remain poorly understood (Lawson Tait, 1974; Bustami, 1988; DeLancey and Starr, 1990; Kearney et al., 2004).

The pelvic floor consists of different muscle layers: the pelvic diaphragm, the urogenital diaphragm, the superficial trigonal muscles, and the lateral muscles (Standring, 2008). The pelvic floor is important for the support of the pelvic organs, to assist fecal and urinary continence, and to improve pelvic and spinal stability; furthermore, it plays a key role in sexual pleasure. The pelvic diaphragm is formed by the levator ani and the coccygeus muscles (International Anatomical Nomenclature Committee, 1983; Kearney et al., 2004).

The coccygeus muscle forms a triangular structure attached to the spine of the ischium and to the lateral surface of the coccyx and S5 (Fig. 4.3). This muscle does not contribute to active movement of the pelvic floor; in fact, the effective contractile support structure is represented by the levator ani muscle. The components of the levator ani muscle are the puborectal, iliococcygeal, and pubovisceral (pubococcygeus) muscles, further subdivided into pubovaginal, puboperineal, and puboanal. This terminology was accepted in 1998 by the Federative Committee on Anatomical Terminology (International Anatomical Nomenclature Committee 1983).

The iliococcygeus originates from the tendinous arch of levator ani and forms a diaphragm between the anus and the coccyx. The puborectalis originates from the pubic bone, forming a ring around the rectum. The pubococcygeus with its three branches originates from the pubic bone and inserts into the perineal body, the vaginal wall, and into the tissue between the internal and external anal sphincter. In the axial plane, the puborectal muscle can be seen lateral to the pubovisceral muscle and decussating dorsal to the rectum. The course of the puboperineal muscle near the perineal body is visualized in the axial plane. The coronal view is perpendicular to the fiber direction of the puborectal and pubovisceral muscles and shows them as "clusters" of muscle on either side of the vagina. The sagittal plane consistently demonstrates the puborectal muscle passing dorsal to the rectum to form a sling that can consistently be seen as a "bump." This plane is also parallel to the pubovisceral muscle

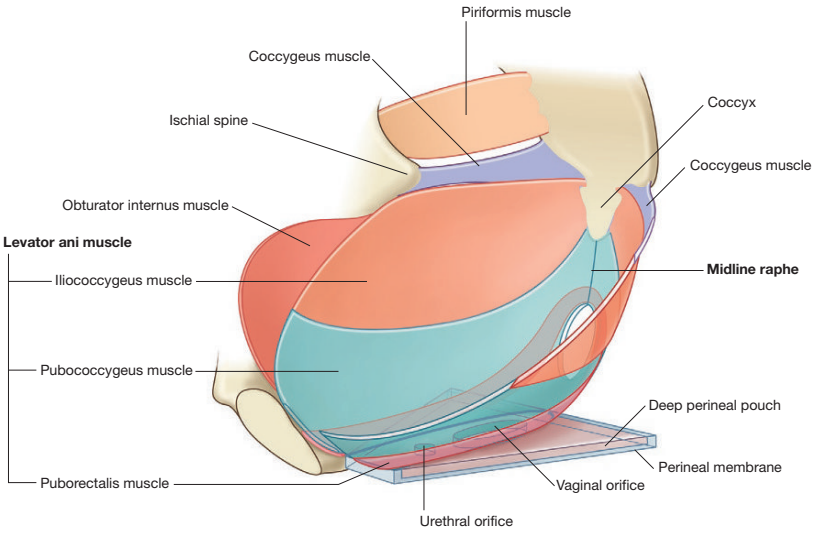

Fig. 4.3. The pevic floor muscles. (Reproduced from Standring, 2008.)

fiber direction and shows the puboperineal muscle (Margulies et al., 2006).

Appearance of the levator ani muscle subdivisions in magnetic resonance images

The urogenital diaphragm consists of the deep transverse perineal muscle with the superior and inferior fascia. The perineal membrane is composed of two regions, one dorsal and one ventral. The dorsal portion consists of bilateral transverse fibrous sheets that attach the lateral wall of the vagina and perineal body to the ischiopubic ramus. This portion is devoid of striated muscle. The ventral portion is part of a solid three-dimensional tissue mass in which several structures are embedded. It is intimately associated with the compressor urethrae and the urethrovaginal sphincter muscle of the distal urethra with the urethra and its surrounding connective tissue. In this region the perineal membrane is continuous with the insertion of the arcus tendineus fascia pelvis. The levator ani muscles are connected with the cranial surface of the perineal membrane. The vestibular bulb and clitoral crus are fused with the membrane's caudal surface (Stein and DeLancey, 2008).

The superficial trigonal muscle is composed of the bulbocavernosus, ischiocavernosus, and superficial transverse perineal muscles in the anterior triangle and the anal sphincter in the posterior triangle. The superficial transverse perinei originates from the ischial tuberosity and inserts on the perineal body (Stein and DeLancey, 2008). The ischiocavernosus muscle extends from the ischial tuberosity to the clitoral crura, inserting on to the body of the clitoris (this muscle compresses the crura of the clitoris and delays the return of blood through the veins, contributing to maintain the erection). The bulbocavernosus muscle occupies each lateral side of the vagina between the perineal body and the clitoris body (it diminishes the orifice of the vagina and with its anterior fibers contributes to the erection of the clitoris) (Standring, 2008).

Female longitudinal anal muscles or conjoint longitudinal coats (CLCs) are attached to the subcutaneous tissue along the vaginal vestibule on the anterior side of the external anal sphincter. Lateral to the CLCs, the external anal sphincter also extends anteriorly towards the vaginal side walls. The anterior part of the CLCs originated from the perimysium of the levator ani muscle. In terms of topographic anatomy, the female anterior CLCs are likely to correspond to the lateral extension of the perineal body (a bulky subcutaneous smooth-muscle mass present in adult women), supporting the vaginal vestibule by transmission of force from the levator ani (Kinugasa et al., 2013).

Female longitudinal anal muscles extend into the subcutaneous tissue along the vaginal vestibule

The lateral walls of the pelvis are composed of the piriformis and obturator internus (muscles of the lower limb). The perineum is a diamond-shaped area limited by the pubic symphysis, ischiopubic rami, sacrotuberous ligaments, and the coccyx (Fig. 4.4). A line that passes through the two ischial tuberosities divides the perineum into two triangles: the anterior urogenital and the posterior anal triangle (Standring, 2008).

The connective system

In addition to muscles, the pelvic organs are supported by connective tissue organized in different layers of fasciae and ligaments. Magnetic resonance studies offer new insights to the traditional anatomic readings (Tunn et al., 2001, 2003).

- The endopelvic fascia covers the pelvic organs and connects them to the lateral pelvic wall. It is made up of a combination of elastin, collagen, mucopolysaccharides, adipose, and neurovascular tissue. The fascia covering the levator ani muscle continues with the endopelvic fascia above, perineal fascia below, and obturator fascia laterally (Yavagal et al., 2011). The levator ani muscles and their superior and inferior fascia combined together form the so-called pelvic diaphragm (Ashton-Miller and De Lancey, 2007).
- The broad ligaments connect the uterus to the lateral pelvic walls on both side, and on its upper end it encases the fallopian tubes, round ligaments, utero-ovarian ligaments, and ovaries (Standring, 2008).
- The round ligaments extend from the lateral side of the uterine body and, passing through the inguinal canal, insert into the labia majora (Standring, 2008).
- The uterosacral ligaments support the cervix and the upper part of the vagina by their attachment to the sacrum, having also an important role of vaginal receptiveness in sexual intercourse (Campbell, 1950).
- The cardinal ligaments or Mackenrodt's ligaments extend from the cervix to the posterolateral pelvic wall (Ramanah et al., 2012).

The obturator fascia

The fascia of the obturator internus covers the pelvic surface of the muscle; it arches beneath the obturator vessels and nerve, completing the obturator canal, and at the front of the pelvis is attached to the back of the superior ramus of the pubis. Below it is attached to the falciform process of the sacrotuberous ligament and to the pubic

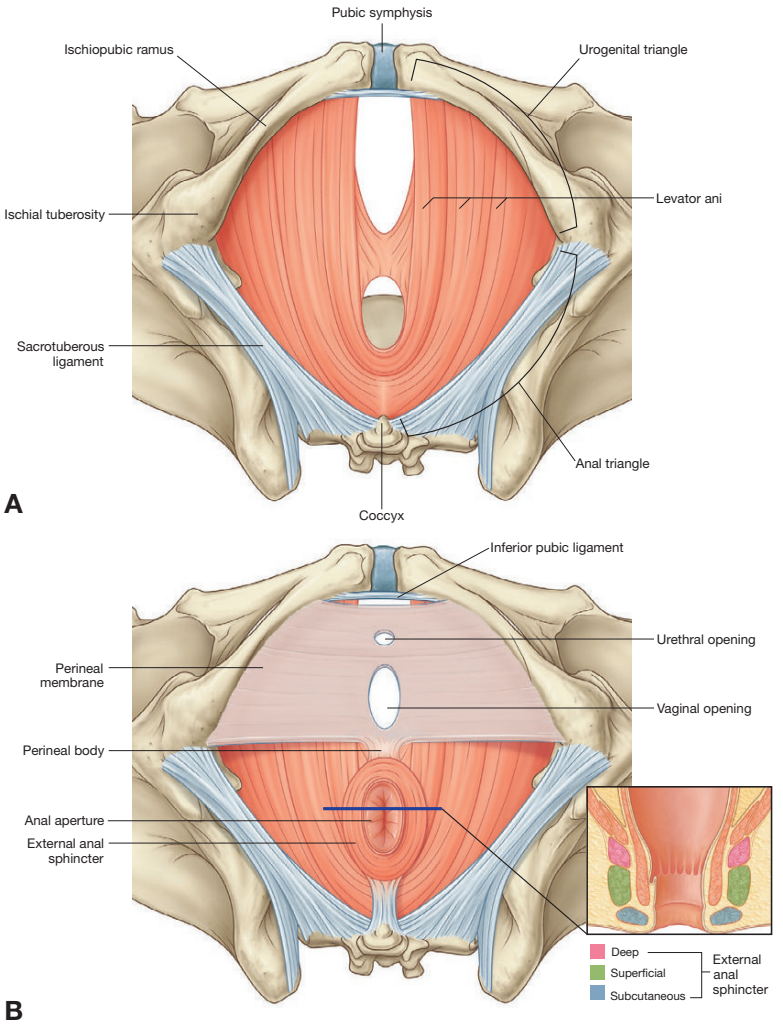

Fig. 4.4. (**A, B**) The perineum. (Reproduced from Standring, 2008.)

arch. Thickening in the obturator fascia is called the arcus tendinous fascia pelvis, extending from the pubis anteriorly to the ischial spine (Ziouziou et al., 2013). Alcock's canal syndrome or pudendal nerve entrapment (Labat et al., 2008) is a condition caused by compression of the pudendal nerve in the canal, resulting in neuralgia in the area of distribution of the pudendal nerve (vulva, vagina, clitoris) (Oelhafen et al., 2013).

THE VASCULAR SYSTEM

External genitalia

The arterial supply of the vulva is derived from the external and internal pudendal arteries. The internal pudendal artery is a branch of the anterior division of the internal iliac artery and the veins drain into the internal iliac vein (Netter, 2010). The inferior rectal artery supplies the anal canal; the perineal artery supplies the superficial perineal muscles; the posterior labial branch provides an artery to the bulbs of the vestibule, dorsal and deep arteries of the clitoris. The superficial and deep external pudendal arteries are branches of the femoral artery and supply the labia majora with branches of the pudendal artery (Beech and Adams, 2009).

The internal pudendal arteries are the key resistance vessels controlling the peripheral circulatory component of sexual response in both males and females. Structurally the pudendal artery has a smaller lumen diameter, wall thickness, and much lower wall-to-lumen ratio compared to that of the male. The lumen of this artery also tapers as it travels distally and becomes the clitoral artery. Based on its smaller wall thickness, as expected, the female pudendal artery does not contract to the same magnitude attained by the male pudendal artery. However, the sensitivity to adrenergic-mediated contraction is not different between men and women (Hannan et al., 2012).

Many of the differences between the male and female pudendal arteries can be explained by the hemodynamic demands of their genital organs. The volume of blood and inflow pressures required to fill the penis are much greater than the demands of the female genitalia when sexual purposes are considered. Furthermore, various clinical studies have confirmed the difference in volume of blood as well as the pressures achieved by the genital organs during orgasm in both sexes. In fact, the volume of blood required to fill the clitoral tissue during sexual response is one-tenth that required to fill the penis (10 mL vs 100 mL) (Kaufman et al., 1993; Maravilla and Yang, 2008). Furthermore, the intracavernosal pressure within the penis reaches suprasystolic values during orgasm/ejaculation, whereas the vaginal, clitoral, and labial pressures only increase approximately 30–40 mmHg at peak sexual response (Kandeel et al., 2001; Sommer et al., 2001). Thus the male pudendal artery needs to be able to withstand greater inflow of blood at higher pressure and these requirements are reflected in the increased wall-to-lumen ratio of the pudendal artery.

The pudendal artery in the female rat is very similar anatomically to that in women. In women, the origin of the internal pudendal artery is also located on the internal iliac artery, but appears to arise much further down after the obturator, vesicular, and inferior gluteal branches (Yamaki et al., 1998; Beech and Adams, 2009). In both species, the internal pudendal artery gives off branches supplying the labia and distal vaginal wall and terminates as the common clitoral artery with branches forming the clitoral cavernous and dorsal clitoral arteries (O'Connell and De Lancey, 2005; Fatu et al., 2006). There is also evidence in both men and women of accessory pudendal arteries which arise off the inferior vescical, obturator, and external pudendal arteriesand supply the genital tissues (Benoit et al., 1999).

The internal pudendal artery has markedly heightened susceptibility to vascular damage compared to other vessels in the body. Evidence suggests that the female may also be susceptible to vascular pathologies contributing to sexual dysfunction. Indeed, vaginal/clitoral engorgement is a central nervous system-driven event, leading to increases in blood flow to the genital organs – an event that precedes arousal (Traish et al., 2010). This increased blood flow to the vagina, clitoris, and labia is responsible for vasocongestion, engorgement, and lubrication in the sexual arousal response.

Internal genitalia

The internal genitalia are supplied by the internal pudendal artery and the uterine artery.

The vagina receives blood from the descending branch of the uterine artery, vaginal artery, and internal pudendal artery. The veins form the vaginal venous plexus into the internal iliac veins (Standring, 2008).

The vascular system of the uterus is based on the uterine artery from the internal iliac or hypogastric artery and on the ovarian artery from the abdominal aorta. These vessels give origin to an important anastomotic trunk with a typical circular disposition. The uterine artery derives from the anterior division of the hypogastric and runs medial to the levator ani muscle; about 2 cm from the cervix it crosses above and in front of the ureter. Reaching the side of the uterus it ascends in a tortuous manner between the two layers of the broad ligament to the junction of the fallopian tube and uterus. It ends joining with the ovarian artery. The uterine veins correspond with the arteries and end in the uterine plexuses.

The arteries of the ovaries and uterine tubes are the ovarian arteries from the abdominal aorta. Each ovarian artery anastomoses in the mesosalpinx, with the uterine artery giving some branches to the fallopian tube and to the ovary. The veins emerge from the hilum in the form of a plexus, the pampiniform plexus (Netter, 2010).

Veins from the ovary have a different ending: the right ovarian vein drains into the vena cava, with an acute incident angle that facilitates blood flow into the bigger leading vein. The left ovarian vein drains into the renal vein, with an orthogonal incidence which reduces the draining flow (Standring, 2008). This mechanic flowing difference is credited as the leading cause of pelvic varices on the left side. It can contribute to chronic pelvic pain, mostly when it is more localized on the left side of the pelvis.

THE LYMPHATIC SYSTEM

The lymphatic vessels of the perineum and of the external genitalia follow the course of the external pudendal vessels, and end in the superficial inguinal and subinguinal glands. Those from the ovary ascend with the ovarian artery to the lateral and preaortic glands. The lymphatic vessels of the uterus consist of two sets, superficial in the peritoneum and deep inside the organ. The vessels of the cervix go into the external iliac glands, to the hypogastric glands, and to the common iliac glands. The vessels of the body of the uterus run in the broad ligament principally and with the ovarian vessels ascend to the lateral and preaortic glands (Standring, 2008).

The innervation of genitals and pelvic floor system

The pudendal nerve arises from the sacral plexus; it is formed by the second, third, and fourth sacral nerve

roots. It passes between the piriformis and coccygeus muscles and leaves the pelvis through the lower part of the greater sciatic foramen. It then crosses the spine of the ischium, being situated between the sacrospinous and sacrotuberous ligament (Robert et al., 1998), and re-enters the pelvis through the lesser sciatic foramen. It goes along the lateral wall of the ischiorectal fossa with the internal pudendal vessels (the pudendal artery lies on its medial side), contained in a duplication of the obturator fascia called Alcock's canal (Shafik et al., 2004) and divides at the level of the perineum into three terminal branches: the dorsal nerve of the clitoris, the perineal nerve, and the inferior rectal nerve, providing the sensory branches to the skin of the perineal area, labia majora, and clitoris (Mahakkanukrauh et al., 2005; Tagliafico et al., 2013). It also innervates the external anal sphincter (inferior rectal nerve) and deep muscles of the urogenital triangle (perineal nerve).

The perineal nerve is situated below the internal pudendal artery and divides into a posterior labial branch and a muscular branch. The dorsal nerve of the clitoris is the deepest division of the pudendal nerve. Considering the relatively small size of the clitoris, even including the crura and bulbs, in comparison to the penis, the size of the dorsal nerve of the clitoris is proportional to its extraordinary sensory capacity, although it is small in absolute terms. The dorsal nerve supplies the clitoris (Peng and Antolak, 2009). The pudendal nerve is the most important human nerve in terms of pleasure perception. At the same time, it is also critical in sexual pain disorders, namely introital dyspareunia and vaginismus.

The lumbar plexus is formed by the loops of communication between the anterior division of the first three and the greater part of the fourth lumbar nerves; it is situated in the posterior part of the psoas major, in front of the transverse processes of the lumbar vertebrae. It divides into many branches, giving origin to the ileoinguinal nerve and genitofemoral nerve, which are important for innervation of the pelvis. The ileoinguinal nerve arises from the first lumbar nerve, giving branches to the obliquus internus muscle and to the skin covering the mons pubis and labia majora. The genitofemoral nerve arises from the first and second lumbar nerves and divides into the external spermatic nerve (which accompanies the round ligament of the uterus and becomes lost on it) and into the lumboinguinal nerve (whicih supplies the skin of the anterior surface of the upper part of the thigh) (Standring, 2008).

THE PHYSIOLOGIC AGING OF WOMEN'S GENITALIA

The female genital tract undergoes anatomic and functional changes from birth to menopause and beyond, due to the levels and roles of estrogen, progesterone, and androgen (testosterone, dehydroepiandrosterone, and androstenedione) production (Venkatesh and Cu-Uvin, 2014). After the menopause, the loss of sexual hormones accelerates the process of aging, with two prominent characteristics:

1. A low-grade inflammation, genital and systemic, leading to a new word "inflammaging" – a process that constitutes the common denominator of cancer, neurodegenerative and cardiovascular diseases, among others (Michaud et al., 2013; Fulop et al., 2014).
2. A progressive involution of all the genital structures, unless a well-tailored hormone replacement therapy (HRT) is considered and prescribed.

Specifically, menopause is defined as the permanent cessation of ovarian follicular activity (Mishra and Kuh, 2011). It is a natural bodily process which has a different clinical expression for each woman. The cessation of estrogen production causes a variety of symptoms and signs (hot flashes, night sweats, breast tenderness, vaginal dryness and atrophy, loss of sexual drive, ostheoarthritis with joint pain, osteoporosis, heart disease, and mood changes) (Hoffman et al., 2012).

Typical aging changes include the following.

Vulvar aging

Prominent features include: reduced epithelial and mucosal trophism, progressive reduction in the volume of labia majora and minora (Fig. 4.5), reduced fibroblastic activity, up to 30%, with reduced production of collagen, elastin, and mucopolisaccharides, reduced sweat and sebaceous gland production, both qualitative and quantitative, with parallel reduction in genital pheromones (Farage and Maibach, 2006).

This change, toghether with the modification of the vaginal ecosystem, secretion, and lubrication, is responsible for the loss of the genital "scent of a woman," critically important as a pleasant trigger for oral sex and for

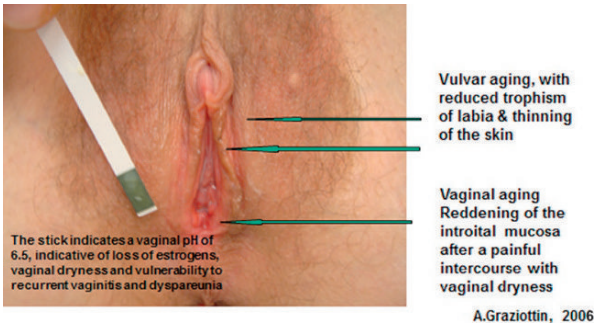

Fig. 4.5. Progessive vulvovaginal aging after the menopause.

erection. Many partners report this specific change as a major impairment in the couple's intimacy liturgy only to the listening and caring gynecologist! Other changes include a progressive involution of the corpora cavernosa, that loses on average 50% volume by the menopause (Tarcan et al., 1999). When the process is particularly accelerated, as may happen in thin, hypoestrogenic postmenopausal women, it may contribute to the clinical complaint that "my clitoris is dead" (Hunter et al., 2008) in terms of loss of congestion and pleasurable sensations up to orgasm during genital foreplay, reported by 20% of postmenopausal women.

Other changes include the involution of peripheral nerves, of skin immune system activity and in hair distribution, color, and density (Tan et al., 2012). Hair whitening may be perceived as an aging-related sexual "insult," particularly by women who undergo a premature menopause and have to face these genital changes in spite of their relative youth, unless appropriate HRT (and hair coloring) is prescribed, when feasible and not contraindicated. Senile atrophy, kraurosis vulvae, leukoplakia, and lichenification are the epiphenomena, the visible tip of the iceberg of a full-thickness aging, involving all the tissue components, as mentioned above. They indicate how the progressive skin, submucosal, vascular, connective, nervous and immune involution may affect vulvar appearance and function (Kingsberg et al., 2013).

Introital dyspareunia up to frank impossibility to accept intercourse because of the extreme narrowing of the vestibular area is the most frequently reported sexual consequence in advanced aging (Krychman, 2011). Vulvar lichen sclerosis, a probable autoimmune disease with accelerated vulvar aging, and a prominent symptom of night itching, may further contribute to the sexual complaint of clitoral hyporesponsiveness, orgamic difficulties, and introital dyspareunia, complained of during and after menopausal transition (Fig. 4.6).

On a positive note, topical treatment with a 2% testosterone propionate powder in Vaseline jelly may dramatically delay and partially reverse vulvar aging and its sexual consequences, more so if timely initiated – the sooner the better (Graziottin and Murina, 2011).

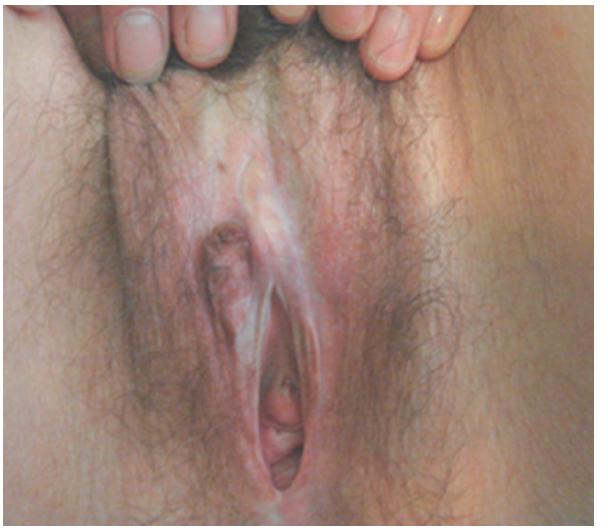

Fig. 4.6. Introital postmenopausal dyspareunia with vulvar dystrophy. Carla, 54 years; three children. Main consulting symptoms: hypoactive sexual desire disorder, itching, vulvovaginal dryness, and introital dyspareunia. Associated symptoms: delayed orgasm, with diminished intensity, mild stress incontinence, leakage during thrusting. (Reproduced from Graziottin and Murina, 2011.)

Ovarian aging

The ovaries undergo aging by a continuous decrease in number of follicles, diminished quality of oocytes, and ovarian hormonal deficiency until the menopause, which is the final step in this aging process (Li et al., 2012). Sexual mechanisms are involved and oxidative stress is considered one of the most important, leading to follicular atresia and reduction of quantity and quality of oocytes (Agarwal et al., 2012). The number of follicles in the ovary has a direct relation with the hormonal levels of estrogen, progesterone, and gonadotropin (Agarwal et al., 2012). During menopause, there is a rise in follicle-stimulating hormone and luteinizing hormone levels with a decrease in the amount of estrogen (Doshi and Agarwal, 2013). Estrogen is synthesized by granulosa cells of the ovary in three forms: estradiol (the most common and potent form which is predominant during the fertile age of the woman), estriol, and estrone (the weaker form, which is prevalent during the postmenopausal phase, derived from the conversion of androstenedione in adipose tissue and liver) (Cooke and Naaz, 2004). In addition, estrogens are synthesized in smaller amounts by other tissue, adrenal glands, fat cells, hepatocytes, and even from muscles, which during physical exercise metabolize dehydroepiandrosterone to estradiol and testosterone. The reduction of estrogen levels increased the oxidative stress in the body depending on the proper chemical structure of the hormone correlating with breaks in genetic material (Lei et al., 2010).

Vaginal aging and atrophy

It has been estimated that 25–50% of postmenopausal women experience vulvovaginal atrophy, with symptoms of burning on urination, vaginal discharge, itching or burning sensation, vaginal dryness, and painful sexual intercourse (MacBride et al., 2010; Tan et al., 2012). The reduction of estrogens removes the trophic stimulus

from the vaginal tissue: the vaginal epithelium becomes thin, vaginal secretions and vascularization decrease, the submucosal layers lose mucopolisaccharides and elastic fibers, and the vagina becomes shorter, narrower, and less elastic, with an increase in the pH level (Freeman, 2010) and in the content of inflammatory cytokines (interleukin-1 (IL-1) and IL-8). The hormonal changes influence the vaginal microbiome, with a continued decrease in lactobacilli, the prominent acid production bacteria typical of the healthy vaginal ecosystem in the fertile age. The consequent change in resident flora contributes to the increased vulnerability to *Escherichia coli* infections, leading to recurrent vaginitis and urinary tract infections (Lamont et al., 2011; Broatman et al., 2014). Pathogenic biofilms produced by and containing *E. coli* and other pathogenic microorganisms of colonic origin contribute to recurrent cystitis and vaginitis in the postmenopausal years.

Uterine and tubal aging

With age, and in the absence of HRT, the uterus and tubes undergo progressive involutive changes. The muscle component is reduced, an increased collagen production is documented, and the endometrium becomes subtle and thin (Bitti et al., 2014). Myomata, previously present in the fertile age, undergo a reduction in size and, sometimes, there are local involutive inflammatory processes with calcifications (Grings et al., 2012).

Vascular aging

Aging is associated with structural and functional changes in the vasculature, including endothelial dysfunction, arterial stiffening and remodeling, impaired angiogenesis, and defective vascular repair with an increased incidence of atherosclerosis (Novella et al., 2012). Cardiovascular risk increases in women after the menopause: it has been correlated with loss of the protective effects of estrogens on vascular endothelium (Stice et al., 2009). Estrogen promotes endothelial nitric oxide production and modulates prostacyclin and thromboxane A_2 release (vasodilator substances) and decreases the production and effects of vasoconstrictors such as endothelin and angiotensin II (Orshal and Khalil, 2004; Khalil, 2013). Early initiation of estrogen replacement produces more favorable results than if started later (Prentice et al., 2009). Specifically, progressive vascular involution of the vaginal vessel is first responsible for the progressive vaginal dryness complained of by an increased percentage of postmenopausal women (Guthrie et al., 2004; Dennerstein et al., 2007).

Pelvic floor aging, sarcopenia, and bone mass loss

Pelvic floor aging involves all the conenctive structures with a prominent involution in the levator ani muscle. Sarcopenia is age-related loss of muscle mass and function, caused by multifactorial mechanisms (impaired regenerative capacity, attenuated ability to respond to stress, elevated reactive oxygen species production, and low-grade systemic inflammation) (Lightfoot et al., 2014).

Sarcopenia at the level of the pelvic floor muscles is of special importance in the aging woman as it may contribute to the prolapse of genital organs, to urinary incontinence, and even anal incontinence in women who suffered from sublclinical anal lesions during delivery.

The decrease of estrogens leads to a bone mass loss which predisposes to osteoporotic fractures (Ahn and Song, 2009) in association with vitamin D insufficiency (Lips et al., 2006; e Silva et al., 2014). Loss of vitamin D may further accelerate the sarcopenia process. This may further contribute to back pain (Silva et al., 2006; Lightfoot et al., 2014).

THE PHYSIOLOGY OF WOMEN'S SEXUAL FUNCTION

The anatomy of the genital organs is a prerequisite for sexual function in both genders. Physiology encompasses all the functions and changes of the systems – nervous, muscular, vascular, mucocutaneous, metabolic, endocrine, immune – that are essential to lead to a complete sexual response (Graziottin and Giraldi, 2006). Physicians should master the basics of the anatomy and physiology of sexual function to to be able to diagnose and treat women's sexual dysfunction (Graziottin, 2007a, b). Sexual function includes desire/interest, central and peripheral arousal with genital congestion and vaginal lubrication, orgasm, resolution, and satisfaction. Recent debate supported a common reading of sexual desire/interest and central arousal in women (Greenberg and Jerrold, 2010).

Sexual desire/interest and central arousal may be activated by both internal and external stimuli (Fig. 4.7). Internal stimuli include erotic and non-erotic dreams, fantasies, memories, love, attachment/intimacy needs, and physical drive. External stimuli include all the sensory signals: olfactory (including pheromones), tactile, gustatory, auditory, and visual. In women the first three are prominent and are also referred to as "cenesthetic signals." Whatever the stimulus, as soon as it is perceived/read as "sexual," it will massively activate a complex neuronal functional response in many different brain

areas (see Chapter 2), a process known as psychoplasticity. This is the functional correlation of the huge neuroplasticity biologically activated by the sexual stimulus, that is constantly modulated during the fertile age by the presence of and changes in sexual hormone levels (see Chapter 10). After the menopause, massive central, peripheral/somatic, and genital changes are induced in women's sexual response by the loss of sexual hormones (Table 4.1).

Once the sexual stimulus is perceived, four major brain systems are activated at the same time (Stoléru et al., 2012):

1. the autonomic *s*ystem, mediating the neurovascular, cardiovascular, respiratory, mucocutaneous, olfactory, salivary, and genital response, preparing the whole body for sexual intercourse
2. the emotional/affective/limbic system, which sets the emotional color/atmosphere of this specific feeling of desire and arousal, which may be enhancing, when a positive, reciprocal response is perceived in the desired partner, or inhibiting, when a negative response is anticipated/perceived and/or when unwanted genital pain is perceived/activated by arousal and/or by the intercourse
3. the cognitive system, which evaluates the wish for and risks of behaving sexually
4. the motor system, usually neglected in classic descriptions; in contrast, it is an absolutely vital part of sexual behavior in both genders. It is involved in two main areas: (a) motor behavior is a vital part of courting, foreplay, hugging, kissing, and caressing, i.e., in the music of loving and sexual bodies; and (b) it is also a critical component of orgasm, by definition a sensory/motor reflex. It seems that decreased blood flow in the left lateral orbitofrontal cortex signifies behavioral disinhibition during orgasm in women, and that deactivation of the temporal lobe is directly related to high sexual arousal. In addition, the deep cerebellar nuclei may be involved in orgasm-specific muscle contractions, while the involvement of the ventral midbrain and right caudate nucleus suggests a role for dopamine in female sexual arousal and orgasm (Georgiadis et al., 2006). It is of special relevance for

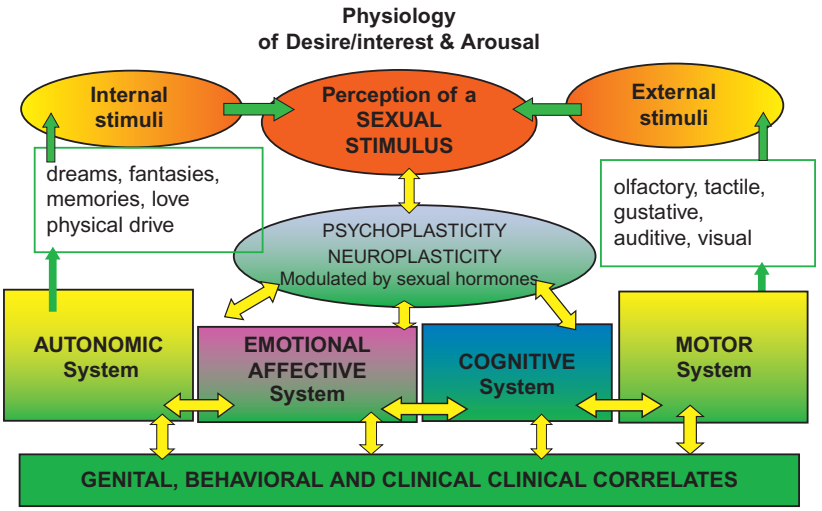

Fig. 4.7. Physiology of sexual desire/interest and central arousal. (Reproduced from Graziottin and Giraldi, 2006.)

Table 4.1

Mean steroid levels in women: values converted to pg/mL

Steroid	Reproductive age	Natural menopause	Iatrogenic menopause
Estradiol	100–150	10–15	10
Testosterone	400	290	110
Androstenedione	1900	1000	700
Dehydroepiandrosterone	5000	2000	1800
Dehydroepiandrosterone sulfate	3 000 000	1 000 000	1 000 000

Reproduced from Lobo (1999).

neurologists, as motor system pathology may affect women's (and men's) sexuality in a complex, and yet not completely understood, way. For example, in multiple sclerosis, cerebellar components of orgasm in women are selectively affected (Gruenwald et al., 2007).

MODELS OF WOMEN'S SEXUAL FUNCTION

Different models of women's sexual function have been proposed over the years. The main change is from a linear reading of the sexual response (Fig. 4.8) (Masters and Johnson, 1966), without desire as a major starting point, to including desire (Fig. 4.9) (Kaplan and Horwith, 1983), to a more sosphisticated model (Basson, 2000) more focused on emotional/affective reading, appreciating the role of intimacy needs in women. In this model (Fig. 4.10) four major contributors modulate the final perception of desire. This model is endorsed mostly by women in long-lasting relationships when intimacy needs may activate a responsive desire to the partner's sexual cues. Basson's key contributors of sexual desire/interest include biologic, psychologic, sociocultural, and relationship factors.

Graziottin's circular model focuses on the biologic component of women's sexual response to help physicians in their basic reading of key functional and dysfunctional biologic contributors (Fig. 4.11) (Graziottin, 2000). It should be considered as a detailed reading of the biologic contributors in Basson's integrated biopsychosocial model. Here the focus will be on the genital physiology contributing to the genital sexual response in women.

During sexual stimulation, the female sexual arousal response is triggered by sensory stimulation, synchronous with central nervous activation, resulting in increased blood flow to the genitals (Berman et al.,

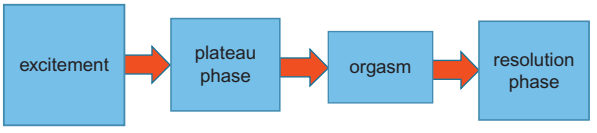

Fig. 4.8. Masters and Johnson's sexual model – a linear model with one phase occurring before the next in the same order.

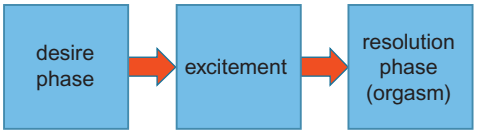

Fig. 4.9. Kaplan's triphasic model – a linear model with implementation of the sexual desire phase.

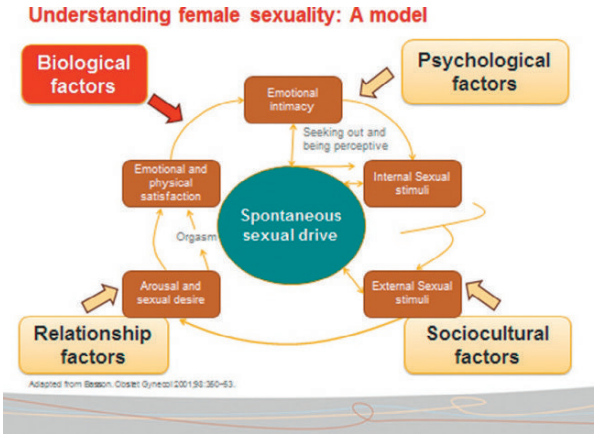

Fig. 4.10. Basson's sexual model. (Adapted from Basson, 2001.)

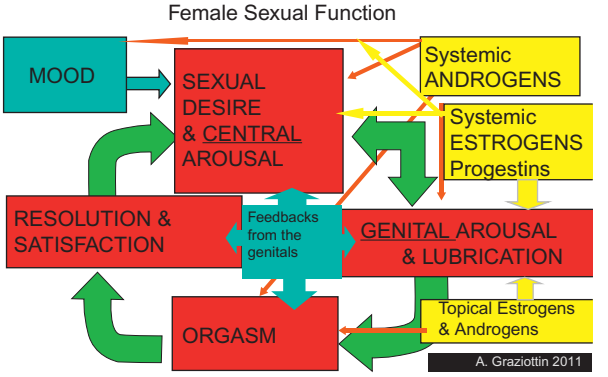

Fig. 4.11. Graziottin's model stresses: (1) the interdependence between desire/interest and central arousal, genital arousal, with cavernosal congestion and vaginal lubrication, orgasm, resolution, and satisfaction, leading to either positive or negative feedback, according to the quality and intensity of the sexual experience; (2) in contrast to previous models, the importance of genital feedback: (a) the quality of cavernosal/vulvar and urethral congestion and vaginal lubrication and the sensations/feelings the woman is having from it (pleasure, indifference ("I feel nothing"), pain and/or burning feelings at penetration); (b) the impact of the man's genital sexual response on the woman's genital arousal (quality of erection, hardness, and duration). These biologically based genital factors may further enhance or inhibit the woman's genital and mental response, through either positive or negative feedback; (3) the model also stresses the role of mood as a central desire/interest modulator encompassing: (a) the biologic mood levels (serotonine/dopamine-correlated); (b) the impact of sexual hormone patterns and fluctuations on mood itself; (c) the impact of the specific sexual experience (whether rewarding, neutral, or negative) on mood; (d) the inhibiting role of negative/painful genital feedbacks (often disregarded/neglected) in women; and (e) the impact of male genital factors (functional/lasting erections vs erectile deficit or premature ejaculation).

1999; Deliganis et al., 2002; Maravilla et al., 2003; Giraldi and Levin, 2006; Cuzin, 2012). During sexual arousal, the cavernosal bodies of the labia/periurethra and clitoris become engorged with blood (increased by two to three times) (Suh et al., 2004). The concomitant activation and secretion of Bartholin's gland liquid contribute to the lubrication of the internal part of the labia minora and of the vestibular region; it is essential to prevent painful coitus (Riley and Riley, 1983).

The clitoris with the clitoral bulbs plays a central role in female sexual function. Under basal conditions, the blood vessels in the clitoris have a high tone (through sympathetic activity) and are mainly closed (Yilmaz et al., 2002), but show evidence of vasomotion (Levin, 2005), the random opening and closing depending on local tissue needs. The neural innervation is through VIPergic nerves releasing vasoactive intestinal peptide (VIP), which dilates the arterial supply and nitric oxide (NO), which promotes relaxation of the smooth muscle of the cavernous sinuses (Martin-Alguacil et al., 2008). In both genders testosterone is a "permitting" factor for NO-mediated vasodilatation; in women, estrogens are the permittng factor for VIP-mediated systemic vasodilatation and vaginal lubrication (Levin, 2005). During sexual arousal, the central reduction of sympathetic tone and the release of the two vasodilator neurotransmitters create an increase in blood flow to the clitoris, relaxing the trabecular smooth muscles, thus promoting clitoral vasocongestion along with increased width of the clitoris during arousal (Salonia et al., 2012).

Since there is no subalbugineal layer between its tunica and the erectile tissue, the clitoris only becomes swollen or tumescent and not rigid, even when fully filled (Toesca et al., 1996). This congestion is usually associated with pleasurable genital feelings of engorgement and lubrication: with positive feedback this contributes to improved mood, positive emotional feelings, and desire/interest/motivation for intercourse and penetration.

The vagina also plays a very active role in sexual arousal with its change in microcirculation. During quiescence, vaginal capillaries are closed due to contraction of the precapillary sphincters; the surface pO_2 of the vagina wall is thus basally at a low, hypoxic level (Wagner and Levin, 1978). When the local area around one of these becomes hypoxic, the released metabolites (pCO_2, lactic acid, K^+, and adenosine triphosphate) cause precapillary sphincter relaxation and the supplied capillaries to open up, washing away the metabolites and refreshing the local area with oxygen and nutrients. This intermittency of the microcirculation is known as "vasomotion" (Levin and Wylie, 2008). The degree of vaginal vasomotion is a sensitive and useful index of genital arousal. Thus, during basal conditions, a high vasomotor tone of the arterial supply through central sympathetic activation and a high level of vasomotion keep the blood flow to the vagina at minimal levels. With sexual stimulus, the central sympathetic tone is reduced and the arterial supply is enhanced through the action of released neuronal VIP and some NO via the sacral anterior nerve root (Wagner, 1979). In this way the recruitment of the capillaries becomes maximal, the vagina becomes fully vasocongested (along with the labia and clitoris), and vasomotion is absent.

Within the sexually aroused vagina, the capillaries of the microcirculation are filled with blood and the increased hydrostatic pressure inside them forces out a plasma transudate (ultrafiltrate) into the interstitial space around the blood vessels (Wagner, 1979; Levin, 2005; Levin and Wylie, 2008). Continued formation of this neurogenic transudate fills up the interstitial space and then passes through and between the cells of vaginal epithelium to leak on to the surface wall of the vagina as vaginal lubrication. The final fluid is a modified plasma filtrate because the cells of the vagina can transfer Na^+ ions vectorially from the lumen back into the blood and add K^+ ions by secretion and cell shedding (Wagner, 1979). The ionic concentrations are different from those in the plasma, having a higher K^+ and a lower Na^+ than plasma (Wagner and Levin, 1980). In contrast, the arousal lubrication fluid has a much higher Na^+ concentration than the basal fluid, approaching that of plasma (Wagner and Levin, 1978). On cessation of sexual arousal, the vaginal Na^+ together with osmotically drawn fluid is transferred back into the blood, thus resetting the vagina to the basal "just moist" condition.

The pelvic muscles are an intrinsic part of the orgasmic process (Levin, 1981). Orgasm is characterized by seven to eight rapid sequential contractions of the levator ani muscles and muscles of the superficial trigonus. Hypoactivity of the muscles (low tone), more frequent after vaginal delivery, leads to poor sexual function and lack of pleasure during coitus and orgasm. A healthy and tonic pelvic floor is significantly associated with better arousal and orgasm (Lowenstein et al., 2010). In contrast, hyperactivity (high tone) may be pathophysiologically linked to the sexual pain disorders called dyspareunia (coital pain) and vaginismus (Graziottin and Giraldi, 2006).

The orgasm in the female is a variable, transient peak of sensation of intense pleasure, creating an altered state of consciousness, usually accompanied by involuntary, reflex rhythmic contractions of the pelvic striated circumvaginal musculature, often with concomitant uterine and anal contractions and myotonia that resolves the sexually induced vasocongestion, usually with an induction of well-being and contentment (Meston et al., 2004). It can be induced by different physical

trigger stimulations, genital (clitoral, periurethral, vaginal, anal), non-genital (breast, nipple, skin), and mental stimulation (erotic dreams, fantasies, sexual daydreams) (Levin, 2001). During orgasm the so-called phenomenon of female ejaculation has been demonstrated (Korda et al., 2010): this consists of the expulsion of a small quantity – no more than one or two teaspoons – of whitish fluid produced by the female prostate, previously called Skene's paraurethral glands (Rubio-Casillas and Jannini, 2011), characterized by the presence of prostate-specific antigen and prostatic specific acid phosphatase (Zaviacic et al., 1988).

RESOLUTION AND SATISFACTION

Orgasm is associated with different changes: (1) somatic: the peak of oxytocin contributes to relaxation of the musculature, lowering blood pressure and heart beat, reducing the frequency of breathing, leading to an overall sense of physical relaxation; (2) emotional affective: oxytocin also mediates a sense of contentment, further accentuated by emotional feelings if the experience has been appreciated as highly rewarding; (3) endocrine: oxytocin released at orgasm increases estrogen and androgen receptors in the genital organs and pelvic floor, thus creating the endocrine basis for further enhancement of the physical response; and (4) finally oxytocin potentiates the couple's bonding through the powerful reward system specifically activated by intercourse with one or more pleasurable orgasms.

CONCLUSION

Anatomy and physiology of women's sexual function still deserve further studies as many aspects remain unclear or controversial. Knowledge and continuous updating are key for all healthcare providers who are willing to really increase their competence in diagnosing and effectively treating women's sexual dysfuntions.

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 5

Anatomy and physiology of the lower urinary tract

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INTRODUCTION

The storage and periodic elimination of urine depend on the coordinated activity of two functional units in the lower urinary tract: (1) a reservoir (the urinary bladder) and (2) an outlet consisting of the bladder neck, urethra, urethral sphincter, and pelvic floor (Fry et al., 2005). Coordination between these organs is mediated by a complex neural control system located in the brain, spinal cord, and peripheral ganglia (Morrison et al., 2005). Thus, urine storage and release are highly dependent on central nervous system pathways. This distinguishes the lower urinary tract from many other visceral structures (e.g., the gastrointestinal tract and cardiovascular system) that maintain a certain level of function even after extrinsic neural input has been eliminated.

The lower urinary tract is also unusual in its pattern of activity and organization of neural control mechanisms. For example, the urinary bladder has only two modes of operation: storage and elimination. Thus, many of the neural circuits have switch-like or phasic patterns of activity (de Groat, 1975; de Groat et al., 1993; de Groat and Wickens, 2013), unlike the tonic patterns characteristic of the autonomic pathways to cardiovascular organs. In addition, micturition is under voluntary control and depends on learned behavior that develops during maturation of the nervous system, whereas many other visceral functions are regulated involuntarily. Micturition also requires the integration of autonomic and somatic efferent mechanisms to coordinate the activity of visceral organs (the bladder and urethra) with that of urethral and pelvic floor striated muscles (Morrison et al., 2005).

Due to the complexity of the neural mechanisms regulating the lower urinary tract, micturition is sensitive to a wide variety of injuries, diseases, and chemicals that affect the nervous system. Thus, neurologic mechanisms are an important consideration in the diagnosis and treatment of voiding disorders. This article reviews: (1) the innervation of the urinary bladder, urethra, and pelvic floor; (2) the organization of the reflex pathways controlling urine storage and elimination; (3) the neurotransmitters involved in micturition reflex pathways; and (4) neurogenic dysfunctions of the lower urinary tract.

PERIPHERAL NERVOUS SYSTEM

Efferent innervation and neurotransmitters

The lower urinary tract receives a bilateral efferent innervation from the thoracic and lumbosacral segments of the spinal cord (Fig. 5.1A). Efferent axons are carried in three sets of peripheral nerves: sacral parasympathetic (pelvic nerves), thoracolumbar sympathetic (hypogastric nerves and sympathetic chain), and sacral somatic nerves (primarily the pudendal nerves) (Morrison et al., 2005) (Fig. 5.1A). Preganglionic axons carrying information from the spinal cord to the bladder and urethra synapse with autonomic ganglion cells widely distributed throughout the peripheral nervous system in: (1) the pelvic plexus; (2) prevertebral sympathetic ganglia (inferior mesenteric ganglia); (3) paravertebral sympathetic chain ganglia; and (4) ganglia on the serosal surface and in the wall (intramural ganglia) of the organs (Langley and Anderson, 1895, 1896; Wozniak and Skowronska, 1967; de Groat and Ryall, 1969; Féher et al., 1978; Fehër et al., 1980). Ganglia on one side are interconnected by numerous fiber tracts and the majority of inputs from the spinal cord occur ipsilaterally. In addition in some species fiber connections between the right and left pelvic plexuses and the inferior mesenteric ganglia occur

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(Tanaka et al., 1981; Fukuda and Fukai, 1985; Kihara and de Groat, 1997) and synaptic interactions between the right and left plexuses have been reported (Harji et al., 1998). The striated muscles of the external urethral sphincter (EUS) (i.e., rhabdosphincter) and pelvic floor (levator ani) are directly innervated by axons originating from motoneurons in the spinal cord (Figs 5.1 and 5.2).

Pelvic and bladder ganglia

The autonomic ganglia contain thousands of postganglionic neurons but are innervated by considerably smaller numbers of preganglionic neurons (PGNs) located in the intermediolateral region of the spinal cord (Nadelhaft et al., 1980, 1983; de Groat et al., 1981, 1982; Nadelhaft and Booth, 1984; Morgan et al., 1986; Nadelhaft and McKenna, 1987; Keast, 1999). Thus, the preganglionic axons exhibit considerable divergence within the peripheral nervous system in order to synapse with multiple ganglionic targets. Synaptic transmission in all ganglia is mediated by acetylcholine acting on nicotinic receptors; although, as discussed later, other neurotransmitters acting on various types of presynaptic and postsynaptic receptors can modulate cholinergic transmission.

The anatomy and function of bladder ganglia vary in different species. For example, in rodents the ganglion cells have no or few very short dendrites (Tabatabai et al., 1986; Rogers et al., 1990) whereas in the cat the cells have a complex morphology with 6–7 long dendrites (Tabatabai et al., 1984; de Groat and Booth, 1993).

This difference in dendritic structure correlates with differences in synaptic physiology. In rats the ganglion cells receive an input from one dominant preganglionic axon that elicits large-amplitude excitatory postsynaptic potentials (EPSPs) and synaptically mediated postganglionic discharges. Thus synaptic transmission occurs with a high safety factor and the ganglia function as simple relay stations that transmit signals from the spinal cord to the bladder muscle. Transmission is relatively constant over a wide range of frequencies (1–20 Hz). On the other hand, in the cat and rabbit ganglionic transmission occurs with a low safety factor and is frequency-dependent. Low-frequency stimuli (<0.25 Hz) elicit small-amplitude EPSPs and no firing. However postganglionic firing gradually increases in amplitude during continuous stimulation and is very prominent at frequencies of 1–20 Hz (de Groat, 1975; de Groat and Saum, 1976; Booth and de Groat, 1979; de Groat et al., 1979a, b; de Groat and Booth, 1980). Maximal

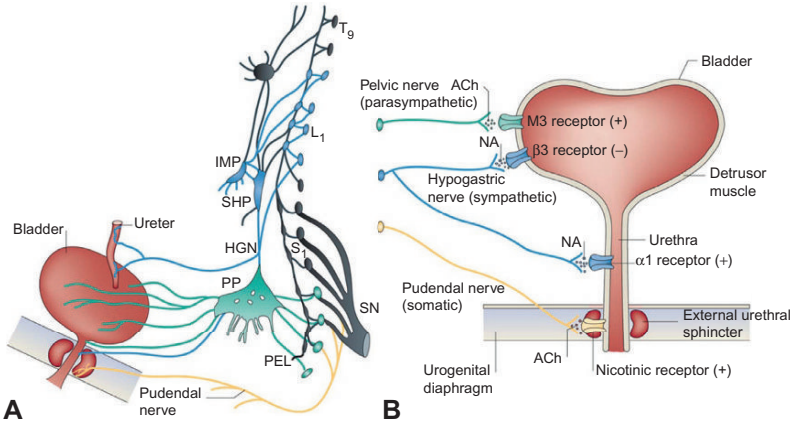

Fig. 5.1. Efferent pathways of the lower urinary tract. (**A**) Innervation of the female lower urinary tract. Sympathetic fibers (shown in blue) originate in the T11–L2 segments in the spinal cord and run through the inferior mesenteric ganglia (inferior mesenteric plexus: IMP) and the hypogastric nerve (HGN) or through the paravertebral chain to enter the pelvic nerves at the base of the bladder and the urethra. Parasympathetic preganglionic fibers (shown in green) arise from the S2–4 spinal segments and travel in sacral roots and pelvic nerves (PEL) to ganglia in the pelvic plexus (PP) and in the bladder wall. This is where the postganglionic nerves that supply parasympathetic innervation to the bladder arise. Somatic motor nerves (shown in yellow) that supply the striated muscles of the external urethral sphincter arise from S2–4 motor neurons and pass through the pudendal nerves. (**B**) Efferent pathways and neurotransmitter mechanisms that regulate the lower urinary tract. Parasympathetic postganglionic axons in the pelvic nerve release acetylcholine (ACh), which produces a bladder contraction by stimulating M_3 muscarinic receptors in the bladder smooth muscle. Sympathetic postganglionic neurons release norepinephrine (noradrenaline: NA), which activates β_3-adrenergic receptors to relax bladder smooth muscle and activates α_1-adrenergic receptors to contract urethral smooth muscle. Somatic axons in the pudendal nerve also release ACh, which produces a contraction of the external sphincter striated muscle by activating nicotinic cholinergic receptors. Parasympathetic postganglionic nerves also release adenosine triphosphate, which excites bladder smooth muscle, and nitric oxide, which relaxes urethral smooth muscle (not shown). L_1, first lumbar root; S_1, first sacral root; SHP, superior hypogastric plexus; SN, sciatic nerve; T_9, ninth thoracic root. (Reproduced from Fowler et al., 2008.)

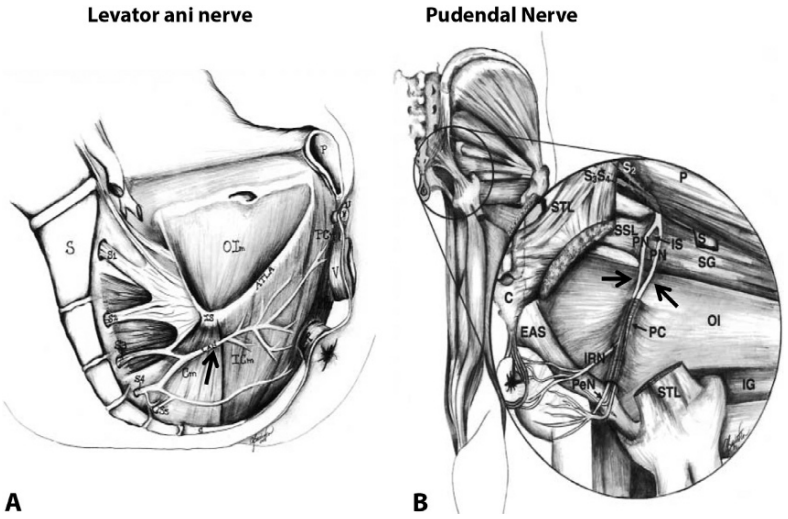

Fig. 5.2. (**A**) Illustration of the course of the levator ani nerve (left hemipelvis, sagittal view). S, sacrum; S1–S5, sacral foramina; Cm, coccygeal muscle; LAN, levator ani nerve; IS, ischial spine; ICm, iliococcygeal muscle; OIm, obturator internal muscle; PCm, pubococcygeal muscle; PRm, puborectal muscle; ATLA, arcus tendinous levator ani; C, coccyx; V, vagina; U, urethra; R, rectum. (**B**) Course of the pudendal nerve through gluteal region and ischiorectal fossa (transgluteal view). The gluteus maximus and the sacrotuberous ligament have been removed. S2–S4, sacral nerve roots; P, piriform muscle; STL, sacrotuberous ligament; SSL, sacrospinous ligament; PN, pudendal nerve; IS, ischial spine; S, sciatic nerve; SG, superior gemellus muscle; C, coccyx; EAS, external anal sphincter; PC, pudendal canal; OI, obturator internal muscle; IRN, inferior rectal nerve; PeN, perineal nerve; IG, inferior gemellus muscle. (Reproduced from Barber et al., 2002.)

facilitation of transmission requires 15–25 stimuli in a train and persists for 30–60 seconds after termination of high-frequency stimulation. Electrophysiologic experiments revealed that frequency-dependent facilitation is mediated by a presynaptic mechanism that enhances acetylcholine release.

Nicotinic transmission in cat bladder ganglia is also modulated by neurotransmitters acting on cholinergic muscarinic and non-cholinergic receptors (de Groat and Booth, 1993). Activation of muscarinic receptors or α_1-adrenergic receptors facilitates transmission while activation of α_2-adrenergic or delta opioid receptors inhibits transmission (de Groat and Kawatani, 1989; Keast et al., 1990). Adrenergic modulation of transmission can be elicited by direct stimulation or reflex activation of sympathetic nerves and opioid receptor modulation is mediated by opioid peptides (enkephalins) released from parasympathetic preganglionic nerves. The synaptic inhibitory mechanisms are effective in suppressing excitatory transmission elicited by low-frequency preganglionic stimulation but relatively ineffective at higher frequencies of stimulation.

Thus synapses in cat and rabbit bladder ganglia function as "high-pass" filters (de Groat, 1975; de Groat and Saum, 1976; de Groat and Booth, 1993) and act as a peripheral gating mechanism to suppress the transfer of low-frequency efferent activity from the spinal cord to the bladder during urine storage, but amplify the transfer of high-frequency activity during micturition. Based on the frequency dependence of synaptic transmission, these bladder ganglia complement the switch-like properties of neural circuits in the central nervous system and can contribute to the maintenance of urinary continence while also promoting bladder emptying. The properties of bladder ganglia in humans have not been studied.

Parasympathetic postganglionic nerves

Excitatory parasympathetic neuroeffector transmission in the bladder is mediated by acetylcholine acting on postjunctional muscarinic receptors (Fig. 5.1B) (Andersson, 1993). Both M_2 and M_3 muscarinic receptor subtypes are expressed in bladder smooth muscle; however use of subtype-selective muscarinic receptor antagonists and muscarinic receptor knockout mice revealed that the M_3 subtype is the principal receptor involved in excitatory transmission (Figs 5.1B and 5.3) (Andersson, 1993; Matsui et al., 2000, 2002; Andersson and Arner, 2004). Activation of M_3 receptors triggers intracellular Ca^{2+} release; whereas activation of M_2 receptors inhibits adenylate cyclase (Fig. 5.3) (Andersson and Arner, 2004). The latter may contribute to bladder contractions by suppressing adrenergic inhibitory mechanisms which are mediated by β-adrenergic receptors and stimulation of adenylate cyclase (Fig. 5.3).

In bladders of various animals stimulation of parasympathetic nerves also produces a non-cholinergic

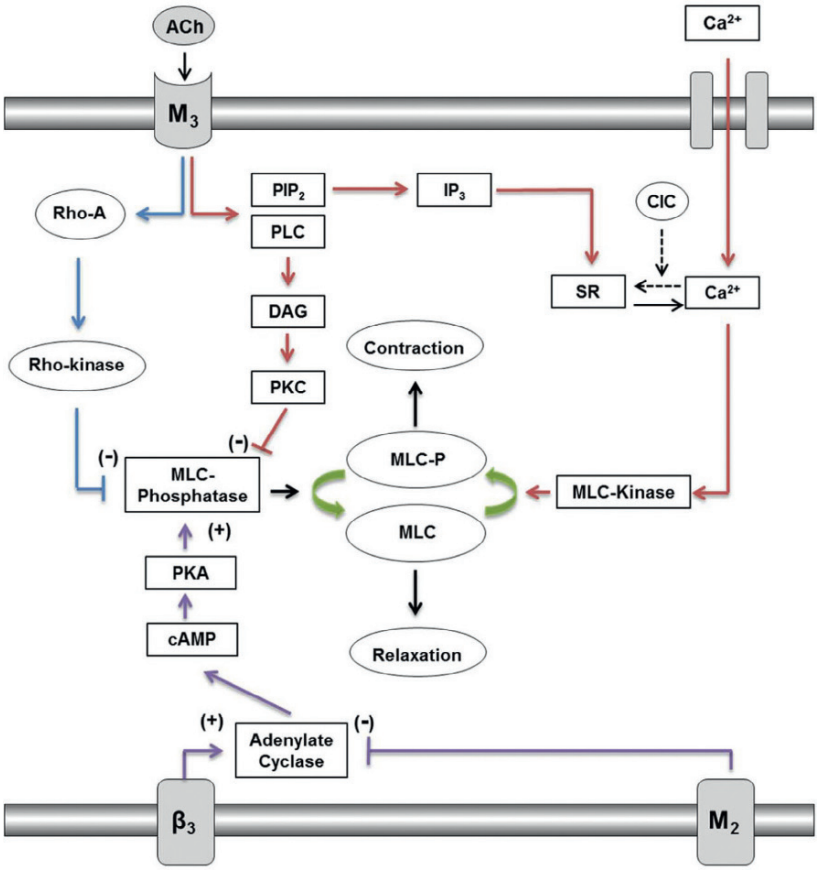

Fig. 5.3. Intracellular signaling pathways involved in activation and relaxation of detrusor contractions via M_2 and M_3 muscarinic and $ß_3$-adrenergic receptors, respectively. ACh, acetylcholine; PLC, phospholipase C; DAG, diacylglycerol; PKC, protein kinase C; PKA, protein kinase A; MLC, myosin light chain; IP_3, inositol trisphosphate; PIP_2, phosphatidylinositol 4,5-bisphosphate; SR, sarcoplasmic reticulum; CIC, calcium-induced calcium release. Intracellular Ca^{2+} release and Ca^{2+} influx contribute to contractions. Activation of M_2 muscarinic receptors inhibits adenylate cyclase and reduces $ß_3$-adrenergic receptor-mediated relaxation.

contraction that is resistant to atropine and other muscarinic receptor-blocking agents. Adenosine triphosphate (ATP) is the excitatory transmitter mediating the noncholinergic contractions (Andersson, 1993; Ralevic and Burnstock, 1998; Burnstock, 2001b; Andersson and Arner, 2004). ATP excites the bladder smooth muscle by acting on P2X receptors which are ligand-gated ion channels. Among the seven types of P2X receptor expressed in the bladder, $P2X_1$ is the major subtype in the rat and human bladder smooth muscle (Ralevic and Burnstock, 1998; Burnstock, 2001b). Purinergic transmission has an important excitatory role in animal bladders but is not important in the normal human bladder. However it appears to be involved in bladders from patients with pathologic conditions such as detrusor overactivity, chronic urethral outlet obstruction, or interstitial cystitis (Palea et al., 1993; Burnstock, 2001b; Zhong et al., 2001).

Parasympathetic input to the urethra induces relaxation during voiding (Andersson et al., 1992; Andersson, 1993; Burnett et al., 1997; Ho et al., 1999; DeLancey et al., 2002; Andersson and Arner, 2004). In various species the relaxation is not affected by muscarinic antagonists and therefore is not mediated by acetylcholine. However inhibitors of nitric oxide (NO) synthase block the relaxation *in vivo* during reflex voiding or block the relaxation of urethral smooth-muscle strips induced *in vitro* by electric stimulation of intramural nerves, indicating that NO is the inhibitory transmitter involved in relaxation (Burnett et al., 1997; DeLancey et al., 2002; Morrison et al., 2002). In some species neurally evoked contractions of the urethra are reduced by muscarinic receptor antagonists or by desensitization of P2X purinergic receptors, indicating that acetylcholine or ATP is involved in excitatory transmission to urethral smooth muscle (Zoubek et al., 1993).

Sympathetic postganglionic nerves

Sympathetic preganglionic pathways that arise from the T11–L2 spinal segments pass to the sympathetic chain ganglia and then to prevertebral ganglia in the superior

hypogastric and pelvic plexus (Fig. 5.1A) and also to short adrenergic neurons in the bladder and urethra. Sympathetic postganglionic nerves that release norepinephrine provide an excitatory input to smooth muscle of the urethra and bladder base, an inhibitory input to smooth muscle in the body of the bladder, and inhibitory and facilitatory input to vesical parasympathetic ganglia (Keast et al., 1990; Andersson, 1993; DeLancey et al., 2002). α-Adrenergic receptors are concentrated in the bladder base and proximal urethra, whereas β-adrenergic receptors are most prominent in the bladder body (Fig. 5.1B) (Andersson and Arner, 2004). These observations are consistent with pharmacologic studies showing that sympathetic nerve stimulation or exogenous catecholamines produce β-adrenergic receptor-mediated inhibition of the body and α-adrenergic receptor-mediated contraction of the base, dome, and urethra (Fig. 5.1B). Molecular and physiologic studies have shown that β_3-adrenergic receptors elicit inhibition and α_1-adrenergic receptors elicit contractions in the human bladder (Andersson and Arner, 2004). The α_{1A}-adrenergic receptor subtype is most prominent in the normal bladder but the α_{1D} subtype is upregulated in bladders from patients with outlet obstruction, raising the possibility that α_1-adrenergic receptor excitatory mechanisms in the bladder might contribute to irritative lower urinary tract symptoms in patients with benign prostatic hyperplasia (Andersson and Arner, 2004).

Sacral somatic nerves

Somatic efferent pathways to the EUS are carried in the pudendal nerve from anterior horn cells in the third and fourth sacral segments of the human spinal cord (Fig. 5.1A) and from various caudal lumbosacral segments in animals. The pudendal nerve passes along the lateral surface of the internal obturator and coccygeus muscles and through Alcock's canal (Fig. 5.2B). As the nerve passes through the canal, it branches into the inferior rectal nerve (which innervates the anal rhabdosphincter), the perineal nerve (which innervates the striated urethral sphincter, the bulbospongiosus muscle, the ischiocavernosus muscle, superficial transverse perineal muscle, and the labial skin), and the dorsal nerve of the clitoris. The branches of the perineal nerve are more superficial than the dorsal nerve of the clitoris and, in most cases, travel on the superior surface of the perineal musculature. The terminal branch of the perineal nerve to the striated urethral sphincter travels on the surface of the bulbocavernosus muscle then penetrates the urethra to innervate the sphincter from the lateral aspects (Fig. 5.2B).

Striated muscles of the pelvic floor, including the levator ani, coccygeus, and puborectalis muscles (Fig. 5.4), receive a different innervation. In human (Fig. 5.2A) (Barber et al., 2002), squirrel monkey (Pierce et al., 2003, 2006, 2008), dog (Thuroff et al., 1982), cat, and rat (Thor et al., 1994; Thor and de Groat, 2010) the levator ani muscles are innervated by the levator ani nerve, although there are reports that the pudendal nerve may also provide an innervation to these muscles in humans (Wallner et al., 2006; Grigorescu et al., 2008). The levator ani nerve primarily arises from sacral spinal roots (e.g., S_3–S_5 in humans) and travels along the intrapelvic face of the levator ani muscle with a high degree of variability in branching patterns (Fig. 5.2A) (Barber et al., 2002).

Modulation of efferent neurotransmission in the bladder

Studies in the urinary bladder of several species (rats, rabbits, human, and guinea pig) have revealed that the efficiency of transmission at postganglionic cholinergic and adrenergic neuroeffector junctions (Tobin and Sjogren, 1998; Somogyi and de Groat, 1999) can vary with the frequency and/or pattern of nerve activity and be modulated by drugs that activate or block receptors for neurotransmitters. This neuroplasticity is dependent in part on homosynaptic and heterosynaptic modulatory mechanisms mediated by the actions of various neurotransmitters (acetylcholine, norepinephrine, neuropeptides, and purines). Postganglionic nerve terminals as well as ganglionic synapses exhibit frequency-dependent gating mechanisms and are sites of "cross-talk" between sympathetic and parasympathetic nerves (de Groat and Saum, 1971, 1972, 1976; Saum and de Groat, 1972; D'Agostino et al., 1986; Somogyi et al., 1995). These properties can alter efferent nerve signals passing from the spinal cord to the bladder.

Afferent innervation and neurotransmitters

Afferent axons in the pelvic, hypogastric, pudendal, and levator ani nerves transmit information from the lower urinary tract and pelvic floor to second-order neurons in the lumbosacral spinal cord (de Groat, 1986; Jänig and Morrison, 1986; Yoshimura and de Groat, 1997a). Pelvic nerve afferents that innervate the bladder and urethra originate in caudal lumbosacral dorsal root ganglia (DRG) and are divided into two populations: small myelinated (Aδ) and unmyelinated C-fibers. The pudendal and levator ani nerves also contain larger-diameter myelinated afferents. Aβ afferents that terminate in the skin are present in the pudendal nerve and Aα afferents that innervate muscle spindles are present in the levator ani nerve (Pierce et al., 2003; Thor and de Groat, 2010).

Receptor properties of afferents

Aδ mechanoreceptor afferents identified in the pelvic nerve (Winter, 1971; Bahns et al., 1987; Downie and

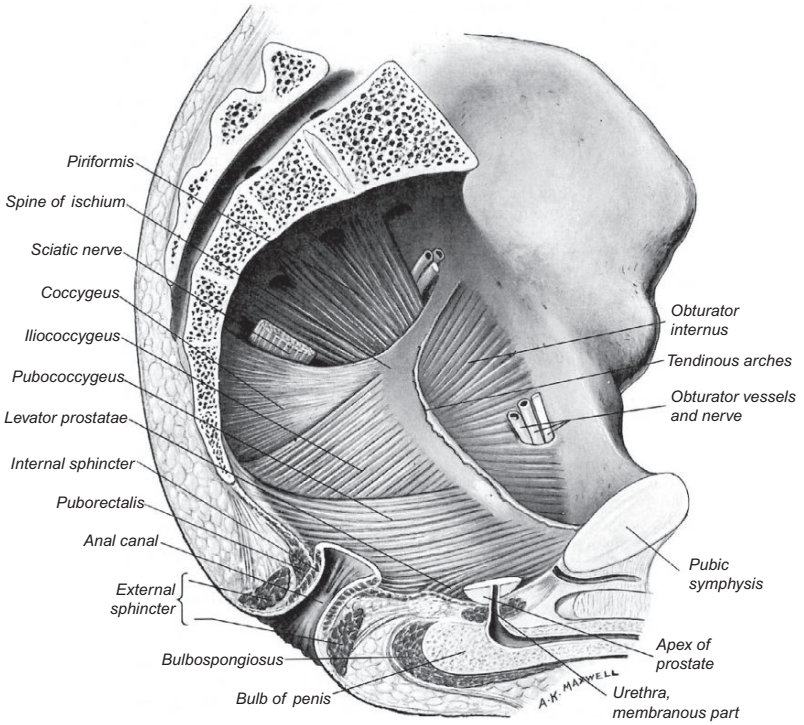

Fig. 5.4. Pelvic aspect of the left levator ani and coccygeus. The superior gluteal vessels and nerve have been cut close to the upper border of piriformis; the anal canal has been divided below the anorectal flexure and the greater part of the prostate has been removed. The constituent parts of levator ani are shown. Note: coccygeus is fused and coextensive with the sacrospinous ligament; the latter is viewed from the gluteal aspect. (Reproduced from Horne, 1995.)

Armour, 1992; Satchell and Vaughan, 1994) or the sacral dorsal roots (Jänig and Morrison, 1986; Häbler et al., 1993) of the cat respond to both passive distension as well as active contraction of the bladder, indicating that they are in series tension receptors. These afferents which have conduction velocities ranging between 2.5 and 15 m/s (Häbler et al., 1993) are silent when the bladder is empty but during slow filling of the bladder display a graded increase in discharge frequency at intravesical pressures below 25 mmHg (Jänig and Morrison, 1986; Bruns et al., 2011). Multiunit recordings exhibit a successive recruitment of mechanoreceptors with different thresholds during bladder filling. The maximal firing rates range from 15 to 30 Hz. All afferents behave like slowly adapting mechanoreceptors with both a dynamic and static component of their discharge. Pressure thresholds for mechanosensitive afferents in the cat fall on the flat, compliant part of the bladder pressure–volume curve at about 25–75% of the pressure at which the curve becomes steep. These thresholds are consistent with intravesical pressures at which humans report the first sensation of bladder filling. Electrophysiologic studies in cats and rats have revealed that the normal micturition reflex is triggered by myelinated Aδ-fiber afferents (de Groat et al., 1981; Mallory et al., 1989; Häbler et al., 1990).

In contrast to the low-threshold mechano-sensitive Aδ-bladder afferents, the C-bladder afferents in cats are generally mechano-insensitive ("silent C-fibers") (Häbler et al., 1990). Many of these afferents are nociceptive and respond to cold stimuli or chemical/noxious stimuli such as high potassium, low pH, high osmolality, and irritants such as capsaicin and turpentine oil (McMahon and Abel, 1987; Fall et al., 1990; Häbler et al., 1990; Maggi, 1993). Following exposure to these substances silent afferents become mechanoreceptive and the sensitivity of bladder mechanoreceptors to distension also increases.

In rats, Sengupta and Gebhart (1994) reported that both Aδ- and C-fiber afferents are mechanosensitive and respond to bladder distension. They also found that 30% of bladder afferents were not responsive to any mechanical stimuli, and these unresponsive bladder afferents included both Aδ- and C-fibers (Fig. 5.5B). Other studies in rats showed that most myelinated Aδ-fiber bladder afferents are mechano-sensitive, while about one-half of unmyelinated C-fiber bladder afferents have no clear mechano-sensitivity (i.e., silent

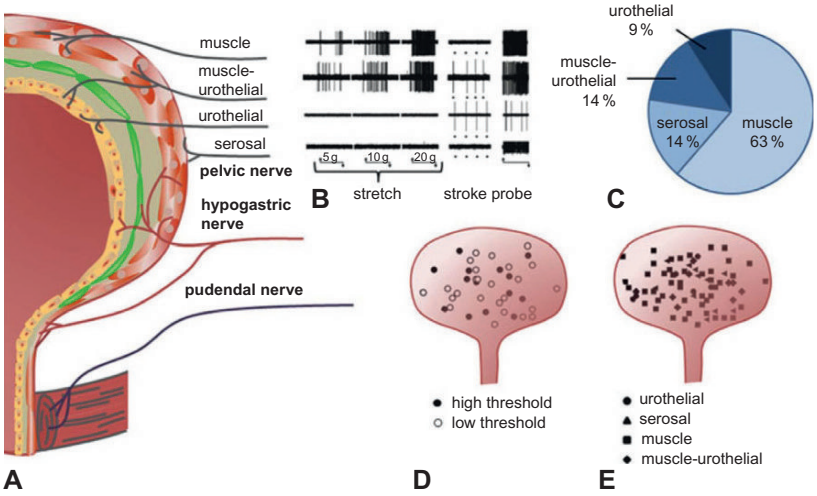

Fig. 5.5. Classes and distribution of afferent nerves in the lower urinary tract of mice. (**A**) The distribution of the different classes of fibers in the bladder wall and urethra. (**B**) In the pelvic nerve, four types of mechanosensitive fibers were identified by stretch, stroke, and probe. (**C**) Proportions of afferent fiber types recorded in the pelvic nerve. (**D**) Distribution of low- and high-threshold receptive fields of pelvic nerve muscle afferent fibers based on responses to stretch. (**E**) Distribution of receptive fields of the four classes of pelvic nerve fibers. (Reproduced from Kanai, 2011.)

C-fibers), but respond to chemical stimuli (Dmitrieva and McMahon, 1996). Neural activity induced by bladder distension is much lower in mechano-sensitive C-fiber bladder afferent fibers than in myelinated Aδ-fibers, suggesting that C-fiber bladder afferents are less excitable than Aδ-fiber afferents in rats. Another study showed that many C-fiber bladder afferents are volume receptors that do not respond to bladder contractions, a property that distinguishes them from "in series tension receptors" (Morrison, 1997).

Because capsaicin, the C-fiber afferent neurotoxin, does not block normal micturition reflexes in cats and rats, it is believed that C-fiber afferents are not essential for normal voiding (de Groat et al., 1990; Maggi and Conte, 1990; Cheng et al., 1993, 1999). On the other hand, the efficacy of capsaicin in reducing bladder overactivity induced by noxious stimuli indicates that C-fiber afferents do play an important role in lower urinary tract dysfunction in pathologic conditions (de Groat and Yoshimura, 2009, 2012; Kanai, 2011).

In the mouse pelvic nerve four classes of bladder afferents (serosal, muscular, muscular/urothelial, and urothelial) have been identified based on responses to receptive field stimulation with different mechanic stimuli, including probing, stretch, and stroking the urothelium (Fig. 5.5). A low-threshold group, representing 65–80% of the total population, and a high-threshold stretch-sensitive population of muscular afferents were identified (Daly et al., 2007; Xu and Gebhart, 2008). The muscular afferents can be sensitized by application of a combination of inflammatory mediators (bradykinin, serotonin, prostaglandin, and histamine at pH 6.0) (Xu and Gebhart, 2008).

In the guinea pig bladder four classes of afferents have also been detected (Zagorodnyuk et al., 2006, 2007). These include: stretch-sensitive afferents in muscle which behave as in-series tension receptors as well as tension-mucosal mechanoreceptors which can be activated by stretch, mucosal stroking or by hypertonic solutions applied locally to the receptive fields in the mucosa. In addition, stretch-insensitive afferents consisting of mucosal mechanoreceptors and chemoreceptors have been identified. Muscle-mucosal mechanoreceptors are activated by both stretch and mucosal stroking, by hypertonic solution, αβ-methylene ATP, but not by capsaicin. Stroking- and stretch-induced firing is significantly reduced by removal of the urothelium. Mucosal high-responding mechanoreceptors are stretch-insensitive but can be activated by mucosal stroking, hypertonic solution, αβ-methylene ATP, and capsaicin. Stroking-induced activity is reduced by removal of the urothelium. Mucosal low-responding mechanoreceptors are stretch-insensitive but can be weakly activated by mucosal stroking but not by hypertonic solution, αβ-methylene ATP, or capsaicin. Removal of the urothelium reduces stroking-induced firing.

Activity of Aδ and C-fiber bladder and urethral afferent axons has been identified in the hypogastric nerves (Winter, 1971; Floyd et al., 1976), lumbar splanchnic nerves, or the lumbar white rami (Bahns et al., 1986). The receptive fields of the units are either single or multiple punctuate sites on the bladder or urethral surface or associated with blood vessels in the peritoneal

attachments to the bladder base. Afferents with receptive fields on or in the bladder wall respond in a graded manner to passive distension or isovolumetric contraction at intravesical pressures from 10 to 70 mmHg with threshold pressures generally below 20 mmHg. Urethral afferents exhibit either no responses to bladder stimulation or low discharge rates at higher intravesical pressures. No functional differences between the Aδ and C-fiber afferent populations in the hypogastric nerve have been reported, except that firing rates are lower in the latter group. In contrast to pelvic nerve afferents the hypogastric afferents often are active with the bladder empty (Winter, 1971; Bahns et al., 1986).

Afferent fibers innervating the urethra are also important for modulating lower urinary tract function. In dogs urethral afferent fibers in the pelvic and pudendal nerves are sensitive to the passage of the fluid through the urethra. Pudendal nerve afferents are more sensitive than pelvic nerve afferents (Talaat, 1937). Afferents in the pelvic nerves of the rat also are activated by high intraurethral pressures (>60 cm H_2O) (Feber et al., 1998). Pudendal nerve afferents responding to urine flow exhibit a slowly adapting firing pattern (Todd, 1964) while small myelinated or unmyelinated urethral afferents in the hypogastric nerves and myelinated urethral afferents in the pelvic nerves responding to urine flow or urethral distension exhibit rapidly adapting responses (Bahns et al., 1986, 1987). Stimulation of flow-sensing urethral afferents by intraurethral saline infusion enhances volume-induced reflex bladder contractions in rats (Jung et al., 1999). Electric stimulation of urethral afferents also evokes reflex bladder contractions in the cat and rat and improves bladder emptying (Chen et al., 2012; McGee and Grill, 2014). Levator ani afferent fibers innervate muscle spindles (Gosling et al., 1981; Pierce et al., 2003) and Golgi tendon organs (Palmieri et al., 1988), which are common in skeletal muscles but absent in the rhabdosphincters (Martin et al., 1974; Rockswold et al., 1980; Gosling et al., 1981; Thuroff et al., 1982; Schroder and Reske-Nielsen, 1983; Borghi et al., 1991).

Nociceptive C-fiber afferents are also present in pelvic and pudendal nerves innervating the urethra (Conte et al., 1993; Thor and Muhlhauser, 1999) and the number of these afferents is higher in the pelvic than in the pudendal nerves (Yoshimura et al., 2003). Activation of urethral C-fibers by intraurethral capsaicin application elicits EUS and pelvic floor striated muscle electromyogram activity and nociceptive behavioral responses, which disappear after pudendal nerve transection (Conte et al., 1993; Lecci et al., 1994; Thor and Muhlhauser, 1999). Urethral C-fiber activation by capsaicin also suppresses reflex bladder contractions in rats (Jung et al., 1999; Yang et al., 2010). Putative C-fiber afferent fibers identified by positive staining for calcitonin gene-related peptide (CGRP) or substance P are present in the subepithelium, the lamina propria, and the muscular layers in all portions of the urethral (Hökfelt et al., 1978; Warburton and Santer, 1994).

Electrophysiologic properties of afferents

Functional properties of dissociated bladder and urethral afferent neurons identified by retrograde axonal transport of fluorescent dyes injected into the bladder or urethra have been investigated using patch clamp techniques (Yoshimura et al., 1996, 2001a, b, 2003; Yoshimura and de Groat, 1997b; Yoshimura, 1999; Zhong et al., 2003; Dang et al., 2005, 2008; Sculptoreanu et al., 2005a, b).

Based on electric and chemical properties, bladder afferent neurons are divided into two populations (Yoshimura et al., 1996). The most common population of neurons (>70%) are small in size, sensitive to capsaicin, and exhibit high-threshold, long-duration action potentials resistant to tetrodotoxin, a Na^+-channel blocker. The other population of bladder afferent neurons which are larger in size and insensitive to capsaicin exhibit low-threshold, short-duration action potentials which are reversibly blocked by tetrodotoxin. Because the majority of bladder afferent neurons with tetrodotoxin-resistant spikes are sensitive to capsaicin, these neurons are likely to be the origin of C-fiber afferent axons (Yoshimura and de Groat, 1999).

Chemical properties of afferents

Immunohistochemical studies reveal that bladder afferent neurons contain various neuropeptides, such as substance P, CGRP, pituitary adenylate cyclase-activating polypeptide (PACAP) and vasoactive intestinal peptide (Keast and de Groat, 1992; Maggi, 1993; Vizzard, 2000), as well as putative excitatory amino acid transmitters, glutamic and aspartic acid (Keast and Stephensen, 2000), and vesicular glutamate transporters (Brumovsky et al., 2013). Peptide-containing axons are distributed throughout all layers of the bladder but are particularly dense in the lamina propria just beneath the urothelium.

Bladder afferent neurons and axons, especially C-fiber afferents, also express various receptors (Fig. 5.6), including the transient receptor potential vanilloid receptor 1 (TRPV1, the capsaicin receptor) (Maggi, 1993; Birder et al., 2001; Avelino et al., 2002), transient receptor potential ankyrin 1 receptor (TRPA1) (Everaerts et al., 2008; Streng et al., 2008), TRPM8, a cold receptor (Everaerts et al., 2008), tyrosine kinase receptor A (TrkA), which responds to nerve growth factor (NGF) (Qiao and Vizzard, 2002a, b), α and β estrogen receptors (Bennett et al., 2003) and tyrosine kinase

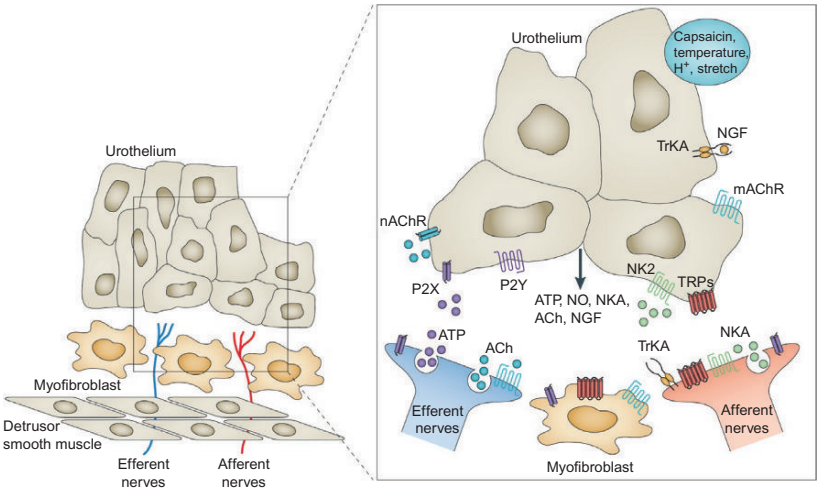

Fig. 5.6. A model illustrating possible chemical interactions between urothelial cells, afferent nerves, efferent nerves and myofibroblasts, in the urinary bladder. Urothelial cells, myofibroblasts, and afferent nerves express common receptors, including purinergic receptors (P2X and P2Y) and transient receptor potential receptors (TRPs), such as the capsaicin receptor (TRPV1). Urothelial cells also express TRPV2, TRPV4, and TRMP8. Activation of receptors and ion channels in urothelial cells by bladder distension or chemical stimuli can release mediators, such as adenosine triphosphate (ATP), nitric oxide (NO), neurokinin A (NKA), acetylcholine (ACh), and nerve growth factor (NGF), that target adjacent nerves or myofibroblasts and might also act in an autocrine or paracrine manner on urothelial cells. Neuropeptides (including NKA) released from sensory nerves and the urothelium can act on the neurokinin 2 receptor (NK2) to sensitize the mechanoreceptive afferent nerve endings. NGF released from muscle or the urothelium can exert an acute and chronic influence on the excitability of sensory nerves through an action on tyrosine kinase A (TrkA) receptors. ATP released from efferent nerves or from the urothelium can regulate the excitability of adjacent nerves through purinergic P2X receptors. ACh released from efferent nerves or from the urothelium regulates the excitability of adjacent nerves through nicotinic or muscarinic ACh receptors (nAChR and mAChR). (Reproduced from Fowler et al., 2008.)

receptor B (TrkB) that responds to brain-derived neurotrophic factor (Qiao and Vizzard, 2002a, b), glial cell line-derived neurotrophic factor (GDNF) receptors that respond to GDNF (GRFα1) and artemin (GRFα3) (Forrest and Keast, 2008), isolectin B4-binding sites (IB4) (Yoshimura et al., 2003), muscarinic receptors, endothelin receptors, and purinergic receptors ($P2X_2$, $P2X_3$, P2Y) that can be activated by ATP (Bennett et al., 1996; Lee et al., 2000; Rong et al., 2002; Zhong et al., 2003; Nishiguchi et al., 2005; Studeny et al., 2005; Everaerts et al., 2008; Streng et al., 2008). Many of these receptors have been detected not only in axons in the bladder but also in the lumbosacral spinal cord in the same locations as the projections of bladder afferent axons. Patch clamp recordings from bladder afferent neurons (de Groat et al., 1998; Yoshimura and de Groat, 1999) have also demonstrated that a high percentage of these neurons not only from lumbosacral DRG (i.e., pelvic nerve afferents), but also thoracolumbar DRG (i.e., hypogastric nerve afferents) respond to ATP, protons, and/or capsaicin (Dang et al., 2005).

Axonal tracing studies have also revealed that a small percentage of lumbosacral afferent neurons innervate multiple pelvic organs. For example, 3–15% of DRG neurons are double-labeled following injections of different tracers into the colon and bladder (Keast and de Groat, 1992; Malykhina et al., 2004, 2012; Christianson et al., 2007). The double labeling occurs more frequently in rostral lumbar (L1–L2) than in caudal lumbosacral (L6–S1) DRG, which provide the major innervation to the bladder and colon. It has been speculated that dichotomizing afferents that send axonal branches to different target organs may contribute to viscero-visceral cross-organ sensitization (Pezzone et al., 2005; Yoshikawa et al., 2015). Furthermore, the suppression of cross-organ sensitization by capsaicin treatment indicates that a large proportion of the dichotomizing afferents are C-fibers.

GROSS ANATOMY OF THE LOWER URINARY TRACT

The bladder can be divided into two parts: a body lying above the ureteral orifices and a base consisting of the trigone and bladder neck (Fig. 5.7). The two areas are different but homogeneous within themselves with respect to neuromorphology and neuropharmacology (El-Badawi and Schenk, 1966). Histologic examination of the bladder body reveals that myofibrils are arranged into fascicles in random directions (Donker et al., 1976).

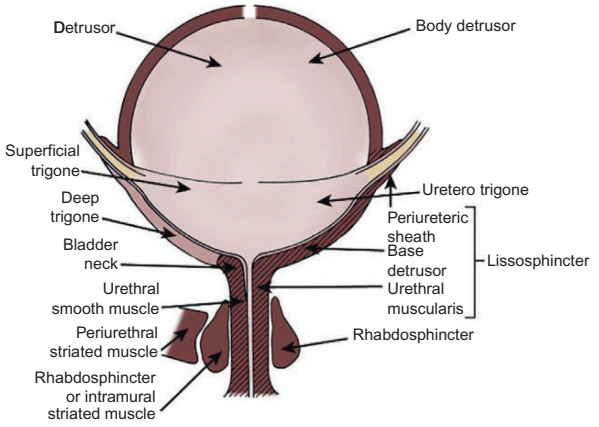

Fig. 5.7. Anatomy of the bladder and its outlet.

This architecture differs from the discrete circular and longitudinal smooth-muscle layers in the ureter or gastrointestinal tract.

The bladder outlet is composed of the bladder base, urethra, and striated urethral sphincter (i.e., rhabdosphincter: Fig. 5.7). The bladder base has a laminar architecture with a superficial longitudinal layer lying beneath the trigone. A muscle layer deep to the superficial layer is continuous with the detrusor (Tanagho, 1982; Dixon and Gosling, 1987; Zderic et al., 1996). The smaller muscle bundles of the deep muscle layer in the bladder base exhibit a predominantly circular orientation.

The urethra begins at the internal meatus of the bladder and extends to the external meatus. In the male, four segments are readily identified. The first is the preprostatic portion, or the bladder neck, which consists of a complete circular collar of smooth-muscle cells that extends distally to surround the proximal portion of the urethra (Gosling, 1999). Because of the location and orientation of the fibers the terms "internal" or "proximal urethral sphincter" have been used to define this component of urinary tract smooth muscle. This smooth muscle is densely innervated by sympathetic nerves which mediate sphincter closure during ejaculation. Although this genital function of the bladder neck is well established, it is not known if the smooth muscle of this region normally plays an active role in maintaining urinary continence. However it has been reported (Barbalias and Blaivas, 1983; Sakakibara et al., 2001) that damage to sympathetic nerves or interruption of autonomic reflex pathways to the lower urinary tract in patients with multiple system atrophy, myelodysplasia, or spinal cord injury produces an open bladder neck at rest. The prostatic urethra then extends throughout the length of the gland, terminating at its apex. The membranous urethra extends from the prostatic apex through the pelvic floor musculature until it becomes the bulbous and penile urethra (fourth segment) at the base of the penis.

In women, an anatomic smooth-muscle sphincter at the bladder neck is not obvious and the majority of muscle bundles in this region extend obliquely or longitudinally into the urethra (Hutch and Rambo, 1967; Tanagho, 1982). The sympathetic innervation is less dense in this region and the function of the bladder neck in maintenance of continence is uncertain because it is preserved in men and some women after destruction or opening of the bladder neck (Chapple et al., 1989). A passive mechanism in women involving vascular filling of the urethral lamina propria is also thought to contribute to a urethral seal effect and continence.

Striated muscle, which is present in the wall of the male and female urethra, forms an EUS (rhabdosphincter) that is separate from, but connected to, the periurethral skeletal muscle of the pelvic floor (Fig. 5.7). In the male, the striated muscle extends from the base of the bladder and the anterior aspect of the prostate to the full length of the membranous urethra. The female has an attenuated striated sphincter mechanism divided into two components: (1) a proximal striated sphincter consisting of circular muscle that forms the outermost layer of the muscle wall and (2) a more distal component comprised of two arch-shaped straps of muscle, the compressor urethrae, that arise laterally near the ischiopubic rami and the urethrovaginal sphincter that closely follows the vaginal wall. The urethral striated muscles that function as true sphincters are attached to the pelvic floor muscles and to each other by connective tissue but do not attach directly to bone. Thus they are anatomically and functionally quite distinct from the striated skeletal muscle of the pelvic floor.

The pelvic floor (Ashton-Miller and DeLancey, 2007) is a bowl-shaped structure comprised of bone, striated muscle, and connective tissue. The rim of the bowl is formed by the bones of the pelvic girdle (sacrum, ilium, ischium, and pubis). The "bottom" of the bowl is lined with striated muscle: the iliococcygeus and pubococcygeus (which together comprise the levator ani muscle), the coccygeus, and puborectalis muscles (Fig. 5.4). The muscles are attached to the bone and to each other with various connective tissue supports and provide support for the pelvic viscera.

Because the EUS does not have "dedicated" attachment to skeletal structures it acts as a true sphincter (i.e., contraction produces virtually no movement except constriction of the lumen). In addition it does not contain muscle spindles or Golgi tendon organs which are present in the levator ani and other striated muscles. This is consistent with the finding that the pudendal nerve pathway to the EUS, in contrast to the nerves in the levator ani muscle, does not contain large myelinated

afferent axons (i.e., types Ia and Ib) that innervate these sensory organs (Martin et al., 1974; Rockswold et al., 1980; Gosling et al., 1981; Thuroff et al., 1982; Schroder and Reske-Nielsen, 1983; Borghi et al., 1991), and does not contain small γ motor neuron axons that innervate muscle spindles.

In women, urinary continence is maintained during elevations in intra-abdominal pressure by three processes. First, there is passive transmission of abdominal pressure to the proximal urethra. DeLancey proposes the "hammock hypothesis" that abdominal pressure transmitted through the proximal urethra presses the anterior wall against the posterior wall. The posterior wall remains rigid if there is adequate pelvic support from muscle and connective tissues. More distally, based on morphologic data, DeLancey and colleagues (DeLancey, 1989, 1997; Sampselle and DeLancey, 1998) have postulated that the urethral attachments to the pubis (pubourethral) and vaginal connections to pelvic muscles and fascia actively change the position of the bladder neck and proximal urethra with urine storage and voiding. This arrangement compresses the urethra against the pubis during bladder filling and straining. These attachments contain both fascia and smooth muscle (Oelrich, 1980; DeLancey, 1989). However, mere transmission of abdominal pressure to proximal urethra does not account for the entire increase in urethral pressure (Constantinou and Govan, 1982). For example, urethral pressure rises before cough transmission. These findings implicate an active urethral continence (neural) mechanism in women (Constantinou and Govan, 1982). A guarding reflex involving contraction of striated muscle of the EUS in conjunction with contraction of smooth muscle of the proximal urethra and bladder neck can transiently promote continence (Enhorning, 1961; Tanagho, 1982). Thus, urinary continence results from the combination of active muscle tone and passive anatomic coaptation.

Understanding voiding and continence requires some working knowledge of the contractile properties of smooth and striated muscle. The contractile properties of bladder smooth-muscle cells are well suited for either urine storage or release. Filling the bladder at a slow physiologic rate maintains an intravesical pressure of less than 10 cm H_2O (Klevmark, 1974). Acute denervation of the bladder does not appreciably alter this low filling pressure (Langley and Whiteside, 1951). This concept has been used to support the hypothesis that the intrinsic myogenic or viscoelastic properties of cellular and extracellular components are major contributors to low-pressure bladder filling and compliance. Conversely, neural input is required for the rapid and sustained smooth-muscle contraction accompanying voiding.

PHYSIOLOGY OF THE LOWER URINARY TRACT

Urinary bladder smooth muscle

Bladder smooth muscle consists of a sheet containing many small, spindle-shaped cells linked together at specific junctions. The bladder muscle has a broad length–tension relationship, allowing tension to be developed over a large range of resting muscle lengths (Uvelius and Gabella, 1980). The thin and thick filaments of smooth-muscle fibers are arranged as myofibrils that cross the fibers obliquely in a lattice-like arrangement. The filaments of contractile proteins are attached to the plasma membrane at the junctional complexes between neighboring cells (Chacko et al., 1999).

Measurements of tissue impedance indicate that the detrusor muscle is less well coupled electrically than other smooth muscles (Brading and Mostwin, 1989; Parekh et al., 1990). Poor coupling could be a feature of normal detrusor to prevent synchronous activation of the smooth-muscle cells during bladder filling. Thus, although individual cells may contract spontaneously, contraction of the bladder as a whole generally requires stimulation by parasympathetic nerves (Andersson, 1993). In response to acetylcholine released from parasympathetic nerve terminals, muscarinic M_3 receptors are thought to induce detrusor muscle contractions by initiation of action potentials and calcium entry through nifedipine-sensitive L-type Ca^{2+} channels (Andersson and Arner, 2004; Andersson and Wein, 2004; Schneider et al., 2004a, b) in addition to increased polyphosphoinositide hydrolysis resulting in inositol 1,4,5-trisphosphate (IP_3) production and release of intracellular calcium stores (Fig. 5.3) (Iacovou et al., 1990; Eglen et al., 1994; Harriss et al., 1995; Hashitani et al., 2000; Fry et al., 2002; Braverman et al., 2006). The rise in cytoplasmic calcium concentration brought on by the action potential results in binding of calcium to calmodulin. Calcium-bound calmodulin is then capable of activating myosin light-chain kinase, permitting it to phosphorylate the myosin type II light chain. Phosphorylation of the light chain allows the myosin to interact with actin, leading to force generation (Fig. 5.3) (White et al., 1993; Chacko et al., 1994; Andersson and Arner, 2004).

Bladder interstitial cells (myofibroblasts)

Although the bladder smooth muscle may be spontaneously active (Brading, 1997, 2006), another population of cells in the bladder, known as interstitial cells or myofibroblasts (Fig. 5.6), has an important role in modulating spontaneous activity (Andersson and Arner, 2004; Kumar et al., 2005). Different types of interstitial cells

have been identified in human and guinea pig ureter, urethra, and bladder body (Kumar et al., 2005; Hashitani, 2006; Fry et al., 2007).

In the human bladder, subepithelial interstitial cells stain for vimentin and smooth muscle α-actin but not for desmin (Fry et al., 2004). These cells are linked by gap junctions consisting of connexin 43 proteins and make close appositions with C-fiber nerve endings in the submucosal layer of the bladder (Fig. 5.6), suggesting that there is a network of functionally connected interstitial cells immediately below the urothelium that may be modulated by nerves (Fry et al., 2004). P2Y purinergic receptors, most notably $P2Y_6$ receptors (Fig. 5.6), and M_3 muscarinic receptors are expressed in suburothelial interstitial cells from guinea pigs (Fry et al., 2007; Grol et al., 2009), and ATP induces inward currents associated with elevated intracellular Ca^{2+} in these cells (Fry et al., 2007). Vimentin-stained suburothelial interstitial cells in bladders from patients with idiopathic detrusor overactivity exhibit increased expression of muscarinic M_2 and M_3 receptors that correlates with urgency scores (Mukerji et al., 2006).

Interstitial cells are also present in the detrusor muscle layer (Kumar et al., 2005). These cells which stain for c-Kit are located along the boundaries of muscle bundles in the guinea pig bladder (McCloskey and Gurney, 2002; Hashitani et al., 2004; Hashitani, 2006). They generate Ca^{2+} waves in response to activation of M_3 muscarinic cholinergic receptors and are spontaneously active, suggesting that they could act as pacemakers or intermediaries in transmission of nerve signals to smooth-muscle cells (McCloskey and Gurney, 2002; Johnston et al., 2008). However, Hashitani and colleagues (2004) have suggested that interstitial cells in the detrusor may be more important for mediating the transmission of Ca^{2+} transients between smooth-muscle cells rather than being the pacemaker of spontaneous activity, because spontaneous Ca^{2+} transients occur independently in smooth muscles and interstitial cells. Glivec, a c-Kit tyrosine kinase inhibitor, decreases the amplitude of spontaneous contractions in the guinea pig bladder (Kubota et al., 2004, 2006) as well as in bladder strips from patients with overactive human bladder which exhibit increased numbers of c-Kit-positive cells (Biers et al., 2006).

Urothelium: neuron-like properties and interaction with afferent nerves

While the urothelium has been historically viewed as primarily a "barrier," there is increasing evidence that urothelial cells display a number of properties similar to sensory neurons (nociceptors and mechanoreceptors), and that both types of cell use diverse signal transduction mechanisms to detect physiologic stimuli (Birder and Andersson, 2013) (Fig. 5.6). Examples of "sensor molecules" (i.e., receptors/ion channels) associated with neurons that have been identified in urothelium include receptors for bradykinin (Chopra et al., 2005), neurotrophins (trkA and p75) (Murray et al., 2004), purines (P2X and P2Y) (Lee et al., 2000; Burnstock, 2001a; Birder et al., 2004; Tempest et al., 2004; Chopra et al., 2008), norepinephrine (α and β) (Birder et al., 2001, 2002b; Limberg et al., 2010; Kullmann et al., 2011), acetylcholine (muscarinic and nicotinic) (Chess-Williams, 2002; Beckel et al., 2006; Kullmann et al., 2008a, b; Beckel and Birder, 2012), protease activated receptors (D'Andrea et al., 2003; Dattilio and Vizzard, 2005), amiloride/mechanosensitive Na^+ channels (Smith et al., 1998; Wang et al., 2003; Araki et al., 2004), prostaglandin E_2 (PGE_2) receptors (EP1) (Wang et al., 2008), and a number of TRP channels (TRPV1, TRPV2, TRPV4, TRPM8, TRPA1) (Birder et al., 2001, 2002a; Stein et al., 2004; Birder and Yoshimura, 2007; Gevaert et al., 2007; Du et al., 2008; Kullmann et al., 2009; Mochizuki et al., 2009; Yamada et al., 2009) (Fig. 5.6).

When urothelial cells are activated via these receptors/ion channels in response to mechanical or chemical stimuli, they can in turn release chemical mediators such as NO, ATP, acetylcholine, prostaglandins, and substance P (Fig. 5.6) (Ferguson et al., 1997; Birder et al., 1998, 2003; Burnstock, 2001a; Chess-Williams, 2004; Birder and Andersson, 2013). These agents are known to have excitatory and inhibitory actions on afferent nerves, which are located close to or in the urothelium (Birder et al., 2001; Andersson, 2002). Thus, it has been speculated that the urothelium plays a role in bladder sensation by responding to local chemical and mechanical stimuli and then sends chemical signals to the bladder afferent nerves, which convey information to the central nervous system (Birder et al., 2005; de Groat, 2006; Yoshimura and Birder, 2007; Birder and Andersson, 2013) (Fig. 5.6).

NO can be released by the urothelium, particularly during inflammation (Birder et al., 1998). The release of NO can be evoked by the calcium ionophore A-23187, norepinephrine, substance P, and capsaicin. Release of NO from bladder strips evoked by adrenergic agonists is reduced by 85% after removal of the urothelium. Given that NO has a minimal direct effect on the detrusor muscle but does exert an inhibitory effect on afferent and reflex activity in the bladder (Ozawa et al., 1999; Pandita et al., 2000; Masuda et al., 2007; Yu and de Groat, 2013) and inhibits Ca^{2+} channels in bladder afferent neurons (Yoshimura et al., 2001a), it is likely that NO is involved in urothelial sensory signaling mechanisms in the bladder and may have a role in modulating inflammatory and nociceptive pathways. Increases in inducible NO synthase expression in the

urothelium and and/or NO levels in the bladder have been demonstrated in bladder pain syndrome/interstitial cystitis (BPS/IC) patients, especially those with Hunner's lesion (BPS/IC European Society for the Study of Interstitial Cystitis (ESSIC) type 3C) (Hosseini et al., 2004; Koskela et al., 2008; Logadottir et al., 2013). In addition, NO synthase expression in afferent neurons is increased in rats with chronic bladder inflammation (Vizzard et al., 1996), raising the possibility that pathologic conditions increase the contribution of NO to bladder function.

ATP released from urothelial cells during stretch can activate a population of suburothelial bladder afferents expressing $P2X_2$ and $P2X_3$ receptors, signaling changes in bladder fullness and pain (Fig. 5.6) (Ferguson et al., 1997; Burnstock, 2001a). Accordingly, $P2X_3$ null mice exhibit urinary bladder hyporeflexia, suggesting that this receptor as well as neural–epithelial interactions is essential for normal bladder function (Cockayne et al., 2000). These findings suggest a mechanism whereby extracellular stimuli such as stretch are translated into changes in afferent function via urothelially released ATP.

Prostaglandins are also released from the urothelium. These are assigned two possible functions: (1) regulation of detrusor muscle activity and (2) cytoprotection of the urothelium, based on effective treatment of hemorrhagic cystitis by prostaglandins (Jeremy et al., 1987). The predominant forms found in biopsies of human urothelium from are 6-oxo PGF > PGE_2 > $PGF_{2\alpha}$ > TXB_2 (thromboxane B_2). Prostacyclin (PGI_2) is also produced. These findings were confirmed and extended in the guinea pig bladder, where the major production of prostaglandins occurs in the urothelium and where production increases greatly with inflammation (Saban et al., 1994). In mice PGE_2 provokes ATP release from cultured urothelial cells, which express EP1 receptors; and bladder overactivity induced by intravesical application of PGE_2 is prevented in EP1 receptor knockout mice, suggesting the involvement of EP1 receptors in the PGE_2-mediated urothelial-afferent interaction (Wang et al., 2008).

The contribution of muscarinic receptors to bladder function extends beyond detrusor contractility to urothelial-afferent interactions. Muscarinic receptors are expressed in the urothelium at high density (Fig. 5.6) (Hawthorn et al., 2000) and there is a basal release of acetylcholine from the urothelium, which is increased by stretch and aging (Yoshida et al., 2003). Activation of the muscarinic receptors in the urothelium releases substances (e.g., ATP) that modulate afferent nerves and smooth-muscle activity (Hawthorn et al., 2000; de Groat, 2004; Kullmann et al., 2008a, b; Birder and Andersson, 2013).

Muscarinic agonists also release substances called urothelium-derived inhibitory factors that decrease the force of detrusor muscle contraction (Hawthorn et al., 2000; Kumar et al., 2005). The molecular identity of this factor is not known; however, pharmacologic studies suggest that it is not NO, a prostaglandin, prostacyclin, adenosine, a catecholamine, γ-aminobutyric acid (GABA), or an agent that acts via apamin-sensitive, small-conductance K^+ channels. It has been shown that the inhibitory response elicited by this factor is attenuated in a fetal model of bladder outlet obstruction (Thiruchelvam et al., 2003). Further studies are required to identify this substance and its role in bladder function.

Urethral outlet

The urethra is composed of smooth and striated muscle. The smooth muscle in humans and larger mammals consists of a relatively thick inner layer that is predominantly longitudinally arranged, and an outer thinner layer of circular muscle. Contraction of the longitudinal smooth muscle could play a role in the opening of the bladder neck during micturition or in stabilizing the urethra and allowing force generated by the circular muscle elements to occlude the lumen during urine storage.

Striated muscle in the urethra forms a rhabdosphincter that is separate from the periurethral skeletal muscle of the pelvic floor. In the male an outer layer of circularly oriented striated muscle forms a horseshoe configuration with an opening posteriorly. Striated muscle also extends throughout the prostate and its capsule (Tanagho, 1982; Dixon and Gosling, 1987). The female has an attenuated striated sphincter mechanism as well as additional muscle structures termed the compressor urethrae and the urethrovaginal sphincter (DeLancey, 1989).

Striated muscles are characterized as slow-type and twitch-type. Twitch-type myofibrils can be further classified as slow and fast on the basis of functional and metabolic characteristics (Padykula and Gauthier, 1967). Slow-twitch fibers seem ideally suited for maintaining sphincter tone for prolonged periods, whereas fast-twitch fibers may be needed to enhance sphincter tone rapidly to maintain continence when intra-abdominal pressure is abruptly increased. The striated muscle of the distal sphincter mechanism contains predominantly slow-twitch fibers (Elbadawi, 1984; Gosling et al., 2000) and provides more than 50% of the static resistance (Tanagho et al., 1989). In the male, the rhabdosphincter consists of 35% fast-twitch and 65% slow-twitch fibers (Padykula and Gauthier, 1970), while in the female, the percentage of fast-twitch fibers is lower (13%). The periurethral striated muscle of the pelvic floor also contains both fast-twitch and slow-twitch fibers.

During bladder distension blocking striated sphincter activity with nicotinic neuromuscular blocking agents

reduces urethral tone, but rarely by more than 40%; while blocking sympathetic nerve control of urethral smooth muscle with α-adrenoceptor blockers reduces intraurethral pressure by about a third, indicating a contribution of both striated and smooth muscles.

Overview of the lower urinary tract activity during storage and voiding

The neural pathways controlling lower urinary tract function are organized as simple on–off switching circuits that maintain a reciprocal relationship between the urinary bladder and urethral outlet. Intravesical pressure measurements during bladder filling in both humans and animals reveal low and relatively constant bladder pressures when bladder volume is below the threshold for inducing voiding. The accommodation of the bladder to increasing volumes of urine is primarily a passive phenomenon dependent upon the intrinsic properties of the vesical smooth muscle and quiescence of the parasympathetic efferent pathway. In addition, in some species urine storage is facilitated by sympathetic reflexes that mediate an inhibition of bladder activity, closure of the bladder neck, and contraction of the proximal urethra. During bladder filling the activity of the sphincter electromyogram also increases (Fig. 5.8), reflecting an increase in efferent firing in the pudendal nerve and an increase in outlet resistance that contributes to the maintenance of urinary continence.

The storage phase of the urinary bladder can be switched to the voiding phase either involuntarily or voluntarily (Fig. 5.8). The former is readily demonstrated in the human infant (Fig. 5.8A) when the volume of urine exceeds the micturition threshold. At this point, increased afferent firing from tension receptors in the bladder produces firing in the sacral parasympathetic pathways and inhibition of sympathetic and somatic pathways. The expulsion phase consists of an initial relaxation of the urethral sphincter followed by a contraction of the bladder, an increase in bladder pressure, and flow of urine. Relaxation of the urethral outlet is mediated by activation of a parasympathetic reflex pathway to the urethra that triggers the release of NO, an inhibitory transmitter, as well as by removal of adrenergic and somatic excitatory inputs to the urethra.

ANATOMY OF THE SPINAL PATHWAYS CONTROLLING THE LOWER URINARY TRACT

The reflex circuitry controlling micturition consists of four basic components: primary afferent neurons, spinal efferent neurons, spinal interneurons, and neurons in the brain that activate or modulate spinal reflex pathways (Figs 5.9–5.11).

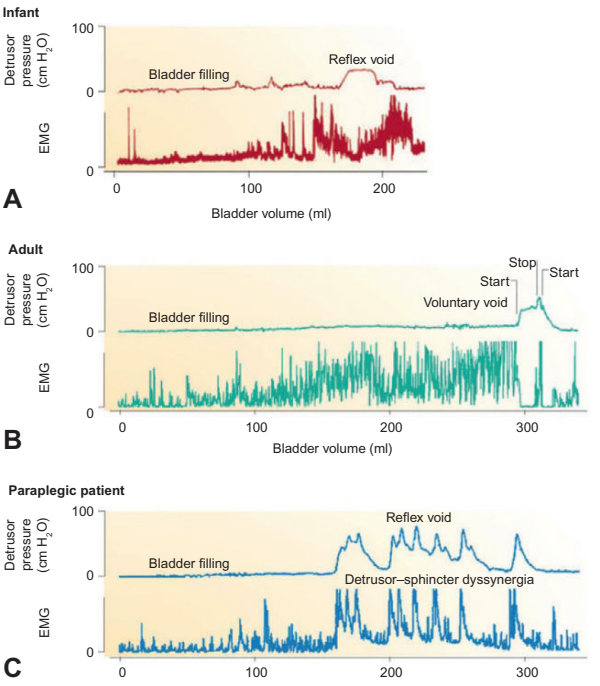

Fig. 5.8. Reflex voiding responses in an infant, a healthy adult, and a paraplegic patient. Combined cystometrograms and sphincter electromyograms (EMGs, recorded with surface electrodes), allowing a schematic comparison of reflex voiding responses in an infant (**A**) and in a paraplegic patient (**C**) with a voluntary voiding response in a healthy adult (**B**). The abscissa in all recordings represents bladder volume in milliliters; the ordinates represent electric activity of the EMG recording and detrusor pressure (the component of bladder pressure that is generated by the bladder itself) in cm H_2O. On the left side of each trace (at 0 mL), a slow infusion of fluid into the bladder is started (bladder filling). In part **B** the start of sphincter relaxation, which precedes the bladder contraction by a few seconds, is indicated ("start"). Note that a voluntary cessation of voiding ("stop") is associated with an initial increase in sphincter EMG and detrusor pressure (a myogenic response). A resumption of voiding is associated with sphincter relaxation and a decrease in detrusor pressure that continues as the bladder empties and relaxes. In the infant (**A**), sphincter relaxation is present but less complete. On the other hand, in the paraplegic patient (**C**), the reciprocal relationship between bladder and sphincter is abolished. During bladder filling, involuntary bladder contractions (detrusor overactivity) occur in association with sphincter activity. Each wave of bladder contraction is accompanied by simultaneous contraction of the sphincter (detrusor sphincter dyssynergia), hindering urine flow. Loss of the reciprocal relationship between the bladder and the sphincter in paraplegic patients thus interferes with bladder emptying. (Reproduced from Fowler et al., 2008.)

Afferent projections in the spinal cord

Sacral afferent pathways from the cat and rat bladder passing through the pelvic nerve project into Lissauer's tract at the apex of the dorsal horn and then send

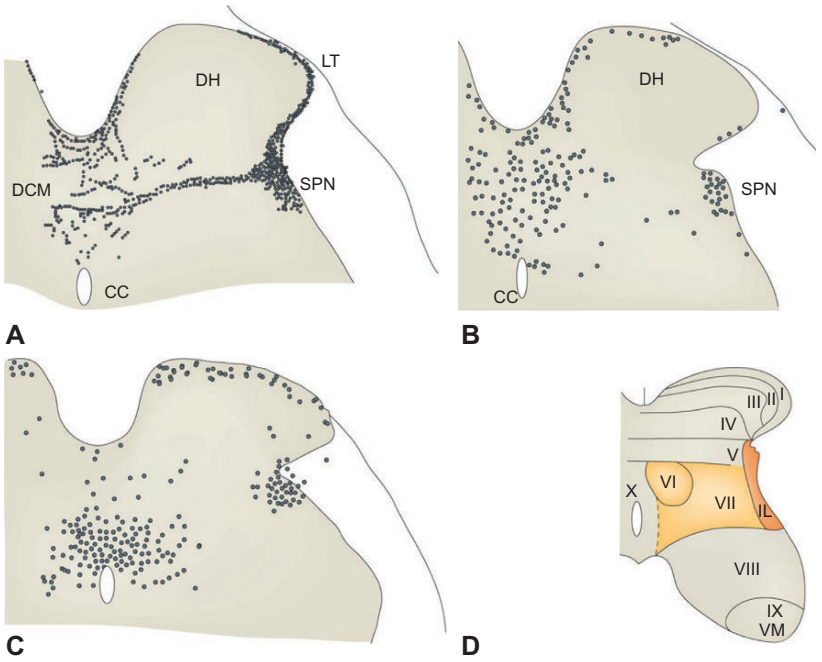

Fig. 5.9. Primary afferent and spinal interneuronal pathways involved in micturition. (**A**) Primary afferent pathways to the L6 spinal cord of the rat project to regions of the dorsal commissure (DCM), the superficial dorsal horn (DH), and the sacral parasympathetic nucleus (SPN) that contain parasympathetic preganglionic neurons. The afferent nerves consist of myelinated (Aδ) axons, which respond to bladder distension and contraction, and unmyelinated (**C**) axons, which respond to noxious stimuli. (**B**) Spinal interneurons that express *c-fos* following the activation of bladder afferents by a noxious stimulus (acetic acid) to the bladder are located in similar regions of the L6 spinal segment. (**C**) Spinal interneurons involved in bladder reflexes (labeled by transneuronal transport of pseudorabies virus injected into the urinary bladder) are localized to the regions of the spinal cord that contain primary afferents and *c-fos*. Some of these interneurons provide excitatory and inhibitory inputs to the parasympathetic preganglionic neurons located in the SPN. (**D**) The laminar organization of the cat sacral spinal cord, showing the location of parasympathetic preganglionic neurons in the intermediolateral region of laminae V and VII (shaded area). CC, central canal; IL, intermediolateral nucleus; LT, Lissauer's tract; VM, ventromedial nucleus (Onuf's nucleus). (Reproduced from Fowler et al., 2008.)

collaterals laterally and medially around the dorsal horn into laminae V–VII and X at the base of the dorsal horn (Figs 5.9A and 5.11) (Morgan et al., 1981; Nadelhaft and Booth, 1984; Steers et al., 1991a). The lateral pathway terminates in the region of the sacral parasympathetic nucleus. Bladder afferents have not been detected in the center of the dorsal horn (laminae III–IV) or in the ventral horn. Afferents from the pelvic viscera of the cat passing through sympathetic nerves to the rostral lumbar segments have similar sites of termination in laminae I, V–VII, and X (Morgan et al., 1986).

Pudendal nerve afferent pathways from the EUS of the cat have central terminations that overlap in part with those of bladder afferents in lateral laminae I, V–VII and in lamina X (de Groat, 1986; Thor et al., 1989). These afferents differ markedly from other populations of pudendal nerve afferents innervating the sex organs as well as cutaneous and subcutaneous tissues of the perineum that terminate in the deeper layers of the dorsal horn (laminae II–IV) (Ueyama et al., 1984; Thor et al., 1989; Kawatani et al., 1994). Spinal projections of afferents from the levator ani muscle have only been detected in medial lamina VI of the lumbosacral spinal cord, an area for termination of large myelinated proprioceptive afferents (Thor and de Groat, 2010). This afferent pathway is very likely involved in the initiation of reflex activity of the pelvic floor.

Efferent neurons in the spinal cord

Parasympathetic PGNs are located in the intermediolateral gray matter (laminae V–VII) in the sacral segments of the spinal cord (Fig. 5.11) (Nadelhaft et al., 1980), whereas sympathetic PGNs are located in medial (lamina X) and lateral sites (laminae V–VII) in the rostral lumbar spinal cord. EUS motoneurons are located in lamina IX in Onuf's nucleus in the human, monkey (Fig. 5.12E), and cat (Fig. 5.11) and in the dorsolateral motor nucleus in

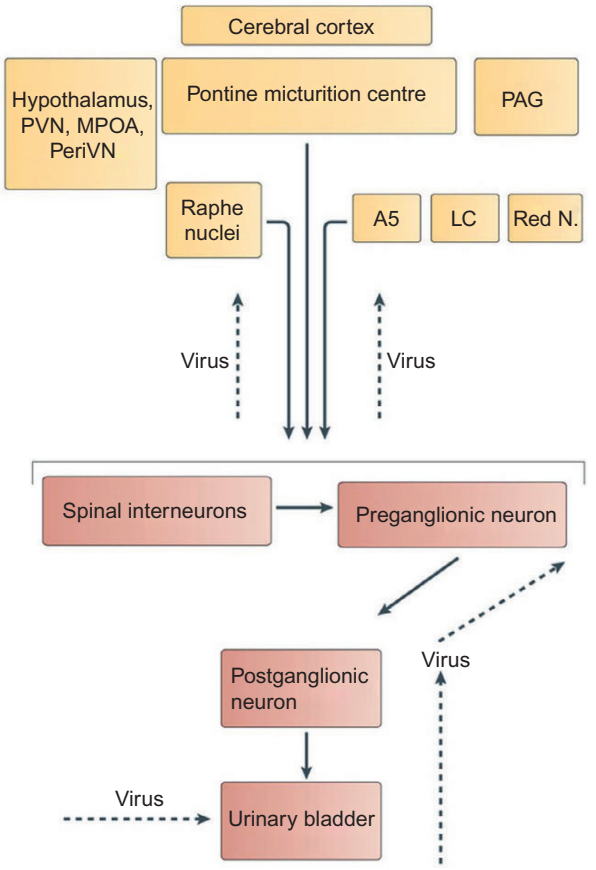

Fig. 5.10. Connections between the lumbosacral spinal cord and brain areas involved in bladder control. The central pathways involved in controlling the urinary bladder can be visualized in rats using transneuronal virus tracing. Injection of pseudorabies virus into the wall of the urinary bladder leads to retrograde transport of the virus (indicated by the dashed arrows) and the sequential infection of postganglionic neurons, preganglionic neurons, spinal interneurons and then various supraspinal neural circuits that are synaptically linked to the spinal preganglionic neurons and interneurons. The supraspinal sites labeled by the virus transport include the pontine micturition center (also known as Barrington's nucleus), the cerebral cortex, the paraventricular nucleus (PVN), the medial preoptic area (MPOA) and periventricular nucleus (PeriVN) of the hypothalamus, the periaqueductal gray (PAG), the locus coeruleus (LC) and subcoeruleus, the red nucleus (Red N.), the raphe nuclei, and the A5 noradrenergic cell group. Synaptic connections are indicated by solid arrows. Synaptic inputs from supraspinal neurons can project to spinal preganglionic neurons or interneurons, as indicated by the bracket. (Reproduced f rom Fowler et al., 2008.)

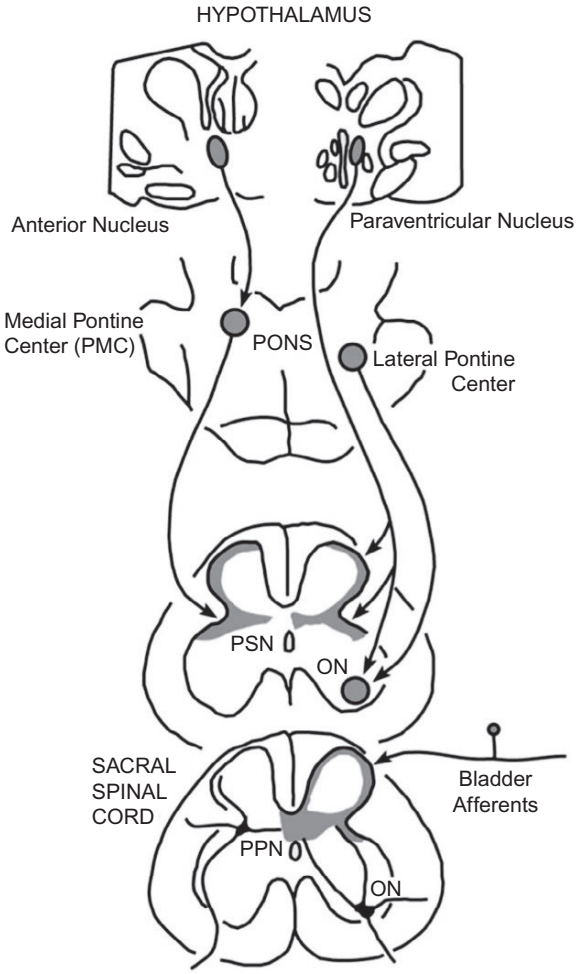

Fig. 5.11. Neural connections between the brain and the sacral spinal cord that may regulate the lower urinary tract in the cat. Lower section of the sacral spinal cord shows the location and morphology of a parasympathetic preganglionic neuron (PPN) in the sacral parasympathetic nucleus (PSN), a sphincter motor neuron in Onuf's nucleus (ON), and the sites of central termination of afferent projections (shaded area) from the urinary bladder. Upper section of the sacral cord shows the sites of termination (shaded areas) of descending pathways arising from the medial pontine micturition center (PMC), the lateral pontine sphincter or urine storage center, and the paraventricular nuclei of the hypothalamus. Section through the pons shows the projection from the anterior hypothalamic nuclei to the PMC.

the rat (Thor and de Groat, 2010). Neurons innervating the levator ani muscles in the squirrel monkey are located medial to Onuf's nucleus and consist of two populations: large α motoneurons and small, presumably γ, motoneurons that are known to innervate muscle spindles (Fig. 5.12B and C). The latter population is not present in Onuf's nucleus, which is consistent with the absence of the muscle spindles in the EUS.

Parasympathetic PGNs exhibit dendrites projecting to four major areas: (1) the lateral and dorsolateral funiculus; (2) lamina I on the lateral edge of the dorsal horn; (3) the dorsal gray commissure; and (4) the gray matter and lateral funiculus ventral to the autonomic nucleus

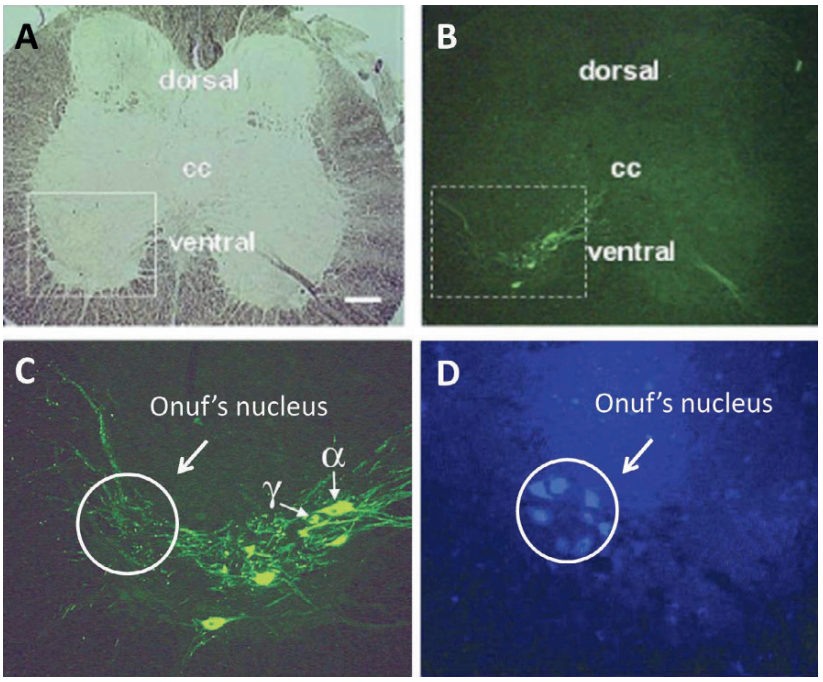

Fig. 5.12. Photomicrographs of a single transverse section of sacral spinal cord from a squirrel monkey with pubocaudalis muscle injected with cholera toxin B (CTB) and the anal rhabdosphincter injected with fast blue. (**A**) Bright field illumination shows cytoarchitecture of gray and white matter; white box indicates area shown in high power in panels **C** and **D**. cc, central canal. (**B**) Epifluorescent illumination showing CTB-labeled (bright green) levator ani motor neurons; white box indicates area shown in high power in panels **C** and **D**. (**C**) High-power photomicrograph of boxed area in panels **A** and **B** using epifluorescent illumination to show CTB-labeled levator ani motor neurons. Note large α and small γ CTB-labeled motor neurons; also CTB-labeled processes extending from levator ani motor neurons into Onuf's nucleus (white circle) and the ventrolateral funiculus. (**D**) Same area and section as panel **C** viewed with epifluorescent illumination to show fast blue-labeled (bright blue) anal sphincter motor neurons in Onuf's nucleus (white circle). Close apposition between CTB-labeled levator ani motor neuron processes and fast blue-labeled rhabdosphincter motor neurons was observed. (From Pierce et al., 2005; Thor and de Groat, 2010.)

(Fig. 5.11) (Morgan et al., 1993). It has been speculated that these dendritic projections reflect the major synaptic inputs to the PGN; i.e., lamina I dendrites receiving primary afferent projections, lateral funiculus dendrites receiving bulbospinal projections, and medial dendrites receiving interneuronal projections from the dorsal commissure and inputs from the contralateral side of the spinal cord. EUS motoneurons have a similar dendritic pattern (Fig. 5.11) (Thor and de Groat, 2010). Processes from levator ani motoneurons extend into two important locations: (1) medial lamina VI, which receives primary afferent input from muscle spindles and Golgi tendon organs; and (2) Onuf's nucleus, where the processes form close appositions with sphincter motoneurons (Fig. 5.12C) (Pierce et al., 2005). Presumably these appositions reflect a neuroanatomic substrate for coordinating the urethral sphincter and the pelvic floor muscles during micturition and defecation.

The most striking feature of the sacral PGNs in the cat is an extensive axon collateral system that projects bilaterally to various regions of the dorsal and ventral horns, including the area around the central canal, the intermediolateral gray matter, the dorsal commissure, and the lateral dorsal horn (Morgan et al., 1991). These axon collaterals are likely to be involved in a bilateral recurrent inhibitory pathway that regulates the parasympathetic outflow to the bladder (de Groat and Ryall, 1968; de Groat, 1976).

Interneurons in the spinal cord

Spinal interneurons involved in lower urinary tract function have been identified by retrograde transneuronal labeling after injection of pseudorabies virus (PRV) into the urinary bladder, urethra, or EUS of the rat. PRV, which is taken and transported from peripheral efferent terminals to efferent neurons in the spinal cord, crosses multiple synapses to infect interneuronal circuitry throughout the central nervous system (Figs 5.9C and 5.10). PRV-labeled spinal neurons are located in the same general regions of the spinal cord that receive afferent input from the bladder, including the dorsal commissure, laminae I and V, and lamina VII just dorsal and medial to the PGN (Nadelhaft et al., 1992; Nadelhaft

and Vera, 1995, 1996, 2001; Vizzard et al., 1995; Marson, 1997; Sugaya et al., 1997). Spinal interneurons in these locations receiving afferent input from the lower urinary tract have also been identified by firing in response to stimulation of bladder afferents (de Groat et al., 1981; McMahon and Morrison, 1982a, b) or by the expression of the immediate early gene, c-*fos,* after chemical or mechanical stimulation of the bladder and urethra (Fig. 5.9B) (Birder and de Groat, 1993; Birder et al., 1999). Some of these interneurons make excitatory and inhibitory synaptic connections with PGN (Araki and de Groat, 1996, 1997; de Groat et al., 1998; Miura et al., 2003) and participate in segmental spinal reflexes (de Groat et al., 1998), whereas others send long projections to supraspinal centers, such as the periaqueductal gray (PAG) (Figs 5.13B and 5.14), pontine micturition center (PMC, Barrington's nucleus), the hypothalamus and thalamus that are involved in the supraspinal control of micturition (McMahon and Morrison, 1982a, b; Blok et al., 1995; Ding et al., 1997; Birder et al., 1999; Duong et al., 1999; Blok and Holstege, 2000; Holstege and Mouton, 2003).

Axonal projections from the spinal cord to the brain

Nociceptive and non-nociceptive sensory input from the lower urinary tract is transmitted to the brain via multiple spinal tracts. Studies of Barrington (1925, 1933) in the cat (Fig. 5.15D) and Nathan and Smith (1951) in humans indicated that the ascending sensory pathways are located in the superficial part of the dorsolateral funiculus in cat and the most lateral part of the spinal cord, about midway between the anterior and posterior horns, in humans (Fig. 5.15A and B). Patients with bilateral lesions of the spinothalamic tract lost the normal sensation underlying the desire to micturate and the sensations of pain and temperature from the bladder and urethra (Nathan and Smith, 1951; Nathan, 1956). Lesions were in the same region of the cord as that conveying impulses interpreted as pain,

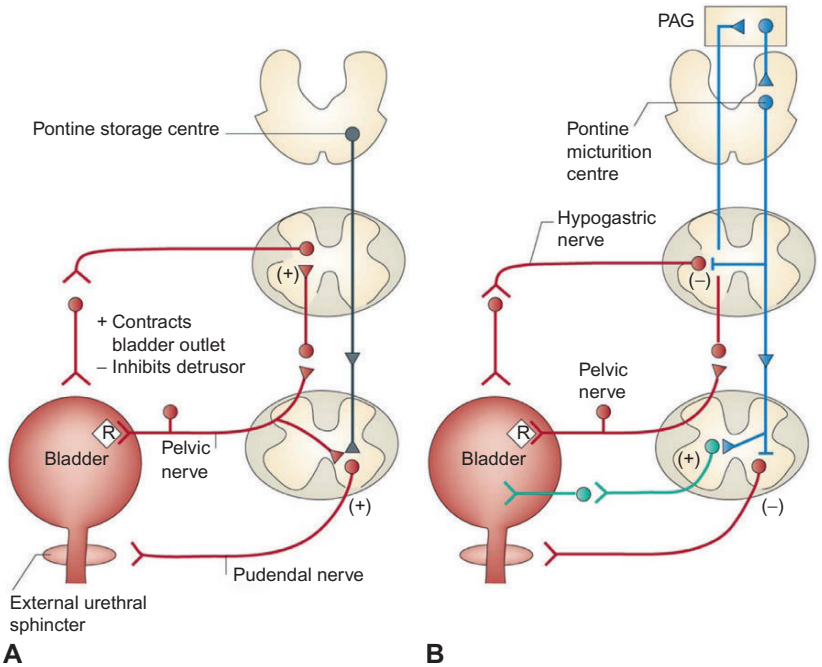

Fig. 5.13. Neural circuits that control continence and micturition. (**A**) Urine storage reflexes. During the storage of urine, distension of the bladder produces low-level vesical afferent firing. This in turn stimulates sympathetic outflow in the hypogastric nerve to the bladder outlet (the bladder base and the urethra) and pudendal outflow to the external urethral sphincter. These responses occur by spinal reflex pathways and represent guarding reflexes, which promote continence. Sympathetic firing also inhibits contraction of the detrusor muscle and modulates neurotransmission in bladder ganglia. A region in the rostral pons (the pontine storage center) might increase striated urethral sphincter activity. (**B**) Voiding reflexes. During the elimination of urine, intense bladder afferent firing in the pelvic nerve activates spinobulbospinal reflex pathways (shown in blue) that pass through the pontine micturition center. This stimulates parasympathetic outflow to the bladder and to the urethral smooth muscle (shown in green) and inhibits sympathetic and pudendal outflow to the urethral outlet (shown in red). Ascending afferent input from the spinal cord might pass through relay neurons in the periaqueductal gray (PAG) before reaching the pontine micturition center. Note that these diagrams do not address the generation of conscious bladder sensations, nor the mechanisms that underlie the switch from storage to voluntary voiding, both of which presumably involve cerebral circuits above the PAG. R, receptors on afferent nerve terminals. (Reproduced from Fowler et al., 2008.)

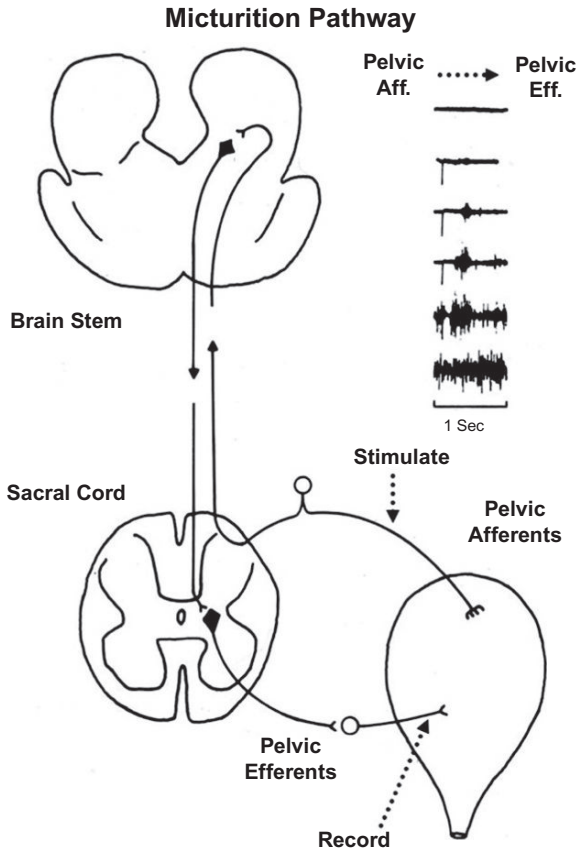

Fig. 5.14. Multiunit recordings of reflex activity on a bladder postganglionic nerve in a chloralose-anesthetized cat during electric stimulation (0.8 Hz, 3 V, 0.05 ms duration) of bladder afferent axons in the pelvic nerve. The bladder was distended with saline to a volume below the threshold for inducing micturition. First tracing at top right is a recording prior to the onset of stimulation showing that the efferent pathway is inactive. The next tracing shows the lack of a response to the first stimulus in a train of stimuli. Further stimulation (lower tracings) induces a gradual increase in the magnitude of a long-latency reflex and the eventual emergence of asynchronous firing (last tracing), which indicates the onset of reflex micturition. The diagram on the left shows the spinobulbospinal micturition reflex pathway and the sites of nerve stimulation and recording.

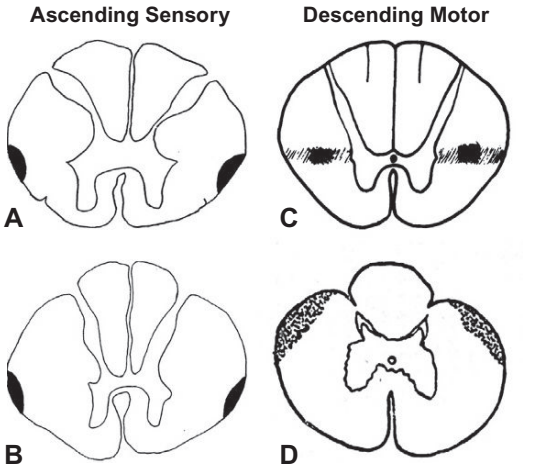

Fig. 5.15. (**A** and **B**) Drawings of transverse sections of the spinal cord. The area containing the centripetal pathway from the bladder and the spine thalamic pathway from the urethra is shaded. (Reproduced from Nathan and Smith, 1951.) (**C**) The region within the spinal cord of the centrifugal pathway for micturition. The majority of the fibers probably lie within the region indicated by cross-hatching. (Reproduced from Nathan and Smith, 1958.) (**D**) Diagram of transverse section of the spinal cord of cat. The area within which the centripetal bladder pathway lies is shown by stippling. (Reproduced from Nathan and Smith, 1951.)

warmth, and cold from the sacral segments of the body. Most patients with unilateral lesions of the spinothalamic tract did not notice any change in bladder function and retained normal sensation of a full bladder and desire to micturate. However a minority of patients reported unilateral sensations (Nathan, 1956). In humans and cats the ascending pathways are partially crossed within the spinal cord. In the cat the spinal tract neurons, which are located on the lateral side of the dorsal horn and in lateral lamina V and VI of the sacral spinal cord segments (Fig. 5.9D), project bilaterally to the PAG but not to the thalamus (Klop et al., 2005).

Following damage to the cauda equina or the spinal cord below mid lumbar level, afferent axons passing through prevertebral sympathetic nerves and the sympathetic chain to the rostral lumbar or caudal thoracic segments can also initiate sensations from the lower urinary tract (Nathan, 1956).

A second spinal ascending pathway from the pelvic viscera that initiates painful sensations is located in the dorsal columns (Kuru, 1965; Al-Chaer et al., 1996, 1998; Hirshberg et al., 1996; Willis et al., 1999). This pathway originates in spinal neurons in the region of the dorsal commissure and projects along the midline to make synaptic connections with neurons in the nucleus gracilis (Fig. 5.16) which then relay information to the ventral posterior lateral nucleus of the thalamus. The pathway has been identified in various species with anatomic and electrophysiologic techniques. In humans destruction of pathway in the dorsal columns has been effective in reducing cancer pain in the pelvic organs (Fig. 5.16) (Nauta et al., 1997, 2000).

Axonal projections from the brain to the spinal cord

Transneuronal PRV tracing methods have also identified many populations of neurons in the rat brain that are involved in the control of bladder (Nadelhaft et al., 1992; Nadelhaft and Vera, 1995, 2001; Sugaya et al., 1997), urethra (Vizzard et al., 1995), and the EUS

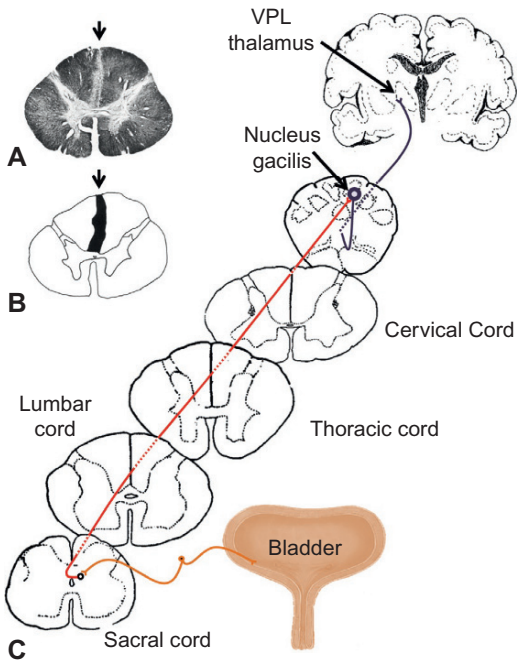

Fig. 5.16. (**A–C**) Diagram showing an ascending spinal sensory pathway in the dorsal columns identified in humans and animals that carries nociceptive information from the pelvic viscera to the nucleus gracilis. The pathway originates from second-order spinal tract neurons located in the dorsal commissure of the sacral spinal cord. The spinal tract neurons receive primary afferent input from the pelvic organs. Neurons in the nucleus gracilis relay information to the ventral posterior lateral (VPL) nucleus of the thalamus. Lesions along the midline in the dorsal columns (shown in spinal sections **A** and **B**) relieve chronic pelvic pain. (Reproduced from Willis et al., 1999.)

(Nadelhaft and Vera, 1996, 2001; Marson, 1997), including the PMC, PAG, medullary raphe nuclei, which contain serotonergic neurons; the locus coeruleus, which contains noradrenergic neurons, and the A5 noradrenergic cell group (Fig. 5.10). More rostral regions in the hypothalamus (lateral medial preoptic and paraventricular nucleus), dorsal thalamus, the primary and secondary motor cortices and entorhinal and piriform cortices also exhibit virus-infected cells. In the cat PRV tracing from the urinary bladder or the EUS identified a cluster of neurons extending from the PMC ventrolaterally into the pontine reticular formation (de Groat et al., 1998).

Other anatomic studies in which anterograde tracers were injected into areas of the cat brain revealed labeled axon terminals in regions of the brain and spinal cord (Fig. 5.11) consistent with the virus-tracing data. Tracer injected into the paraventricular nucleus of the hypothalamus labeled terminals in the sacral parasympathetic nucleus as well as the sphincter motor nucleus (Holstege and Mouton, 2003; Beckel and Holstege, 2011). Injections of tracers into the anterior hypothalamus or PAG (Blok and Holstege, 1994) labeled terminals in the PMC, whereas tracers in the PMC labeled axonal projections to the sacral parasympathetic nucleus, the lateral edge of the dorsal horn, and the dorsal commissure (Blok et al., 1997a; Blok and Holstege, 1997), areas containing dendrites of PGNs, sphincter motoneurons, and afferent inputs from the bladder (Fig. 5.11). Conversely, projections from neurons in the ventrolateral pons in the cat, an area identified as the pontine urine storage center (PUSC) (Kuru, 1965), terminate rather selectively in the sphincter motor nucleus (Fig. 5.11) (Holstege et al., 1986). Thus the sites of termination of descending projections from the pons are optimally located to regulate reflex mechanisms at the spinal level.

In humans the descending tracts subserving conscious control micturition and coordination of bladder function are located within the lateral columns in close association with the ascending sensory pathway at the level of the central canal throughout the length of the spinal cord (Fig. 5.15D) (Nathan and Smith, 1958). In animals the descending pathways from the PMC cross extensively within the lumbosacral segments (Kuru, 1965).

SUBCORTICAL URINE STORAGE MECHANISMS

Sympathetic storage reflex

Although the sympathetic input to the lower urinary tract is not essential for the performance of micturition, it does contribute to the storage function of the bladder. Surgical interruption or pharmacologic blockade of sympathetic innervation can reduce urethral outflow resistance, reduce bladder capacity, and increase the frequency and amplitude of bladder contractions recorded under constant volume conditions (de Groat et al., 1993).

Sympathetic reflex activity is elicited by a sacrolumbar intersegmental spinal reflex pathway that is triggered by vesical afferent activity in the pelvic nerves (de Groat and Lalley, 1972) (Fig. 5.13A). The reflex pathway is inhibited when bladder pressure is raised to the threshold for producing micturition. This inhibitory response is abolished by transection of the spinal cord at the lower thoracic level, indicating that it originates at a supraspinal site, possibly the PMC (Fig. 5.13B). Thus, the vesicosympathetic reflex represents a negative-feedback mechanism that allows the bladder to accommodate larger volumes during bladder filling but is turned off during voiding to allow the bladder to empty completely.

Urethral sphincter storage reflexes

Motoneurons innervating the striated muscles of the EUS exhibit a tonic discharge that increases during bladder filling (Thor and de Groat, 2010). This activity is mediated in part by a spinal reflex pathway (the guarding reflex) activated by low-level afferent input from the bladder (Fig. 5.13A). Studies in cats have also suggested that neurons in the ventrolateral region of the pontine reticular formation provide a tonic excitatory input to the EUS motoneurons (Holstege et al., 1986; Holstege and Mouton, 2003). Electric stimulation in this region (termed the pontine urine storage center: Fig. 5.13A) (Kuru, 1965; Kuru and Iwanaga, 1966) excites the EUS motoneurons and induces contractions of the EUS (Kuru, 1965; Koyama et al., 1966; Holstege et al., 1986).

Contraction of the EUS also induces firing in afferent axons in the pudendal nerve which in turn activate inhibitory interneurons in the spinal cord that suppress reflex bladder activity (McGuire et al., 1983; de Groat et al., 2001) by inhibiting PGN and interneurons on the micturition reflex pathway (de Groat, 1978; de Groat et al., 1982). Thus the bladder-to-EUS-to-bladder reflex pathway represents a second negative-feedback mechanism in the spinal cord that promotes urinary continence. Activation of afferents in the pudendal nerve, some of which very likely innervate the EUS, also elicits reflex contractions of the EUS and contributes to continence (Thor and de Groat, 2010). During micturition the firing of sphincter motoneurons and the negative feedback is inhibited. This inhibition, which is mimicked by electric stimulation of the PMC and activation of bulbospinal pathways (Fig. 5.13B) (Kruse et al., 1990, 1991), is less prominent in chronic spinal animals (Thor and de Groat, 2010), and is therefore dependent in part on supraspinal mechanisms.

Analysis of urethral closure mechanisms during sneeze-induced stress conditions in anesthetized female rats revealed that the pressure increases in the middle portion of the urethra are mediated by reflex contractions of the EUS as well as the pelvic floor muscles (Kamo et al., 2003). Transection of the pudendal nerves reduces reflex responses by approximately 70% and transection of the nerves to the iliococcygeus and pubococcygeus muscles reduces urethral responses by an additional 25%.

Brainstem-spinal storage mechanisms

Electric stimulation of the PUSC located ventrolateral to the PMC (Fig. 5.13A) not only excites the EUS but also inhibits reflex bladder activity, increases bladder capacity, and inhibits the bladder-excitatory effect of PMC stimulation (Sugaya et al., 2005). Neurons in the region of the PUSC project to the nucleus raphe magnus in the medulla which contains neurons that in turn project to the lumbosacral spinal cord. Electric (McMahon and Spillane, 1982; Morrison and Spillane, 1986; Sugaya et al., 1998; Athwal et al., 2001; de Groat, 2002) or chemical (Chen et al., 1993) stimulation in the nucleus raphe magnus induces serotonergic inhibition of reflex bladder activity. Thus neurons in the PUSC may activate descending inhibitory pathways to the sacral parasympathetic nucleus (Sugaya et al., 2005).

Electric stimulation of the rostral pontine reticular formation (RPRF) ventral to the PMC in an area also known as the nucleus reticularis pontis oralis inhibits reflex bladder contractions in cats and rats (Sugaya et al., 1987, 2005; Kimura et al., 1995; Nishijima et al., 2005). Neurons in this region project to the spinal cord and also to nucleus reticularis gigantocellularis located in the rostrodorsal medulla. The RPRF projects to lumbosacral glycinergic-inhibitory neurons that may mediate the inhibitory effects of RPRF stimulation (Sugaya et al., 2005).

VOIDING MECHANISMS

Brainstem circuitry: spinobulbospinal micturition reflex

Role of PMC

Voiding, which can be initiated voluntarily or reflexly, is mediated by activation of the sacral parasympathetic efferent pathway to the bladder and urethra as well as reciprocal inhibition of the somatic pathway to the urethral sphincter (Fig. 5.13B). In contrast to storage mechanisms that are dependent on spinal reflex pathways, voiding is dependent on neural circuitry in the brain and spinal cord (Figs 5.9B, 5.10, and 5.11) (Barrington, 1925; Langworthy et al., 1940; Ruch and Tang, 1956; Kuru, 1965; de Groat and Ryall, 1969; de Groat, 1975).

Studies in cats using brain-lesioning and electrophysiologic techniques revealed that reflex micturition is mediated by a spinobulbospinal pathway consisting of an ascending sensory limb that passes from the sacral spinal cord to circuitry in the rostral brainstem, leading to activation of neurons in the PMC that send excitatory signals back to the sacral spinal cord to complete the reflex circuit (Figs 5.13B and 5.14). In animals reflex micturition is preserved after removal of the forebrain by supracollicular decerebration but is abolished after bilateral destruction of the PMC or transection of the neuraxis at any level caudal to the PMC (Kuru, 1965).

Anterograde axonal tracing studies in cats revealed that neurons in the PMC project directly to bladder PGNs in the sacral spinal cord (Blok and Holstege, 1997). Labeled fibers from the PMC that were filled with round

vesicles and that formed a symmetric synaptic cleft terminated on the soma and dendrites of the PGNs. These data suggest that the descending pathway makes monosynaptic connections and has an excitatory function. On the other hand, electrophysiologic experiments in cats in which EPSPs were evoked in bladder PGNs by stimulation of the PMC indicate that the descending pathway from the PMC to bladder PGNs is polysynaptic and strongly facilitated during the micturition reflex (Sasaki and Sato, 2013). The latter finding is consistent with other electrophysiologic studies in cats indicating that the descending PMC–spinal cord limb of the micturition reflex requires afferent feedback from the bladder to induce large-amplitude bladder contractions and that it can be modulated at the spinal level, possibly at an interneuronal site by segmental afferent inputs (Kruse et al., 1991, 1992).

Recordings of electrical activity in bladder efferent nerves (Fig. 5.14) support the concept that the micturition reflex is mediated by a pathway passing through a switching center in the rostral pons. Stimulation of bladder afferent nerves evokes long-latency discharges (120–150 ms) on bladder postganglionic nerves (Fig. 5.14) that persist after supracollicular decerebration but not after transection of the spinal cord at the thoracic level (de Groat and Ryall, 1969; de Groat, 1975). The evoked reflexes are unmasked by partial filling of the bladder to elicit a basal level of afferent firing. They also exhibit an unusual temporal facilitation in which the first stimulus during a train (0.5–1 Hz frequency) does not evoke a response and the next few stimuli evoke gradually increasing responses (wind-up), eventually producing a self-sustaining micturition reflex (Fig. 5.14). These observations indicate that, even under optimal conditions with tonic afferent input from bladder mechanoceptors, electric stimulation of bladder afferents only activates the micturition switching circuit after a delay of several seconds.

Bladder afferent nerve stimulation evokes neuronal firing in the PMC at latencies ranging from 30 to 40 ms; and electric stimulation in the PMC evokes bladder contractions and postganglionic nerve firing at latencies of 60–75 ms (de Groat, 1975; Noto et al., 1991). The sum of the latencies of the putative ascending (afferent-mesencephalic-pontine) and descending limbs (pontine-sacral efferent neuron) of the reflex approximates the latency of the entire reflex pathway (120 ms). The reflex firing elicited in cats and rats is not altered following supracollicular decerebration but is eliminated by acute transection of neuraxis at any level caudal to the PMC (de Groat and Ryall, 1969; de Groat, 1975; de Groat et al., 1981).

In the rat 79% of neurons in the PMC (Barrington's nucleus) are activated by bladder distension consistent with its role as a PMC (Rouzade-Dominguez et al., 2003). Although no neurons were selectively activated by distension of the colon, the majority of bladder-responsive neurons (73%) were also activated by colon distension. These data support the proposals based on PRV tracing experiments that neurons in the PMC coordinate the functions of the colon and the lower urinary tract (Valentino et al., 2000; Vizzard, 2000; Rouzade-Dominguez et al., 2003).

Properties of neurons in the PMC

Single-unit recording in the PMC of the cat (Fig. 5.17) (Bradley and Conway, 1966; Koshino, 1970; de Groat et al., 1998; Sasaki, 2002, 2004, 2005a, b; Sugaya et al., 2003, 2005; Tanaka et al., 2003) and rat (Elam et al., 1986; Willette et al., 1988) with the bladder distended under isovolumetric conditions revealed several populations of neurons exhibiting firing correlated with reflex bladder contractions, including: (1) neurons that are silent in the absence of bladder activity but fire prior to and during reflex bladder contractions (direct neurons, 21%) (Fig. 5.17A); (2) neurons that are active during the period between bladder contractions and are inhibited during contractions (inverse neurons, 51%) (Fig. 5.17B); and (3) neurons that fire transiently at the beginning of bladder contractions (on–off neurons, 4%). Tonic firing that was not correlated with bladder activity was also identified in a large percentage (25%) of PMC neurons (termed independent neurons) (Fig. 5.17C). All of these neurons are localized primarily in the region of the locus coeruleus complex.

Subpopulations of direct and inverse neurons in the cat have also been identified based on slow changes in firing during and between bladder contractions (Sasaki, 2004). Approximately 50% of direct neurons (type 2) exhibit tonic firing between bladder contractions, whereas the remainder (type 1) are quiescent until 0.5–1.2 seconds prior to a bladder contraction. The majority of inverse neurons (84%) stop firing during a bladder contraction after a delay of 4–11 seconds, whereas a small number exhibit only a reduction in firing. A large percentage of direct neurons project to the lumbosacral spinal cord (Sasaki, 2002, 2005b; Sugaya et al., 2003), whereas only a small percentage of inverse neurons send projections to the cord. Thus it has been speculated that inverse neurons function as local inhibitory neurons in the PMC. Both direct and inverse neurons exhibit excitatory synaptic responses to electric stimulation of afferent axons in the pelvic nerve (de Groat et al., 1998). Direct neurons fire at a mean latency of 62 ms after a stimulus, whereas inverse neurons fire at a shorter latency of 25–30 ms, followed by an inhibition at a latency of 80 ms and then a late excitation at 250–300 ms.

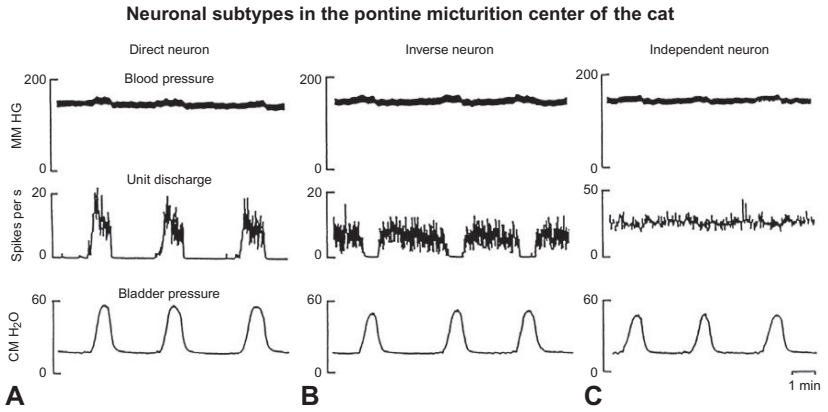

Fig. 5.17. Relationship between single-unit activity in the pontine micturition center of a decerebrate, unanesthetized cat and reflex contractions of the urinary bladder. Top tracings are blood pressure; middle tracings are ratemeter recordings of unit activity in spikes per second; and the bottom tracings are bladder pressure in cm H_2O. Three types of neuronal activity are illustrated: (**A**) a direct neuron that only fired during a bladder contraction; (**B**) an inverse neuron that fired between bladder contractions and was inhibited during contractions; and (**C**) an independent neuron that exhibited continuous firing unrelated to bladder contractions. Small increases in blood pressure occurred during bladder contractions. The bladder was distended with saline and maintained under isovolumetric conditions. Horizontal calibration represents 1 minute. The three neurons were studied at different times in the same animal. (Reproduced from de Groat and Wickens, 2013.)

Role of the PAG

Early studies in cats (Langworthy and Kolb, 1935; Kabat et al., 1936; Skultety, 1959; Koyama et al., 1962; Gjone, 1966) revealed that stimulation at sites in the PAG could either excite or inhibit bladder activity. The effects of stimulation were dependent on the state of the bladder. For example, when stimulation was applied with the bladder partially full and relatively inactive, excitatory effects were commonly elicited; however when the bladder was full and exhibiting large-amplitude reflex contractions stimulation at the same site produced inhibition. Reflex bladder activity was also enhanced by elimination of parts of the PAG by focal lesions or serial transections through the mesencephalon (Langworthy and Kolb, 1933; Tang, 1955; Ruch and Tang, 1956). This finding raised the possibility that a mesencephalic bladder inhibitory center tonically controls micturition. An inhibitory region seems to be located in the dorsolateral margin of the rostral PAG (Numata et al., 2008) because chemical or electric stimulation at this site inhibits reflex bladder contractions as well as the contractions induced by electric stimulation of the PMC. Injection of bicuculline, a $GABA_A$ receptor antagonist, into the PMC blocks the PAG-induced inhibition of PMC stimulation, indicating that GABA is the transmitter in the inhibitory pathway (Numata et al., 2008).

Other sites in the PAG seem to have a facilitatory role in micturition. Electric stimulation in the ventrolateral region of the PAG evokes bladder contractions (Noto et al., 1989; Matsuura et al., 2000; Taniguchi et al., 2002) and firing on bladder postganglionic nerves (Noto et al., 1991), while injections of cobalt chloride, a synaptic inhibitory agent (Matsuura et al., 1998), or an opioid receptor agonist (Matsumoto et al., 2004) into this region suppresses reflex micturition. These data raised the possibility that the ventrolateral PAG is an essential component of the micturition reflex.

Electric recordings in the PAG indicate that it may serve as a relay and coordinating center on the ascending limb of the micturition reflex pathway. In the rat electric stimulation of bladder afferents in the pelvic nerve elicits negative field potentials in the dorsal PAG at a mean latency of 13 ms, which is considerably shorter than the mean latency of field potentials in the region of the PMC (42 ms) (Noto et al., 1989). In the cat a similar difference between latencies of pelvic afferent evoked field potentials in the PAG (11 ms) (Duong et al., 1999) and in the PMC (30–40 ms) (de Groat, 1975) has been noted.

Subsequent studies in the cat and rat provided further support for the idea that bladder afferent information is relayed through the PAG. Axonal tracing studies in the cat revealed that spinal tract neurons located in lamina I on the lateral edge of the sacral dorsal horn, a region receiving primary afferent input from the bladder (Morgan et al., 1981), send a prominent direct axonal input through the lateral funiculus to the PAG (Blok et al., 1995; Holstege and Mouton, 2003) (Figs 5.13 and 5.18). Injection of retrograde tracers into the lateral funiculus at the lumbar level labels the same group of sacral spinal tract neurons (de Groat et al., 1981). The

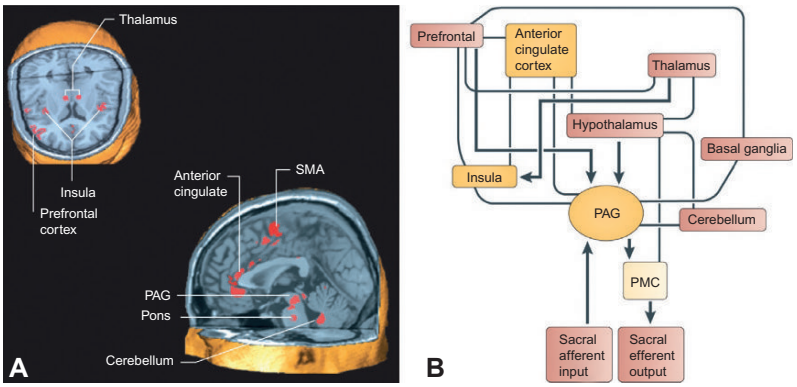

Fig. 5.18. Brain areas involved in the regulation of urine storage. (**A**) A meta-analysis of positron emission tomography and functional magnetic resonance imaging studies that investigated which brain areas are involved in the regulation of micturition reveals that the thalamus, the insula, the prefrontal cortex, the anterior cingulate, the periaqueductal gray (PAG), the pons, the medulla, and the supplementary motor area (SMA) are activated during the urinary storage. (**B**) A preliminary conceptual framework, based on functional brain-imaging studies, suggesting a scheme for the connections between various forebrain and brainstem structures that are involved in the control of the bladder and the sphincter in humans. Arrows show probable directions of connectivity but do not preclude connections in the opposite direction. PMC, pontine micturition center. (Reproduced from Fowler et al., 2008.)

PMC, on the other hand, receives a weaker input directly from the spinal cord and this input does not terminate on the PMC output neurons that send information back to the sacral parasympathetic nucleus. Axonal tracing methods also identified projections from the PAG to the PMC (Blok and Holstege, 1994; Kuipers et al., 2006), raising the possibility that ascending afferent information from the bladder is relayed through synapses in the PAG to the PMC. Thus it has been proposed that the PAG has an essential role in the spinobulbospinal micturition reflex pathway (Noto et al., 1989; Holstege and Mouton, 2003).

However experiments in cats by Takasaki et al. (2011) have raised questions about the importance of the PAG in reflex micturition. When the mesencephalon was serially transected at various levels, that interrupted the connections between the PAG and the PMC. Reflex bladder contractions persisted after transections at rostral levels that eliminated connections with the dorsal half of the PAG. Reflex micturition also persisted after more caudal transections that eliminated connections with both the dorsal and ventral half of the PAG or eliminated the most rostral part of the PMC. On the other hand, transections caudal to the PMC abolished reflex micturition. The authors concluded that the PAG does not have an essential role in reflex micturition but rather is involved in transmitting bladder-filling information to higher brain centers. Subsequently, the techniques used in transection experiments were questioned by other investigators (Stone et al., 2011), who noted that the PAG lesions in the experiments of Takasaki et al. (2011) were often incomplete and a part of the caudal ventrolateral PAG was preserved in some experiments.

In the rat the role of the PAG is even less clear because prominent ascending projections from the lumbosacral spinal cord have been detected in the PMC as well as the PAG (Ding et al., 1997; Blok and Holstege, 2000). Thus the organization of the ascending limb of the micturition reflex is uncertain and may vary in different species. Brain imaging studies (Tai et al., 2009) in the rat revealed that neuronal activity in the PAG increases during slow bladder filling (Fig. 5.19), indicating that afferent activity from the bladder is received and processed in the PAG prior to micturition; however, a similar signal was not detected in the PMC during filling (Fig. 5.19). On the other hand, during micturition, signals were detected in the PAG and the PMC. Similar results have been reported during brain imaging in humans (Fig. 5.18). These results suggest that the PAG in the rat serves as a relay station for transmitting afferent information from the bladder to the PMC but that the switch from urine storage to voiding occurs in the PMC.

Properties of neurons in the PAG

Single-unit recordings in the PAG and adjacent mesencephalic reticular formation in decerebrate unanesthetized cats during rhythmic reflex bladder contractions under isovolumetric conditions revealed firing patterns similar to those recorded in the PMC, including: (1) tonic storage neurons that are partially inhibited during bladder contractions (43%); (2) phasic storage neurons that are completely inhibited during bladder contractions (15%), similar to inverse neurons in the PMC; (3) phasic micturition neurons that are only active during micturition (13%) (Liu et al., 2004), similar to direct neurons in

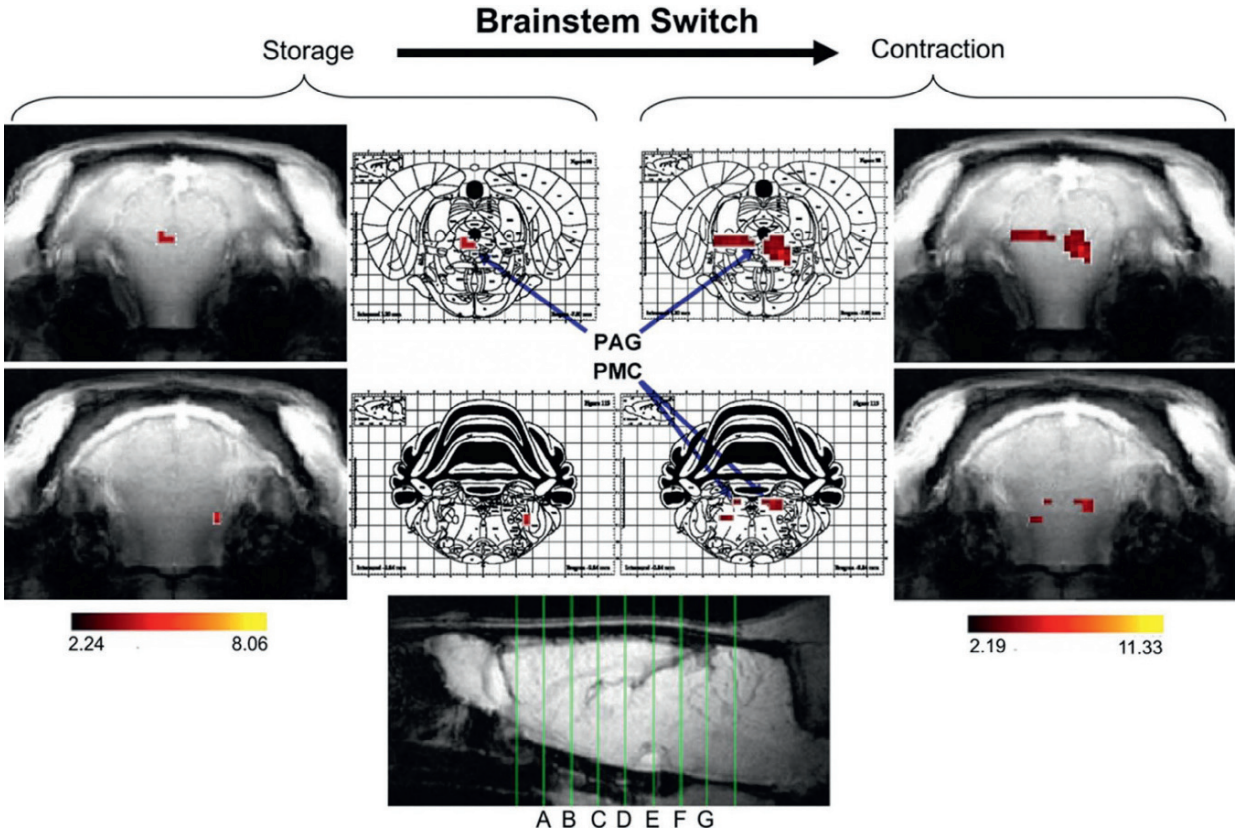

Fig. 5.19. Blood oxygen level-dependent (BOLD) images from the rat showing brainstem activation associated with switching from the bladder storage phase to the bladder contraction phase. The locations of coronal brain sections (**F** and **G**) are indicated in the sagittal brain image at the bottom, which corresponds to the Bregma coordinates in the anterior–posterior direction at 2.28, 0.24, 1.80, 3.84, 5.88, 7.80, and 9.84 mm. Region of interest (ROI) analysis was performed on the brainstem at coronal sections **F** and **G** to detect the activation. The periaqueductal gray (PAG) and pontine micturition center (PMC) are indicated by the blue arrows. The color scale bars indicate the *t* value. (Reproduced from Tai et al., 2009.)

the PMC. A fourth type of neuron (29%), classified as tonic micturition neurons that are active throughout storage and micturition but increase their firing during bladder contractions, may be similar to the transient neurons identified in the PMC. Among the 84 neurons recorded in this study, 16 were located in the PAG and the remainder were located just ventral to the PAG. In the PAG storage neurons seemed to be located in the middle part of the PAG (H-C coordinates: P 0–1), whereas micturition neurons were distributed in a broader area. Simultaneous unit recordings in the PAG and PMC or in the PAG and the PUSC did not reveal significant time correlations in 100-ms windows between unitary activity in the these locations.

The PMC–PAG switch

Pharmacologic studies indicate that circuitry in the PMC and PAG allows the spinobulbospinal micturition reflex pathway to function as a switch that is either in a completely "off" mode (storage) or maximally "on" mode (voiding). Injections of excitatory amino acids into the PMC (Mallory et al., 1991) or PAG (Taniguchi et al., 2002) evoke bladder contractions in cat and rat. On the other hand, microinjections of low doses of inhibitory agents such as $GABA_A$ receptor agonists (muscimol) or opioid peptides at these sites increases the bladder volume threshold for inducing micturition without altering the magnitude of the micturition reflex measured as the amplitude of voiding contractions (Mallory et al., 1991; Noto et al., 1991; Matsumoto et al., 2004; Stone et al., 2011). Conversely, injections of $GABA_A$ receptor (bicuculline) or opioid receptor antagonists (naloxone) reduce the bladder volume threshold, indicating that tonic activation of inhibitory receptors in these centers can alter the set point of the micturition switch (Mallory et al., 1991; Noto et al., 1991; Stone et al., 2011). Because pharmacologic modulation of the PAG circuitry clearly alters the bladder volume threshold it seems reasonable to conclude that PAG input to the PMC switching circuit also regulates the set point for the micturition switch.

Subcortical modulatory circuits

Experiments in animals using a variety of techniques (axonal tracing, electrophysiologic stimulation and recording, lesions) have identified four subcortical regions: (1) cerebellum (Connor and German, 1941; Chambers and Sprague, 1955; Bradley and Teague, 1969; Nishizawa et al., 1995); (2) hypothalamus (Tang, 1955; Ruch and Tang, 1956); (3) substantia nigra–ventral tegmental area (SN/VTA) (Yoshimura et al., 1992; Sakakibara et al., 2002b); and (4) PUSC (Kuru, 1965; Koyama et al., 1966; Holstege et al., 1986; Nishizawa et al., 1987; Sakakibara et al., 2002a) that modulate voiding. Neurons in the SN/VTA and PUSC promote urine storage by inhibiting the neural pathways to the bladder or activating the pathways to the urethral sphincter. Neurons in the cerebellum and hypothalamus have both excitatory and inhibitory effects on voiding. Brain imaging studies in humans have shown activation in the cerebellum (Griffiths et al., 2005; Kuhtz-Buschbeck et al., 2005; Seseke et al., 2006; Takao et al., 2008) and the caudal hypothalamus (Athwal et al., 2001; Griffiths et al., 2007) in response to bladder distension (Fig. 5.18). More detailed information about these modulatory circuits has appeared in recent reviews (Sugaya et al., 2005; de Groat and Wickens, 2013).

Forebrain control of micturition

Lesioning and electric stimulation studies indicate that voluntary control of micturition depends on connections between the frontal cortex and other forebrain structures, including the anterior cingulate gyrus, insula, amygdala, bed nucleus of the stria terminalis and septal nuclei, where electric stimulation elicits excitatory bladder responses (de Groat et al., 1993; Andersson and Pehrson, 2003). Damage to the cerebral cortex, due to tumors, aneurysms, or cerebrovascular disease, appears to remove inhibitory control of the PMC, resulting in bladder overactivity. Pharmacologic studies in rats indicate that decerebration or brain damage induced by occlusion of the middle cerebral artery induces bladder overactivity in part by eliminating tonic glutamatergic and dopaminergic inhibitory mechanisms and unmasking a dopaminergic excitatory mechanism (Yokoyama et al., 2002).

Human and animal brain imaging studies using various methods have examined the areas of the brain involved in the control of micturition (Blok et al., 1998; Athwal et al., 2001; Kavia et al., 2005; Fowler, 2006; Griffiths et al., 2007; Fowler and Griffiths, 2010; Griffiths and Fowler, 2013). Some studies evaluated the brain areas responsible for the perception of bladder fullness and the sensation of the desire to void during bladder filling (Athwal et al., 2001; Tadic et al., 2013). Others have examined brain activity during micturition (Blok et al., 1997b, 1998; Nour et al., 2000) or voluntary contractions of the pelvic floor during urine withholding (Blok et al., 1997b). During urine storage activation occurs in the PAG, thalamus, insula, prefrontal cortex, anterior cingulate, pons, medulla, and supplementary motor area (Fig. 5.18). These results are consistent with the notion that the PAG receives information about bladder fullness and then relays this information (possibly through the thalamus) to other brain areas involved in the control of urine storage. The insula, where normal visceral sensations such as desire to void are thought to be mapped, is regarded as a key center for processing bladder afferent input. During voiding activation occurs in the prefrontal cortex, insula, hypothalamus, PAG, and in a region of the dorsal pons (Fig. 5.18) comparable to the location of the PMC in rats (Fig. 5.19) and cats.

Insights into possible brain circuitry controlling micturition (Fig. 5.20) have been obtained using various types of analyses, including: (1) measurements of white-matter hyperintensities globally and in specific white-matter tracts in the brains of patients with urinary urgency and/or incontinence and the correlation of white-matter hyperintensities with brain activity during fMRI and bladder filling (Tadic et al., 2010); (2) a physiophysiologic interaction method (Tadic et al., 2008; Griffiths et al., 2009) or functional connectivity analysis of functional magnetic resonance imaging (fMRI) data from normal or urinary-incontinent human subjects during bladder filling and voiding (Shy et al., 2014); (3) information about bladder dysfunction induced by brain lesions (Sakakibara et al., 2010) (Table 5.1) and (4) the organization of forebrain neural networks involved in micturition in animals (Kuru, 1965; Birder et al., 2009). The importance of the prefrontal cortex in bladder control was established in clinical studies by Ueki (1960) and Andrew and Nathan (1964) that revealed lesions clinically demonstrated to have long-term effects on bladder function, including urgency, frequency, and sometimes incontinence, were located in white-matter tracts in the medial prefrontal regions between the superior frontal gyrus and the cingulate gyrus. On the other hand, medial prefrontal gray-matter lesions led to relatively short-term incontinence. Therefore axonal pathways from the prefrontal cortex are thought to be important in modulating the pontine–mesencephalic micturition reflex circuitry. Anatomic studies in cats showed that the PMC receives direct connections from only five brain regions, including ventrolateral and dorsomedial PAG, medial preoptic area of the hypothalamus, posterior hypothalamus, and ventromedial pontomedullary tegmental field. Thus a large part of the forebrain modulation of the PMC output to the spinal

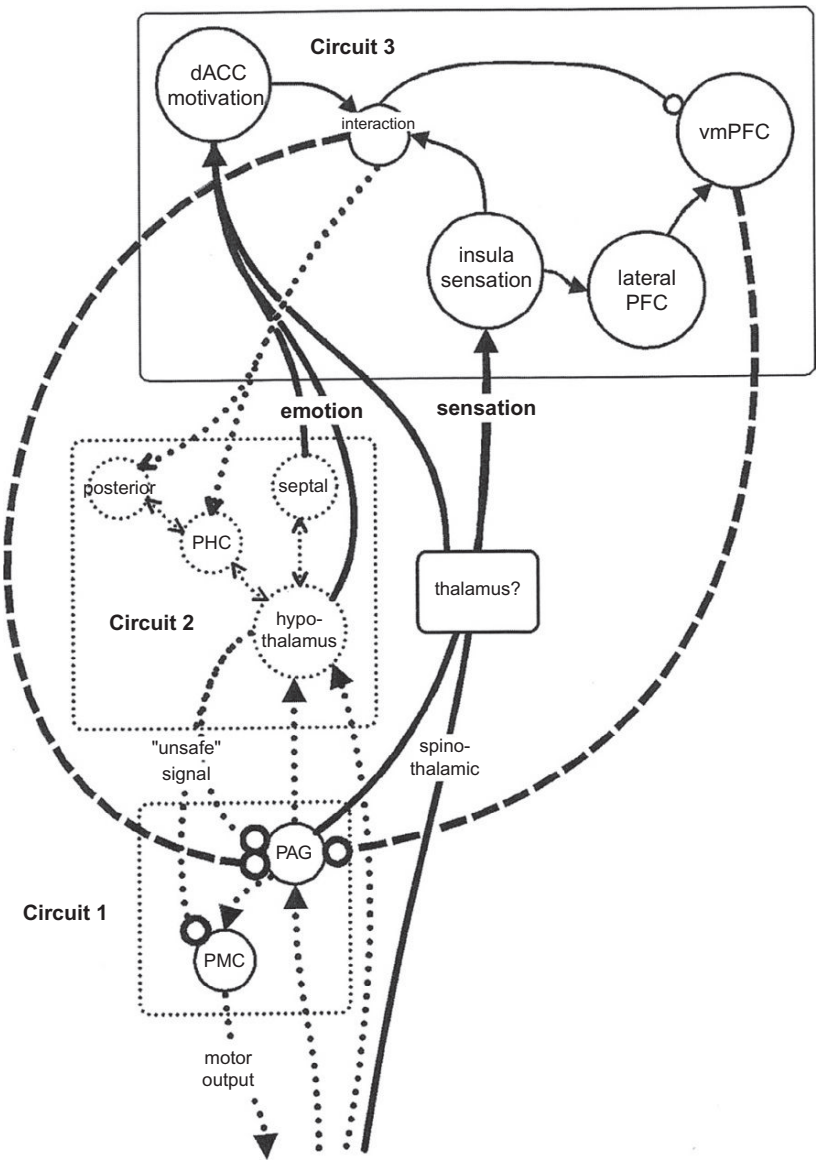

Fig. 5.20. Putative forebrain neural circuitry, based on human brain-imaging studies that control the periaqueductal gray (PAG)/pontine micturition center (PMC) micturition reflex circuit (circuit 1). Sensory input from the bladder is processed in the insula which in turn sends signals to the prefrontal cortex (circuit 3) that provides inhibitory feedback to the PAG in circuit 1. The anterior cingulate cortex which is also part of circuit 3 has bidirectional interactions with septal/hypothalamic nuclei (circuit 2) which also sends inhibitory signals to the PAG to control reflex activity mediated by circuit 1. Solid lines, principal connections of circuit 3; dashed lines, descending output from circuit 3; circles, inhibitory synapse; PFC, prefrontal cortex; vmPFC, ventromedial prefrontal cortex; dACC, dorsal anterior cingulate cortex; posterior, posterior cingulate and precuneus; PHC, parahippocampal complex. The "interaction" region in circuit 3 may be the thalamus, although it is shown separately. (Reproduced from Griffiths and Apostolidis, 2010.)

cord must be mediated indirectly via circuitry in the hypothalamus and/or the PAG. Indeed, Andrew and Nathan (1964, 1965) speculated that cortical control of septal and hypothalamic nuclei was important for integrating micturition into normal daily activities.

On the other hand, anatomic tracing studies in rats (Valentino et al., 1994, 1999) have revealed direct pathways to the PMC from the motor, insular, and infralimbic cortices, the bed nucleus of the stria terminalis, a region near the medial amygdaloid nucleus just lateral to the supraoptic nucleus, as well as from the hypothalamic and PAG areas identified in the cat.

Figure 5.20 shows putative brain circuitry involved in processing sensory information received by the PAG and

Table 5.1

Lesion literature for bladder pathophysiology

Key brain regions	Pathology	Number of cases	Effect on bladder behavior
Frontal	Various causes of frontal-lobe pathology (Andrew and Nathan, 1964)	36	Altered bladder sensation and incontinence in absence of intellectual deterioration or retention Three cases had retention
	Brain tumors (Ueki, 1960)	50	Disturbances of micturition
	Frontal-lobe tumors (Maurice-Williams, 1974)	7	Frequency, urgency incontinence
	Frontal abscess (Yamamoto et al., 1995)	1	Retention
	Frontal abscess/hematoma (Lang et al., 1996)	2	Retention
	Anterior cerebral vascular lesions (Sakakibara et al., 1996a)		Various bladder disorders and hemiparesis
Anterior cingulate gyrus	Bilateral infarction of anterior cingulate gyri (Laplane et al., 1981)	1	Complex behavioral changes and incontinence
	Glioma of anterior cingulate gyrus and supplementary motor cortex (Duffau and Capelle, 2005)	1	Urgency incontinence with loss of sensation
Insula	Glioma of insula and inferior frontal gyrus (Duffau and Capelle, 2005)	1	Incontinence without loss of bladder sensation
Hypothalamus	Ruptured anterior cerebral aneurysms (Andrew et al., 1966)	6	Pre- or postoperative disturbances of micturition
	Pituitary tumors extending into the hypothalamus (Yamamoto et al., 2005)	3	Urgency incontinence, weight loss, psychiatric symptoms
	Cystic lesion of hypothalamus (Andrew and Nathan, 1965)	1	Frequent incontinence
Periaqueductal gray	Presumed inflammatory lesion (Yaguchi et al., 2004)	1	Urinary retention
Pons	Posterior fossa tumors (Holman, 1926)		Voiding difficulty
	Brainstem tumors (Ueki, 1960)	46	Predominantly voiding difficulties
	Brainstem vascular lesions (Sakakibara et al., 1996b)	34	Predominantly voiding difficulties
	Brainstem gliomas in children (Renier and Gabreels, 1980)	24	Voiding difficulty
	Presumed dermoid (Betts et al., 1992)	1	Urinary retention and disordered eye movements
	Low-grade glioma (Manente et al., 1996)	1	Paraparesis, urinary retention and disordered eye movements
	Herpes encephalitis (Sakakibara et al., 1998)	1	Urinary retention and disordered eye movements
	Presumed rhombencephalitis (Komiyama et al., 1998)	1	Urinary retention and horizontal diplopia

Reproduced from Birder et al. (2009).

thalamus from ascending spinal tract pathways and the integration of that input with hypothalamic–limbic circuits that might be concerned with emotional aspects of voiding. Inhibitory feedback from cortical and subcortical circuitry, including the hypothalamus, is thought to regulate the pontomesencephalic micturition reflex circuitry by modulating synaptic transmission in the PAG. More detailed information about the forebrain circuitry involved in voluntary control of voiding based on human brain imaging studies is presented in Chapter 7.

Spinal micturition reflex pathways

Spinal cord injury rostral to the lumbosacral level eliminates voluntary and supraspinal control of voiding. This

loss of control leads initially to an areflexic bladder and complete urinary retention, followed by a slow development of automatic micturition and bladder hyperactivity mediated by spinal reflex pathways. However, voiding is commonly inefficient due to simultaneous contractions of the bladder and urethral sphincter (bladder sphincter dyssynergia) (Fig. 5.8C). Electrophysiologic studies in animals (de Groat and Ryall, 1969; de Groat et al., 1981, 1990) have shown that the spinal micturition reflex is mediated by a spinal segmental pathway that has a short central delay of approximately 5 ms and is triggered by a C-fiber afferent limb (Fig. 5.21). This fast reflex contrasts with the spinobulbospinal micturition reflex in normal animals that occurs after a much longer central delay (60–70 ms) and in response to myelinated Aδ afferent input from the bladder. In normal cats, capsaicin, a neurotoxin known to disrupt the function of C-fiber afferents, did not block reflex contractions of the bladder or the bladder reflex evoked by A-δ fibers. However, in cats with chronic spinal injury, capsaicin completely blocked bladder reflexes (Fig. 5.21) evoked by C-fibers (de Groat et al., 1990; de Groat, 1997; Cheng et al., 1999). Evidence of the contribution of C-fiber bladder afferents to bladder hyperactivity and involuntary voiding in humans has been obtained from studies in which capsaicin or resiniferatoxin, another C-fiber afferent neurotoxin, was administered intravesically to patients with neurogenic detrusor overactivity due to multiple sclerosis or spinal cord injuries (Fowler, 2006). In these patients the toxins increased bladder capacity and reduced the frequency of incontinence.

Several mechanisms seem to underlie the emergence of bladder reflexes mediated by C-fibers. These mechanisms include changes in central synaptic connections and alterations in the properties of the peripheral afferent receptors that lead to sensitization of the "silent" C-fibers and the unmasking of responses to mechanical stimuli (de Groat and Yoshimura, 2006; Vizzard, 2006). In rats, bladder afferent neurons undergo both morphologic (i.e., neuronal hypertrophy) (Steers et al., 1991a) and physiologic changes (i.e., upregulation of tetrodotoxin-sensitive Na^+ channels and downregulation of tetrodotoxin-resistant Na^+ channels) following spinal cord injury or urethral outlet obstruction (Yoshimura and de Groat, 1997b). This neuronal plasticity may be mediated by the actions of neurotrophic factors, such as nerve growth factor released within the spinal cord or the urinary bladder (Steers et al., 1991b; Steers and Tuttle, 2006; Vizzard, 2006; Liu and Kuo, 2008). The production of neurotrophic factors, including nerve growth factor, increases in the bladder after spinal cord injury (Vizzard, 2006) and chronic administration of nerve growth factor into the bladder of rats induces

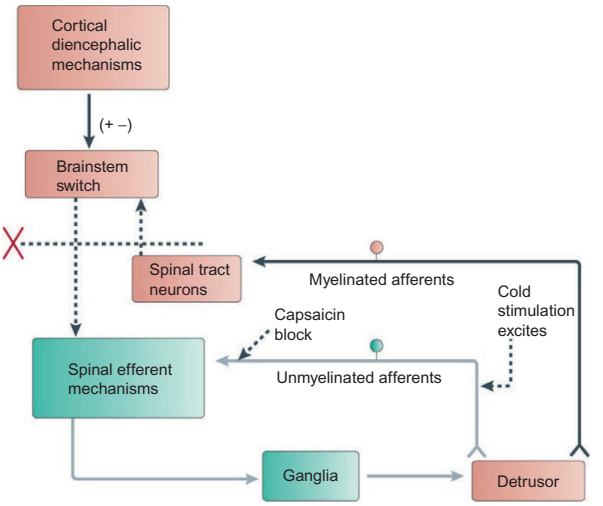

Fig. 5.21. Organization of the parasympathetic excitatory reflex pathway to the detrusor muscle. This scheme is based on results from electrophysiologic studies in cats. Micturition is initiated by a supraspinal reflex pathway that passes through a center in the brainstem. The pathway is triggered by myelinated afferents (Aδ-fibers), which are connected to the tension receptors in the bladder wall. Injury to the spinal cord above the sacral segments interrupts the connections between the brain and spinal autonomic centers and initially blocks micturition. However, following cord injury a spinal reflex mechanism (shown in green) emerges that is triggered by unmyelinated vesical afferents (C-fibers); the A-fiber afferent inputs are ineffective. The C-fiber reflex pathway is usually weak or undetectable in animals with an intact nervous system. Stimulation of the C-fiber bladder afferents by instillation of ice water into the bladder (cold stimulation) activates voiding responses in patients with spinal cord injury. Capsaicin (20–30 mg, subcutaneously) blocks the C-fiber reflex in cats with spinal lesions but does not block micturition reflexes in spinal-intact cats. Intravesical capsaicin also suppresses detrusor hyperreflexia and cold-evoked reflexes in patients with neurogenic bladder dysfunction. (Reproduced from Fowler et al., 2008.)

bladder hyperactivity and increases the firing frequency of dissociated bladder afferent neurons (de Groat and Yoshimura, 2006; Yoshimura et al., 2006). On the other hand, intrathecal application of antibodies against nerve growth factor, which bind nerve growth factor and neutralize its actions in the spinal cord, suppresses detrusor hyperreflexia and detrusor sphincter dyssynergia in spinal cord-injured rats (Seki et al., 2002, 2004).

Spinal cord injury in cats and rats also causes the re-emergence of a neonatal exteroceptive micturition reflex that is activated by tactile stimulation of cutaneous afferent axons in the perineum (i.e., the perineal-to-bladder reflex) (de Groat, 2002). In neonatal animals, this reflex is activated by the mother licking the perineal region of the young animal. The stimulation is essential

for survival of the neonate because isolation of the newborn from its mother leads to urinary retention. The adult form of reflex voiding, which is triggered by bladder distension, does not become functional until several weeks after birth. As the adult reflex is appearing, the neonatal perineal-to-bladder reflex becomes progressively weaker and eventually disappears (de Groat et al., 1981). Thus, postnatal maturation of voiding function is associated with a prominent reorganization of synaptic connections in bladder reflex pathways, leading to downregulation of primitive spinal mechanisms and upregulation of mature supraspinal mechanisms. It seems likely that this developmental switching mechanism is dependent upon competition between brain and spinal pathways because spinal cord injury in adult animals and humans, which interrupts brain–spinal cord connections, causes the re-emergence of the neonatal perineal-to-bladder reflex (de Groat, 2002; de Groat and Yoshimura, 2006). Spinal cord injury in humans also unmasks a bladder reflex elicited by instillation of cold water into the bladder (Geirsson et al., 1993; Fowler et al., 2008). This cold-evoked bladder reflex, which is activated by C-fiber afferents, is not present in normal adults but occurs in neonates and is then suppressed during postnatal maturation of the nervous system.

Influence of aging on lower urinary tract function

Lower urinary tract symptoms, such as increased voiding frequency, urgency, urge incontinence, and poor bladder emptying, are common and troublesome problems in older men and women (Resnick, 1995; Naughton and Wyman, 1997; Nuotio et al., 2002; Smith, 2010). Previous studies have reported various changes in lower urinary tract function, including a reduction in bladder capacity, increased bladder sensation, and detrusor overactivity (Diokno et al., 1986, 1988; Homma et al., 1994; Hald and Horn, 1998; Madersbacher et al., 1998, 1999; Nuotio et al., 2002). However, there are few studies that address the normal changes in the lower urinary tract that occur with aging. Pfisterer et al. (2006b) have examined age-related changes in bladder function among 85 community-dwelling female volunteers and demonstrated that detrusor contractility, bladder sensation, and intraurethral pressure decline with age and that a reduction in bladder capacity associated with age may be related to detrusor overactivity rather than to aging itself, because small bladder capacity associated with detrusor overactivity is similarly seen in younger and older women (Pfisterer et al., 2006a). Thus, aging appears to induce a reduction in bladder and urethral function in humans.

In animal studies, impaired bladder function, as evidenced by increased voided volume per micturition associated with a high micturition pressure threshold, has also been demonstrated in aged rats in comparison with young rats (Chun et al., 1988; Chai et al., 2000). In addition, aged rats exhibit reduced sensitivity of pelvic nerve afferents in response to increased bladder volume, but not pressure, and a reduction in the maximal bladder pressure generated during pelvic nerve stimulation (Hotta et al., 1995), although the frequency–response curve for electrically evoked contractions of bladder muscle strips was similar in young and old rat bladders (Yu et al., 1996). A significant linear reduction in the amount of acetylcholinesterase-positive nerves was observed with increasing age in the human bladder (Gilpin et al., 1986), suggesting a reduced parasympathetic innervation of the aged bladder. The expression of neuropeptides such as CGRP and substance P in lumbosacral DRG neurons decreases with age (Mohammed and Santer, 2002), and there is a marked reduction in the density of PACAP innervation of the subepithelial plexus and of the muscle layer of the bladder base in old rats (Mohammed et al., 2002). Aged mice up to 26 months old also exhibited an impaired ability to respond to the challenge of continuous bladder filling while voiding detrusor contraction strength did not degrade with aging (Smith et al., 2012). Taken together, these results suggest that impaired activity of the aged bladder is likely to be at least in part due to reduced function of efferent and afferent nerves innervating the bladder.

Changes in the central nervous system in relation to lower urinary tract function have also been demonstrated in aged animals. For example, immunohistochemical analyses in aged rats revealed significant age-associated declines in the serotonergic (5-HT) and adrenergic innervation of various spinal cord regions, including the intermediolateral cell nucleus, sacral parasympathetic nucleus, dorsal gray commissure, and in the area of the ventral horn that contains Onuf's nucleus, although 5-HT innervation of the sacral parasympathetic nucleus and tyrosine hydroxlase-like immunoreactivity in the ventral horn nucleus were maintained (Ranson et al., 2003). Sympathetic PGNs in the L1–2 spinal cord that project to the major pelvic ganglion also exhibit a number of age-related degenerative changes, such as reductions in the cell number, the length of their dendrites, and the synaptic contacts made by glutamate-immunoreactive boutons on to the dendrites, although these changes are not seen in parasympathetic PGNs in the L6–S1 spinal cord (Santer et al., 2002). Frequent voiding produced by apomorphine-induced dopamine receptor activation is more pronounced in aged rats compared with young rats, suggesting that aged rats are more

susceptible to altered central neurotransmitter mechanisms that induce bladder overactivity, even though baseline bladder function declines with aging (Chai et al., 2000).

In contrast to altered nerve activity in old animals, there appears to be no significant difference in detrusor contractile responses to cholinergic stimulation in these animals (Chun et al., 1989; Longhurst et al., 1992; Lieu et al., 1997; Lin et al., 1997; Schneider et al., 2005), even though old rats have a reduced density of muscarinic receptors in the bladder (Schneider et al., 2005). In contrast, there are some reports of age-related changes of the detrusor response to adrenergic stimulation (Latifpour et al., 1990). Some studies show that detrusor contractile responses to norepinephrine are increased in old male and female rats (Saito et al., 1991, 1993; Nishimoto et al., 1995). Aged female rats also exhibit increases in expression of α_{1D}-adrenoceptors and α_{1D}-receptor-mediated contractions of the bladder (Dmitrieva et al., 2008). However, another study showed no age-dependent changes in α_1-adrenoceptor properties such as phenylephrine-induced contractile responses, total receptor density, and mRNA expression of α_1-adrenoceptor subtypes (α_{1A}, α_{1B}, and α_{1D}) in the rat bladder base and dome (Yono et al., 2006). The detrusor response to β-adrenergic stimulation is reduced in old male rats (Nishimoto et al., 1995) along with a reduction in the density of β-adrenergic receptors and a decreased cAMP production (Nishimoto et al., 1995) in response to β-adrenergic stimulation. The combination of an increase in the α-adrenergic excitatory responses and decreased β-adrenergic inhibitory responses results in a net contracting effect of norepinephrine on the aged bladder in contrast to the relaxing effect of norepinephrine in the young bladder, although the contribution of these changes in adrenoceptor properties to age-related alterations in lower urinary tract function is still to be determined.

Computer model of micturition switching circuit

Computer model of the PMC and PAG switching circuitry that underlies the spinobulbospinal micturition reflex in a decerebrate animal

Based on neuronal firing patterns recorded in the PMC and PAG during rhythmic bladder contractions as well as antidromic responses to stimulation of the spinal cord and synaptic responses to stimulation of bladder afferent nerves, a neural circuit has been designed in an attempt to model the switching properties of the spinobulbospinal micturition reflex in a decerebrate animal (Fig. 5.22) (de Groat and Wickens, 2013). The circuit includes the peripheral afferent and efferent pathways between the bladder and the spinal cord plus connections between the spinal cord, PAG, and PMC.

The ascending sensory limb of the circuit consists of a mechanosensitive bladder primary afferent neuron that synapses with a second-order spinal tract neuron. The latter projects to excitatory neurons in the PAG that in turn relay information to the PMC. The PMC contains several types of neurons. Direct neurons (indicated by D in Fig. 5.22) that send information back to the sacral parasympathetic nucleus represent the descending limb of the spinobulbospinal micturition reflex (Fig. 5.22). These neurons (type 1 direct neurons) are silent during bladder filling but are activated prior to and during micturition. In the model the type 1 direct neurons receive tonic inhibitory input from independent neurons and bladder volume-dependent inhibition from inverse neurons, shown in Figure 5.17B. Inverse neurons (I) that are activated by afferent input from the PAG and fire during bladder filling make inhibitory connections with direct neurons to provide feed-forward inhibition of the micturition reflex during bladder filling. The inverse neurons are inhibited during micturition, which in turn removes inhibitory input to the direct neurons and facilitates the micturition reflex. Transient neurons (T) which are activated by bladder afferent stimulation via a relay (B) through the PAG and fire at the beginning of a bladder contraction are postulated to inhibit the inverse neurons and play an important role in the initiation of the micturition reflex. Type 2 direct neurons (indicated by R in Fig. 5.22) which exhibit continuous firing during bladder relaxation but are strongly activated at the onset of micturition are postulated to receive excitatory axon collaterals (pathway C) from type 1 direct neurons and mediate reciprocal inhibition of inverse neurons. This would further enhance the development of the micturition reflex by suppressing inhibitory input to the type 1 direct neurons.

In the PAG it is postulated that neurons tonically active during bladder filling or between micturition contractions represent relay neurons that transmit excitatory signals (pathway A) to inverse neurons in the PMC that in turn generate feed-forward inhibition of the micturition reflex. Conversely, excitatory neurons in the PAG that relay bladder afferent information to PMC direct neurons are likely to be "phasic micturition neurons," identified by Sakakibara et al. (2002a). It is known that a GABAergic inhibitory mechanism in the PAG tonically controls the bladder volume set point for initiating micturition (Stone et al., 2011). In the hypothetical circuit in Figure 5.22, this mechanism is represented by an independent inhibitory neuron synapsing with the PAG relay neuron. Similarly, GABAergic or enkephalinergic independent inhibitory neurons in the

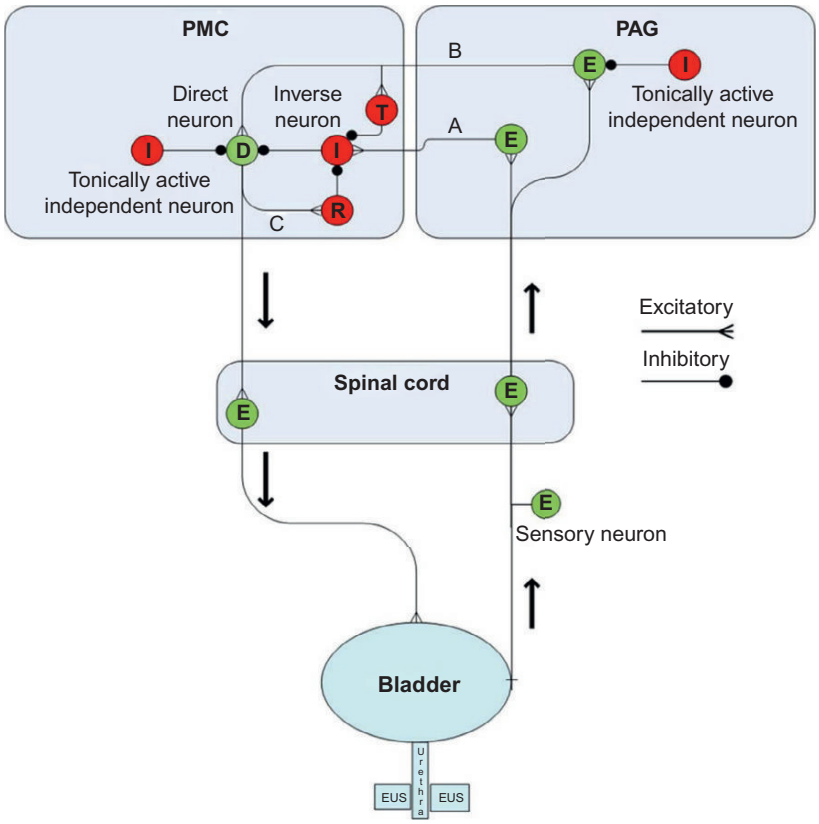

Fig. 5.22. Computer model of pontine micturition center (PMC)–periaqueductal gray (PAG) switching circuits. Diagram illustrating the putative pathways in the PAG and PMC that contribute to urine storage and voiding. This circuitry shows the neuronal elements and connections used in the computer model. The right side illustrates the ascending afferent limb of the spinobulbospinal micturition reflex that projects to the PAG, and the left side shows the descending limb that connects the PMC direct neuron to the bladder efferent neuron in the sacral spinal cord. During urine storage, as the bladder slowly fills, a low level of afferent activity activates an excitatory neuron (**E**) in the PAG which relays information (pathway **A**) to an inverse neuron (**I**) in the PMC that in turn provides inhibitory input to the type 1 direct neuron (**D**) to maintain continence. Bladder afferent input is also received by a second neuron in the PAG (**E**) that is on the excitatory pathway (pathway **B**) to the PMC type 1 direct neuron (**D**) and to a transiently active PMC neuron (**T**) that fires at the beginning of micturition. However, the PAG excitatory relay neuron (**E**) is not activated during the early stages of bladder filling because it is inhibited by a tonically active independent neuron (**I**). The PMC type 1 direct neuron is also inhibited by a tonically active independent neuron (**I**) located in the PMC. Bladder afferent firing gradually increases during bladder filling, which increases feed-forward inhibition of the direct neuron via the PAG–PMC inverse neuron pathway. However, at a critical level of afferent firing, excitatory input to the PAG excitatory relay neuron surpasses the tonic inhibition of the independent neuron and sends signals to the PMC transient neuron which briefly inhibits the inverse neuron, reducing inhibitory input to the direct neuron, allowing it to overcome tonic inhibition and fire action potentials which activate by an axon collateral (pathway **C**) a reciprocal inhibitory neuron (**R**) that suppresses the inverse neuron (**I**) and further reduces inhibition of the direct neuron (**D**). The direct neuron then switches into maximal firing mode and sends excitatory input to the spinal efferent pathway to the bladder, inducing a large bladder contraction and more afferent firing which further enhances synaptic transmission in the PAG–PMC micturition reflex pathways. The reflex circuitry returns to storage mode as the bladder empties and afferent firing declines. Excitatory neurons are green and inhibitory neurons are red. (Reproduced from de Groat and Wickens, 2013.)

PMC are likely to control the set point for micturition by tonically inhibiting the type 1 direct neurons.

In summary, GABAergic or enkephalinergic inhibitory control of the micturition switching circuit may occur at several sites on the spinobulbospinal pathway, including: (1) the ascending limb in the spinal cord; (2) relay centers in the PAG; (3) synapses on type 1 direct neurons in the PMC. However it is presumed that the switch from storage to voiding occurs at the level of the direct neurons because their firing is closely linked with PGN firing and reflex bladder contractions, indicating that transmission of descending signals through the sacral parasympathetic nucleus occurs with a high safety factor. Therefore excitatory synapses on the descending limb of the micturition reflex pathway in the spinal cord function as relays rather than switches

and transmit signals from the PMC switch to the bladder with high fidelity.

Computer model of the spinal urine storage and micturition circuitry

Spinal storage circuitry, which is not shown in Figure 5.22, is also part of the computer model (see de Groat and Wickens, 2013, for details). This circuitry includes the spinal vesicosympathetic and vesicosphincter reflex mechanisms (Fig. 5.13A), described in a previous section. For simplicity these reflex mechanism have been modeled (Fig. 5.13A) as monosynaptic reflexes, although it is probable that they are multisynaptic pathways. As indicated in Figure 5.13B, these two storage reflexes are inhibited by descending input from the type 1 direct neurons in the PMC, thereby promoting urethral outlet relaxation during micturition. The model includes a third storage mechanism in which sphincter afferents activate spinal inhibitory neurons that suppress bladder PGNs and interneurons on the ascending and descending micturition reflex pathway. The model also includes a recurrent inhibitory circuit in which preganglionic axon collaterals activate interneurons that in turn inhibit excitatory interneurons on the ascending and descending limbs of the micturition reflex pathway (de Groat and Ryall, 1968; de Groat, 1975). A urethral-bladder excitatory mechanism which facilitates micturition in response to flow of urine through the urethra (Barrington, 1925; Kuru, 1965) is also included in the model and not shown in Figure 5.22.

Computer simulation of the storage–voiding cycle using the PMC-PAG and spinal models

The model of the spinobulbospinal pathway consisting of the supraspinal components shown in Figure 5.22 and the spinal components which are not shown was used to simulate a reflex storage–voiding cycle and estimate various parameters, including bladder pressure, bladder volume, bladder afferent firing, and bladder efferent firing during filling of the bladder at a rate of 30 mL/min (Fig. 5.23). The model of the urinary tract used in this simulation has two interconnected components: a mechanical component that models the bladder and outlet, and an artificial neural network that models the neural reflex pathways controlling the lower urinary tract. This approach is similar to several other attempts to model the lower urinary tract (van Duin et al., 1998; Fry et al., 2011) but also includes putative supraspinal circuitry based on unit recordings in the PMC and PAG. The mechanical component was taken from the model produced by Bastiaanssen et al. (1996). The neural component was based on the electrophysiologic properties of individual neuronal groups in the PMC and PAG. The mathematical details for producing the neural

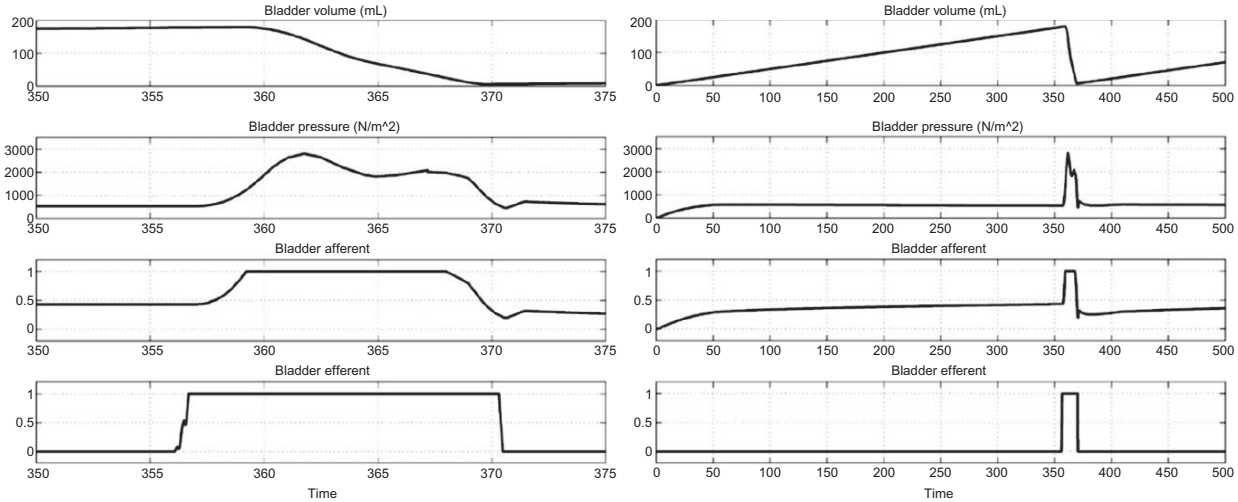

Fig. 5.23. Computer simulation of the storage–voiding cycle. Simulated bladder volume (top tracing) and pressure (second tracing), bladder afferent firing (third tracing) and bladder efferent firing (bottom tracing) during bladder filling (30 mL/min) and during reflex voiding using the computer model of spinal, periaqueductal gray and pontine micturition center neural pathways and the myocybernetic model of Bastiaanssen et al. (1996) to predict the properties of the bladder, urethra, and the afferent firing arising in these structures. Note that, as bladder volume increases, bladder pressure remains low, bladder efferent firing is absent, but bladder afferent firing gradually increases, eventually reaching a threshold for inducing a micturition reflex, as evidenced by an abrupt increase in efferent firing, which induces an increase in bladder pressure, increased afferent firing, and bladder emptying. Bladder efferent firing peaks early during micturition and is maintained until the bladder is empty. The voiding phase is shown on an expanded timescale in the tracings on the right side. (Reproduced from de Groat and Wickens, 2013.)

component are included in a recent paper (de Groat and Wickens, 2013).

Based on the Bastiaanssen et al. (1996) model, during bladder filling bladder pressure remains low but bladder afferent firing slowly increases as bladder wall tension increases (Fig. 5.16). Bladder efferent firing, which represents activity in the spinobulbospinal micturition reflex pathway, remains low during the filling because the PAG-PMC switching circuit is in the off mode. At a critical bladder volume threshold the PAG-PMC switch is turned on and efferent firing markedly increases, inducing a prominent increase in bladder pressure followed by an increase in bladder afferent firing, a relaxation of the urethral outlet (not shown) and then voiding evident as a decrease in bladder volume. The model generates an all-or-none reflex response, reflected as maximal efferent discharge throughout voiding, even as bladder volume decreases. The model generates efficient voiding, resulting in complete bladder emptying. Reducing the strength of the inhibitory input from the PMC tonically active independent neuron to the direct neuron reduces bladder capacity, while increasing the strength of the inhibition increases bladder capacity.

NEUROTRANSMITTERS IN CENTRAL PATHWAYS CONTROLLING MICTURITION

Excitatory neurotransmitters

Excitatory transmission in central pathways controlling the lower urinary tract depends on several types of neurotransmitter, including glutamate, neuropeptides, NO, and ATP (de Groat and Yoshimura, 2001; Miura et al., 2001; Seki et al., 2005; Yoshiyama and de Groat, 2008). Pharmacologic experiments in rats have revealed that glutamate is an essential transmitter in the ascending, pontine, and descending limbs of the spinobulbospinal micturition reflex pathway and in spinal reflex pathways controlling the bladder and EUS (Yoshiyama and de Groat, 2005; Chang et al., 2006). Glutamatergic synaptic mechanisms involving both *N*-methyl-D-aspartate (NMDA) and non-NMDA receptors appear to interact synergistically to mediate transmission in these pathways.

Inhibitory neurotransmitters

Several types of inhibitory transmitter, including inhibitory amino acids (GABA, glycine) and opioid peptides (enkephalins), can suppress the micturition reflex when applied in the central nervous system. Experimental evidence in anesthetized animals indicates that GABA and enkephalins exert a tonic inhibitory control in the PMC and regulate bladder capacity (Mallory et al., 1991; de Groat et al., 1993; Morrison et al., 2005). These substances also have inhibitory actions in the spinal cord. Glycine or GABA has been implicated in: (1) recurrent inhibition in the sacral parasympathetic pathway to the bladder of the cat; (2) inhibition of reflex bladder activity by stimulation of the distal bowel in the rat; (3) inhibition of motor neurons innervating the EUS during micturition; and (4) inhibition of bladder activity induced by electric stimulation of the RPRF (de Groat, 1976; de Groat and Yoshimura, 2001; Shefchyk, 2001; Sugaya et al., 2005).

Transmitters with mixed excitatory and inhibitory actions

Some transmitters, including dopamine, 5-HT, norepinephrine, acetylcholine, and non-opioid peptides such as vasoactive intestinal polypeptide and corticotropin-releasing factor, have both inhibitory and excitatory effects on reflex bladder activity (de Groat et al., 1993; Pavcovich and Valentino, 1995; Andersson and Pehrson, 2003; Lee et al., 2003; Nakamura et al., 2003; Yoshiyama et al., 2003; Klausner et al., 2005; Tai et al., 2006). In some instances, different effects are mediated by different types of receptor. For example, the inhibitory effects of dopamine are mediated by D_1-like (D_1 and D_5) receptor subtypes; and the facilitatory effects, by D_2-like (D_2, D_3 and D_4) subtypes. Loss of forebrain dopaminergic inhibitory mechanisms after middle cerebral artery occlusion in rats (Yokoyama et al., 2002) or in patients with idiopathic Parkinson's disease is associated with bladder hyperactivity (de Groat and Yoshimura, 2001).

Interest in the role of 5-HT in the central control of micturition has increased following the introduction of duloxetine, a 5-HT–norepinephrine reuptake inhibitor, for the treatment of stress urinary incontinence (Thor, 2003). 5-HT has complex effects on the lower urinary tract that vary in different species (de Groat, 2002). In the cat, activation of central 5-HT_{1A} receptors inhibits reflex bladder activity, whereas activation of 5-HT_2 receptors enhances activity of the urethral sphincter (Thor, 2003). On the other hand, activation of central 5-HT_{1A} receptors in the rat enhances bladder and sphincter reflexes (Chang et al., 2006, 2007). The similarities in the effects of duloxetine in cat and human indicate that micturition in the cat may be a useful model for developing centrally acting serotonergic agents for the treatment of lower urinary tract dysfunction.

CONCLUSIONS

The functions of the lower urinary tract to store and periodically eliminate urine are regulated by a complex neural control system that performs like a simple switching circuit to maintain a reciprocal relationship between the bladder and urethral outlet. The switching circuit is modulated

by several neurotransmitter systems and is therefore sensitive to a variety of drugs and neurologic diseases. Further research is needed, particularly in humans using brain imaging techniques, to identify the pathways in the forebrain that exert voluntary control over primitive micturition reflex circuitry in the brainstem and spinal cord. More information is required about the neuroplasticity underlying the postnatal development of bladder control in children, the loss of that control in adults after neural injury, and the partial recovery of bladder function after spinal cord injury. It is also important to define the contribution of neurotrophic factors released in the bladder or in the central nervous system to neuroplasticity. Detailed studies of peripheral afferent pathways, including the role of the urothelial cells in bladder sensory transduction mechanisms, are necessary to explore the pathophysiology of urinary urgency sensations and urgency incontinence. A more complete understanding of the peripheral and central neural mechanisms involved in bladder and urethral control will no doubt facilitate the development of new diagnostic methods and therapies for lower urinary tract dysfunction.

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 6

Human sexual behavior related to pathology and activity of the brain

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INTRODUCTION

Most of our knowledge of how the brain controls sexual behavior is still based upon the effects of various brain lesions. In this chapter, we describe several types of brain damage, resulting from traumatic head injury and non-traumatic lesions, e.g., ischemic stroke, from surgery, and their effects on sexual behavior, and also sexual phenomena occurring due to epilepsy. The clinical aspects of sexual dysfunction in stroke, multiple sclerosis (MS), and epilepsy is more extensively discussed in Chapters 16, 20, and 22.

More recently, imaging of regional brain activity in response to sexual stimulation, arousal, and orgasm has provided a new and different perspective on human sexual response. The evidence generated by studies of these differing brain phenomena in relation to sexual behavior is reviewed herein toward a better understanding of how our brain generates this salient perceptual and behavioral phenomenon.

BRAIN ACTIVITY AND BEHAVIOUR

There is a fundamental problem with attempting to attribute a specific function to a specific brain region. Does damage to a specific brain region interfere with the actual performance of a function or with the motivation to perform the function? For example, in traumatic brain injury (TBI)-related erectile dysfunction, does the brain damage interfere with the actual autonomic control of erection, or does it create a depressed mood and body image that interferes with erection without directly affecting the autonomic control?

Similarly, when a deficit is observed in recorded or imaged brain activity related to a behavioral deficit, is the activity deficit the controlling mechanism (i.e., "cause") of the behavioral deficit, or is the activity deficit a response to a disrupted input to that brain region (i.e., "effect")? With a growing appreciation and sophistication regarding this fundamental interpretational complexity, concepts of brain function have evolved beyond control "centers" or functional magnetic resonance imaging (fMRI) "blobs" toward a concept of connections among neural systems, i.e., their "functional connectivity" (Hillary et al., 2015).

The basic principle of the functional connectivity approach is: using fMRI, multiple regions of interest (ROIs) are selected, and the "profile" of the fluctuations in the activity of the multiple ROIs over time are correlated with each other. The closer the congruence of particular different temporal profiles, the greater is the "functional connectivity" between or among those particular ROIs. This analysis can be performed during a "resting state" when the person is not performing any task, and just "resting." As pointed out by Hacker et al. (2012), the "resting state" functional connectivity analysis is valuable in making it possible to assess abnormalities in the relation among brain systems in the absence of motor activity, thus avoiding the problem of ascertaining whether a particular brain region is producing or responding to the movement. Studies demonstrate that there are many major brain regions that, despite having no direct neuroanatomic connections, nevertheless vary their activity profiles in time with each other, e.g., the amygdala and hippocampus (Roy et al., 2009), and hence are "functionally connected." In this

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case, an implication is that there is a source external to both the amygdala and the hippocampus that drives them both in parallel.

Studies of brain activity in TBI, Parkinson's disease (PD), and MS have shown significant differences in functional connectivity between these pathologies and healthy controls. The functional connectivity approach is a modernized form of the previous "cross-correlation" analysis methodology that was applied to electroencephalogram (EEG) data, with the advantage of much more precise structural localization now using fMRI. It is noteworthy that a basic underlying concept of brain function developed using EEG – i.e., the neurophysiologic mechanism underlying synchronization versus desynchronization of the EEG waveform – informs the interpretation of functional connectivity analysis in a way that has not yet been fully appreciated and utilized.

The modern blood oxygen level-dependent (BOLD) fMRI functional connectivity methodology is implicitly based on the same underlying concept as previously used in EEG synchronization/desynchronization studies, but with an important new element, as follows.

Multiple recent fMRI functional connectivity studies of TBI, PD and MS provide evidence of abnormally high functional connectivity among certain brain systems, e.g., between striatum and cortex. This can be interpreted as a loss of the healthy and necessary temporal differentiation of activity, i.e., independent functioning, between these systems. In EEG parlance, this condition is a greater synchrony in their activity cycles, leading to a more "seizure-like" pattern. The important new element is that, in TBI, PD, and MS brain compared to healthy brain, in addition to increased synchrony, even termed "hyperconnectivity" (Hillary et al., 2015), among certain brain regions, there is also lower functional connectivity between certain other brain regions, e.g., between lower brainstem and striatum. In the case of PD, there is both increased functional connectivity between striatum and specific parts of the cerebral cortex, and decreased functional connectivity with the "extended" brainstem, i.e., cerebellum, pons, midbrain, and thalamus (Hacker et al., 2012). A likely reconciliation of these two apparently diametrically opposite types of findings is that certain brain systems depend on direct, tightly linked (synchronized) connection for their proper function (e.g., dopamine release into the striatum), whereas other brain systems (e.g., cortical connection to striatum) require flexibly linked (desynchronized) connection for their proper function.

These seemingly discrepant findings using functional connectivity, in which behavioral pathology can be associated with both higher and lower functional connectivity depending on which neural systems, reveal a new level of brain function that can be appreciated because of the ability of fMRI to identify regional brain activity throughout the entire brain, which was beyond the resolving power of EEG.

A preliminary generalization that emerges is that, if input from one neural system to another is necessary for the receiving system to function, a decrease in functional connectivity between them interferes with the proper functioning of the receiving system. By contrast, if two systems depend on their proper functioning by a flexible reciprocity, then an increase in the measure of their "functional connectivity" implies a decrease in the flexibility of their interaction, leading to a more rigid, less differentiated, more pathologic, process.

LOCALISED BRAIN LESIONS AND SEXUALITY

Various focal brain lesions of different etiologies have been recognized by clinicians to cause changes in sexual function and behavior. The accumulation of this knowledge sheds some light on the brain control of sexuality which is slowly upgraded by functional imaging studies. The following paragraphs recount what can be deduced regarding brain control of sexuality from focal brain lesions resulting from stroke, MS, TBI, and surgery.

Localized brain lesions due to disease and sexual symptoms

In unilateral stroke patients (26 men) Coslett and Heilman (1986) found that the prevalence of major sexual dysfunction was greater after right-hemisphere (9/12) than left-hemisphere (4/14) lesions. Stroke-related lesions in the right cerebellum were associated with ejaculation disorder, whereas lesions in the left basal ganglia were associated with decreases in sexual desire (Jung et al., 2008). By contrast, "hypersexuality" was reported in cases of temporal-lobe lesions resulting from stroke (Monga et al., 1986). A caveat in interpreting "hyper" behavior resulting from brain pathology is that disinhibition of behavior is a commonly reported correlate. Hence, it is important to differentiate a general disinhibition of behavior, of which the "hyper" pattern is just one component, from a "hyper" pattern that is unique. This issue of whether the behavioral disinhibition is generalized or unique and specific is a recurring problem in the clinical cases reviewed herein. For example, according to Miller et al. (1986):

> *hypersexual behavior following brain injury is uncommon but when seen is often associated with basal frontal or diencephalic lesions. . . patients manifested disinhibited public expression of their increased drive. This sexual disinhibition was often associated with a general disinhibition of behaviour.*

In the case of a hemorrhagic stroke in a 39-year-old male involving the basal frontal areas bilaterally, with involvement of the septal region, they reported that the patient publicly masturbated and attempted to have intercourse with his wife and with female nurses in front of his three roommates, and shortly thereafter became comatose and died.

Thalamic lesions resulting from cerebrovascular accidents were associated with erectile dysfunction to a greater extent than lesions of frontal lobe, other cortical regions, or basal ganglia (Jeon et al., 2009). Erectile dysfunction of psychogenic origin was correlated with atrophy of gray matter (measured by MRI) in left nucleus accumbens and left hypothalamus (Cera et al., 2012). Hemorrhagic lesion of the nucleus accumbens in a 55-year-old male led to a loss of libido, amnesia, and a "flattening of emotional reactions. . .He said: 'There is nothing which makes me really happy or really sad. It's all far away'" (Goldenberg et al., 1999). As is always the problem with single case studies, caution must be exercised in generalization; for example, in patients with atrophy in the regions mentioned, what proportion have erectile dysfunction? Nevertheless, it is tempting to speculate that these two reported cases involving the nucleus accumbens are consistent with evidence of a "hedonic" role for the nucleus accumbens and its activation at orgasm (Komisaruk et al., 2004; for review, see Komisaruk et al., 2009). See Chapter 16 for a general discussion on stroke and sexuality.

Sexual dysfunction in MS is common (Chapter 20) and is commonly assumed to be primarily a consequence of spinal involvement. However, there are case reports of "hyperlibidinism" in cases of MS in which frontal (Gondim and Thomas, 2001) and temporal and frontal (Huws et al., 1991) lesions were found. In another case report, septal and hypothalamic inflammatory demyelination in a male was associated with a sexual paraphilia related to women's breasts; the lesions also extended to the right sides of the internal capsule, substantia nigra, and red nucleus (Frohman et al., 2002). Other case studies in which septal damage was correlated with sexually disinhibited behavior are described below.

Seizures and sexual symptoms

According to Cummings (1997), ictal events that have sexual manifestations (e.g., sexual auras, ictal orgasm, and sexual automatisms) have been associated more with right-sided temporal-lobe foci than left-sided seizures, whereas ictal sexual automatisms are associated more with frontal (motor) seizures. Blumer (1970) described 29 of 50 patients, male and female, with temporal-lobe epilepsy who were characterized by a global hyposexuality: "Most outstanding was their inability to experience orgasm." Twenty of the 29 had experienced orgasm less than once per year; 10 had experienced orgasm once or never. Consistent with the Klüver–Bucy syndrome, after these patients received temporal lobectomy, their seizures ceased, and they became chronically hypersexual. In two patients, seizures recurred, at which time their hypersexuality ceased. These patients underwent removal of the anterior portion of the temporal lobe on one side that was generating the seizure (i.e., unilateral removal of the epileptogenic temporal lobe, removing the limbic structures of the medial portion of the gyrus – presumably hippocampus and amygdala). One male patient underwent temporal lobectomy, but about 1 year later, the seizures recurred. At that time, about 20 minutes after the attacks,

> *he would seek sexual relations with his wife. . . His wife had started to look forward to this happening. Normally he would not seek sexual relations more than once a week. However, if a seizure occurred following sexual relations – even only one hour later – he would desire sexual relations again (Blumer, 1970).*

Another patient rejected surgical intervention for his seizures:

> *At that time his wife told the neurosurgeon that he was regularly demanding intercourse immediately after his attacks. At times when he was having several attacks a day, his impatient demands were difficult for his wife, but she always acquiesced. By contrast, in the absence of seizures several weeks might pass without his experiencing sexual arousal (Blumer, 1970).*

By contrast, one of the patients "experienced the feeling of sexual climax with each of his seizures" (Blumer, 1970).

A "focal paraneoplastic limbic encephalitis presenting as orgasmic epilepsy" was described by Fadul et al. (2005). It was the case of a 57-year-old woman with a 2-month history of daily spells that consisted of a sudden pleasure-provoking feeling that was described as "like an orgasm" (Fadul et al., 2005), lasting for 30 seconds to 1 minute. MRI revealed a tumor in the left anterior medial temporal lobe of the forebrain, that the authors claimed was probably due to metastasis from lung cancer that was diagnosed when she presented for medical care. The EEG showed a focal left midtemporal abnormality. After carbamazepine to control the seizures and tumor medication, the tumor regressed, and the seizures subsided.

There are many other cases reported of sexual feelings and orgasm occurring during, as well as before or after, temporal-lobe seizures and seizures of other brain regions. Thus, there are numerous reports of men and women who describe orgasmic feelings just prior to the onset of an epileptic seizure. This experience has been termed "orgasmic aura" (Calleja et al., 1988; Reading and Will, 1997; Janszky et al., 2002, 2004). The most common brain region from which these orgasmic auras originate is the right temporal lobe of the forebrain, which contains the hippocampus and the amygdala. The site of origin of the epileptic activity is ascertained electroencephalographically. The aura may have a spontaneous onset or may be triggered by some specific stimulus, for example, orgasmic aura triggered in a woman when she brushes her teeth (Chuang et al., 2004). While seizure-related orgasms may be described as "unwelcome" (e.g., Reading and Will, 1997), in other cases they have been described as pleasurable. One woman was reported to have refused antiepileptic medication or brain surgery because she enjoyed her orgasmic auras and did not want to have them eliminated (Janszky et al., 2004).

It is important to note that these orgasmic auras are not necessarily experienced as involving genital sensation: They are perceived as non-genital orgasms. There are other reports of epileptic seizures that originate in the genital projection zone of the sensory cortex. In those cases the individuals report that they experience genital sensation that develops into an orgasm, and the orgasm feels as if it were indeed generated by genital stimulation (e.g., Calleja et al., 1988).

The genital sensory "homuncular map" region of Penfield and Rasmussen (1950) is the paracentral lobule. Their map is based on their studies using direct cortical electric stimulation and asking awake patients to state where on the body they perceived that the stimulation originated. The paracentral lobule also responds to actual genital stimulation in women and men as recorded using fMRI (Komisaruk et al., 2011b, 2013). Seizures originating in the paracentral lobule, perisylvian (temporal) region, or anterior cingulate region produced genital sensations in men and women and orgasm in a woman (Stoffels et al., 1980). These authors reported that the patients often then applied genital self-stimulation in the postictal phase.

Thus, the temporal lobe, paracentral lobule, and other brain regions are clearly involved in sexual feelings-related epileptic seizures; what is less clearly understood is how the seizures themselves, the period before or after the seizures, or temporal lobectomy, which eliminates the seizures, can each induce sexual feelings and/or orgasms. Perhaps the apparent discrepancy could be resolved by more precise characterization of the qualities of the sexual feelings before, during, and after seizure activity and before and after temporal lobectomy to alleviate the seizures.

Sexual dysfunction related to traumatic brain injury

Cognitive impairment, personality change, and sensorimotor disability (each from minimal to extensive, in various combinations) often remain after TBI and may be accompanied by sexual dysfunction as a consequence of either the cerebral lesion or psychosocial factors. Among patients with closed-head injury admitted for 24 hours or more, significant sexual dysfunction was found in 50% over a 15-year time span (O'Carroll et al., 1991). Decreased or increased sexual desire, erectile failure, and retarded ejaculation may occur, at least in part as a consequence of posttraumatic pituitary dysfunction (Agha et al., 2004), but hormonal therapy was not reported in that study, leaving the possible role of the pituitary dysfunction unresolved. Frontal and temporal lesions seem to result more often in sexual disturbances than parieto-occipital lesions. A major difficulty in relating the effects on sexual behavior to the neurologic effects of TBI has been summarized concisely by Aloni and Katz (1999):

> *The causes and effects of sexual functioning after TBI are very confusing and the literature does not clarify this confusion. One cannot accurately differentiate between primary and secondary sexual problems and, therefore, cannot evaluate the contribution of each problem to the presented sexual dysfunction ... One cannot assume that, even when injury to a critical area is proven, the sexual dysfunction is definitely a result of that injury.*

The effects of the lesion may be direct, on the physiologic control (e.g., penile erection), or indirect, e.g., emotional reactions to one's self-esteem, body image, or sexual identity (Aloni and Katz, 1999).

TBI produces variable effects on sexual behavior, including decreased or increased libido, loss of genital sensation, reduced lubrication, erectile and ejaculatory dysfunction, anorgasmia, and socially and sexually uninhibited, inappropriate behavior, including unwelcome advances and exhibitionism, contrasting with the individual's pre-trauma behavior (Rees et al., 2007). These cases of sexual disinhibition have been attributed predominantly to damage to frontal or temporal cortical regions.

Simpson et al. (1999) emphasize that, in persons with brain damage, a distinction should be made between "hypersexuality" and "disinhibition,"; disinhibition may lead to "sexually aberrant behavior." The authors

suggest that hypersexuality is associated with bilateral temporal-lobe lesions, whereas sexual disinhibition is associated with injury of the frontal lobes. Their distinction, which contains gray zones, is based on the idea that the temporal lobes normally directly inhibit performance of sexual behavior *per se*, whereas the frontal lobes normally inhibit learned socially inappropriate behavior in general. They point out, however, that "little is known about the mechanisms of hypersexuality and disinhibition as causal agents of sexually aberrant behavior."

Malloy and Richardson (1994) came to the conclusion that, "Given the paucity of material, a relationship between focal neurologic dysfunction and erotomania remains to be demonstrated."

Aloni and Katz (1999) suggest that:

> *Many times "hypersexuality" is not an indication of greater sexual needs, but rather a general loss of control in sexuality as in other areas of life . . . It usually consists of hedonistic behaviour with no awareness of the needs of the other person, leading to anger, withdrawal, and feelings of dislike.*

TBI and sexual dysfunction in men

After TBI, in a study by Katz and Aloni (1999) of 67 men based on reports in the literature that did not specify the causes or anatomic correlates of the injuries, during the "desire stage" of sexual response, 28 reported reduced libido, 13 reported increased libido, and 14 reported "hypersexuality with loss of control." During the "arousal stage," of 29 men, 20 reported "impotence" and another five reported "loss of sensation." During the "orgasm and ejaculation stage," among nine men, one reported anorgasmia.

Fonteille et al. (2012) reviewed the literature on the association between brain lesions and pedophilia, concluding that in most cases of pedophilia associated with brain lesions, the lesions were located in frontal or temporal cortex. Mendez and Shapira (2011) differentiated aspects of pedophilia in relation to specific brain lesions, i.e., "a predisposition of sexual attraction for children through disinhibition with frontal disease, sexual preoccupation with right temporal disease, or hypersexuality with subcortical disease in non-motor basal ganglia, hypothalamus, or septal nuclei." From this information it is not possible to discern the degree to which these lesions exert a "primary" effect on pedophilic behavior or release a pre-existing predilection for the behavior. Thus, as Poeppl et al. (2011) point out, while the cingulate and insular cortices are activated in pedophiles by viewing prepubescents, the same brain regions are activated in non-pedophile adult males viewing erotica. Thus, it may be less likely that these cortical regions "cause" pedophilia than that they respond to the preference, which has a different source.

TBI and sexual dysfunction in women

Bell and Pepping (2001) point out an important difference between women and men in the effects of TBI on sexual behavior that is related to significant cultural expectations and demands. Specifically, "woman's roles as wife, mother, and daughter are likely to result in a different constellation of family dynamics when TBI is introduced." And this problem is exacerbated by the fact that "much of the literature on family needs after TBI focuses exclusively on female spouses of men with TBI." These authors describe a set of "disinhibition" symptoms resulting from a severe frontotemporal TBI in a "composite" woman's case, which include "childlike" behavior, giddiness, impulsivity, flirtatiousness, animosity toward female staff, argumentation, minimization of response to feedback, and a tendency to deny, rationalize, and minimize problems. More specifically, they emphasize unique problems caused by TBI in women, which include pain and endocrine issues, reproduction, and sexual functioning. Thus,

> *mesial temporal lobe foci of seizures were associated with hypogonadotropic hypogonadism, resulting in infertility, amenorrhea, oligomenorrhea, and dysfunctional uterine bleeding, . . . and alterations in secondary sexual characteristics such as hirsutism, worsening of acne, voice change, and obesity.*

They suggest that damage to the neural control of the pituitary, resulting in a decrease in estradiol production, could be the basis of at least some of these effects. Older women with TBI, in particular, described more difficulties with thyroid conditions, sleep disturbances, loss of urinary control, and arthritic changes (Bell and Pepping, 2001).

Changes in sexual behavior after frontal lobotomy

Damage to the frontal lobes can lead to increases in sexual behavior, indicating a normal inhibitory role for this part of the brain, which is disinhibited by the various forms of damage. That pattern is consistent with reports of the effects of frontal lobotomy, i.e., psychosurgery, that was performed in the 1930s and 1940s, primarily for the treatment of schizophrenia and psychosis, prior to the advent and application of psychoactive drugs. In an extensive review of the function of the frontal lobes published in 1953, Ervin characterized the

personality changes following frontal lobotomy in people with psychosis as including "slight impairment in ability to generalize, a tendency to perseverate, euphoria, apathy, procrastination, facetiousness, temper outbursts and distractability, impaired judgment, lack of planning for the future, and loss of creative imagination" (Ervin, 1953).

McKenzie and Proctor (1946) noted increased sexuality in some 25% of their frontal-lobotomized patients. While Freeman and Watts (1950) commented that "sexual behavior in the majority of cases does not seem to undergo any great alteration following prefrontal lobotomy," they did make the following observation:

> *In summing up our observations on the relation of prefrontal lobotomy to sexual activity... it would seem that the postoperative inertia manifested by some patients reduces the tendency of the individual to seek sexual gratification. On the other hand, the suppression of the restraining forces may lead to a freer expression of the personality along sexual lines.*

Thus, the conclusion by Freeman and Watts implies that, rather than there being a specific sexual behavior function that is intrinsic to the frontal lobes, the lobotomy produces a general social disinhibition, one expression of which may be manifested in (hyper)sexual behavior, with its concomitant stresses on social interaction.

The "higher functions" of the brain, such as the learning of socially acceptable, rather than aberrant, behavior is a complex, longest-in-latency-to-develop process involving finely tuned inhibitions. When the frontal regions are disconnected from the rest of the brain, that complexity is lost and, with it, the complex, intricate social inhibitions and graces. Prominently disinhibited is sexual behavior, along with other complex sociocultural behavior patterns. Perhaps there are parallels in normal development. These finely tuned sociocultural patterns are the last to emerge in the developing child, and the first to be lost in senile dementia, as in "last hired, first fired." Thus, they are the most highly differentiated and complex, and the most vulnerable, brain functions.

Temporal-lobe ablation for control of epilepsy and sexual sequelae

Terzian and Dalle Ore (1955) reported their case of a 19-year-old male who had received bilateral surgical removal of the anterior portion of the temporal lobes, the amygdala, and the anterior portion of the hippocampus for control of medication-resistant temporal-lobe epilepsy. After the surgery

> *he displayed to the doctor, with satisfaction, that he had spontaneous erections followed by masturbation and orgasm ... became exhibitionistic ... wanted to show his sexual organ erect to all doctors ... showed indifference [to women] in contrast with his behavior before the operation ... Homosexual tendencies ... were soon noticed ... practices self-abuse several times a day ... picked up objects ... the same object again and again ... and ate at least as much as four normal persons.*

The authors recognized the similarities of these behavior patterns to a behavioral syndrome initially demonstrated in rhesus monkeys, which subsequently was named after the discoverers – the Klüver–Bucy syndrome.

The Klüver–Bucy syndrome

In their study that became eponymous, Klüver and Bucy performed bilateral surgical removal of the temporal lobes, including the amygdala, in rhesus monkeys (Bucy and Kluver, 1955). They characterized the effects of this surgery as follows:

> *(1) forms of behavior indicative of an agnosia [i.e., inability to recognize or comprehend] in various sense fields [they also referred to this as* Seelenblindheit *("psychic blindness") – e.g., a lesioned monkey handling a snake, of which it is normally fearful)], (2) strong oral tendencies [i.e., mouthing objects as if trying to identify them or play with them using the mouth], (3) an excessive tendency to attend and react to every visual stimulus [termed "hyper-metamorphosis"], (4) profound changes in emotional behavior [e.g., placidity], (5) striking changes in sexual behavior, particularly in the form of hypersexed behavior [i.e., attempts at mating with animals of other species and inanimate objects and frequent masturbation], and (6) changes in dietary habits (e.g., eating of meat).*

In humans, the Klüver–Bucy syndrome was observed in the case of posttraumatic bitemporal-lobe lesions (Goscinski et al., 1997). The researchers' patients showed at least three of the following: hypersexuality, hypermetamorphosis, memory disorder, placidity, loss of people recognition, bulimia. The authors claimed symptomatic response to carbamazepine, which augments gamma-aminobutyric acid receptor activity. These authors' observation of "loss of people recognition" is consistent with the claim by Rasia-filho et al. (2000) that bilateral

amygdala damage can compromise the recognition of fear in facial expressions.

Jha and Patel (2004) review a wide variety of human brain pathologies that result in a Klüver–Bucy syndrome, which they characterize as psychic blindness (inability to recognize familiar objects), hypermetamorphosis, increased oral exploration, placidity, indiscriminate hypersexuality, change in dietary habits, aphasia, amnesia, dementia, and seizures. The pathologies include TBI, Alzheimer's disease, Huntington's disease, herpes simplex encephalitis, toxoplasmosis, hypoglycemia, acute intermittent porphyria, tuberculous meningitis, heat stroke, shigellosis, neurocysticercosis, anoxia, and ischemic encephalopathy. Some authors suggest a brain laterality difference in the effects of these lesions.

Thus, in a review of clinical literature, Braun et al. (2003) concluded that hypersexual behavior was associated with right-temporal-lobe lesions, whereas hyposexual behavior was associated with left-temporal-lobe lesions. Changes in social behavior, inconsistent with the patients' behavior prior to the surgery, were reported, including exhibitionism, hetero- and homosexual advances to strangers, public masturbation, and pedophilia. The "hypersexuality" reported after surgical removal of portions of the temporal lobe containing hippocampus and amygdala may be a combination of loss of discrimination of appropriate sexual objects, loss of social inhibitions, and increased sexual desire.

In addition to frontotemporal cortex lesions the Klüver–Bucy syndrome was reported as a consequence of involvement of the anteroventral thalamus in a case study using positron emission tomography, showing bilateral damage by ischemic lesions (Muller et al., 1999).

Hypersexuality and socially inappropriate sexual behavior after other brain lesions

There are also several reports of hypersexuality in humans after surgery that damaged the septal region. These cases involved an increase in sex-related activities rather than an increase in orgasmic activity. Gorman and Cummings (1992) reported the case of a 75-year-old man living in a nursing home who developed hydrocephalus and had a shunt placed in his brain to drain the fluid. After this surgery, there were many reports of the patient approaching and fondling female patients, crawling into bed with other patients with sexual intent, and using sexually explicit language, requiring restraint – a marked change in character. The authors performed a computed tomography (CT) scan and found that the tip of the shunt was lodged in the septum. Similarly, Miller et al. (1986) stated that:

> *hypersexual behavior following brain injury is uncommon but when seen is often associated with basal frontal or diencephalic lesions [that encroach on the septum] . . . patients manifested disinhibited public expression of their increased drive. This sexual disinhibition was often associated with a general disinhibition of behaviour.*

Miller et al. (1986) described a 59-year-old man who underwent surgical removal of a subfrontal meningioma revealed by a CT scan. They reported that:

> *after surgery his desire for sexual activity increased from once per week to 1–4 times per day. Intercourse frequently lasted longer than 1 hour and he had some difficulty achieving orgasm . . . Two years after surgery he became increasingly preoccupied with sex and developed a manic syndrome. He was admitted to hospital where he publicly masturbated and sexually propositioned both male and female patients and staff (he had a past history of previous homosexual contacts).*

The same authors described the case of a 34-year-old man with a glioma involving the thalamus, hypothalamus, ventral midbrain, and pons (Miller et al., 1986). The man began to make sexual proposals to his 7-year-old daughter and her friends, made increasingly more public sexual advances toward young children, and frequently embarrassed his wife by showing pornographic pictures to visitors at their home. He was arrested for propositioning children in his neighborhood.

Similar changes in behavior were observed after surgical damage to the septal region, basal forebrain, and upper or lower brainstem regions.

Psychosurgery in treatment of socially inappropriate sexual behavior

Psychosurgical brain lesions were used in the 1970s in Germany in an attempt to control pedophilia and "sexual delinquents" through the use of surgical unilateral removal of the ventromedial or medial anterior hypothalamus. As described by the authors,

> *following a stereotactic ventromedial hypothalamotomy not only are the dynamic aspects of sexuality, such as compulsion and impulsivity, diminished, but also organic components, which have to do with completion of the sex act. In contrast, the structure of the patient's sexual organization remains unchanged: A pedophilic character, for example, is still retained. However,*

it is possible for the subject to adapt his sexual behavior to the specific conceptions and expectations of our society (Dieckmann et al., 1988).

FUNCTIONAL IMAGING STUDIES

Brain activity related to sexual arousal and orgasm

The neural pathways to and from the brain involved in sexual response have been reviewed recently (Komisaruk and DelCerro, 2014). With the advent of functional regional brain imaging technology utilizing fMRI, positron emission tomography, and functional near-infrared spectroscopy, recent studies have correlated activity in discrete brain regions in men and women with sexual arousal induced by visual stimulation, and orgasm and ejaculation induced by self- or partner-induced stimulation. While there is general agreement among studies as to activity in specific brain regions under similar circumstances, there does not yet seem to be a clear, consistent picture that relates the findings in brain imaging studies with the effects of brain pathologies on sexual behavior. Of course, there is a fundamental difference in the phenomena observed in brain pathology studies (e.g., behavioral effects of lesions, surgery, or seizures) versus functional brain imaging studies (e.g., correlates with reported "sexual arousal," orgasm, or ejaculation). That is, the brain pathology studies measure mainly overt behavior, whereas the brain imaging studies measure mainly perception. While erection, ejaculation, and orgasm are overt responses in both types of studies, at the present state of knowledge, there are at best scant direct links between specific behavioral effects of regional brain pathologies and overt correlates of specific regional brain activities. Furthermore, there is increasing evidence of important differences between the role of the left versus the right brain regions in sexual and other behavior in the effects of lesions and brain imaging, and laterality is often not specified in the literature.

In the case of the temporal lobe, lesions of which induce the Klüver–Bucy syndrome, findings of the brain activity of the temporal cortex, hippocampus, and amygdala do not readily inform the syndrome. Thus, amygdala activity was reported to increase upon visual stimulation-induced sexual arousal in men (Karama et al., 2002; Hamann et al., 2004; Feretti et al., 2005) and women (Karama et al., 2002; Hamann et al., 2004; Rupp et al., 2013), but more actively in men (Hamann, 2005), and at orgasm in women (Hamann et al., 2004; Komisaruk et al., 2004, 2010; Rupp et al., 2013), but decrease during ejaculation in men (Holstege et al., 2003). Hippocampal activity was reported to increase during sexual arousal in men (Cera et al., 2012) and orgasm in women (Hamann et al., 2004; Komisaruk et al., 2004, 2010; Rupp et al., 2013). Temporal-lobe activity was reported to decrease at ejaculation in men (Holstege and Huynh, 2011), although the middle temporal gyrus activity increased (Holstege et al., 2003).

In other brain regions, Huynh et al. (2012) reported that primary and secondary visual cortices became deactivated in women watching erotic films, and Ortigue et al. (2007) reported a correlation between the "quality" of orgasm that women self-rated and the degree of activation of their left anterior insular cortex in response to subliminal presentation of their partner's name.

A further intrinsic problem in interpreting the brain activity data is that the methodology does not readily distinguish the outcome of activation of excitatory versus activation of inhibitory neurons, thus complicating the interpretation of the observed brain activity if there is excitation of inhibitory neurons.

If we attempt to interpret the disinhibition of sexual behavior that was reported in some cases of frontal lobotomy, there is considerable variability in the literature in the frontal cortical regions that are activated and deactivated during sexual arousal and orgasm. In men and women during sexual arousal, activation was reported in medial prefrontal cortex (Karama et al., 2002), orbitofrontal cortex (Spinella, 2007), and dorsolateral prefrontal cortex (Leon-Carrion et al., 2007), and, during ejaculation, in orbitofrontal cortex (Holstege et al., 2003). Frontal cortical activation was also observed in women during orgasm (Komisaruk et al., 2004, 2010; Wise, 2014). Wise (2014) presents fMRI evidence in women that physical genital stimulation and thinking of genital stimulation each activate the paracentral lobule (genital sensory cortex), but the frontal cortex is much more highly activated by thinking of genital stimulation than by physical genital stimulation. The frontal cortex is a heterogeneous brain region; one cannot yet predict on the basis of the regional brain activity which subdivisions could account for the various sexual behavioral effects observed.

CONCLUSION

Attempts to apply brain imaging data toward understanding the effects of brain damage, pathology, and surgery on sexual behavior are in the embryonic – not even infancy yet – stage. Nevertheless, there is good agreement on a number of brain regions that are active in relation to sexual arousal and orgasm, even though it is not clear what roles they play. In other words, we are

not able to construct the full spectrum of "sexual arousal" or "orgasm" from what is known about the various brain regions that increase or decrease their activity. For example, there are multiple reports that during sexual arousal in response to visual erotic stimulation, there is activation of hypothalamus (Karama et al., 2002; Hamann et al., 2004; Feretti et al., 2005; Kuhn and Gallinat, 2011), anterior cingulate cortex (Karama et al., 2002; Feretti et al., 2005; Kuhn and Gallinat, 2011; Cera et al., 2012; Oei et al., 2012), insula (Karama et al., 2002; Kuhn and Gallinat, 2011; Cera et al., 2012), and amygdala (Karama et al., 2002; Holstege et al., 2003; Feretti et al., 2005). During orgasm in men and women, activation was reported in cerebellum (Holstege et al., 2003; Komisaruk et al., 2004, 2010, 2011a), anterior cingulate (Holstege et al., 2003; Komisaruk et al., 2004, 2010, 2011a), and the dopaminergic pathway from ventral tegmentum (Holstege et al., 2003) to nucleus accumbens (Komisaruk et al., 2004, 2010, 2011a). We observed widespread activation throughout the brain during orgasm in women (Fig. 6.1) (Komisaruk et al., 2011a). However, except for some unsurprising correlates, e.g., increased activity in sensorimotor cortex and cerebellum (motor activity), hypothalamus (oxytocin secretion at orgasm), the dopamine pathway ("reinforcement" system), we are hard-pressed to "reverse engineer" the unique erotic experiential qualities of sexual arousal and orgasm from what is known about the functions of the brain regions whose activity we find correlated with these processes.

Much remains to be learned.

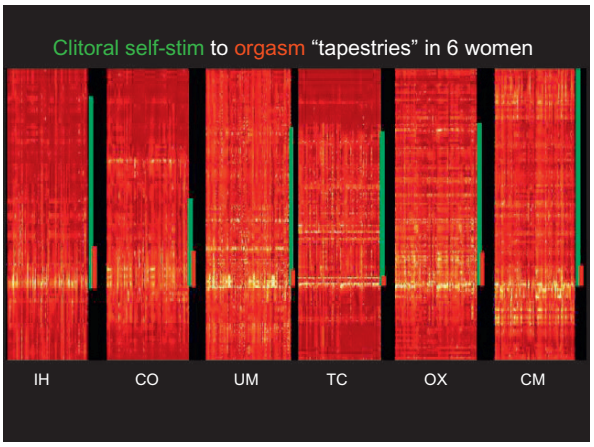

Fig. 6.1. "Tapestry" depiction of genital self-stimulation to orgasm in six different women, showing evidence of intense global activation in the brain at orgasm. For each woman, each of 80 brain regions ("Brodmann areas") is represented by a column. Each row represents a successive 2-second scan starting from the top. The activity in each region relative to its maximum during the scan is represented as a "hot metal" analog, in which dark red is the lowest activity and "white hot" is the highest. The vertical green bars indicate when clitoral self-stimulation was applied. The red bars represent the onset and duration of orgasm, after which self-stimulation stopped. Note the different temporal and spatial patterns leading up to orgasm and the widespread intense activation at orgasm. In order to facilitate comparisons, the approximate time of occurrence of the orgasms is aligned among the six samples, which necessitated "stretching" the time bases differentially along the vertical axis.

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 7

Functional imaging of structures involved in neural control of the lower urinary tract

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BACKGROUND

The primary function of the lower urinary tract (LUT) is beguilingly simple: it is to switch back and forth between two phases, storage of urine and voiding, depending on the volume currently in the bladder, the suitability or unsuitability of the occasion for bladder emptying, and volitional control. Prior to the advent of functional brain imaging, knowledge of how the brain might control the LUT rested largely on animal experiments and observations of the effects of brain lesions in human patients. Lesions are uncontrollable in location and extent. Moreover, because voiding is a bodily function normally under voluntary control (and voluntary control is impaired by anesthesia), suitable animal models are hard to find. Early work suggested that the bladder was controlled by a number of reflexes (Guyon, 1900), and this point of view was elaborated by Barrington in a series of experiments on the cat (Barrington, 1915, 1931, 1941). This work led to extensive animal investigation of potential spinal and cerebral reflexes, of which 32 were ultimately described (Elbadawi, 1988). A few of these reflexes were confirmed in humans by physiologic (what would now be called "urodynamic") experiments conducted by Denny-Brown and Robertson (Vilensky et al., 2004). Despite the simple function of the LUT, however, it has always been difficult to distill from the series of reflexes a clear understanding of the ultimate control of the LUT.

An early attempt to provide a simple picture of overall neural control was made by Bradley and his coworkers, who suggested that control was exerted by four "loops" (neural circuits) (Bradley et al., 1975; Hald and Bradley, 1982). Loop I, consisting of connections between the brainstem and the frontal cortex, forms part of a neural circuit still believed to be important today (circuit 1 in Fig. 7.1). Loop II, running spinally between brainstem and the sacral parasympathetic nucleus, is actually the spinobulbospinal micturition reflex. Loops III and IV survive in the spinal reflexes that are important in the storage phase (Fowler et al., 2008; Griffiths and Apostolidis, 2010).

Over the past 15 years, functional brain imaging has emerged as the most powerful technique for studying human brain function, in particular for understanding the relationship between activity in certain brain areas and specific functions. The science behind it appeared two decades ago with the advent of improved scanning of whole brain images and powerful computer tomographic analysis. Initially single-photon computerized tomography (SPECT) was used, followed by positron emission tomography (PET). Both techniques required injection of a radioactive substance which was concentrated in metabolically active brain regions. The spatial and temporal resolution of PET were better than those of SPECT, so that this method proved very valuable, and it was using PET that many of the early functional brain imaging discoveries were made. Later, PET was complemented by functional magnetic resonance imaging (fMRI), which has the advantage of being non-invasive and free of radioactivity. However, its signal-to-noise ratio is low, so that repeated captures of event-related data are usually necessary.

For studies of bladder function using fMRI this has meant that subjects have been required to do repeated pelvic floor contractions with either full or empty bladder (Kuhtz-Buschbeck et al., 2005, 2007; Zhang et al., 2005; Seseke et al., 2006) or had alternating bladder infusions and fluid removal via a catheter (Griffiths et al., 2005; Mehnert et al., 2008; Krhut et al., 2012).

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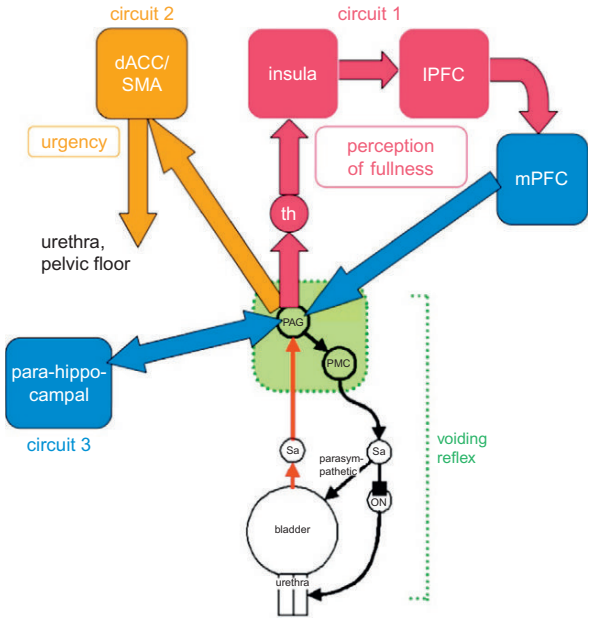

Fig. 7.1. A simple working model of the lower urinary tract control system, showing the voiding reflex with its rostral terminus in the brainstem (green), and circuits 1, 2, and 3 of the control network (in red, orange, and blue respectively). The return path of circuit 1 is in blue to signify that medial prefrontal cortex (mPFC) deactivation plays an important role in continence control. Sa, sacral parasympathetic area; ON, Onuf's nucleus; PAG, periaqueductal gray; PMC, pontine micturition center; th, thalamus; lPFC, lateral prefrontal cortex; dACC, dorsal anterior cingulate cortex; SMA, supplementary motor area. (Modified from De Groat et al., 2015.)

Because of these limitations and the need for scanning in an unnatural position, other methods such as near-infrared spectroscopy (NIRS) have been tried. NIRS is used for non-invasive assessment of regional brain function in human subjects by detecting (through the intact skull) changes in blood hemoglobin concentrations associated with neural activity. It has much better temporal, though more limited spatial, resolution than fMRI, but up to now only a few exploratory studies of bladder control have been reported using this method (Matsumoto et al., 2009, 2011).

Amongst the extensive brain imaging literature the number of studies that have focused on brain control of LUT function is tiny. The complete literature on this topic (excluding review articles) amounted in November 2013 to only 50 papers. Nevertheless, they have fundamentally changed our thinking about brain control of the bladder.

The current working model of bladder control

As mentioned above and in recent reviews (Fowler et al., 2008; Griffiths and Fowler, 2013), the neural circuitry of the LUT behaves as a switch between two phases, storage of urine and voiding, the basis of which is a bulbospinal neural circuit that is under the control of a network of interconnected brain regions (Fig. 7.1). The switching action itself is mediated by a long-loop spinobulbospinal voiding reflex which has its rostral terminus in the brainstem (see the lower part of Fig. 7.1).

During urine storage, as the bladder fills, bladder (sacral) afferent signals increase in strength until they exceed a threshold set in the brainstem, specifically the midbrain periaqueductal gray (PAG). The switch is then thrown and the reflex fires, i.e., the pontine micturition center (PMC, also referred to as the "M-region" or "Barrington's nucleus" (Holstege, 2005)) is activated, the urethral sphincter relaxes, the bladder contracts, and voiding occurs. When the bladder is empty, urine storage resumes. Brain imaging in the rat (Tai et al., 2009) has confirmed this picture: during storage, the PAG was activated (presumably by afferent input from the bladder) while the PMC was inactive. When the bladder volume reached the micturition threshold, the switch from storage to voiding was associated with enhanced PAG activity and PMC activation.

If this voiding reflex operated in isolation without restraining influences from higher brain centers (the cerebral bladder control network), it would fire automatically whenever the bladder volume, and therefore the bladder afferents, reached the threshold level, precipitating involuntary voiding (incontinence). Normal adults however can postpone or advance the moment of firing voluntarily and thus ensure that urination occurs only if it is consciously desired and socially appropriate. Moreover even normal subjects may not be able to micturate on command in all circumstances – voiding can only occur if it is judged emotionally "safe" also. Inability to exert such control is abnormal: it may occur as a consequence of functional or structural changes in the above-mentioned neural circuitry, and is indeed encountered in the varieties of LUT dysfunction observed in lesions affecting the central nervous system (CNS).

A simple working model that encapsulates our current understanding of the control system is shown in Figure 7.1. In this model the brainstem contains two nuclei concerned with micturition, the midbrain PAG and the PMC, which have different functions. The PAG is the location of the switch from storage to voiding and back. It projects to many parts of the forebrain, including amygdala, bed nucleus of the stria terminalis, hypothalamus, and thalamus, and via these structures to other parts of the bladder control network. This cerebral LUT control network projects back to the PAG. The PAG also receives ascending afferents from the bladder, and sends descending signals back via the PMC to the bladder and urethra. The ascending and descending inputs synapse in different parts of the PAG (Holstege, 2005;

Linnman et al., 2012), allowing interneurons to perform the signal processing required to adjust the threshold for voiding (Beckel and Holstege, 2011), and thus modulate its onset.

The PMC on the other hand receives input almost exclusively from the PAG. (It may also receive a "safe to void" signal from the hypothalamus (Holstege, 2005).) When activated by the PAG, the PMC passes on a signal to the sacral spinal cord, where inhibitory interneurons in Onuf's nucleus relax the urethral sphincter at the same time as the bladder contracts. In this sense the PMC ensures coordinated, synergic voiding. It may also coordinate elimination and voiding behavior, at least in rats (Valentino et al., 2011). Onuf's nucleus is larger in males than females, consistent with the more powerful striated sphincter in males (Forger and Breedlove, 1986). Early work suggested that initiation and maintenance of voiding should be distinguished (Barrington, 1931, 1941) and, in fact, once the voiding reflex has been triggered it seems to run its course without further control from higher centers (Tai et al., 2009).

In this model the PAG is not only concerned with initiation of voiding, but it plays an important role in the storage phase too. Its pivotal location between brain and bladder enables it to pass sensory information about the bladder to higher parts of the brain, and also receive information back from the cerebral neural control network, after processing, so as to maintain continence by appropriate action such as further suppression of the voiding reflex (Fig. 7.1).

There is some evidence for the involvement of a third brainstem nucleus, lateral and ventral to the PMC and not directly connected to it (Blok and Holstege, 1999). It is not included in the working model but, in the cat, electric stimulation of this region (the L-region or the pontine continence center (Sugaya et al., 2005)) causes tightening of the urethral sphincter (Holstege et al., 1986). This is believed to occur in humans also (Blok et al., 1997a; Athwal et al., 2001; Kuhtz-Buschbeck et al., 2005; Seseke et al., 2006), possibly accompanied by inhibition of bladder contraction. Indeed, the putative L-region was activated in men and women who tried to void in the MRI scanner but could not do so (Blok et al., 1997a, 1998).

Functional brain imaging studies

Prior to the widespread use of functional brain imaging, animal experiments and clinical observations had revealed numerous brain areas with excitatory or inhibitory effects on voiding (Fig. 7.2) (Torrens, 1982). Functional brain imaging in humans, starting with SPECT by Fukuyama et al. in 1996, has enabled simplification of this picture to a few essential elements (Fig. 7.1). It has also provided clarity about both normal function and what can go wrong in pathologic conditions due to overt neurologic lesions or other conditions implying impaired bladder control, such as urgency incontinence or overactive bladder (OAB, a portmanteau expression for urgency incontinence with or without urgency and frequency of micturition (Abrams et al., 2002)).

In 1997 Holstege's group published a study of brain activation during filling and voiding in men (Blok et al., 1997a), using PET. It established a framework of thinking that has guided studies in this area ever since. Activation was demonstrated in the dorsal pons, the presumptive location of the PMC, in subjects who were able to void in the scanner, and also in the medial prefrontal cortex (mPFC) (Fig. 7.3). In those who tried to void but

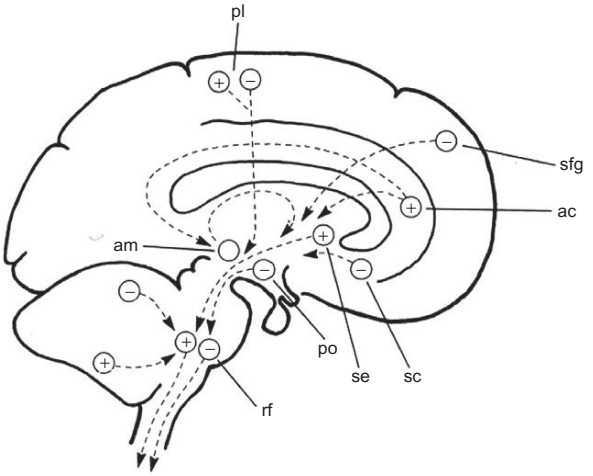

Fig. 7.2. A representation (made prior to the advent of functional brain imaging) of cerebral areas involved in micturition. + facilitation; – inhibition; ac, anterior cingulate gyrus; am, amygdala; pl, paracentral lobule; po, preoptic nucleus; rf, pontine reticular formation; sc, subcallosal cingulate gyrus; se, septal area; sfg, superior frontal gyrus. (Reproduced from Torrens, 1982.)

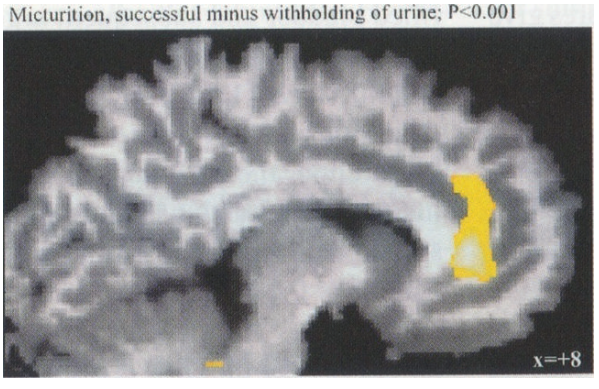

Fig. 7.3. The medial frontal region and presumptive pontine micturition center are activated during voiding, as shown in yellow on a sagittal cross-section of the brain. (Reproduced from Blok et al., 1997a, with permission.)

could not do so there was activation in the putative pontine L-region, while medial prefrontal activity was less pronounced.

A review of human functional brain imaging experiments conducted using PET or fMRI in these and other early studies (Griffiths and Tadic, 2008) summarized the midbrain and pontine locations of activation that had been found. Activations were clustered near the PMC (mostly during voiding), more rostrally near the PAG, and also near the putative L-region (Fig. 7.4).

In PET imaging experiments and also more recent fMRI studies, the PAG was activated on bladder filling (Athwal et al., 2001; Griffiths et al., 2005), consistent with the arrangement of bladder control shown in Figure 7.1. The rat study referred to above has confirmed the pontine location of the storage/voiding switch (Tai et al., 2009).

Recently, fMRI has become the method of choice because it is relatively inexpensive and requires no radioactivity or radiation. Ideally, to obtain reliable data from the rather noisy fMRI signal, averaging of numerous repetitions of the behavior to be studied, recorded over several minutes, is desirable. Protocols ("paradigms") have been developed to do this during storage and during simulated voiding (relaxation of the pelvic floor without actual voiding) (Kuhtz-Buschbeck et al., 2005; Seseke et al., 2006). An fMRI paradigm to study real voiding has been achieved only recently (Krhut et al., 2012). Most studies however have been made during storage, using a variety of paradigms to examine the brain's reaction to bladder filling: during repeated, rapid infusion and withdrawal of an aliquot of liquid via a syringe; or before and after natural or slow bladder filling; or combined with repeated contraction of the pelvic floor muscles. These different solutions to the problems of drift, noise, and physiologic accuracy yield different, but presumably complementary, results. For example, according to PET (Blok et al., 1997a) and SPECT (Yin et al., 2008) observations in male subjects, the inferior frontal gyrus is activated bilaterally after filling the bladder to capacity, but this region is less evident on fMRI. It has been incorporated under the name "lateral prefrontal cortex" (lPFC) in Figure 7.1.

A potential problem in interpreting imaging data is that neuronal activations (which are derived from local blood oxygen changes) may represent either excitatory or inhibitory activity: it is usually not known which. Another is that regional deactivation as well as activation may be encountered. Deactivation means that, in response to an event such as bladder filling, activity in the given location falls to below its initial resting value. It is commonly observed in a specific "default mode network" that is active during resting conditions (Raichle and Snyder, 2007). Deactivation seems to be a sign that resting activity is suspended while the brain uses its resources to process an event requiring conscious attention.

Table 7.1 summarizes human brain imaging observations of the principal regions shown in Figure 7.1.

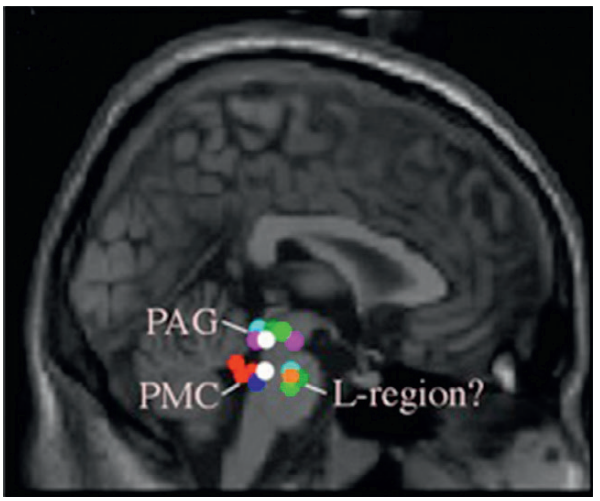

Fig. 7.4. Brainstem and midbrain areas activated during withholding of urine or with a full bladder, or during voiding, projected on a sagittal section of the brain. PAG, periaqueductal gray; PMC, pontine micturition center; L-region is a putative pontine continence center. Based on positron emission tomography, functional magnetic resonance imaging, and single-photon emission computed tomography studies in healthy controls. (Adapted from Griffiths and Tadic, 2008.)

NEURAL CIRCUITS INVOLVED IN BLADDER CONTROL

To understand LUT neural control and loss of control it is helpful to arrange the relevant brain regions in neural circuits that play different roles (Fig. 7.1). Of course these interpretations are speculative and one obvious limitation is that they are based to a large extent on observations made when there is strong desire or urgency to void. Moreover there is little functional information about the pathways that connect the various brain regions in the assumed circuits. Bearing in mind these limitations, three circuits (Fig. 7.1) can be postulated to represent the neural control of LUT. The observations on which these postulates are based are presented below.

Circuit 1: Prefrontal cortex and insula

Circuit 1 (Fig. 7.1) appears to include the thalamus, insula, lPFC, and mPFC, as well as the PAG.

Insula

The insula has come to be regarded as the homeostatic afferent cortex that registers visceral sensations (Craig, 2003; Kuhtz-Buschbeck et al., 2005). It receives

Table 7.1

Selected observations of four principal regions of the working model concerned with bladder control during the storage phase (with bladder filling or withholding, or with full bladder and urgency but without bladder contraction)

Region	Authors	Coordinates/BA	Subjects	Notes
mPFC	Griffiths et al. (2009)	6, 62, 24	Women	Deact
	Tadic et al. (2010a)	−8, 52, 22 BA 9	Women with OAB, urgency	Deact
	Tadic et al. (2010b)	−6, 38, −4 BA 32	Women with OAB	Deact
	Blok et al. (1997a)	8, 24, 24 BA 24,32	Normal men	Deact, PET
dACC/SMA	Griffiths et al. (2007)	−6, 14, 34	Women with OAB	
	Griffiths et al. (2009)	0, 6, 30	Normal women	
	Tadic et al. (2010a)	−10, 4, 50 BA 24	Women with urgency	
	Athwal et al. (2001)	−2, 18, 22	Normal men	PET
	Matsuura et al. (2002)	8, 43, 7 BA 32	Normal men	PET
Insula	Blok et al. (1998)	38, 10, 12	Normal women	PET
	Nour et al. (2000)	−40, 14, 2	Normal men	PET
	Blok et al. (1997a)	32, 24, 12	Normal men	PET
	Matsuura et al. (2002)	−26, −3, 15	Normal men	PET
	Griffiths et al. (2007)	50, −4, 2	Normal women	
	Griffiths et al. (2007)	34, 8, 16	Women with OAB	
	Tadic et al. (2008)	44, 6, 4	Normal women	
	Tadic et al. (2008)	38, −4, 16	Women with OAB	
	Griffiths et al. (2009)	34, 8, 16	Normal women	
	Tadic et al. (2010a)	34, 24, 4 BA 13	Women with urgency	
	Seseke et al. (2013)	36, 8, 8	Men with prostate ca	
	Tadic et al. (2012)	32, 20, 4 BA 13	Women with UUI and DO	
lPFC	Tadic et al. (2012)	38, 30, 6 BA 47	Women with UUI and DO	
	Tadic et al. (2008)	50, 8, 14	Women with urgency	
	Tadic et al. (2008)	58, 6, 14	Normal women	
	Athwal et al. (2001)	56, 40, 16	Normal men	PET
	Yin et al. (2008)	66, 30, −2 BA 45, 47	Normal men	SPECT
	Seseke et al. (2013)	52, 3, 21	Men with prostate cancer	
	Blok et al. (1998)	44, 44, 12 BA 47	Normal women	PET

BA, Brodmann area; mPFC, medial prefrontal cortex; Deact, deactivation; OAB, overactive bladder; PET, positron emission tomography; dACC, dorsal anterior cingulate cortex; SMA, supplementary motor area; lPFC, lateral prefrontal cortex; UUI, urgency urinary incontinence; DO, detrusor overactivity; SPECT, single-photon emission computed tomography.
Based on functional magnetic resonance imaging except where noted. Coordinates of bilateral activations are reported on the predominant side.

homeostatic information ("the sense of the physiologic condition of the entire body," including the viscera) via afferent input from small-diameter fibers in lamina 1 of the spinal cord, relayed in the thalamus. A critical element of this information is an appreciation of the degree of bladder filling. Consistent with this concept, insular activation has been observed in most studies of urine storage (see, for example, Fig. 7.5), and in healthy controls activation increases with bladder filling and therefore with desire to void (Griffiths et al., 2005; Kuhtz-Buschbeck et al., 2005). It is relatively weaker in older subjects (Griffiths et al., 2009), who correspondingly have less pronounced bladder sensation (Pfisterer et al., 2006). A recently published abstract (Tadic

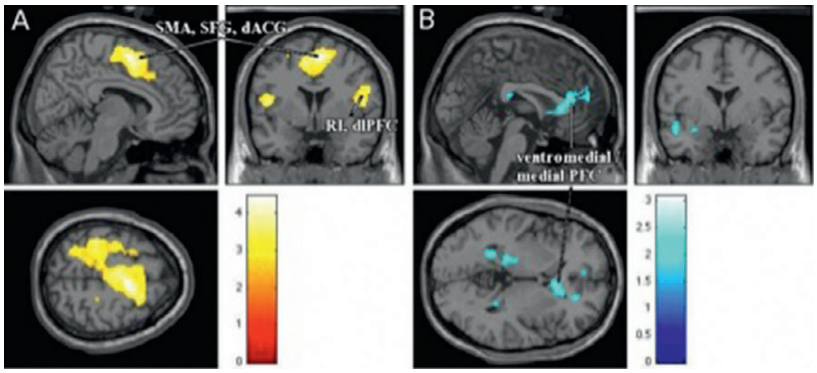

Fig. 7.5. In older urgency-incontinent women, regions activated (**A**: yellow) and deactivated (**B**: blue) during urgency. SMA, supplementary motor area; SFG, superior frontal gyrus; dACG, dorsal anterior cingulate gyrus; RI, right insula; dlPFC, dorsolateral prefrontal cortex. (Reproduced from Tadic et al., 2012.)

et al., 2012) confirms that the insula is activated in normal elderly women and in those with urgency urinary incontinence (UUI) responsive to behavioral therapy. In those with UUI refractory to therapy, however, lack of insular activation may suggest that proper use of homeostatic information is important for continence. The insular activations are bilateral (Fig. 7.5: see below for further discussion). The role of the thalamus in processing and relaying bladder signals to the right and left insula (and many other cortical regions) is supported by imaging studies that have shown thalamic excitation in response to bladder filling (Kavia et al., 2005).

Medial prefrontal cortex

The importance of the prefrontal cortex in bladder control was established by clinical studies by Ueki (1960). Subsequently Andrew and Nathan (Andrew and Nathan, 1964; Fowler and Griffiths, 2010) pointed out that the location of lesions which were clinically demonstrated to have long-term effects on bladder function was in white-matter tracts in the medial prefrontal region. Medial prefrontal gray-matter lesions led to relatively short-term incontinence (Fig. 7.6). Further evidence for the importance of the mPFC is provided by children with primary nocturnal enuresis, who have difficulty controlling the bladder at night and show abnormal connectivity in the resting state in this region (Lei et al., 2012).

Ventromedial regions of the prefrontal cortex are involved in decision making in an emotional and social context (Damasio, 1996). They have extensive interconnections with the limbic system – the hypothalamus and amygdala – as well as the insula and anterior cingulate cortex (ACC). The more lateral parts of the prefrontal cortex are involved in aspects of cognition, especially working memory (Bechara et al., 2000), and several bladder studies have shown activation of lPFC (or

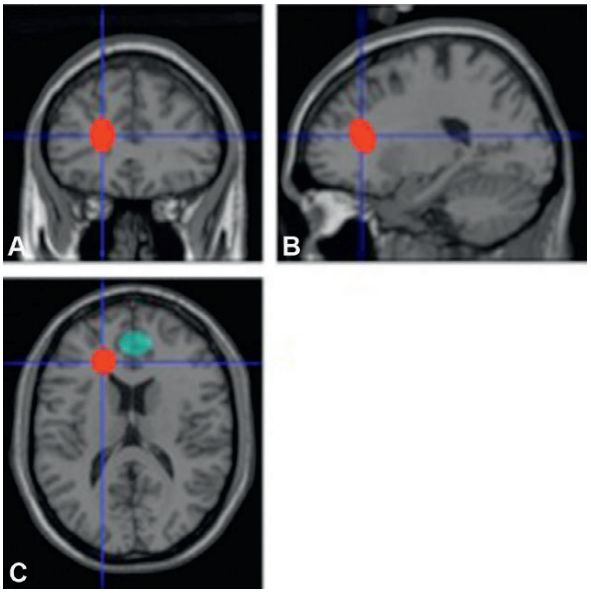

Fig. 7.6. Regions where cortical lesions led to temporary urinary incontinence (turquoise, in gray matter) or permanent urinary incontinence (red, in white matter), or occasionally other voiding dysfunction. (Modified from Andrew and Nathan, 1964, with the help of a sketch made by Nathan and kindly provided by Dr. Clare Fowler (private communication).)

inferior frontal gyrus) (Table 7.1) (Blok et al., 1997a). Connections with the ventromedial PFC give access to the limbic system and other parts of the brain.

PET studies show that, during voiding, the medial prefrontal area is activated (Fig. 7.3). During withholding of urine or with full bladder, however, the observations suggest that, especially in urgency incontinence, the medial parts of the prefrontal cortex are deactivated rather than activated in response to bladder filling (Athwal et al., 2001; Griffiths and Tadic, 2008; Tadic et al., 2012) (Table 7.1 and Fig. 7.5). Suggestively, the

mPFC is part of the default mode network mentioned above (Raichle and Snyder, 2007), but up to now it has not been clear whether mPFC deactivation is dysfunctional, a cause of incontinence, or a sign that the voiding reflex is being suppressed, a mechanism promoting continence. If the latter interpretation proves to be correct, this will suggest a continence mechanism that operates as follows: if involuntary voiding or leakage threatens, excitation of the insula and lateral PFC leads (via an inhibitory connection) to reduced input to the mPFC and correspondingly the PAG (via the return pathway in Fig. 7.1). This presumably raises the threshold level or reduces PAG activity, so stabilizing the voiding reflex and promoting continence. This mechanism of continence would be used only by those attempting to avoid inappropriate bladder contractions. In entirely normal subjects this circuit is not activated, at least under experimental circumstances such as urodynamic testing or functional brain scanning.

Circuit 2: Dorsal anterior cingulate cortex and supplementary motor area

A key feature of interoceptive sensations is their association with an affective, motivational aspect and hence their value in homeostasis. For example, an increasingly unpleasant desire to void as the bladder fills ensures that the bladder is regularly emptied, even though the exact time and place are under voluntary control. The ACC can be considered as the limbic motor cortex (Devinsky et al., 1995), responsible for motivation and modulation of bodily arousal states (Critchley et al., 2003). In the cardiac system, dorsal ACC activation is associated with sympathetic control of heart rate (Wager et al., 2009). Similarly, ACC activation may help to control LUT function via the sympathetic β- and α-adrenergic receptors on these peripheral organs. Moreover, the dorsal part of the ACC (dACC) is usually coactivated with the adjacent supplementary motor area (SMA), where activation is associated with contraction of the pelvic floor and striated sphincter muscles (Seseke et al., 2006; Kuhtz-Buschbeck et al., 2007; Schrum et al., 2011). Together therefore, if UUI threatens, the dACC and the SMA appear to be able to react by generating both the sensation of urgency and a contraction of the urethral sphincter, thus motivating a toilet visit while reinforcing the ability to postpone voiding until the toilet is reached.

Circuit 2, as sketched incompletely in Figure 7.1, indicates no clear connecting pathways, but in reality the afferent signal from the PAG to the dACC/SMA may be relayed by the thalamus. The path of the return signal is unclear but it may involve sympathetic nuclei in the brainstem, the PAG, or even the L-region. As indicated above, this circuit seems to be a short-term back-up continence mechanism that is employed by patients with urgency incontinence or OAB when they experience urgency. In normal subjects, who have less imperative sensation, the dACC/SMA is activated by bladder filling less strongly or not at all, just as for circuit 1.

Circuit 3: Subcortical mechanisms

In normal individuals for over 99% of the time, the bladder is slowly filled with urine, presumably with unconscious monitoring by brain circuits, but without sensation reaching consciousness. Correspondingly, fMRI measurements made during bladder filling, when the bladder volume is small and there is little, if any, sensation, indicate activation of a subcortical network that includes the PAG and parahippocampal parts of the temporal cortex (Fig. 7.7) (Tadic et al., 2013). Cortical circuits 1 and 2 do not appear to be involved, consistent with absence of bladder filling sensation.

Among women with idiopathic inability to sense or to empty the bladder, restoration of bladder sensation by sacral neuromodulation leads to changes in a similar brainstem/parahippocampal network (Fig. 7.7) (Kavia et al., 2010), suggesting that this may be the route by which the PAG normally monitors bladder behavior and exchanges bladder-related signals with the rest of the brain. Since the parahippocampal cortex is close to the amygdala, the seat of emotion, one would expect this circuit to be particularly concerned with the emotional aspects ("safety") of voiding, perhaps providing output

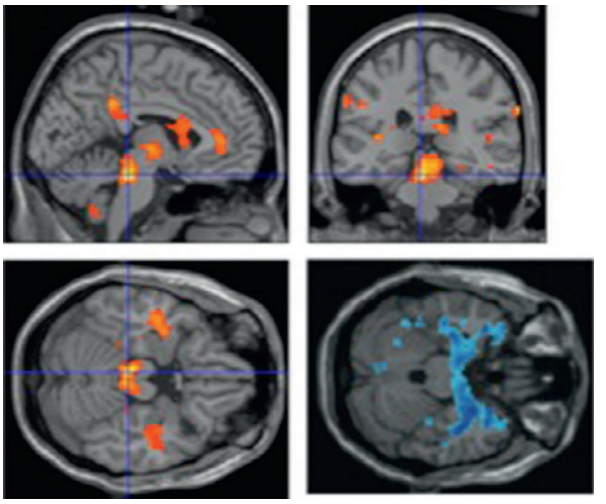

Fig. 7.7. In yellow/orange, sections showing areas activated by bladder filling, in normal women with small volume in the bladder and little sensation. Bottom left section shows periaqueductal gray and parahippocampal activation. In blue, bottom right, midbrain and parahippocampal circuit affected by successful neuromodulation in Fowler's syndrome. (Reproduced from Tadic et al., 2013, and Kavia et al., 2010.)

to the brainstem nuclei via the postulated "safe" signal from the hypothalamus. The subcortical circuitry is included in a schematic way in the working model (Fig. 7.1).

CEREBRAL CONTROL OF THE URETHRAL SPHINCTER

Control of the urethral sphincter mechanism has not been studied as systematically as that of the bladder itself, but there seem to be several ways to control the sphincter. We have seen already that the wiring of the voiding reflex (Fig. 7.1) – in particular the presence of an inhibitory interneuronal connection in the sacral nucleus of Onuf – ensures synergic relaxation of the sphincter when the bladder contracts for voiding. Moreover, excitation of the pontine L-region is associated with sphincter contraction that seems to play a part in preventing urination if it is judged involuntarily to be unsafe.

Suggestively, the anterior cingulate (or midcingulate) cortex shown in the working model and in observations such as those in Figure 7.5A, appears to be the same brain region that exerts sympathetic control over heart rate (Critchley et al., 2003; Wager et al., 2009). Speculatively therefore, the dACC might be involved in sympathetic control of the LUT, which has always been difficult to identify in humans. Under conditions of urgency or strong desire to void, dACC excitation by bladder filling would help to maintain continence through bladder relaxation and sphincter contraction, using sympathetic descending pathways that terminate respectively on β-adrenergic inhibitory terminals in the bladder body and α-adrenergic excitatory terminals in the smooth muscle of the proximal urethra and bladder base. These pathways thus form part of circuit 2 of the control network, a part that is left uncompleted in Figure 7.1.

During bladder filling, dACC activation usually extends into an adjacent region of the frontal cortex, the SMA (Fig. 7.5). According to Kuhtz-Buschbeck and coworkers (2007), this same region is activated during voluntary contraction of the pelvic floor and striated urethral sphincter, suggesting that there are connecting pathways from SMA to these muscles (again part of circuit 2). Bladder filling with urgency would therefore recruit these striated muscles also, promoting continence.

Other authors have investigated the supraspinal correlates of voluntary sphincter contraction. Blok and coworkers (1997b) used PET imaging with repetitive pelvic floor contractions to show that in women there was a pelvic floor motor area in the superomedial precentral gyrus, slightly anterior to the SMA. By contrast, the SMA itself seemed to be more strongly activated by abdominal straining. Seseke and coworkers (2006) pointed out that pelvic floor muscle control cannot be separated from the micturition process. They found that, compared with pelvic floor relaxation, pelvic floor contraction was accompanied by greater activation in the medial sensorimotor cortex. This region is close to the superomedial precentral gyrus described by Seseke et al.

Kuhtz-Buschbeck and coworkers (2007) performed a careful study of the location of activity during rhythmic contractions of the pelvic floor muscles. The main center of activation was in the superior frontal gyrus, Brodmann area (BA) 6, at Montreal Neurological Institute (MNI) coordinates [1 to 3, −9 to 3, 45 to 66] (Fig. 7.8). Taken together, these studies support the view that different parts of the brain may be used for voluntary and involuntary control of the urethral sphincter and pelvic floor muscles.

LATERALITY OF CEREBRAL CONTROL NETWORK

PET and fMRI studies have identified activations of the insula, inferior frontal gyrus, and dorsolateral prefrontal cortex that are typically bilateral (Fig. 7.5), although whenever a preference has been reported it has been for the right side (Blok et al., 1997a, 1998; Nour et al., 2000; Griffiths et al., 2005; Seseke et al., 2006). This is evident in Table 7.1, where insular and lPFC activations are reported predominantly on the right, regardless of whether the subjects were men or women (and indeed whether they were uniformly right-handed or mixed left- and right-handed). An early clinical study of

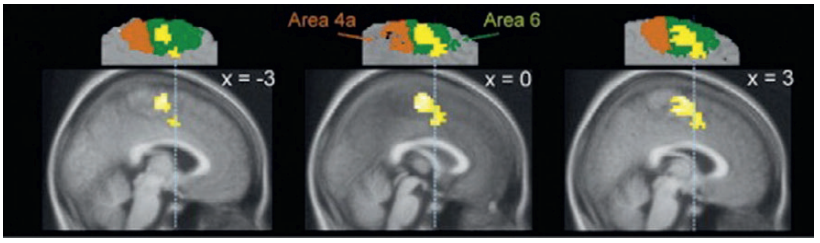

Fig. 7.8. Location of principal region active during rhythmic pelvic-floor muscle contractions (in yellow). Brodmann area (BA) 4 and BA 6 are shown in red and green respectively. (Reproduced from Kuhtz-Buschbeck et al., 2007.)

patients with frontal brain tumors (Maurice-Williams, 1974) and a SPECT study of brain perfusion in the frail elderly (Griffiths, 1998) also suggested a right-sided preponderance.

CONNECTIVITY OF CEREBRAL CONTROL NETWORK

One limitation on our knowledge of the finer functional details of the mechanisms of conditions such as OAB, urgency incontinence, or chronic retention of urine (which occur idiopathically as well as a consequence of known brain lesions) is that the functional imaging studies performed to date have been based mainly on observations of activity in specific brain regions. They can give only incomplete information about how the cerebral network ultimately controls or fails to control bladder behavior, because the pathways that connect the regions are equally important.

However, only scattered studies of connectivity, based on a variety of methods, have been published. In normal subjects, bladder filling revealed polysynaptic connections of the dACC and insula with frontotemporal and sensorimotor cortex, forebrain, midbrain, and pontine regions (Tadic et al., 2008), in particular with the bilateral putamen (Griffiths et al., 2009), a region not included in our working model (Fig. 7.1). Similarly, patterns of functional connectivity differ greatly between empty and full bladder (Nardos et al., 2014), while during attempted micturition the connectivity of the right insula is weaker than at baseline (Kuhtz-Buschbeck et al., 2009). Thus connectivity varies greatly, even in normal subjects, depending on circumstances (including the age of the subjects: Griffiths et al., 2009).

Unsurprisingly, connectivity differs from normal in pathologic situations also. In urgency-incontinent adults (Tadic et al., 2008) the effective connectivity seems to be shifted (compared to normal) to a parietotemporal complex. Similarly, in children with impaired bladder control (manifested by monosymptomatic nocturnal enuresis) resting-state connectivity is abnormal in regions that form part of the neural circuits in Figure 7.1: the left inferior frontal gyrus (part of the lPFC), the mPFC (BA 10), and the left midbrain (Lei et al., 2012).

Reduced integrity of the white-matter connecting pathways in the brain, manifested as white-matter hyperintensities on structural MRI, is common in the elderly and is associated with several geriatric syndromes, including urgency incontinence. Sakakibara et al. (1999), Kuchel et al. (2009) and Tadic (Tadic et al., 2010a; Gary et al., 2013) have shown that the presence and severity of urgency incontinence in older women, and the corresponding changes in cerebral activity, are correlated with the degree of white-matter damage as assessed by the global volume of white-matter hyperintensities seen on structural MRI. These authors present some weaker evidence that focal damage in specific white-matter tracts (e.g., those serving mPFC or dACC/SMA) may contribute causally to incontinence.

CEREBRAL CONTROL NETWORK AND OTHER NEUROGENIC LOWER URINARY TRACT DYSFUNCTION

Cerebral lesions

Very little functional brain imaging has been performed in patients with presumed isolated lesions above the brainstem, due for example to stroke or traumatic brain injury. The contribution of Andrew and Nathan (1964) has been discussed above. The work reviewed so far suggests potential sites in the CNS where an overt lesion might result in impaired bladder control (manifested as OAB or urgency incontinence, or possibly urinary retention). They include the regions of circuits 1 and 2 and their connecting pathways. Lesions in the subcortical circuit 3 may also be involved, although this circuit has been little studied. The LUT effects of lesions studied by other methods are discussed in Chapter 15. Two striking case reports regarding circumscribed surgical lesions, demonstrated by structural MRI (Duffau and Capelle, 2005), suggest that a lesion in the anterior cingulate and SMA abolishes bladder sensation while a lateral frontal lesion leads to inability to postpone voiding. These observations are consistent with the working model and its interpretation put forward in Figure 7.1.

Other types of neurogenic LUT dysfunction

Functional brain imaging in other diseases has also suggested sites where cerebral damage may lead to LUT dysfunction.

Idiopathic normal-pressure hydrocephalus is a central abnormality which characteristically results in urinary incontinence, along with gait disturbance and dementia. A brain imaging study using SPECT (Ishii et al., 2011) showed reduced regional blood flow around the corpus callosum and sylvian fissure, areas where lesions would be expected to interrupt white-matter connecting pathways between the prefrontal cortex and the PAG (see circuit 1 in Fig. 7.1). Another SPECT study of this disease (Sakakibara et al., 2012) showed that LUT dysfunction was closely related to underperfusion of the frontal lobes, especially on the right, again suggesting damage to a critical part of circuit 1.

In patients with Parkinson's disease and urinary symptoms, SPECT imaging of dopamine transporter showed marked decline in the striatum, particularly the putamen. This region is not identified explicitly in

Figure 7.1, but presumably forms part of the subcortical circuit 3. It has been implicated in the network of LUT control, for example by connectivity studies (Griffiths et al., 2009). Parkinson's disease can be significantly improved by subthalamic deep-brain stimulation (Herzog et al., 2006), which normalizes the perception of urinary bladder filling. A PET study (Herzog et al., 2008) showed that this type of stimulation significantly affected activity in the posterior thalamus and the insular cortex. Both regions are concerned with relaying and processing of afferent LUT information from the PAG (Fig. 7.1). Thus the clinical improvement caused by deep-brain stimulation seems to be the result of enhanced processing of afferent information.

Multiple systems atrophy presents with both storage and voiding symptoms, such as urgency incontinence and hesitancy in starting voiding. A SPECT study (Sakakibara et al., 2004) showed reduced activation of the vermis of the cerebellum during both storage of urine and voiding. The cerebellum is not shown in Figure 7.1, but is frequently reported in imaging studies.

Even subcerebral lesions have central effects. For example, spinal cord injury has prominent, well-known, and clinically important effects on LUT dysfunction, varying from urinary retention to incontinence, with or without detrusor sphincter dyssynergia (lack of coordination of bladder and urethral muscles). The type of dysfunction depends strongly on the level of the lesion (Blaivas, 1982), but incomplete lesions are common and may have unpredictable effects. One brain imaging study (Zempleni et al., 2010) has shown that the central representation of bladder filling sensation, involving activation of several of the regions shown in Figure 7.1 (e.g., PAG, bilateral insula, dACC, and SMA), is preserved in the subacute stage of incomplete spinal cord injury. In contrast to healthy subjects (see, for example, Mehnert et al., 2008), however, there was decreased neural response in right prefrontal and insular areas, consistent with impairment of control emanating from the right side, which is normally predominant. There was increased response on the left side, presumably in compensation.

Peripheral lesions such as radical prostatectomy are also reflected in changed function of the CNS. Prior to surgery contraction of the muscles of the pelvic floor and urethral sphincter is associated with activation in many of the regions of Figure 7.1, including pons, PAG, thalamus, putamen, inferior frontal cortex, insula, anterior cingulate, SMA, sensorimotor cortex, and inferior parietal cortex. Surgery appears to partially decentralize these muscles, a factor contributing to post-operative iatrogenic incontinence. Correspondingly, many brain responses to contraction are diminished after prostatectomy, presumably reflecting diminished afferent and efferent innervation (Seseke et al., 2013), although the overall pattern of activation is relatively unchanged.

CONCLUSION

To summarize, after 15 years of functional brain imaging, the picture of LUT control that has been built up is as follows. A CNS control network (Fig. 7.1) maintains inhibition of the voiding reflex during urine storage and monitors unusual or unexpected bladder events. At small bladder volumes this occurs largely unconsciously and presumably relies on a subcortical network (circuit 3). Further bladder filling generates a bladder sensation that gradually increases in intensity, reflecting insular activation and desire to void. In normal individuals however, despite the increasing volume and sensation, the voiding reflex is not excited. If and when voiding would be mechanically appropriate, emotionally safe, socially appropriate, and consciously desired, voluntary voiding occurs by exciting an mPFC region that in turn sends a signal to switch the PAG from storage and to voiding. The PAG then activates the PMC, which coordinates bladder and sphincter behavior to ensure complete emptying of the bladder.

In OAB imperative urgency develops during the storage phase, indicating a threat of leakage. OAB is sometimes a consequence of a cerebral lesion, but often it is idiopathic, implying that there is a subtle lesion whose nature has not yet been revealed. It may involve damage to cerebral connecting pathways, or dysfunction of the subcortical control circuit, or any other dysfunction that compromises the stability of the spinobulbospinal voiding reflex.

If urgency develops, additional continence mechanisms can then be recruited in an attempt to maintain bladder control. They are based on neural circuits involving respectively activation of the dACC/SMA, deactivation of the mPFC, and (possibly) changes in subcortical function. All three circuits provide input to the PAG or other brainstem nuclei, aimed at suppressing the firing of the voiding reflex.

Of course, this is a simplified and incomplete working model that omits many features of supraspinal control. Even this short survey has identified brain regions, not included in Figure 7.1, that seem to play an important part, for example, the cerebellum, the putamen, and the parietal cortex. Clearly, improvement and correction of the working model are inevitable and to be welcomed, both for intellectual satisfaction and for medical utility. In the long term, understanding of how the LUT – a relatively simple mechanical system – is controlled may help us understand the mechanisms that control more complex organ systems.

ACKNOWLEDGMENTS

I am very grateful to Clare Fowler for providing the basis of the ideas put forward in this manuscript, which is based in part on reviews published jointly (Fowler et al., 2008; Fowler and Griffiths, 2010; Griffiths and Fowler, 2013; De Groat et al., 2015). David Vodusek gave me very helpful and much needed editorial guidance. Stasa Tadic, Neil Resnick, Andrew Murrin, Chet de Groat, and many other colleagues in Pittsburgh and London provided essential help and stimulating discussions. I gratefully acknowledge support from the University of Pittsburgh and the US Public Health Service.

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Section 3

Approach to the patient

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 8

Approach to the male patient with sexual dysfunction

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INTRODUCTION

In their book *Theories of Human Sexuality*, James Geer and William O'Donohue (1987) emphasized that there are many different ways to approach patients with sexual dysfunction (SD). These approaches include, in somehow random order, the theological, historic, feminist/political, phenomenologic, developmental, anthropologic, sociologic, sociocultural, cognitive, as well as the psychoanalytic and physiologic approach. In a patient with a neurologic disorder, the physiologic approach seems to be the most appropriate to formulate relevant diagnostic and therapeutic procedures; however, the other dimensions of sexuality should be kept in mind.

This chapter is partly based on guidelines of the European Federation of Neurological Societies Task Force on Neurosexology (Lundberg et al., 2001). Further information can be found in Fugl-Meyer et al. (1999), Lundberg et al. (2005), Flink and Lundberg (2010), and in a series of chapters in Kandeel et al. (2007).

CLINICAL EXAMINATION

The approach to SD patients follows the traditional steps of the clinical approach to all patients, with special and specific modifications and inclusions. History must include a special emphasis on sexual functions and needs to be taken not only from the patient, but also, if possible, from his partner; clinical examination needs of course to include specific attention to the sex organs and surrounding areas; laboratory tests may include not only blood and urine, but also semen. There are specific tests for testing particular aspects of sexual function which, at present, are interesting for research, but not relevant for everyday practice (Porst, 2012; Giuliano and Rowland, 2013).

It should be borne in mind that the patient needs to be examined not only in order to diagnose the nature of his SD, but also to assess his underlying neurologic condition. The diagnosis of the underlying disorder is particularly relevant in cases of isolated appearance of SD. It is also important to stress that, in patients with a known or suspected neurologic condition, the general area of sexual function should be explored in all cases.

PATIENT HISTORY

History should clarify the nature and characteristics of SD, uncover any underlying (and possibly treatable) organic cause, and document the existence of primary or secondary psychologic factors. It includes a survey of the patient's medical history, particularly concerning psychologic and psychiatric disturbances, cardiovascular, endocrine, and neurologic disorders, disorders of the sex organs, prior trauma and surgical procedures, the use of prescription drugs, smoking and alcohol habits, and drug abuse. From the sexologic point of view, history needs to define the patient's sexual expectations, needs, and behavior and should identify sexual problems as well as misconceptions. Psychologic factors are often involved, either as an emotional reaction to SD or as a consequence of a socially or physically disabling disease. Dependence and lack of acceptance of the SD by the patient or his partner, self-perceived unattractiveness, and reduced self-esteem also play a relevant role. It is important not only to interview the partner (if the patient has one who is available), but also to evaluate the quality of the partner relationship.

The sexual complaint itself should be noted, described in detail, and its chronology defined. The patient should be asked about the following items.

Onset of SD

Has the problem been there all the time, or did it have an onset at a specific time? Was the onset rapid or gradual,

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the course progressive or episodic? A possible relation between the sexual symptoms and an underlying neurologic disorder should be elucidated. Taking seizures as an example, hyperventilation during sexual activity and genital stimulation during intercourse and masturbation can trigger a seizure. Sexual phenomena can be part of a seizure if the epileptic focus involves cerebral genital areas (e.g., a parasagittal tumor). One needs also to remember that many antiepileptic drugs have sexual side-effects.

Sexual desire

The patient should be asked about sexual desire. Does the patient experience spontaneous sexual desire? Is the desire easily evoked by commonplace situations? Is there a lack of desire but the patient wishes to have it? Do any particular stimuli – visual, auditory, tactile, or emotional – play an important role? Is there a persistent or recurrent deficiency or absence of sexual fantasies, thoughts, desire for sexual activity, alone or with a partner? Is the patient unable to respond to sexual cues that would be expected to trigger responsive sexual desire? In most cases, to be significant, these symptoms need to be causing personal distress.

Sensory aspects of sexual function and pleasurable feelings

The patient is asked to describe sensory experiences of sexual arousal in different parts of the body. One should ask for present or past disturbances of sensation. Obviously the regions corresponding to the lumbosacral segments are of particular relevance. Is there another area of the body from where sexual feelings can be provoked? This is of particular importance for the patient with loss of sensation in the lumbosacral region.

Pain and headache

Is there pain in the pelvic or lower abdominal region? Does the pain start or is it enhanced during sexual arousal or intercourse? Is it localized in the genital and/or pelvic area? Does sexual activity provoke headache attacks? chest pain? dyspnea?

Penile erection

Description of erections is important. Does the patient have nocturnal erections, morning erections, erections evoked by visual, auditory, or psychogenic stimuli and erections evoked or enhanced by genital stimulation? What is the quality of penile tumescence? Is erection sufficient for penetration? Is there a premature loss of erection during sexual intercourse? Does the patient have episodes of priapism or painful nocturnal erections?

Ejaculation

Ejaculation should be described. Does the patient have premature or retarded ejaculation? Are there spontaneous, unprovoked ejaculations? Are there ejaculations without erection? Is there no ejaculation at all (anejaculation)? Is the ejaculation dribbling, i.e., are there emissions of semen through the urethra without contractions of pelvic floor muscles? Is there lack of emission of semen? Could the ejaculations be retrograde, which means ejaculation into the bladder with presence of sperm in the urine after climax?

Orgasm

Orgasm can be defined as the sum of all physiologic events that happen in the body during the sexual climax and the individual experience of these. Orgasms should be described. What is the capacity to achieve an orgasm? Are there spontaneous orgasms? Multiple orgasms? Does the person actually feel the pelvic floor muscle contractions? How is the quality of orgasmic sensations experienced? Note that an orgasm may also be anhedonic, i.e., without any pleasurable sensations. Some or all orgasms may be painful. In such a case, where is the pain localized?

Fertility

The fertility history should be investigated.

Galactorrhea

The symptom of galactorrhea (with or without raised blood prolactin levels) is rare in males but when it does occur it is of great importance, both as an indication of hypothalamopituitary dysfunction and a cause of SD.

Sexual side-effects of prescription drugs

A large number of prescription drugs have been reported to have sexual side-effects. For instance, antihypertensive drugs may cause impotence; alpha-adrenergic drugs may cause priapism and disturb ejaculation; antidepressant drugs, in particular selective serotonin reuptake inhibitor preparations, may influence libido and orgasm, dopaminergic drugs may increase libido (Lundberg, 2010). The sexual side-effects of antiepileptic drugs has been mentioned above.

THE USE OF QUESTIONNAIRES

Formal questionnaires may be used to obtain standardized information. Some have been validated in different languages and are useful in studies of treatment efficacy in patients with SD. Two of the forms that are most often

used are the Brief Male Sexual Function Inventory for Urology (O'Leary et al., 1995) and the International Index of Erectile Function (IIEF, 1997). Questionnaires are uncommonly used for the routine clinical assessment of patients with SD.

PHYSICAL EXAMINATION OF THE MALE PATIENT WITH SEXUAL DYSFUNCTION

General clinical examination

Sexual development, body height and weight, changes in pigmentation and body hair, nevi, hypertrichosis, feet deformity, and the presence of galactorrhea are noted. External genitalia and the size of the testes (normal 15–25 mL) should be examined, peripheral pulses (arms, legs, penis) palpated, blood pressure measured.

Neurologic examination

A standard neurologic examination, including assessment of mental state, could reveal signs of an underlying neurologic disease. Examination should always address particular information derived from history.

Focused neurologic examination

The sacral segments should be examined with particular care. Skin sensitivity is tested for touch and pain perception in the perineum, perianal and genital skin. The perineal muscles can be palpated, and tested for voluntary and reflex contraction. Anal sphincter and levator ani (pubococcygeus muscle) tone and voluntary and reflex contraction can be palpated, but are usually not examined in the male. The cremasteric reflex (testing the L1 segment), and the bulbocavernosus and external anal reflexes (testing the S2–4/5 segments) should be evaluated. The bulbocavernosus reflex is elicited by squeezing the glans and assessing contraction of the perineal muscles or the anal sphincter (by palpation). The anal reflex is tested by repetitive pricking (or a scratch) delivered to perianal skin (on both sides) and observing anal sphincter contraction.

ESTABLISHING THE DIAGNOSIS

The aim of the history and physical examination is to acquaint the clinician with the state of the general and neurologic health of the patient, including his sexual attitudes, wishes, and above all his functioning. Of the methods available for further diagnostics we can distinguish those for objectively testing sexual function, those objectively defining the neurologic lesion(s), and those clarifying the etiology of the underlying disease, which has caused SD. The specific tests for SD are, at present, neither recommended nor widely used in clinical practice, but are interesting for research (Porst, 2012; Giuliano and Rowland, 2013).

INVESTIGATION OF SEXUAL FUNCTION

Investigation of erectile function

Although essential data will be obtained by history, it is possible to obtain an objective evaluation of erection. Spontaneous and physiologically induced erection can be studied with a variety of techniques. Spontaneous nocturnal penile tumescence (NPT) and rigidity can be measured in the sleep laboratory using strain gauges (measuring penile expansion), visual inspection, and measuring the buckling force (for assessment of rigidity), with polygraphic confirmation of sleep phases; such a procedure is considered the most accurate for determining erectile function (Karacan and Ilaria, 1978; Wasserman et al., 1980). Various low-cost screening tests for NPT have been proposed, but their validity is questionable (Condra et al., 1987). Continuous monitoring of NPT and rigidity can be obtained by a rigidometer during normal sleeping conditions at home (Kaneko and Bradley, 1986), and also during daytime napping (Morales, 1994) or in the awake sexually stimulated examinee (Thase et al., 1988). The utility and limitations of the NPT test have been comprehensively discussed by Morales et al. (1990). Screening tests for NPT were once considered useful to distinguish psychogenic from other causes of erectile dysfunction, but it is now established that they are insufficient on their own to reach such a conclusion. They are no longer recommended as routine tests in the neurologic patient with SD.

Erectile capacity can be tested pharmacologically: given that no major vascular problem is present, an intracorporeal injection of a vasoactive substance (papaverine, combination of papaverine + phentolamine, prostaglandin E_1) will lead to an erection, thus providing "evidence" that erection is possible.The addition of self-stimulation is considered to increase test sensitivity (Lue, 1990). Such testing is not a part of the first-line testing of the neurologic patient with SD.

INVESTIGATING THE NEUROLOGIC LESION

The primary tools to define a possible neurologic lesion are history and clinical examination. This is routinely accompanied by imaging, particularly magnetic resonance imaging for demonstrating structural changes (both in the central but also to some extent in the peripheral nervous system structures). Changes of nervous system function may be demonstrated by clinical neurophysiologic testing. Apart from penile electromyography (EMG) and sensory neurography of the dorsal

penile nerve, the clinical neurophysiologic tests are not specific for innervation of genitalia, but test the lumbosacral segments of the nervous system which are relevant for innervation of the uro-ano-genital region with all its organs. Further information on these tests can be found in Chapter 9.

Clinical neurophysiologic tests

Clinical neurophysiologic tests are, generally, direct extensions of the clinical examination of nervous function; the tests can contribute objective numeric data and often a refinement of the diagnosis, which cannot be achieved by clinical means alone (Vodusek and Fowler, 2004). However, the available neurophysiologic tests are not seen as relevantly benefitting the decision-making process in the individual male patient with SD (Giuliano and Rowland, 2013). The tests are, however, interesting and useful in research on neurogenic SD.

Electrophysiologic tests

In patients with erectile and ejaculatory dysfunction and a suspected neurologic disorder, a diagnosis of involvement of neural and muscular structures related to the genitals and sexual function may be – if relevant – strengthened, refined, and documented by clinical neurophysiologic tests. There are several different methods, classified according to the neuroanatomic subsystem whose function they test. Motor (somatic and autonomic), and sensory (somatosensory and viscerosensory) tests may be distinguished. The methods used are described in Chapter 9.

EMG has been used to demonstrate activation patterns of striated muscles within the sexual response – kinesiologic EMG; as, for instance, demonstrating the pattern of perineal striated muscle activity during ejaculation (Gerstenberg et al., 1990). Concentric needle EMG can identify changes due to both recent denervation and chronic reinnervation, and is considered the method of choice to diagnose lower motor neuron involvement in the lower sacral segments (Vodusek, 1998; Vodusek and Fowler, 2004). Clinical neurophysiogic testing has been much discussed in the past, when the separation of psychogenic and somatic erectile dysfunction seemed more relevant (Haldeman et al., 1995). Of particular interest were the methods testing penile autonomic innervation and smooth-muscle function (corpus cavernosum EMG). Electric activity, spontaneous and evoked by a variety of stimuli, can be recorded by surface or needle electrodes from the penis. (Whether the mechanisms underlying spontaneous and evoked activity and their characteristics are the same has to be clarified.) Both the global pattern of the electric activity, focusing on its appearance and disappearance during flaccidity, tumescence, and detumescence, and the analysis of "individual potentials" (defining the values of parameters such as amplitude, duration, polyphasity) have been advocated. Computer analysis of the signals has been introduced (Wagner and Jiang, 2006). The method seems valid, but results from different laboratories are difficult to compare, and there are open questions related to the sensitivity and specificity of test results. The method is not advocated for routine use in patients.

Testing sensory perception

In addition to clinical testing for sensation, special devices and algorithms can be used for quantifying sensory perception on the genital organs. Such testing has been much discussed in the past, when the separation of psychogenic and somatic erectile dysfunction seemed more relevant, and sensory deficit in the genital area (even subclinical) was hypothesized to be significant in causing SD. Measuring vibratory perception (biothesiometry/vibrametry) on the penis has been found to correlate with results of electrodiagnostic testing (Padma-Nathan, 1988). More informative on nervous control of erection should be tests evaluating small-fiber function, i.e., testing for penile thermal sensation (Yarnitsky et al., 1996). Guidelines for quantative sensory testing have been given by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (Shy et al., 2003). Quantitative sensorimetry is not advocated for routine use in neurologic patients with SD.

Cystometry, other urodynamic tests, and anorectal function tests may strengthen the suspicion of lumbosacral autonomic dysfunction; cardiovascular autonomic testing can strengthen the diagnosis of a systemic autonomic nervous system dysfunction. Such testing is, however, not recommended in the routine assessment of the neurologic patient with SD.

In summary, defining the neurologic lesion is always the first step of the neurologic examination. Defining the etiology of the lesion comes next. In addition to this tenet there is, in an individual patient with neurogenic SD, the question of the particular neurologic lesion responsible for SD (if the effect on the nervous system is complex, as it is in many diseases of both the central and the peripheral nervous system). At present, the issue of the "relevant neurologic lesion" is not routinely pursued in the individual patient; often it is not feasible with the available diagnostic methods, and it does not affect therapy.

It has to be stressed that all testing which diagnoses the neurologic lesion does not "automatically" test neurogenic SD as such; the relationship of test abnormality and actual SD in the individual patient has proven to be

elusive, because partial lesions may not result in overt dysfunction (Vodusek and Zidar, 1987).

INVESTIGATING THE ETIOLOGY OF SD

Laboratory investigation of blood and urine

Basic laboratory data (including sedimentation rate, C-reactive protein, blood cell count, fasting blood sugar, serum lipids, urinanalysis) as well as serum parameters screening for hepatic, kidney and thyroid function should be obtained in every patient suspected of suffering from organic SD. Prolactin and testosterone levels have been proposed as screening tests, but consultation by an endocrinologist is to be preferred for patients suspected of suffering hormone deficiency. Which hormones to be studied depends on the circumstances (sex, age, onset of symptoms) (Lundberg and Wide, 1978).

Laboratory testing of erectile capacity

The diagnosis of the etiology of erectile dysfunction was advanced with the introduction of pharmacologically induced erections. Given that no major vascular problem is present, an intracorporeal injection of a vasoactive substance (papaverine; combination of papaverine +phentolamine; prostaglandin E_1) will lead to an erection, thus strengthening the suspicion of a neurogenic or psychogenic etiology of erectile dysfunction (Mueller and Lue, 1988; Haldeman et al., 1995). The addition of self-stimulation is considered to increase test sensitivity (Lue, 1990).

If intracorporeal injection testing of penile tumescence has strengthened a suspicion of vascular etiology in the male patient with erectile dysfunction, further investigations may be contemplated, and are, as a rule, performed by urologists. Penile blood pressure can be measured using a simple Doppler method and then related to the arm blood pressure. Vascular competence can be measured by angiography, color ultrasonography, and dynamic cavernosography. Intracavernosal pharmacotesting, including color Doppler or duplex sonography of penile arteries to rule out vascular etiology, has been proposed for primary erectile dysfunction (Porst, 2012).

It has been stressed that the purpose of testing should always be defined: pharmacotesting may be sufficient for the majority of patients, and the invasive tests reserved for those in whom surgery is contemplated (Meuleman and Diemont, 1995; Porst, 2012).

The described testing is performed by specialized urologists and is not a part of the first-line testing of the neurologic patient with SD.

CONCLUSION

One cannot stress enough the frequency, and impact, of SD in men of all ages and the current availability of anti-SD drugs does not appear to have changed matters very much. A recent survey (Jannini et al., 2014) shows that one in every 20 young men (age 18–39 years) across different European countries experiences SD and this may well be an underestimate. Compared with controls, SD patients have a significantly higher psychopathologic comorbid burden, a decrease in quality of life, and an impairment in work productivity/activity.

This chapter shows how neurologists need to approach the male patient with SD from the physiologic perspective, keeping in mind that the sexual functioning of the patient has important psychosocial dimensions. The aim of the neurologists is to establish a diagnosis of the neurologic disorder on one hand and the type of SD on the other hand. For the latter, a thorough history is the most important tool, as clinical examination for the SD as such is not possible, and there is no evidence that the various tests will change first-line management decisions.The goal for the neurologist is to distinguish patients in whom treatment of SD can be introduced (see Chapter 24) from those who should be referred to other specialists.

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 9

Approach to the male patient with lower urinary tract dysfunction

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INTRODUCTION

Proper personalized management of every patient requires specific clinical and diagnostic data. How much is needed, determining the number and extent of diagnostic tests, when the tests should be done, and if they need to be followed up will depend on the cause and type of neurologic bladder and the individual patient. In practical terms, it also depends on the setting where the patient is seen, i.e., whether it is a neurologic patient evaluated by a neurologist, a uroneurologist (a term coined by Clare Fowler and meaning neurologist with special expertise in neurogenic lower urinary tract (LUT), bowel and sexual dysfunction), or a neurourologist (the "traditional" specialist with expertise in neurologic disorders of LUT, bowel and sexuality, as a rule with urologic background, but possibly also a gynecologist or rehabilitation specialist).

The neurologic patient with LUT symptoms would, as a rule, have a treating neurologist, who should, ideally, have an understanding of the neurologic LUT dysfunction (LUTD), of the basic aspects of its assessment, and of the first-line treatment. The neurologist should communicate well with the (neuro)urologist when consultation is necessary, and continue to integrate the uroneurologic follow-up of the patient into the general care of all the wide-scale symptomatology that neurologic disease leads to. The patient will undergo specific urologic testing which will indicate objectively how LUT function is altered by the neurologic disease.

The patient originally seen for LUT problems by the urologist will after initial testing be referred to the neurologist if there are symptoms or signs indicative for unsuspected neurologic pathology. LUT symptoms can indeed be the first to appear in diseases such as multiple sclerosis. Frequently primary neurologic testing will not permit a definitive diagnosis of a particular neurologic disease at that time. The urologist will have to start symptomatic treatment but should follow the patient closely. If neurologic signs become more evident, the patient should be referred to the neurologist again.

One can summarize the diagnostic procedure in the neurologic patient with LUT symptoms as: "who, where, and how." "Who" is the particular patient, "where" is the involvement of the nervous system, and "how" relates to how this affects LUT function. In other words, to clarify a particular health problem in an individual patient it is helpful to distinguish between the need to diagnose the neurologic lesion, to rule out "urologic" pathology, and to know the details of the functional disturbance of LUT. Information from patient history, physical exam, imaging and, if necessary, additional testing clarifies the neurologic and/or urologic diagnosis of the lesion and its etiology; with regard to LUTD, physical exam contributes little to understanding, but patient history and functional testing, rationally integrated, reveal the faulty function and allow one to plan management.

An overview of assessment of the male patient with suspected neurogenic LUTD is provided in this chapter.

CLINICAL EXAMINATION

Patient history

The aim of history taking is to gather relevant information to be able to proceed rationally with physical examination and testing. It is helpful to start the assessment with a general overview of the patient's condition: keep in mind his age (is he young, or elderly?); his race; his general condition – good general health or clearly

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suffering; and estimation of his body mass index. Is it possible to communicate with him with regard to language, cognitive abilities, and cooperation?

After this general overview one can proceed with a more detailed history taking.

What is the known neurologic disease?

An inventory of the available data should be made. What is the neurologic diagnosis? How long has the neurologic condition been going on for? Is it a static or progressive condition? What is the extent/grade of the lesion? For instance, in a patient with Parkinson's disease, what is the result of the Hoehn and Yahr scale (Hoehn and Yahr, 1967)? What is the type and stage of progression in a patient with multiple sclerosis (primary or secondary progressive, relapsing, remitting, progressive relapsing or clinically isolated) (Milo and Miller, 2014)? In stroke, the modified National Institutes of Health Stroke Score gives useful information (Meyer and Lyden, 2009). For spinal cord injury (SCI), the American Spinal Injury Association Impairment Scale (AIS) classification can be used: level of lesion, AIS sensory, and motor complete or incomplete (Ditunno et al., 1994, DeVivo et al., 2011). Overall, the examiner should get an understanding of the lesion of the nervous system responsible for LUTD, of the general condition of the patient in terms of sensory deficits, motor and cognitive functions (dementia), and of the prognosis of the disease.

Specific urologic questioning includes previous disease, infections, interventions, and drug intake. The history should also include the assessment of sexual and bowel function, as all pelvic organs are neurologically strongly interrelated, and have a serious impact on quality of life (QoL).

Symptoms to be asked specifically related to urinary symptoms relate both to the storage and the evacuation functions of the LUT.

Storage symptoms are experienced during the storage phase of the bladder and include daytime frequency and nocturia (Abrams et al., 2002).

Daytime frequency is the number of times the bladder needs to be emptied a day. Up to eight times a day is still considered normal for individuals with normal drinking habits and preserved sensation of filling. With loss of sensation and/or need to catheterize the optimal number of emptying times will correspond to the number of catheterizations done. Apart from the neurogenic changes in LUT function, the presence of urinary tract infection (UTI), the intake of bladder-relaxing drugs, and the presence of postvoid residual urine (PVR) influence the number of micturitions.

Nocturia is where the individual has to wake once or more during the night to empty: zero to once is considered normal. In patients with diminished mobility, nocturia can represent a high percentage of total daily output due to pooling in the lower extremities, changes in antidiuretic hormone secretions, and medication (e.g., diuretics). Nocturia must be distinguished from voiding before sleep or after awakening. In neurologic patients, however, such distinction cannot always be made easily, as the emptying at night may be induced by fear of leaking, or may be part of bladder re-education.

Urgency is a sudden compelling desire to pass urine which is difficult to postpone. It does not necessarily coincide with detrusor contractions. Urgency is a sensation and thus is not present where there is complete loss of sensation in the LUT.

Urinary incontinence is any involuntary leakage of urine, and should be further described by type, frequency, severity, precipitating factors, social impact, effect on hygiene and QoL, and the measures used to contain the leakage. Less prevalent in men, it mostly has a severe impact on QoL. Rarely, there may be the need to distinguish incontinence from profuse sweating. Types of urinary incontinence include the following:

- Stress urinary incontinence is involuntary leakage on effort or exertion, on sneezing or coughing. It indicates a loss of resistance at the level of the bladder neck or urethral sphincter.
- Urgency urinary incontinence is accompanied by, or immediately preceded by, urgency.
- Mixed urinary incontinence combines both.
- Nocturnal enuresis is the loss of urine that occurs during sleep.
- Continuous leakage can be the consequence of either bladder overfilling or loss of urethral function.

Sensation is the prerequisite for conscious bladder control. Sensation is considered normal if the patient is aware of how full his bladder is. A distinction between desire to void and strong desire to void can be difficult if sensation is partly absent. Non-specific sensations may be associated with bladder filling (e.g., abdominal fullness, vegetative symptoms, spasticity).

Voiding symptoms are experienced during the emptying phase. In men with neurologic lesions it is important to distinguish between symptoms caused by mechanic obstruction (prostate enlargement) and by deficient LUT function. Information is gathered on the position taken to void, if emptying can be started voluntarily, or if reflex activation or straining is necessary.

Slow stream is reported as reduced urine flow, compared with previous performance or in comparison to others. It may be the consequence of outflow obstruction, weak detrusor function, or both.

Splitting or spraying of the urine stream is due to uneven opening of the urethral canal.

Intermittent stream is the term used when the urine flow stops and starts. This can be the consequence of intermittent urethral spasticity, or bladder contraction that waxes and wanes.

Hesitancy is the term used when an individual describes difficulty in initiating micturition, with delay in onset. It can be caused by bladder neck or urethral sphincter obstruction/spasticity, or by slowly building up bladder contraction.

Straining to void describes the abdominal muscular effort used to initiate, maintain, or improve the urinary stream. It used to be a technique of emptying the denervated bladder, but it has proved to be potentially dangerous and is to be avoided, apart from very rare and well-specified conditions of low pressure and complete voiding with continence between voids.

Terminal dribble is when the final part of micturition has slowed to dribbling.

Postemptying symptoms are experienced immediately after micturition.

A feeling of incomplete emptying can relate to incomplete emptying or to irritation of the LUT.

Postmicturition dribble is the involuntary loss of urine immediately after leaving the toilet. It indicates weak stream or obstruction either in the urethra or externally. It can also be the consequence of improper use of a catheter in the end stage of self-catheterization, with urine left in the catheter.

Gathering information on LUT symptoms should provide a clinical hypothesis of whether it is storage or emptying the bladder which is the main problem. Furthermore, information on previous and present management of LUTD needs to be collected, as well.

Emptying by catheterization

How often intermittent catheterization is done per day, who performs it, which material is used, and which technique is used are problems encountered during catheterization. If an indwelling catheter is permanently used, is it transurethral or suprapubic, which type, what is the interval between changes, are any problems encountered?

Indications of complications

Urinary complications are amongst the most frequent. Warning signs such as hematuria, blood on a catheter, fever, pain, very cloudy urine, blockage of catheters, autonomic dysreflexia, spasticity, and stone fragments found in a collecting device warrant further urologic investigation.

In patients with progressive disease it is useful to know the onset of symptoms, which will often differ from the time of diagnosis, and eventual changes in symptom severity. Patients with a "fixed" neurologic condition, such as after SCI, may report symptom changes if prompted.

Voiding diary (frequency/volume chart)

A frequency/volume chart is an important diagnostic aid, recording fluid intake and urine output per 24-hour period of daily life. The chart gives objective information on the number of times of voiding, the distribution of voiding between daytime and nighttime, and each voided volume. The chart can also be used to record grades of desire to void and leakage and the number of incontinence pads used. The urinary diary is also useful in patients who perform intermittent catheterization. Important information that can be gained are time and volume for each voiding or catheterization, total volume over the period of the recording or 24-hour volume, diurnal variation of volumes, voiding and incontinence interval, and fluid intake (De Wachter and Wyndaele, 2003a). For patients who use catheterization, one can assess residual urine.

A frequency/volume chart is generally recommended in the routine evaluation of the neurologic patient with LUT symptoms, although there is no consensus on the necessary number of days during which the data should be collected. Three consecutive days are a practical compromise between too short to be representative and too long to obtain compliance with the test (Naoemova et al., 2008). Examples of frequency/volume charts are presented in Tables 9.1 and 9.2.

Questionnaires

Collecting a relevant standardized set of patient data has become indispensable to conduct research. This has led to the development of a large number of questionnaires for different patient populations and different pathologies. In addition specific questionnaires have been developed to assess QoL. QoL is considered the most important outcome measure today.

We list the relevant questionnaires available for neurogenic bladder dysfunction (Welk et al., 2013). As a rule these are used in research, but not in routine clinical practice.

There are data sets for use in SCI individuals (Biering-Sørensen et al., 2008; http://www.iscos.org.uk/international-sci-lower-urinary-tract-function-data-sets), and for a variety of neurogenic conditions from the National Institutes of Health Common Data Elements (http:/www.commondataelements.ninds.nih.gov).

Derived from the King's Health Questionnaire, the International Consultation on Incontinence Questionnaire (ICIQ) modules are patient-completed questionnaires evaluating QoL in urinary-incontinent patients and thus not specific for those with neurogenic bladder.

Table 9.1

Sensation-related frequency/volume chart as used in daily practice

Frequency/volume chart

Date:
Name+given name:
Hour getting up:
Hour going to bed:

Time	Volume fluid intake (mL)	Volume voided (mL)	Reason for voiding (1–5)	Urine leakage	Quantity lost (1–3)	Awakening for voiding

Reason for voiding: 1, no desire to void/convenience void; 2, light desire to void; postponing for at least 30 minutes is possible; 3, normal desire to void; postponing longer than 15 minutes is not possible; 4, strong desire to void; postponing is not possible for longer than 5 minutes; 5, urgency, pain.
Quantity lost: 1, drops; 2, underwear wet; 3, garments wet.
Adapted from De Wachter and Wyndaele (2003a); Naoemova et al. (2008).

Table 9.2

Frequency/volume chart of a patient with neurogenic urgency and urgency incontinence

Frequency/volume chart

Date: dd/mm/yyyy
Name+given name: Patient one
Hour getting up: 07.20
Hour going to bed: 22.00

Time	Volume fluid intake (mL)	Volume voided (mL)	Reason for voiding (1–5)	Urine leakage	Quantity lost (1–3)	Awakening for voiding
5.20		150	4			+
7.00	150					
7.23		90	2			
7.25	200					
7.38		75	4	+	1	
8.50		165	3			
8.52		50	1			
10.00	100					
11.25	75					
11.26		150	3			
12.55	200					
15.16		160	4	+	1	
16.06	150					
16.08		130	3			
17.00	75					
17.45	75					
17.56		70	4	+	2	
18.24	100					
20.07		140	3			
20.30	75					
21.50		50	3			
23.45		70	4	+	1	+
02.45		160	4			+
06.23		190	4			+

Reason for voiding: 1, no desire to void/convenience void; 2, light desire to void; postponing for at least 30 minutes is possible; 3, normal desire to void; postponing longer than 15 minutes is not possible; 4, strong desire to void; postponing is not possible for longer than 5 minutes; 5, urgency, pain.
Quantity lost: 1, drops; 2, underwear wet; 3, garments wet.

But the ICIQ is a detailed and robust measure to assess the impact of urinary incontinence with specific reference to social effects. It has been translated into many languages.

Instruments for QOL measurement are available for specific populations, such as the Quality of Life Profile for Adults with Physical Disabilities (Renwick et al., 2003) or the Multiple Sclerosis Quality of Life-54 (Vickrey et al., 1995). The Qualiveen (Costa et al., 2001) was developed to measure urinary-related QoL among SCI patients. It has been used in other neurologic conditions and translated into Italian (Bonniaud et al., 2011), Portuguese (D'Ancona et al., 2009), English (Bonniaud et al., 2005), German (Pannek et al., 2007), and Spanish (Ciudin et al., 2012). The Neurogenic Bladder Symptom Score is a tool to measure urinary symptoms and consequences among patients with acquired or congenital neurogenic bladder. It was found to have appropriate psychometric properties (Welk et al., 2014).

QoL data should be interpreted critically. Though important, QOL scores do not allow a clinician to assess specific clinical domains or relate changes to specific clinical parameters. An intervention may significantly change bladder symptoms – as measured, for example, by the American Urology Association Symptom Score (Barry et al., 1992) – without improving QoL (Welk et al., 2013). A separate QoL question assesses the impact of those symptoms. The two sections do not necessarily correlate: severe symptoms can have no impact on a person's QoL, and some patients rate their QoL as poor despite only mild symptoms.

Some questionnaires and QoL instruments developed for non-neurogenic conditions have been validated in the neurogenic bladder population (Schurch et al., 2007). In a recent review, 13 QoL instruments were compared: the Patient Reported Impact of Spasticity Measure (PRISM), Quality of Well-being Scale, Qualiveen, Sickness Impact Profile (SIP68), Short Form (SF)-36, SF-36 V, SF-12, SF-6D, Quality of Life Index, Quality of Life Profile for Adults with Physical Disabilities (QOLP-PD), Satisfaction with Life Scale, Sense of Well-being Index (SWBI), and the World Health Organization Quality of Life-BREF scale (WHOQOL-BREF). The SF-36 and WHOQOL-BREF have been widely used and validated. The SIP68, QOLP-PD, SF-36 V, and SWBI were found to be promising with limited investigation. The Qualiveen and PRISM performed well in SCI patients (Hill et al., 2010). Because of the importance of looking into bladder, bowel, and sexual functions together, questionnaires exist that evaluate them at the same time in a single patient (Wyndaele et al., 2011). The validated tests are now in the process of being evaluated for their specific usefulness in neurologic patients.

Physical examination

Physical examination builds on the information gathered by history and should be tailored to the individual patient. An outline is provided here for guidance. It will include testing of motor, sensory, and reflex function in the lower sacral segments (see below); also observation of signs accompanying LUTD, such as endocrinologic malfunction, spinal deformities, dysraphism, and foot deformities.

The examination includes the following tests:

- Testing sensation of the perineum for light touch and pain with cotton wool and pin (both sides) (Fig. 9.1). The different dermatomes correspond with T11–S5 innervation and give some information in relation to the hypogastric, pelvic, and pudendal nerve part of the innervation of the LUT. Presence of sensation means that a neurologic lesion is incomplete and permits afferent information from the respective part of the body to reach the somatosensory cortex. Testing sensation is probably the most dependable and informative part of the neurologic examination of the patient with LUT symptoms, but requires the general caveats of sensory testing. It is worthwhile blinding the testing for the patient and including non-stimulation with stimulation in order to control the accuracy of the responses. An individual with a neurologic deficit may strongly want to feel without being able to. (Sensation of bladder is tested in the context of urodynamic testing.)
- Basic tone of the anal sphincter is tested by finger palpation/insertion into the anal canal. The sphincter is lax when there is peripheral motor denervation and spastic in cases of decentralization.
- Voluntary contraction of the bulbospongiosus, anal sphincter, and pelvic muscles should be tested and in males is normally present if the corticospinal tract is

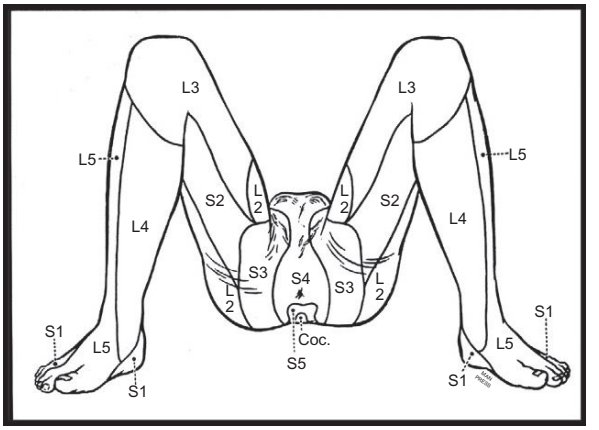

Fig. 9.1. Dermatomes corresponding with somatic and parasympathetic lower urinary tract innervation: S2–S4.

preserved up to the level of the lowermost segments in the body.

- Reflexes (Table 9.3):
  - The cremaster reflex tests the L1–2 segments, which is at the same level as sympathetic innervation of the bladder and bladder neck. It is tested by a short stroke/scratch of the skin (with a finger or a wooden stick) at the inguinal level and the upper inner thigh. A brisk elevation of the ipsilateral scrotum is the normal response. The reflex should be tested on both sides. Distinction should be made with contraction of the dartos muscles by touching the scrotal skin.
  - The bulbocavernosus reflex (BCR) corresponds with the spinal cord levels S2–5, at the level of both the parasympathetic and pudendal innervation of the LUT. It is elicited by a brisk squeeze of the glans; contraction of the perineal muscles and the anal sphincter can be observed visually; digital palpation of the response is probably more sensitive.
  - The anal reflex tests the lowermost sacral segments, S4–5. It is tested by pricking the perianal skin unilaterally with a pin and observing contraction of the anal sphincter. The reflex should be tested on both sides. Another technique consists of making a brisk lateral movement with the fingertip brought into the anus: The sphincter will grab the finger.

The results from the exam need to be interpreted with some caution, taking into account the possibility of poor cooperation and physiologic variability.

The clinical neurologic evaluation tests give additional indirect information on the lesion which has been formulated with information from the history. Testing for sensory loss and reflexes has been traditionally assumed to demonstrate well the neurologic lesion responsible for neurogenic LUT dysfunction. Blaivas et al. (1981a) found absence of BCR in a male patient highly suggestive of a neurologic lesion. Compared to a neurologically normal male (98% clinically present reflex and 100% on electromyography (EMG)), in patients with complete sacral lesion there was 100% absence of clinical and EMG reflex, and in incomplete lesions the reflex was clinically present in 44% (in 78% on EMG). In a group with suprasacral spinal cord lesions 90% had demonstrable BCR (93% on EMG). Loss of pinprick sensation in patients with T12–L1 fractures and SCI correlated with poor recovery of LUT function (Schurch et al., 2003).

A negative neurologic exam does not, however, rule out neurogenic LUTD, since it is only the somatic nervous system which is tested clinically. Watanabe et al. (1998) found in patients with thoracolumbar vertebral fracture that occult LUTD was present in 62% with intact pinprick sensation and in 59% with intact BCR.

Knowledge about the neurologic lesion is important *per se*; extrapolation from the neurologic lesion to the nature of the neurogenic LUTD is, however, only possible to a certain extent (Norris and Staskin, 1996). Wyndaele (1997) found, for instance, a correlation between different levels of spinal cord lesion, the function of bladder neck and sphincter, and the anal reflex and BCR. In practice, predicting bladder function from results of clinical examination may be feasible in some groups of patients, but, generally, it has severe limitations. Clinical neurologic findings in 47 children with lumbosacral myelodysplasia did not correlate with LUTD as diagnosed by urodynamic studies. The level of intact skin sensation, and the presence or absence of bulbocavernosus and anal reflexes could not significantly predict the function of the detrusor muscle, proximal urethra, and striated urethral sphincter. Thus, clinical neurologic examination cannot outline the urologic management in these patients (Wyndaele and De Sy, 1985). Similarly, in patients with T12–L1 fractures and SCI it proved impossible to predict neurogenic voiding dysfunction by sensory evaluation in the perineal area (Schurch et al., 2003).

Table 9.3

Somatic reflexes corresponding with the peripheral innervation of the lower urinary tract

	L1	Cremaster reflex
Knee reflex	L2	
	L3	
	L4	
Ankle reflex	L5	
	S1	
	S2	Bulbocavernosus reflex
	S3	
Anal reflex	S4	
	S5	

Prostate palpation

The (neuro)urologist will also look for urologic conditions to be ruled out as a reason for LUT symptoms in the neurologic patient, such as penile and scrotal abnormalities. Here, we shall only include examination of the prostate.

Transrectal palpation of the prostate is an integral part of clinical neurourologic diagnosis in men. In animal experiments, it has been known for a long time that neurogenic factors play an important role in prostate hypertrophy. Prostate growth is detectable in SCI individuals (Pannek et al., 2003) but recently it was described that the prostate volume of men with complete SCI was significantly smaller than that of able-bodied men,

implying that sustained central innervation of the prostate plays an important role in prostate growth (Pannek et al., 2013). An inverse relationship between age at onset of the neuropathy and volume has been described (Bartoletti et al., 2009).

During the palpation and further testing one must be aware that prostate cancer has been described in aging patients with neuropathy, though with lower incidence then in the general population (Wyndaele et al., 1998; Gignoux et al., 2007). Searching for carcinoma should mostly be done in patients with a life expectancy greater than 10–15 years. If prostate cancer is discovered it tends to be of a more advanced stage and grade, possibly related to decreased use of screening (Scott et al., 2004).

Laboratory tests

Urinary tests

UTI is prevalent in neurogenic LUTD, and should be ruled out first. The interpretation of a urine sample test in a man with neurogenic bladder must take into account the way of bladder emptying, presence of indwelling catheter, symptoms, previous history and treatment, and confounding diseases.

Urinalysis in patients with neurogenic bladder is done with midstream specimen if this is functionally possible or by catheterization (Barnes et al., 1992). The frequency of examining urine samples differs greatly between studies. Several investigators advocate daily use of a dip slide technique during the acute phase of a UTI after SCI, once a week during the subacute phase and monthly or a few times a year in long-term care, though this is not recommended by all (National Institute on Disability and Rehabilitation Research Consensus Statement, 1992).

Because catheter urine specimens are not as likely to be contaminated by periurethral flora as are voided urine specimens, low colony counts more easily represent true bladder bacteriuria in patients performing intermittent catheterization (Hooton et al., 2010). Unfortunately, there is no standard definition for significant bacteriuria in samples from catheterization. A colony count of 10^2 cfu/mL specimen had optimal sensitivity and specificity, compared with paired suprapubic aspirates (Gribble et al., 1988). Most patients have colony counts of 10^5 cfu/mL. The international guideline on catheter-associated UTI suggests a quantitative count of at least 10^3 cfu/mL as a reasonable compromise between sensitivity in detecting UTI and feasibility for the microbiology laboratory in quantifying organisms (Hooton et al., 2010). One also needs to take into consideration the bacterial species. *Escherichia coli* and other Gram-negative bacteria are more virulent and could most likely be the causative agent even in low bacterial concentrations, while other bacteria, such as coagulase-negative staphylococci, or some streptococci, are doubtful pathogens, even in higher concentrations.

Also in meningomyelocele/spina bifida, explicit definitions for UTI are heterogeneous (Madden-Fuentes et al., 2013).

E. coli is considered the dominant species in several studies (Wyndaele et al., 2012). From the bacteria on the periurethra, *E. coli* is most frequently associated with bacteriuria (Schlager et al., 1999). *E. coli* isolates from patients who develop symptomatic UTI may be distinguished from bacteria recovered from patients who remain asymptomatic and possibly from normal fecal *E. coli* (Hull et al., 1998).

Pyuria is evidence of inflammation in the genitourinary tract, but is not helpful in establishing a diagnosis in patients with neurogenic bladder (Cardenas and Hooton, 1995). In a feverish catheterized patient without pyuria a different diagnosis than UTI is probable.

A standardized format for the collection and reporting of a minimal amount of information on UTIs in daily practice or research has been developed for SCI individuals (Goetz et al., 2013).

UTI in a neurologic patient, in whom LUT function has not been assessed as yet, calls for further diagnostics, in the first step testing for PVR.

Blood tests

Blood tests done to evaluate general condition, renal function, and inflammation are routinely performed.

In male patients with neurogenic bladder the prostate-specific antigen (PSA) may need special interpretation. It has been shown that serum PSA value distributions in neurogenic men are very similar to those of the general population, though lower values of PSA and serum testosterone have been found in SCI men (Bartoletti et al., 2009). The presence of an indwelling catheter and older age may result in higher PSA levels (Konety et al., 2000; Pannek et al., 2003). In SCI patients, clean intermittent catheterization can double the PSA value (Torricelli et al., 2011).

Recently new research data have challenged the clinical value of PSA for screening. However this does not make the test overall invalid. A high PSA level in a patient with LUTD can indicate prostatitis or carcinoma. Further evaluation is the role of the urologist.

TESTING LOWER URINARY TRACT FUNCTION

Measuring postvoid residual urine

Measuring PVR is a basic diagnostic procedure in a neurologic patient with LUT symptoms, and should already be ordered by, or performed in, the neurology department. In practice, it is assessed with ultrasonography

(bladder scan is specific equipment for this). This will give a good estimate of PVR; catheterization provides a more exact volume measurement and is typically performed after uroflowmetry/pressure–flow study (see below). The amount of "normal" PVR is a matter of dispute. In neurologic patients, amounts above 100 cc are usually considered as reasons for introducing active management (as a rule, intermittent catheterization).

Urodynamic tests

Urodynamic testing is the objective evaluation of LUT function. Through measurement of urinary flow, pressures in hollow spaces, potentially combined with EMG of sphincter muscles, and imaging, information is obtained on LUT behavior during bladder filling and voiding, and some quantitative data, valuable for management decision making and follow-up of patients (Fig. 9.2).

Classic urodynamic techniques – uroflowmetry, filling cystometry, and pressure–flow study – provide an assessment of several functional parameters in patients with neurogenic bladder (Wyndaele, 1984) (Fig. 9.3). This does not need very elaborate equipment because even a one-channel measuring technique can provide helpful information in the hands of an experienced investigator (Wyndaele et al., 2009) (Fig. 9.4).

The International Urodynamic Basic Spinal Cord Injury Data Set proposed data to be included in the urodynamic evaluation of patients with SCI. Variables included bladder sensation during filling cystometry, detrusor function, compliance during filling cystometry, function during voiding, detrusor leak point pressure, maximum detrusor pressure, cystometric bladder capacity, and PVR. Technical details can be found in the urologic literature (Biering-Sørensen et al., 2008). Some specific investigational aspects are discussed in more detail below.

Measuring urinary flow

With a watch and measuring jug, a time/volume evaluation of male voiding is easily possible, but only average flow is measured thus. With a specific flowmeter a more detailed evaluation can be done: time of flow onset, maximum flow, average flow, volume voided. A curve permits also more detailed information on how the flow actually occurs, with peaks, slow start, or postvoid dribbling. To be accurate, a minimal volume voided is needed (estimated as >150 mL), the position used by the patient in normal circumstances, and a voiding recognized by the patient as corresponding to that in daily life. One uroflow measurement is generally considered not to be representative and the test should be repeated two to three times.

In neurologic patients with newly present LUT symptoms, urinary flow measurement with PVR determination is useful to rule out urinary outflow obstruction as the cause of symptoms. Many patients with neurogenic bladder, however, cannot fulfill the conditions for valid uroflowmetry because of the impossibility of starting to void voluntarily, leakage, or positioning problems.

Cystometry

Cystometry allows the measurement of detrusor pressure. It is imperative to diagnose too high intravesical pressure (during filling or with attempts to void) as this is considered the main cause of neurogenic upper urinary tract (UUT) and LUT complications. UUT complications – ultimately kidney failure – are the most ominous threat to well-being and life itself in patients with neurogenic LUTD. Bruschini et al. (2006) evaluated the UUT and LUT in myelomeningocele patients without adequate urologic management with clinical, urodynamic, and imaging evaluation. The urodynamic data

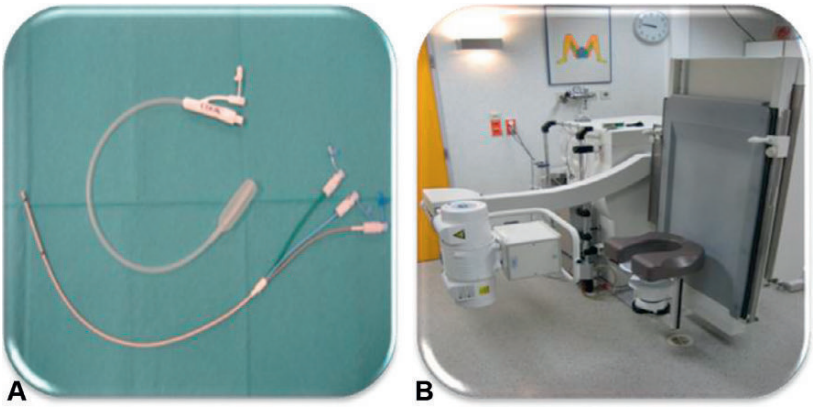

Fig. 9.2. Equipment used for videourodynamic assessment. (**A**) Different catheter for measurement of bladder, urethral, and bowel pressure. (**B**) Radiologic table for video urodynamic testing and integrated urodynamic equipment (University Hospital Antwerp, Belgium).

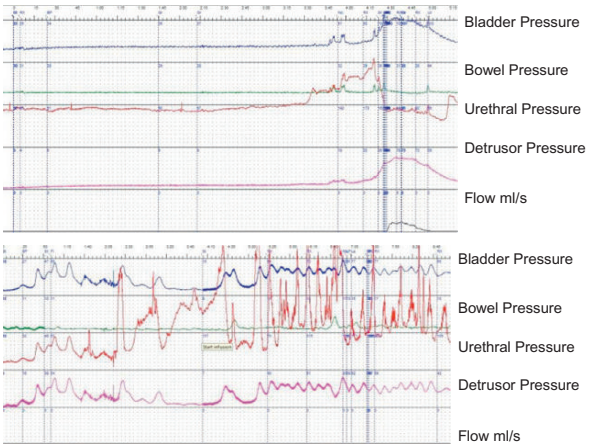

Fig. 9.3. Urodynamic traces in patients with neurogenic bladder. During filling an overactive, involuntary contraction occurs with involuntary voiding but synergic opening of the urethral sphincter.

During filling repeated overactive, involuntary contractions occur with simultaneous strong dyssynergic contractions of the urethral sphincter, preventing leakage but creating a very unsafe high-pressure bladder.

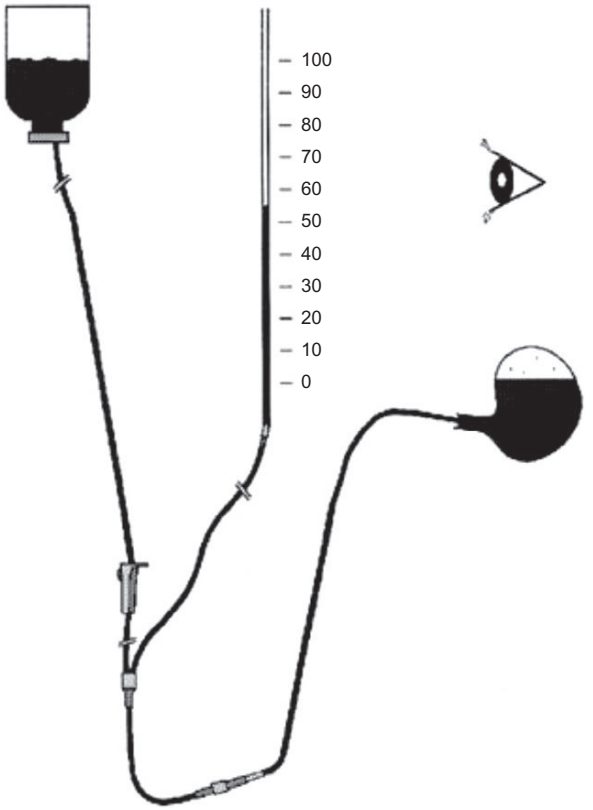

Fig. 9.4. One-channel urodynamic testing. As shown on the figure, there is only one pressure-measuring channel in the bladder and pressure changes are observed on an open pressure line. This testing is inexpensive and permits good basic information if properly performed (Wyndaele et al., 2009).

were correlated with the status of UUT. Cystometry showed normal parameters in only 1% of patients and major dysfunctions in the rest. Detrusor leak point pressure over 40 cm H_2O was associated with UUT damage. Patients with reduced functional bladder capacity $\leq$33% had more renal scars than their counterparts. The figure of maximal pressure of 40 cm H_2O reflects maximal physiologic activity in the ureter in most circumstances.

Interpretation of pressure measurements needs to be done with care. Not only pressure as such but also the duration of the dangerous pressure, and leakage, have to be taken into account. Leakage can be a natural protection against too high pressure. Incontinence treatment must be done together with treatment to lower bladder pressure. The cystometrogram (CMG) filling rate is very important, especially in neurologic patients: De Gennaro et al. (1996) performed urodynamic monitoring over 6 hours and found that this was feasible and permitted a better diagnosis than standard cystometry. Zermann et al. (1997) detected new findings in 45% of children when natural filling was used instead of classic conventional videocystometry. Ko et al. (2002) used filling with diuretics in patients with SCI and neurogenic bladder and found significant differences in neurogenic overactive bladders, but not in hypoactive bladders. The experienced investigator will balance the need for accurate numeric function diagnosis with the time needed for a test, and critically assess the changes in cystometric parameters induced by the technique.

As a rule it is not practical to empty the bowel just before leaving for a urodynamic test, as often bowel evacuation will start after the rectal balloon has been introduced. It is needed to treat a UTI before or accept that the results may be influenced by the infection.

Testing bladder sensation

Cystometry not only allows detrusor pressure to be measured, but importantly also tests bladder sensation. During routine cystometry bladder sensation is assessed by recording first sensation of bladder filling, first desire to void, and strong desire to void. In 52 SCI patients, 26% of those with a supposed complete lesion had sensation of bladder filling during cystometry (Wyndaele, 1991). Also in 41 patients with myelodysplasia the perception of bladder filling proved, rather unexpectedly, to be present in the majority of patients (Wyndaele, 1992). A large cohort study clearly showed that impaired perception of bladder filling during CMG is a sign of a neurologic condition (Wyndaele, 1993a). Ersoz and Akyuz (2004) found bladder-filling sensation in SCI patients present to some degree in all "incomplete patients," in 82.4% of patients with "complete" lesions below T10, and in 38.9% of

patients with "complete" lesions above T11. Bladder-filling sensation investigations were reproducible in terms of bladder-filling sensation category in 36 SCI patients who had a second CMG, offering the potential for sensation-dependent bladder emptying. However, safety is dependent on the urodynamic situation (Shin et al., 2008).

Measurements of electric thresholds add clinically non-obtainable information to sensory function of the LUT (Markland et al., 1965). Several authors have studied their value in neurogenic bladder dysfunction (Frimodt-Moller, 1972; Kieswetter, 1977; Powell and Feneley, 1980). Wyndaele (1993b) found that disturbed electrosensation indicated the possibility of an unsuspected neurologic condition. Electrosensation was present in many meningomyelocele patients with absent skin sensation and absent reflexes and in many patients with suspected complete SCI on clinical evaluation (Wyndaele, 1991, 1992). Standardization is necessary to obtain reproducible results (De Wachter and Wyndaele, 2003b).While there are some data showing that determining threshold of different fiber types selectively may be possible with sinusoidal current (Fujihara et al., 2011), such fiber selectivity needs to be further studied (De Laet et al., 2005). Palmar sympathetic skin response (SSR) and perineal surface EMG recordings have been used to demonstrate sensations more objectively during cystometry. The activity of both appears and increases in parallel with the first sensation of bladder filling, and with the first desire to void, respectively (Reitz et al., 2003). There is no established clinical use for any of the described tests other than simple reporting of sensation during cystometry. However when sensations are reported during bladder filling they have an important impact on urologic treatment possibilities.

Electromyography during cystometry

EMG is performed during cystometry to obtain information on striated sphincter muscle behavior during bladder filling, and, particularly, voiding.

In health, voiding is characterized by cessation of motor unit firing in the urethral sphincter prior to detrusor contraction, as can be demonstrated by recording of "kinesiologic sphincter EMG." Bladder sphincter coordination is often impaired with lesions between the upper pons and the lower sacral spinal segments. Consequently, sphincter activity is not inhibited, and often increases before and during detrusor contraction (this finding is called detrusor sphincter dyssynergia).

Other pelvic floor muscles (i.e., pubococcygeus) reveal similar activity patterns as the urethral and anal sphincters but formal studies have only been performed in women. The pubococcygeus relaxes during voiding; the muscles on either side act in unison (Deindl et al., 1993). Little is known about the complex activity patterns of different pelvic floor muscles (the urethral sphincter, anal sphincter, other perineal muscles, and different parts of the levator ani) during different maneuvers, particularly in males, where, apart from sphincter muscles during voiding, only perineal muscle activity during ejaculation has been formally studied by kinesiologic EMG. It is generally assumed that all pelvic and perineal muscles act in a coordinated fashion (functionally as one muscle), and thus the recording of the external anal sphincter (EAS) EMG is often substituted for the EMG of the external urethral sphincter during urodynamic testing. The striated urethral sphincter is situated in the male deep at the apex of the prostate, and is not easily accessible; its EMG is a more invasive and more operator-dependent technique than the EAS EMG. However, coordinated behavior of pelvic and perineal muscles may be lost in abnormal conditions.

In routine urodynamic testing urologists will often use surface electrodes placed on the perineum. They permit a qualitative information of pelvic muscular activity.

In routine diagnostics (kinesiologic or "urodynamic"), EMG has been included in urodynamic testing to determine the causes of incomplete emptying of the bladder, i.e., detrusor sphincter dyssynergia (Sundin and Petersén, 1975; Mayo and Kiviat, 1980). Blaivas et al. (1981b) described, on the basis ofCMG-EMG, three types of dyssynergia: type 1 had a crescendo increase in EMG activity that reached a maximum at the peak of the detrusor contraction; type 2 had clonic sphincter contractions interspersed throughout the detrusor contraction; and type 3 was characterized by a sustained sphincter contraction that coincided with the detrusor contraction. Using EMG recordings, Aoki et al. (1985) could define interferences caused by the urethral catheter used for urodynamic measurements. The authors also found that the Credé maneuver exaggerated the detrusor sphincter dyssynergia. Pavlakis et al. (1983) studied CMG concomitant with perineal floor and rectus abdominis EMG and concluded that the addition of EMG can improve the recognition of intravesical pressure elevation owing to voluntary contraction of the abdominal musculature. Videourodynamic data and continuous pressure measurement in the urethra were found to be less reliable for the diagnosis of detrusor sphincter dyssynergia than adding EMG during urodynamic testing (De et al., 2005).

There are other clinical situations that mimic detrusor sphincter dyssynergia. Sphincter contraction or failure of relaxation during involuntary detrusor contractions can be seen in patients with Parkinson's disease. The pelvic floor muscle contractions mimicking dyssynergia may be a learned abnormal behavior – dysfunctional voiding (Rudy and Woodside, 1991), and of Fowler's

syndrome, although in the latter the EMG activity is in fact abnormal spontaneous activity of muscle fibers, not inappropriate activation of motor units. Fowler's syndrome has only been described in women (Fowler et al., 1988).

Videourodynamics

Videourodynamic testing permits urodynamic measurement along with imaging of bladder, bladder neck, and urethral sphincter activity during filling and voiding (Fig. 9.5). It is considered the gold standard of diagnostics of LUT function, and its use is advocated in complex neurogenic LUTD (Madersbacher, 1977; Sakakibara et al., 2001). There is limited access to videourodynamics in many places since not all urologic departments possess a radiologic table or it is not possible to perform the testing in the radiology department.

Ultrasonography during urodynamic testing also has proven clinical utility (Perkash and Friedland, 1987).

Cystometry complications

Hematuria due to the urethral catheter, the development of edema in the urinary bladder wall, and the development of urinary bladder spasm are most frequently reported (Pannek and Nehiba, 2007). Symptomatic UTI developing after cystometry warrants antibiotic prophylaxis (Latthe et al., 2008).

Recommendations for urodynamic testing

Urodynamic testing in neurologic patients with suspected neurogenic LUTD is generally postulated by neurourologists, and the standards adhered to have been published (Abrams et al., 2002).

Many studies illustrate the need for urodynamic testing, particularly in patient groups with pathology of the spinal cord and cauda equina. No difference in cystometric capacity and intravesical leak point pressure at terminal detrusor overactivity was shown between complete and incomplete SCI patients in a survey by Moslavac et al. (2008): incomplete SCI patients with neurogenic detrusor overactivity should be tested with cystometry and observed with the same caution as complete SCI patients. In men with SCI, cystometric variables and detrusor overactivity remain consistent over sequential studies, as shown in a study by Ockrim et al. (2005). The importance of urodynamic tests for diagnosis and follow-up is particularly clear in patients with tethered-cord syndrome (Kang et al., 2006; Abrahamsson et al., 2007). Pressure–flow study can demonstrate high-pressure voiding also in neurologic patients due to urethral relaxation failure (Nitti et al., 1996, Sakakibara et al., 2000).

Neurourologists tend to recommend urodynamic tests in all cases of neurologic bladder dysfunction, but, for various reasons, they are rarely performed (Kitahara et al., 2006. However, patients with known or suspected lesions within the spinal canal should definitely have the opportunity to be assessed in depth by urodynamic measurements. Other neurologic patient groups should be tested if basic evaluation and treatment failed, or complications occur.

It should be kept in mind that neither neurologic disease nor the LUTD as its consequence are stable conditions; thus neurourologic assessment needs to be followed up and urodynamics repeated if symptoms persist, return, or change.

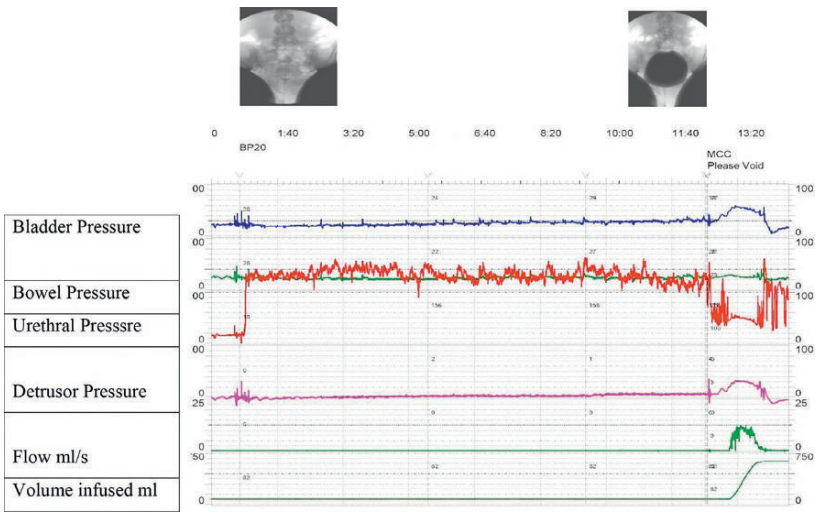

Fig. 9.5. Videourodynamic trace. The different lines represent different pressures measured in the bladder, bowel, and urethra; flow; and volume infused. Video images enable the process to be followed on radioscopy. A normal trace is shown with normal bladder filling, voluntary initiation of voiding with detrusor contraction, and relaxation of the urethral sphincter.

It should also be acknowledged that urodynamic testing has shortcomings and pitfalls. The interpretation can only be done properly after education, training, and expertise.

Additional test to help assess the neurologic lesion responsible for LUTD

Any particular dysfunction of LUT may be neurogenic, but as a rule this is "proven" by inference and by ruling out non-neurologic causes. A neurologic disease *per se* is no proof that the incontinence or the retention in a patient is "neurogenic." One approach to solve this conundrum is to focus on testing specifically the innervation of LUT itself by all means possible, but particularly by clinical neurophysiologic tests – see below.

Of course it would be desirable to have specific tests to prove in the "end organ" (LUT) itself that its affection is neurogenic. For this purpose, special neurourologic tests have been introduced specifically to prove the neurogenic nature of LUTD. Although described many years ago, these tests are not as yet generally accepted and unfortunately are not often used. They have clinical utility and should be further explored.

Ice-water test

The ice-water test (IWT) is based on the principle that mucosal temperature receptors can elicit a spinal reflex contraction of the detrusor, a reflex that is normally inhibited by supraspinal centers. If a neurologic lesion interrupts these inhibitory pathways, a reflex can develop. IWT is of course negative if the bladder is denervated.

Though originally developed for bedside use, a simultaneous measurement of intravesical pressure permits false-negative tests to be ruled out. A positive test has been shown in around 95% of patients with complete and 91% of those with incomplete neurologic detrusor overactivity. About 75% of patients with multiple sclerosis, Parkinson's disease, or previous cerebrovascular accident had a positive IWT. All patients with lower motor neuron lesions, or pure stress incontinence, had a negative IWT (Geirsson et al., 1994; Ronzoni et al., 1997). Repeating the IWT two to three times consecutively has been shown to increase its positivity (Van Meel et al., 2007). Combining the IWT and electric perception threshold will reinforce the results of both tests and can indicate more clearly the possibility of an unsuspected neurologic pathologic finding in patients with idiopathic overactivity of the detrusor. In multiple sclerosis it may clarify the nature of the lesions (Ismael et al., 2000).

In SCI patients, autonomic hyperreflexia can occur during the IWT, and one has to watch carefully for signs, particularly if an investigation is done in a patient with spinal cord lesion at T6 or above.

Bethanechol supersensitivity test

Based on the knowledge that, following denervation, an organ develops hypersensitivity to its excitatory neurotransmitter, Lapides et al. (1962) introduced the bethanechol supersensitivity test in order to distinguish between a neurologic and a myogenic etiology of detrusor hypocontractility. In a study on patients with neurologic and non-neurologic detrusor areflexia, the sensitivity of the bethanechol supersensitivity test for detecting neurologic areflexia was 90%, and specificity 95.6% (Sidi et al., 1988). The test was positive in patients with acute idiopathic autonomic neuropathy (Sakakibara et al., 2004). The test is not generally accepted and several authors caution about the many variables that influence the outcome of the test. Bethanechol as a muscarinic agonist has furthermore been suggested for treatment of poor bladder emptying; a positive response to the test, however, does not predict improved voiding function after subcutaneous or oral administration of the drug (Wein et al., 1980). Bethanechol has also been used for treatment of poor bladder emptying in patients with non-neurologic LUTD (De Wachter et al., 2003).

SPECIAL UROLOGIC INVESTIGATIONS

The urologist can decide to perform endoscopy, more elaborate imaging, and ultrasonography in patients with neurologic LUTD who report alarm signs or in whom LUTD management proves difficult (Şekerci et al., 2014).

CLINICAL NEUROPHYSIOLOGIC TESTING

Traditionally, the diagnosis of neuromuscular system pathology is supported and "objectified" by clinical neurophysiologic testing. Such testing in the uroanogenital region has also been called "uroneurophysiologic." Its role in research in LUT function generally, and in neurogenic LUTD in particular, is recognized but its role in routine diagnostics of patients with suspected neurogenic LUTD is limited; mostly it is helpful to patients with peripheral nervous system involvement, who need a more detailed diagnosis thereof. Historically, clinical neurophysiologic techniques have been swiftly introduced to the uroanogenital region shortly after original tests were formulated for "general clinical neurophysiology," i.e., investigation of muscles, and nerves in the limbs. Primarily, their usefulness was recognized for research, for instance to elucidate the innervation of pelvic floor muscles, and to study the physiology of sacral reflexes. Eventually they were also

adopted in routine diagnostics of patients with neurogenic LUT dysfunction (also anorectal and sexual dysfunction), as the striated pelvic floor and perineal muscles (along with their innervation) were part of the complex "pelvic organ functional systems." They were also suggested as indicators of a lesion in the lower sacral segments: tests to establish involvement of the somatic nervous system were taken as substitute indicators of neurogenic lesions involving the innervation of pelvic organs, as no direct tests for the autonomic innervation of smooth muscle were available.

In routine diagnostics in the individual patient, clinical neurophysiologic tests are an extension of the neurologic examination. Results correlate with function of neural control, but not directly with LUT function (i.e., storage or voiding). This is important to stress since expectations, in the past, that neurophysiologic testing should say something about, for instance, incontinence, were misplaced.

A functional anatomic classification of clinical neurophysiologic tests makes most sense; thus there are techniques testing the somatic and autonomic nervous systems, and the motor and sensory parts of these. The somatic motor system tests are EMG, terminal motor latency measurements/motor nerve conduction studies, and motor evoked potentials (MEP); sensory system tests are electrosensitivity tests and viscerosensory and somatosensory evoked potentials (SEP). Reflex responses test the particular reflex arcs, including the afferent and efferent pathways. Autonomic nervous system tests in the uroanogenital region are the SSR and smooth-muscle EMG. This chapter provides basic information on the available investigations, their applications, usefulness, and limitations; physiologic background and technical details should be checked elsewhere (Vodušek, 2006; Podnar and Vodušek, 2012).

To date, there are no universally accepted standards for conducting individual urogenital-anal neurophysiologic tests, but the variations in testing between different laboratories are minor.

TESTING PERINEAL MUSCLES AND THEIR MOTOR INNERVATION

Electromyography

The term EMG is used by workers in the field for several different procedures, the common denominator of which is the recording of bioelectric activity from muscle. The different usages imply different ways of analyzing muscle electric activity. Most commonly, EMG is used for two purposes: first, to assess patterns of individual muscle activity/inactivity during defined maneuvers ("kinesiologic" EMG, typically recorded simultaneously with other physiologic parameters during urodynamic testing); and second, EMG is used to differentiate between normal and denervated/reinnervated muscle (there seems to be little clinical relevance to the investigation of perineal muscles in patients with myopathy).

In kinesiologic EMG, the electric activity from a muscle indicates the presence or absence of its "activity," i.e., a substitute indicator of its contraction. Its relevance for diagnostics has been discussed above for urodynamics. The prerequisite for the rational application of kinesiologic EMG is that the muscle observed is actually innervated (i.e., the muscle is not denervated). Thus, kinesiologic (urodynamic) EMG testing of the striated sphincter muscle can only be interpreted clearly in patients with known or suspected "upper motor neuron-type" LUTD.

The neurogenic changes in the pelvic floor and perineal muscles (due to, for instance, a cauda equina lesion) are well recognized and routinely evaluated, and the preferred technique is concentric needle EMG (Podnar and Vodušek, 2012). The pelvic floor and perineal muscles can be examined, including the levator ani, the bulbocavernosus muscle, and the striated anal and urethral sphincter muscle. The EAS is the most practical indicator muscle for lower sacral myotomes because it is easy to access, has enough muscle bulk for exact EMG analysis, and its examination is not too uncomfortable (Podnar et al., 1999, 2000). Generally there are three different techniques of motor unit potential (MUP) analysis (manual MUP, single MUP, and multi-MUP) and one technique of interference pattern analysis (turn/amplitude (T/A)) to differentiate between normal and abnormal muscle. Both the template-based multi-MUP analysis of MUP and T/A analysis of interference pattern are fast (5–10 and 2–3 minutes per muscle, respectively), easy to apply, and, technically, represent clinically useful techniques. Quantitative MUP and interference pattern analyses of the EAS are facilitated by the availability of normative values (Podnar et al., 2000). Following a lesion of its peripheral innervation, the MUPs of pelvic floor and perineal muscles are prolonged and polyphasic, of increased amplitude, area, and number of turns (Podnar and Vodušek, 2012). Abnormalities of parameters evaluated by concentric needle EMG are in principle non-specific, and usually only a few are selected to define abnormality – often MUP duration, thickness, and number of turns (Pino et al., 2008). The other EMG technique, such as using a different needle electrode to differentiate between normal and neuropathic muscle, is single-fiber EMG, and the parameter that reflects motor unit morphology is fiber density. This method has often been used in research, particularly by British authors, but is not routinely applied in diagnostics.

Recently, surface EMG recording using non-invasive electrode arrays and multichannel EMG amplifiers was introduced to the EAS and puborectalis. Although observations in normal and pathologic conditions have been published (Merletti et al., 2008), the clinical value of these methods in diagnosing neurogenic sacral disorders has not yet been demonstrated.

The abnormalities revealed in EAS by EMG analysis are non-specific. The cause of denervation (i.e., trauma, neurologic disease affecting the lower motor neurons of Onuf's nucleus, cauda equina, the sacral plexus, the pudendal nerve) has to be established by other means. In a series of 194 consecutive patients referred for electrodiagnostic evaluation of EAS, quantitative needle EMG supported a diagnosis of a cauda equina or conus medullaris lesion in 36 patients, a direct lesion of the EAS muscle in six, a pudendal nerve lesion in two, and a sacral plexus lesion in one patient. Findings were compatible with multiple system atrophy (MSA) in 11, and a severe polyneuropathy in two patients. In 11 patients, the etiology of the pathologic findings could not be established at time of electrodiagnostic testing (Podnar, 2006). EMG abnormalities in some other patient populations have also been reported, for instance, patients with spinal dysraphism (Torre et al., 2002), and iatrogenic lesions (Hale et al., 1999).

While neuropathic EMG changes are expected in cases of known effect on the peripheral nervous system, due to either trauma or neuropathy, in cases of neurologic diseases primarily involving the central nervous system the abnormal EAS EMG is a reflection of concomitant Onuf's nucleus degeneration. Histologically, neuronal loss has been demonstrated in Onuf's nucleus in MSA (Sung et al., 1979), and in Machado–Joseph disease (Scaravilli et al., 2000). In the individual patient suffering from either of these diseases, EAS EMG would be expected to be abnormal if the process already involved Onuf's nucleus. Neuropathic changes have been reported in sphincter muscles of patients with MSA; among 30 patients with a pathologic diagnosis of multisystem atrophy, 24 had abnormal, five had borderline, and only one had a normal sphincter EMG (Paviour et al., 2005). Sphincter EMG has been proposed to differentiate MSA from Parkinson's disease, but it may not be sensitive in the early phase of the disease, and is not specific after 5 years of parkinsonism (Vodušek, 2001). The changes of chronic reinnervation may also be found in in Machado–Joseph disease (Shimizu et al., 2010), and in progressive supranuclear palsy (Valldeoriola et al., 1995), In patients with acute idiopathic autonomic neuropathy and LUTD the EMG of external sphincter muscles was reported to be normal (Sakakibara et al., 2004), as well as in Huntington disease (Kolenc et al., 2014).

These and other EMG reports concern the vast majority of patients with neuropathic involvement of the sacral (peripheral) nervous system, which as a rule is associated with LUTD. Only few reports deal with pelvic floor muscle EMG in generalized myopathy. In a nulliparous woman with limb girdle muscular dystrophy, histology revealed involvement of pelvic floor muscles, but concentric needle EMG of the urethral sphincter was normal (Dixon et al., 1990). In a group of patients with myopathy, no abnormalities were revealed either (Caress et al., 1996), but myopathic EMG changes were observed in the puborectalis and the EAS in patients with myotonic dystrophy (Herbaut et al., 1992).

Motor conduction tests

The recorded EMG signal is also used to indicate that muscle has been activated through its motor nerve, either by stimulation applied to motor pathways (M-wave, MEP) or to sensory pathways (reflex response).

Conduction velocity of the pudendal nerve can only be tested by applying stimulation with needle electrodes (Chantraine et al., 1973), and the measurement of the length of the nerve between the stimulation sites can only be indirect. As this is impractical, the common parameter used to assess conduction in the pudendal nerve is measuring the (terminal) latency of the EMG response from a perineal muscle (on electric stimulation of the pudendal nerve by different types of electrodes). Distal motor latency can be measured by recording with a concentric needle electrode from the bulbospongiosus, the EAS, and the urethral sphincter muscles in response to bipolar surface stimulation placed in the perianal/perineal region, with selective needle stimulation of the pudendal nerve (branches) in the perineum, or other types of electrode (Vodušek, 2006). The most widely published technique to obtain pudendal nerve terminal motor latency uses stimulation with a special surface electrode assembly fixed on a gloved index finger, known as the St. Mark's stimulator. The set has stimulating electrodes at the tip, and recording electrodes at the base of the same finger (Kiff and Swash, 1984). If a catheter-mounted electrode is used for recording, EMG responses from the striated muscle of the urethral sphincter can be obtained. In patients with LUT disorders the test was never much used, and in patients with fecal incontinence it is no longer recommended (American Gastroenterological Association, 1999). Electric stimulation with needle electrodes at vertebral laminae T12–L1 elicits M-waves in the bulbocavernosus and EAS muscle by depolarizing anterior spinal roots (Sato and Nagai, 2002). Electric stimulation identifies the particular nerve root before introducing therapeutic electric stimulation. However, the real clinical value of the test has yet to be established.

On stimulation of motor cortex MEPs from the EAS, the urethral sphincter, the bulbospongiosus muscle, and the levator ani muscle have been reported, but normative

values have only been obtained (for transcranial magnetic stimulation) for the urethral sphincter and the puborectal muscle in adult women (Brostrom et al., 2003). A central conduction time of 15–16 ms without and 13–14 ms with facilitation is obtained for pelvic floor and sphincter muscles (Schmid et al., 2005). Substantially longer central conduction times have been found in patients with multiple sclerosis and spinal cord lesions as compared to healthy controls, and have been suggested to be useful in patients with unclear localization of spinal lesions (Schmid et al., 2005).

Demonstrating the presence of a perineal M-wave or MEP (on magnetic or electric stimulation over lumbosacral spine) may occasionally be helpful in a patient with a suspected peripheral lesion, or in a patient in whom demonstrating an intact sacral root is relevant for a decision on treatment with electric stimulation. MEP on cortex stimulation may be useful for intraoperative monitoring, and indeed this may be the only routine application of this test at present (Sala et al., 2013).

Importantly, MEPs have opened an avenue of research on excitability of motor cortex. It has been demonstrated that, in comparison to the motor area for hand muscles, the anal sphincter motor cortex has less intracortical inhibition (Lefaucheur, 2005).

Testing LUT sensation

Perineal surface sensation is routinely tested clinically; bladder sensation is assessed by recording first sensation of bladder filling, first desire to void, and strong desire to void during cystometry, as described above. Measurement of electric thresholds in LUT has been proposed and has also already been mentioned (see sections on testing bladder sensation and cystometry, above).

Quantitative sensory testing

Quantitative sensory testing sensory modalities applied to the evaluation of sensation in patients with LUTD include vibration, temperature, and electric current. There is no commonly accepted standardized test. The physiologic, psychophysiologic, and methodologic issues and controversies will not be addressed in this chapter.

Sensory neurography

Nerve conduction velocities of the dorsal nerve of the penis can be calculated by placing a pair of stimulating electrodes across the glans and a pair of recording electrodes across the base of the penis. A nerve action potential can be recorded with amplitude of about 10 μV. It can also be recorded by stimulating transrectally or transperineally (Vodušek, 2006). There is no known association between penile sensory neuropathy and bladder/sphincter dysfunction.

Afferent activity in posterior sacral roots can be recorded on electric stimulation of the dorsal penile nerve during surgery (when the sacral roots are exposed) (Vodušek et al., 1993). This intraoperative mapping technique helps to preserve roots mediating perineal sensation in spastic children undergoing dorsal rhizotomies, and to reduce the incidence of postoperative voiding dysfunction (Huang et al., 1997). This test is limited to very specific intraoperative indications.

Somatosensory evoked potentials

Pudendal SEPs assess conduction in the large-fiber afferent pathway from the penis. Stimulating electrically the dorsal penile nerve and recording with surface electrodes at the level of the T12–L2 vertebrae reveals the postsynaptic segmental spinal cord activity (the spinal SEP). Unfortunately, this spinal SEP may be difficult to record even in normal (particularly obese) subjects. In contrast, the cerebral SEP can be recorded easily and reproducibly at the central recording site over the parietal somatosensory cortex (electrodes on Cz: 2 cm: Fz of the international 10–20 electroencephalogram system) (Podnar and Vodušek, 2012). In principle, although not in all normal subjects, visceral (cerebral) SEP can be recorded on stimulation of proximal urethra and bladder. If we are only interested in an objective test to assess preservation of autonomic (visceral) afferent nerves from the LUT in spinal cord lesions, an SSR recording above the spinal lesion level after proximal urethral/bladder neck electrostimulation can be performed (Vodušek, 2006).

Pudendal SEP has been used in research, for instance in studying the mechanism of sacral neuromodulation (Malaguti et al., 2003), although its usefulness in routine diagnostics has often been asserted, but never clearly demonstrated. Cerebral SEP on electric stimulation of the dorsal penile nerve (i.e., the pudendal SEP) has been advocated in patients with neurogenic bladder dysfunction and various neurologic disorders, particularly in multiple sclerosis (Sau et al., 1999). Even in patients with multiple sclerosis and bladder symptoms, however, the tibial cerebral SEP was more often abnormal than the pudendal SEP. The combination of an abnormal pudendal SEP with a normal tibial SEP suggests isolated conus involvement (Rodi et al., 1996). The pudendal SEP is not much used clinically, as neurologic examination for identifying neurologic disease in patients with urogenital symptoms is more sensitive than pudendal SEP (Delodovici and Fowler, 1995). Tibial and pudendal SEPs have been suggested to correlate with predicted recovery of bladder control following SCI (Curt et al., 1997).

Cerebral SEP during penile stimulation may be useful for intraoperative monitoring, and indeed this may be the only routine application of this test at present (Sala et al., 2013).

Sacral reflexes

Two reflexes are commonly elicited clinically in the lower sacral segments: (1) the BCR (also penilocavernosus); and (2) the anal reflex. EMG recording of the sacral reflex has been shown to be more reliable than the clinically assessed response (e.g., observing and palpating the contraction) (Wester et al., 2003). The reflex recorded by EMG can be elicited by mechanic, electric, or magnetic stimulation. Electric stimuli can also be applied in the perianal region, and, using a catheter-mounted ring electrode, to the bladder neck/proximal urethra (Vodušek, 2006).

Electric stimulation of the dorsal penile nerve elicits (somatosomatic) reflexes in perineal muscles with a typical latency of about 33 ms in men (Podnar, 2007a), traditionally called the BCR. In addition to single-pulse electric stimulation, two identical electrical pulses separated by a 3-ms interval can be used (i.e., double-pulse electric stimulation), which is more efficient in eliciting sacral reflexes (Podnar, 2007a). In men, values of 40, 36, and 36 ms have been suggested as the upper limit of normal for the shortest latency obtained on eliciting a series of BCR responses using single, double, and mechanic stimulation, respectively (Podnar, 2007a). Sacral reflex responses recorded with needle or wire electrodes can be analyzed separately for each side from the EAS or bulbospongiosus muscle. Using unilateral dorsal penile nerve blocks, the existence of two unilateral BCR arcs has been demonstrated. Thus, by detection from the left and right bulbospongiosus (and also the EAS) muscles, separate testing of right and left reflex arcs can be performed. In cases of unilateral (sacral plexopathy, pudendal neuropathy) or asymmetric lesions (cauda equina), a healthy reflex arc may obscure a pathologic one on clinical elicitation, but not on neurophysiologic measurements of the sacral reflexes.

The BCR was shown to be a complex response, often forming two components. The first component, with a typical latency of about 33 ms, is the response that has been most often called the BCR. It is stable, does not habituate, and has other attributes of an oligosynaptic reflex response (Vodušek and Janko, 1990).

In men with cauda equina lesions BCR could not be elicited in 64% / 47% of patients on single/double electric stimulation, respectively. Measurement of the reflex latency increased the sensitivity to record abnormalities for 17% and 36%, respectively. BCR measurement increased sensitivity of quantitative EMG of the EAS muscles from 73% to 83% (Podnar, 2007b). In those subjects in whom BCR is difficult to elicit, double electric stimuli should be used. A complete reflex arc lesion should not be inferred by absence of a response if only single pulse is used for stimulation (Podnar and Vodušek, 2012).

"Simple" electrophysiologic BCR testing has been studied extensively and is used in many laboratories in everyday practice to demonstrate objectively the integrity of the S2–4 reflex arc. BCR testing is suggested as a complementary test to concentric needle EMG (CNEMG) examination of pelvic floor muscles in patients with suspected peripheral nervous lesions (Tubaro et al., 2013).

In addition to latency, a number of other parameters can also be measured using electric stimulation, such as, for instance, the reflex threshold, thus evaluating the excitation level of the sacral reflex pathway. Normative data are available (Podnar, 2007a). The excitation level of the sacral reflex pathway changes physiologically during voiding; BCR cannot normally be elicited during detrusor contraction but in the presence of spinal cord lesions such as myelodysplasia this normal suppression is lost. Recording of BCR during the voiding cycle has been called "dynamic BCR recording" (Walter et al., 1994). It is an interesting concept, revealing the underlying changes of reflex threshold, which has, however, so far no established clinical usefulness.

Continuous intraoperative recording of BCR on penile stimulation is being performed in specialized centers to protect innervation of pelvic organs during particular surgeries (Sala et al., 2013).

Stimulation of the perianal skin, bladder neck, or proximal urethra elicits sacral reflexes with latencies significantly longer than BCR. The reflex responses elicited from on bladder neck or proximal urethra stimulation have a visceral afferent reflex limb (fibers accompanying the pelvic nerves). With visceral denervation (e.g., following radical pelvic surgery) the viscerosomatic reflexes (from both bladder and urethral stimulation) may be lost while the bulbocavernosus (penilocavernosus) reflex is preserved.

Autonomic function tests

Cystometry evaluates detrusor contraction and thus indirectly parasympathetic innervation to the bladder. "Direct" methods for diagnostic evaluation of the autonomic nerves innervating the bladder are not available. Cardiovascular autonomic function tests are useful for identifying generalized autonomic dysfunction in patients with LUT symptoms.

Sympathetic skin response

On noxious stimulation (such as a sudden noise or electric pulse) a potential shift (SSR) can be recorded with surface electrodes from the skin of the palms and the soles, as well as the perineum. In the setting of investigating patients with neurogenic pelvic organ dysfunction, the stimulus

used is electric, and usually applied to the arm. The SSR is a reflex which consists of a particular afferent limb (which can vary according to the stimulation set up), a complex central integrative mechanism, and a sympathetic efferent limb with postganglionic non-myelinated C fibers innervating the region where recordings are done. The test is technically and physiologically valid, and has been used in patients with hereditary polyneuropathies to demonstrate involvement of sympathetic nerve fibers. In patients with pelvic organ dysfunction it has so far only been used in research. SSR has been suggested to aid in clarifying the characteristics of incomplete spinal cord lesions. Sparing of the descending sympathetic spinal tract as demonstrated by SSR was correlated with bladder neck function in SCI patients (Rodic et al., 2000). A clear-cut clinical usefulness of the test has as yet not emerged.

Dartos reflex

The dartos muscle is a sympathetically innervated dermal layer within the scrotum, distinct from the somatically innervated cremaster muscle. The scrotal skin contraction, elicited by electric cutaneous stimulation of the thigh, can be recorded; this dartos reflex is a test of lumbal sympathetic function (Yilmaz et al., 2006).

Smooth-muscle electromyography

Technical problems are precluding smooth-muscle EMG of the detrusor muscle in patients (Kinder et al., 1998). Needle EMG of genital smooth muscle (penis) has been reported, but no clinical utility of the test has emerged (Tubaro et al., 2013).

RECOMMENDATIONS FOR CLINICAL NEUROPHYSIOLOGIC TESTING

As knowledge about the lesion(s) of LUT neural control is essential for an understanding of neurogenic LUTD, and also necessary for rational application of more sophisticated therapeutic methods (such as electric stimulation techniques), there seems to be a continuing place for clinical neurophysiology in routine diagnostics (and in research on neurogenic LUTD). As is generally true for electrophysiologic tests, uroneurophysiologic examinations are particularly useful for substantiating the diagnosis of a lesion to the somatic peripheral nervous system, which might be difficult to diagnose otherwise. The potential usefulness of testing in the individual patient needs to be analyzed in the overall clinical setting.

Concentric needle EMG to diagnose denervation and reinnervation of pelvic floor and perineal muscles, and sacral reflex testing to assess the continuity of the sacral reflex arc, are the recommended tests (Tubaro et al., 2013). Proposals for standardization for EAS CNEMG (Podnar and Vodušek, 2001) and the bulbocavernosus (penilocavernosus) reflex have been made (Podnar, 2007a), and seem to be widely adopted.

Although SEP on stimulation of the pudendal nerve, MEP on (magnetic) stimulation of the motor cortex, and SSR recorded in the urogenital region are valid tests, their clinical usefulness is limited, due to the fact that the same or similar information can be obtained by other means.

CONCLUSION

Neurologic patients form special groups which as a rule need special management. Most suffer from chronic neurologic conditions. In addition, many are elderly, and many may also suffer from non-neurologic LUT pathology. It is therefore important to rule out non-neurologic problems, which as a rule is easier than to be certain that symptoms and signs are uniquely neurogenic.

Because of multiple factors, including safety, patient comfort, and financial considerations, the diagnostic work-up must be tailored to the individual patient, but a good history and clinical examination are always of fundamental importance. Much information can be gathered by an experienced examiner by fairly simple means.

Basic assessment, consisting of history, clinical examination, a frequency/volume chart, urinalysis, and PVR determination allows the mildly affected neurologic patient with LUT symptoms to start basic treatment. Together with kidney ultrasonography these tests also constitute the basic long-term follow-up. If, however, pathophysiology of a LUTD is uncertain, especially if irreversible treatment is contemplated, gathering quantitative knowledge of the dysfunction is good clinical practice and allows for a rational treatment choice.

Generally, valid tests are helpful in the assessment of neurogenic LUTD because they contribute to "knowledge-based medicine." So far, good controlled studies oriented to prove the usefulness of particular testing for outcome measures are scarce (and difficult to do). Although to judge the importance of "knowledge-based medicine" may require different criteria, we should seek evidence for and against particular testing. Any test should be subjected to three questions: (1) Does the test have good technical validity? (2) Does the test have good diagnostic validity, ideally against a "gold-standard" measure? (3) Does the test have good therapeutic validity, that is, does the use of the test alter clinical management, does the use of the test improve outcome?

Urodynamic and clinical neurophysiologic testing should demonstrate evidence that testing improves

outcome (through treatment choice and patient selection), which would provide a strong basis for its use. To some extent, testing and therapeutic intervention are different concepts, and (physical as well as laboratory) assessment has another important objective, which is not applicable to interventions and lies at least to some extent outside the scope of evidence-based medicine in the narrow sense (i.e., data based on research using double-blind controlled studies). The objective is to generate knowledge about the situation to be managed in a given patient, so that the practitioner can formulate rational treatment options based on knowledge rather than do so blindfold; that is, the clinician should practice "knowledge-based medicine," even if there are not enough data (yet) to allow for "evidence-based medicine."

In conclusion, every neurological patient with LUT symptoms needs clinical assessment of his problem. In many patient groups with neurogenic LUTD, the pathophysiology is unpredictable and comprehensive urodynamic evaluation is essential in order to practice rational medicine. In selected patients from these groups, clinical neurophysiologic testing will add to information on lesions of the peripheral innervation of the LUT.

ACKNOWLEDGMENT

The authors wish to thank François Boller for editing the chapter.

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 10

Sexual and bladder comorbidity in women

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INTRODUCTION AND GENERAL OVERVIEW

Sexual dysfunction

Sexual dysfunction (SD) in women is defined as disorders of sexual desire, arousal, orgasm, and/or sexual pain which result in significant personal distress and may have a negative effect on women's health and an impact on quality of life (QoL) (Basson, 2000; Basson et al., 2004; see Chapter 2, this volume). Even more than in men, SD in women is a multifactorial condition with anatomic, physiologic, medical, psychologic, and social components.

Historically, US population census data suggest that approximately 10 million American women aged 50–74 years self-report complaints of diminished vaginal lubrication, pain and discomfort during intercourse, decreased arousal, and difficulty in achieving orgasm (Laumann et al., 1999). Among women with any SD, on average 64% (range: 16–75%) experienced desire difficulty, 35% (16–48%) experienced orgasm difficulty, 31% (12–64%) experienced arousal impairment, and 26% (7–58%) complained of sexual pain. Only a handful of epidemiologic studies have also assessed the proportion of women with SD-related distress, showing a prevalence ranging between 12% and 67% (Hayes et al., 2006; Shifren et al., 2008). Overall, Laumann et al. (1999) reported that SD is even more prevalent in women (43%) than in men (31%) and is associated with various psychodemographic characteristics such as age, education, and poor physical and emotional health.

Since the early descriptions of the sexual response cycle by Masters and Johnson (1966) and, later, Kaplan (1974), the stages originally suggested have been challenged (Basson, 2000). Substantial advances have occurred in the understanding of the physiologic aspects of female sexual function (SF) and SD, mainly driven by the increasingly sophisticated methods of their measurement. In this context, the rate of SD in women increases with age; moreover, impairment of SF is significantly associated with the menopausal transition and the menopausal period itself (Goldstein and Teng, 1991; Dennerstein et al., 2003, 2007; Nappi et al., 2010a). In this context, for instance, postmenopausal women often complain of low sexual desire, discomfort during intercourse, dryness, and diminished arousal of the vagina (Semmens and Semmens, 1984; Mongomery and Studd, 1991; Nappi et al., 2010b; Rosen et al., 2012).

Although SD in women is a very prevalent, multifaceted problem, it continues to be underrecognized and undertreated (Giraldi et al., 2011; Bitzer et al., 2013a, b; Fugl-Meyer et al., 2013). Healthcare professionals are aware of the high prevalence of SD among women but infrequently initiate a discussion of SF with their female patients or conduct a comprehensive evaluation for SD (Bachmann, 2006).

Based on traditional classification criteria and more recent reconsiderations of the available clinical observations (Basson et al., 2003; Clayton, 2007), SD in women may be subdivided into:

- sexual desire/interest disorders
- arousal disorders (subjective sexual arousal disorder; genital sexual arousal disorder; combined sexual arousal disorder; persistent sexual arousal disorder; genital arousal disorders; generalized sexual arousal disorders; missed sexual arousal)

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- orgasm disorders
- vaginismus
- dyspareunia.

Each results in significant personal distress and may have negative effects on women's health and QoL. Although each specific condition can be defined separately in medical terms, there is significant clinical overlap in affected patients. Similarly, each of these "categories" involves both psychologic and physiologic aspects and requires subjective and objective evaluations. The last two conditions (vaginismus and dyspareunia) are discussed in detail in Chapter 23 of this volume.

Urinary tract symptoms

Urinary tract symptoms in women are connected to a large group of comorbid conditions related to micturition. As a whole, the most common and meaningful urinary dysfunctions in women include (Chen et al., 2013): (1) overactive bladder (OAB), currently redefined as a syndrome characterized by urinary urgency, with or without urgency urinary incontinence (UUI), usually with increased daytime frequency and nocturia, with no proven infection or other obvious pathology (Abrams et al., 2010; Drake, 2014); (2) UUI, defined as a loss of urine associated with a sudden overpowering urge to void (Abrams et al., 2012); (3) stress urinary incontinence (SUI), which is the complaint of involuntary urine leakage with effort or exertion, upon sneezing or coughing, or with other maneuvers involving sudden increased intra-abdominal pressure; and (4) mixed urinary incontinence (MUI: combined SUI and UUI). The Fourth International Consultation on Incontinence defines urinary incontinence as a storage symptom with the complaint of any involuntary loss of urine (Abrams et al., 2010). This definition is suitable for epidemiologic studies, but when the prevalence of bothersome incontinence is sought, the previous definition of an "involuntary loss of urine that is a social or hygienic problem" can be useful. Urinary incontinence is one of the most important health problems confronting modern society because the symptoms connected with this disease have important social implications and cause discomfort, shame, and loss of self-confidence, and may negatively affect the woman's QoL (Ekelund et al., 1993; Grimby et al., 1993; Abrams et al., 2002, 2010). Moreover, nocturnal enuresis, which is any involuntary loss of urine occurring during sleep, postmicturition dribble, and continuous urinary leakage denote other symptomatic forms of urinary incontinence.

According to the literature, 11–73% of women complain of some urinary tract symptom throughout their lifespan (Barber et al., 2005; Wehbe et al., 2010a, b; Markland et al., 2011). More precisely, 12–46% experience some degree of urinary incontinence (Botlero et al., 2008). A recent population-based cross-sectional postal evaluation of all female patients registered at a single medical practice in the United Kingdom showed a total of 40% of respondents suffered urinary incontinence, which caused significant problems in 8.5% (Cooper et al., 2014). Stress urinary incontinence was the most common type of incontinence, while 10% had symptoms of voiding dysfunction (Cooper et al., 2014).

Overall, urinary tract symptoms may lead to a QoL impairment of more or less significant severity, and in severe cases may result in complete social isolation. In this context, urinary incontinence is a particularly embarrassing and potentially disabling condition that may lead to depression, social isolation, and a worsening general health status (Swithinbank and Abrams, 1999; Landefeld et al., 2008).

Combined sexual and lower urinary tract dysfunction

Lower urinary tract symptoms (LUTS) are frequently associated with female SD (FSD) and/or sexual discomfort (Salonia et al., 2004; Patel et al., 2006). Between 19% and 50% of women with urinary incontinence or pelvic floor disorders, such as prolapse, may experience FSD, dyspareunia, a reduction in sexual interest, and/or a decline in their frequency of sexual activity (Berglund and Fugl-Meyer, 1996; Handa et al., 2004; Sand et al., 2006; Sen et al., 2007; Tennstedt et al., 2007; Nilsson et al., 2011; Shindel et al., 2012). As a whole, sexually active women attending a urogynecologic outpatient clinic showed a prevalence of FSD ranging between 48% and 64%, which is even higher than the traditionally quoted 43% for the US population (Laumann et al., 1999).

Although of clinical importance, FSD is unlikely to be the only reason for women to consult their urogynecologist when attending an outpatient clinic. Indeed, only 10% of women with FSD spontaneously seek medical help for their sexual problems at a urogynecology clinic. Likewise, women seeking care in a urological context are at significant risk of suffering from stressful SD which has never before been investigated, and urologists should be aware of these potential coexisting problems (Bekker et al., 2009; Chen et al., 2013). In this regard, Salonia et al. (2004) were the first to assess the prevalence and predictors of SD in women with urinary incontinence and/or LUTS as compared to a general female population. SD was diagnosed in 99 out of 216 patients (46%). Of these, 34 (34%) reported hypoactive sexual desire, 23 (23%) reported sexual arousal disorder; 11 patients (11%) complained of orgasmic deficiency, and 44 (44%) suffered from sexual pain disorder (e.g.,

dyspareunia or non-coital genital pain). Women reporting low sexual desire commonly suffered from SUI (47%). It was found that 60% of the women with sexual arousal disorders and 61% of those with sexual pain disorders also complained of recurrent bacterial cystitis. Of those complaining of orgasmic-phase difficulties, 46% also reported a troublesome urge incontinence. It was concluded that women reporting urinary incontinence or LUTS also complained of SD to a significantly higher degree than the general, healthy female population, suggesting that an investigation of female sexuality is appropriate for these patients (Salonia et al., 2004). Thereafter, OAB and urinary incontinence were also associated with a large group of dysfunctional mechanisms in terms of SF, thus including declines in desire, arousal, lubrication, orgasm, general sexual satisfaction, along with a potential increase in terms of sexual pain, as compared with women without urinary tract symptoms (Aslan et al., 2005; Cohen et al., 2008; Heidler et al., 2010; Coyne et al., 2011; Chen et al., 2013; Ergenoglu et al., 2013). Younger and sexually active women have the most to lose, and they tend to complain of greater sexual distress associated with lower urinary tract disorders (Aslan et al., 2005; Sand et al., 2006; Zahariou et al., 2010). Some reports have also suggested that urinary symptoms may eventually lead to cessation of sexual activity, with 40% of women describing sexual intercourse as either an instigating or exacerbating event for urinary tract symptoms (Serati et al., 2009a; Wehbe et al., 2010a). In these cases, appropriate medical attention may permit a woman to resume a satisfying sexual life (Graziottin and Leiblum, 2005; Rivalta et al., 2010; Filocamo et al., 2011; Witek et al., 2013).

Urinary tract infections (UTIs) are extremely common clinical entities affecting women throughout the lifespan (Wagenlehner et al., 2009). Acute uncomplicated UTIs are among the most commonly encountered bacterial infections in women (Gupta et al., 2011), with a reported incidence of 0.5–0.7 episodes per woman each year (Hooton et al., 1996). Roughly 25–35% of women between the ages 20 and 40 have experienced an uncomplicated UTI (Gupta et al., 2011), and a subset of these women complains of recurrent UTIs (rUTIs). Sixty percent of rUTIs in women are postcoital (Hooton et al., 1996; Foxman and Brown, 2003; Wagenlehner et al., 2009; Epp et al., 2010; Gupta et al., 2011). Uropathogenic *Escherichia coli* (UPEC) is the pathogen that causes uncomplicated UTIs in 75–90% of cases because UPEC has special features that allow it to take advantage of the bladder's environment (Foxman and Brown, 2003; Nicolle, 2008). Salonia et al. (2013) recently showed that three out of five Caucasian–European, heterosexual, sexually active women of reproductive age complaining of rUTIs as their primary disorder also suffered from secondary provoked vestibulodynia, a condition in which pain is triggered by simple physical contact, touch, pressure, or the stretching of the tissue around the vaginal opening, eventually resulting in an inability to engage in both coital and non-coital sexual attempts. More specifically, provoked vestibulodynia is significantly more frequent in women with uncomplicated UPEC-related rUTIs than in those with UTIs associated with other uropathogens.

OVERACTIVE BLADDER

OAB is a symptom syndrome consisting of urinary urgency, usually accompanied by frequency and nocturia, with or without UUI, in the absence of a causative infection or pathologic conditions (Haab, 2014). The prevalence of OAB is approximately 11–19% in both men and women, and leads to a significant negative effect on a patient's health-related QoL. OAB is also associated with comorbidities such as UTI and an increased risk of falls (Haab, 2014). Neurogenic detrusor overactivity is a bladder dysfunction frequently observed in patients with conditions such as multiple sclerosis (MS) and spinal cord injury (SCI) (Nicholas et al., 2010; Haab, 2014). In these specific patients, increased storage pressure can put the upper urinary tract at risk of deterioration, and reducing this risk is a primary aim of therapy. Urinary incontinence is reported by approximately 50% of MS patients, and most SCI patients will develop some bladder dysfunction (Ruffion et al., 2013; Haab, 2014). Random-effect meta-analysis found the prevalence of urinary incontinence was 50.9% in patients with MS, 52.3% with SCI, 33.1% with Parkinson's disease, and 23.6% with stroke (Ruffion et al., 2013).

Several studies have suggested that women with wet OAB – defined as UUI associated with detrusor overactivity – complain of dissatisfaction, and poor QoL, and have high rates of sexual impairment (Quarto et al., 2007; Coyne et al., 2011; Hall et al., 2012; Tapia et al., 2013). Despite a significant heterogeneity in findings, the literature suggests that health-related QoL in patients with urinary incontinence due to neurogenic detrusor overactivity is worse than patients with urinary incontinence in general or those with the same underlying neurologic condition without urinary incontinence (Tapia et al., 2013).

In a urodynamic study of 118 sexually active women, individuals were separated into SUI, UUI, and MUI groups. Of these patients, MUI patients had the lowest (i.e., best) Pelvic organ prolapsed/urinary Incontinence Sexual Questionnaire (PISQ-12) scores, followed by patients with SUI. Patients with UUI and urodynamic evidence of detrusor overactivity had the highest (worst)

PISQ-12 scores (Coksuer et al., 2011). Because women with dry OAB (i.e., without UUI) were not enrolled, the incremental sexual impairment of OAB alone versus OAB with UUI could not be determined from that specific study.

A relatively small cohort study from Korea using non-validated instruments for the assessment of sexual activity suggested that OAB and urinary incontinence (not otherwise specified) were both associated with worse SF; OAB emerged to be significantly more predictive of sexual problems than SUI (Kim et al., 2005). Similarly, in a population-based study from Taiwan in which women were invited to complete a translated version of the Bristol Female Urinary Tract Symptoms Questionnaire, findings suggested a progressively greater prevalence of interference in sexual life and a lowering of overall QoL in women with SUI, OAB, and MUI (Chen et al., 2003). In a study of women with urodynamically proven OAB or SUI, it was determined that women with OAB had generally poorer marital adjustment scores (as assessed by the Dyadic Adjustment Scale) and lower scores for overall sexual satisfaction (as assessed with the Derogatis Sexual Functioning Inventory) as compared to women with normal lower urinary tract function (Yip et al., 2003). There was no significant difference in sexual interest between women with OAB and healthy women. Interestingly, a trend towards similar relationships was noted in women with SUI, but the relationship was less robust; in this context, only scores regarding the global marital adjustment were significantly lower in women with urinary incontinence compared to those of women without urinary symptoms. Of note, the women in the OAB group were younger than those in the other two arms of the study (mean age 43 years versus 49 and 50 years, respectively); this may influence the importance and trouble ascribed to sexual symptoms in different groups (Yip et al., 2003).

The Epidemiology of Lower Urinary Tracts Symptoms (EpiLUTS) study, which includes a total of 14 400 men and women, showed that OAB negatively affects sexual enjoyment and activity in both sexes (Coyne et al., 2011). Moreover, the EpiLUTS study showed significant links between OAB and both lower desire and arousal scores in women, along with greater rates of erectile dysfunction and ejaculatory dysfunction in men. The authors reported that rates of decreased sexual enjoyment were 25% and 20% in incontinent and continent women suffering from OAB, respectively; in contrast, decreased sexual enjoyment was reported in only 2% of women with minimal or no urinary tract symptoms (Coyne et al., 2011).

Nilsson and coworkers (2011) investigated a relatively large cohort of sexually active women ($n = 147$), aged 18–74 years, with urinary incontinence and urgency using a dedicated semistructured instrument and the Bristol Female Lower Urinary Tract Symptoms questionnaire. Their findings showed that most women considered urinary incontinence and urgency *per se* as having a negative impact on their sexual life, which in turn was perceived as being very important in their lives. One-third of the women enrolled had urinary leakage during sexual activity. Half reported that sexual life was more or less spoiled due to their urinary incontinence or urgency and they were worried about having urinary leakage during intercourse, and almost two-thirds worried about odor and felt unattractive. Women's dissatisfaction with their sexual lives was strongly correlated to lack of satisfaction with psychologic health, orgasmic disability, and worry about urinary leakage during intercourse. As a whole, insufficient vaginal lubrication, lack of satisfaction with psychologic health, and ill health of partners were all significantly correlated with decreased sexual desire (Nilsson et al., 2011). Therefore, the authors outlined how a dialogue about SF in women with urinary symptoms should become an integral component in clinical management.

URGENCY URINARY INCONTINENCE

As previously highlighted, the EpiLUTS study showed that OAB with UUI was associated with a greater likelihood of decreased sexual activity (men: odds ratio (OR) = 9.3; women: OR = 11.2) and decreased sexual enjoyment (men: OR = 9.1; women: OR = 8.9) than OAB without UUI (decreased sexual activity, men: OR = 7.0; women: OR = 8.6; decreased sexual enjoyment, men: OR = 7.2; women: OR = 6.8) (Coyne et al., 2011). Additional evidence regarding the detrimental impact of UUI on sexual health was found in another study. Based on data from 2365 men and women aged 19–99 years from Austria, Heidler and coworkers (2010) showed that the rate of decreased sexual activity was significantly higher in subjects with wet OAB (25% out of 100 subjects) than in those with dry OAB (14% out of 229 subjects; $P < 0.005$). In a cross-sectional study of 118 sexually active women with UUI, SUI, or MUI, who were adequately matched for age, parity, and body mass index (BMI) values, women with MUI reported significantly worse SF (19.6 mean score at PISQ-12; range 0–48) than those with either UUI or SUI (mean score 24.9 and 22.3, respectively; all $P < 0.001$ vs MUI) (Coksuer et al., 2011).

In the United States, a survey of 276 sexually active identical twin sisters demonstrated that UUI ($P = 0.009$) and parity ($P < 0.001$) were the only independent variables that significantly predicted SD based on a multivariate logistic regression analysis after controlling

for several other possible risk factors (Botros et al., 2006). In a case–control study including 279 obese (BMI $\geq$30 kg/m^2) women from a hospital obesity unit and 430 age-, gender-, and county-matched controls conducted in 2003–2007 in Sweden, UUI emerged as an independent risk factor for FSD, as assessed with the PISQ-12 (adjusted OR = 2.0; 95% confidence interval (CI): 1.3–3.1) relative to obesity without UUI and non-obesity, after adjusting for age, BMI, parity, comorbidity, menopause, hormonal replacement therapy, and depression (Melin et al., 2008). A further study conducted on 102 sexually active women demonstrated that UUI (adjusted OR = 2.1; 95% CI: 1.2–8.7) was independently associated with FSD, as assessed with the Female Sexual Function Index (FSFI), after controlling for depression, sleeping problems, and the contemporary intake of multiple pharmacologic therapies (Worly et al., 2010). Likewise, Jiann et al. (2009) used the FSFI as a section of a self-administered questionnaire given to 2159 woman employees of two hospitals to assess their SF and its correlates. Among the 930 women's data eligible for analysis with a mean age of 36.1 years (range 20–67), 43.8% had sexual difficulty in one or more domains, thus including low desire in 31.3%; low arousal, 18.2%; low lubrication, 4.8%; low orgasmic function, 10.4%; low satisfaction, 7.3%; and sexual pain, 10.5%. As expected, compared with the younger women (20–49 years), the oldest age group (50–67 years) had a significantly higher prevalence of low desire, low arousal, and low lubrication, but this was not true of the other domains. Even more importantly, based on multivariate logistic regression analyses, age and UUI were associated with low lubrication and sexual pain. Conversely, most comorbidities were not related to these difficulties, with the exception of diabetes, being related to low desire (Jiann et al., 2009).

Interestingly enough, findings of a multivariate analysis regarding 2005 Korean adults aged 40–89 years indicated that UUI was a significant risk factor for a negative impact on male (adjusted OR = 4.4; 95% CI: 1.7–10.9; $P = 0.002$) but not on female sexual life (OR = 2.0; 95% CI: 0.8–4.7; $P = 0.113$) (Choo et al., 2007).

As a whole, the results of the EpiLUTS study (Coyne et al., 2011) and of smaller studies indicate that UUI is associated with impaired SF in both men and women, although the data are not completely unambiguous (Sand et al., 2006; Nilsson et al., 2011; Chen et al., 2013; Coyne et al., 2013). From the real-life perspective, although more clinical information is certainly needed to strengthen the association between UUI severity and FSD, sexual health issues of women complaining of UUI should be assessed, and vice versa. In this context, treatment of UUI-related/UUI-associated FSD should be regarded as part of, and not only as an epiphenomenon of, the treatment of UUI, in the context of an adequate promotion of sexual health and overall woman's health (Chen et al., 2013). With this aim, for instance, a 12-week, double-blind, randomized, placebo-controlled trial followed by a 12-week open-label phase of tolterodine extended release in sexually active women with OAB and UUI showed that tolterodine resulted in improvements in OAB symptoms and health-related QoL that were maintained or improved with 6 months of use.

Long-term compliance with OAB pharmacotherapy emerged as being important for optimal treatment outcomes (Rogers et al., 2009). Likewise, Giuseppe and coworkers (2007) treated 37 women complaining of urinary incontinence, of whom 23 also had FSD, with transvaginal electric stimulation (TES). TES was conducted for 15–30 minutes twice weekly for 3 months, using a biphasic intermittent current with a frequency of 50 Hz for SUI and 20 Hz for UUI, and the most tolerable intensity of stimulation. After TES, only 2 of the 10 women with UUI experienced leakage incidents; patients with SUI were completely dry during TES. The FSFI scores of patients complaining of urinary incontinence showed significantly lower desire and sexual satisfaction and higher sexual pain than controls. After 3 months, the 23 women with FSD reported remarkable improvements in their sexual life, as depicted by an amelioration of the FSFI (Giuseppe et al., 2007).

STRESS URINARY INCONTINENCE

Salonia and colleagues (2004) reported that SD was diagnosed in 99 out of 216 patients (46%) evaluated for urinary incontinence and/or LUTS as their primary disorders. Of these, 34 (34%) reported reduced sexual desire, 23 (23%) reported sexual arousal disorder; 11 patients (11%) complained of orgasmic deficiency, and 44 (44%) suffered from sexual pain disorder (e.g., dyspareunia or non-coital genital pain). Salonia's data about female SD and LUTS, including SUI, have already been showed through this text; more recently, Oh and colleagues (2008) reported that a greater proportion of women with SUI versus those with OAB complained of dyspareunia; likewise, women with SUI also showed a trend to report coital incontinence (CI) more frequently using the Bristol Female Lower Urinary Tract Symptoms questionnaire to assess SD. The authors determined that global SD was slightly, though non-significantly, higher in women with SUI ($P = 0.096$) (Oh et al., 2008).

A study from Japan reported that SUI was associated with generally worse SF outcomes compared to other urinary complaints (Sako et al., 2011). Among 576 female hospital workers, 72 of 146 evaluable women reported that they had experienced generic urinary symptoms,

17 had UUI, and 35 had SUI. Women with SUI had significantly lower FSFI scores for the desire, arousal, and lubrication domains compared to women without SUI. The difference in FSFI was not significant between women with or without other urinary symptoms (Sako et al., 2011).

A number of non-surgical treatments for SUI may promote improvements in women's sexual health. Oldham and colleagues (2013), for instance, showed that a novel disposable "tampon-like" electrostimulation device (Pelviva) plus unsupervised pelvic floor muscle training (PFMT) is more successful than unsupervised PFMT alone in treating urinary incontinence. More specifically, urinary incontinence was troublesome during sex to a lesser extent in the Pelviva group ($P = 0.026$). Similarly, Liebergall-Wischnitzer et al. (2012) compared the effectiveness of the Paula method (circular muscle exercises; $n = 66$) vs PFMT exercises ($n = 60$) on SF and QoL parameters of women with SUI. Using the PISQ-12, the authors found that the improvements in postintervention SF scores were significant in both groups (Paula, $P = 0.01$; PFMT, $P = 0.05$), as were the QoL scores (Paula: $P < 0.001$; PFMT: $P \leq 0.001$), with no significant difference between groups. There was a significant correlation between the mean SF score and the mean QoL score after the intervention (Paula: $r = 0.4$, $P = 0.002$; PFMT: $r = 0.4$, $P = 0.009$). Moreover, a mild to moderate significant correlation was also found between the SF score and the pad test results in both groups postintervention (Liebergall-Wischnitzer et al., 2012). Similar positive findings were also reported by other groups (Zahariou et al., 2008) However, in a recent review paper, Bø (2012) confirmed level 1, grade A evidence that PFMT is an effective treatment for SUI. In this context, supervised and more intensive training emerged as being more effective than unsupervised training. Although there were no adverse effects, Bø outlined the lack of randomized controlled trials addressing the effect of PFM training on FSD.

COITAL INCONTINENCE

CI – i.e., the loss of urine during coital sexual activity – is surprisingly prevalent among women. Data suggest a prevalence of CI ranging between 10% and 67% in women seeking medical help for LUTS (Hilton, 1988; Shaw, 2002; Serati et al., 2009a; Jha et al., 2012b; Dursun et al., 2013), and in as many as 2–10% of the general female population (Shaw, 2002). CI appears to be most prevalent in women with SUI; in this context, CI has been detected in up to 89% of women with SUI compared to 33% of women with OAB (Serati et al., 2008).

CI may be subdivided into penetration incontinence (i.e., the loss of urine with vaginal penetration) and orgasm-related incontinence (i.e., the loss of urine at orgasm). Interestingly, the subtype of CI seems to vary according to the baseline urinary tract disorder. More specifically, in a cohort of women suffering from penetration incontinence, 70% had SUI and 4% had OAB; in women with orgasm incontinence the prevalence for SUI and OAB was 42% and 3%, respectively (Hilton, 1988). More recently, Serati et al. (2008) showed that penetration incontinence was a complaint in 84% and 9% of women with SUI and OAB, respectively. Moreover, El-Azab et al. (2011) reported that unstable detrusor contractions or the amplitude of those contractions, as measured by urodynamics, did not correlate with the severity of CI. Conversely, 24% of those with OAB experienced orgasm-related incontinence as compared with 5% of patients with SUI (Serati et al., 2008, 2011a). Overall, despite prevalence rates which vary with the different studies, data suggest that penetration incontinence is more often associated with SUI, whereas orgasm-related incontinence may occur in both conditions (Pace and Vicentini, 2008). Factors significantly associated with CI were parity, prolapse, and SUI (El-Azab et al., 2011). The ultrasound measurement of bladder wall thickness allowed an indirect evaluation of detrusor muscle thickness, giving a potential index of detrusor activity (Serati et al., 2011b).

As a whole, the literature does not contain any convincing arguments for favoring one treatment over another on the basis of SF outcome (Fatton et al., 2014). Moreover, women with CI show a lower pharmacologic cure rate than those with detrusor overactivity alone (Serati et al., 2009b). Likewise, no synergistic effect of local estrogens and antimuscarinics in the treatment of OAB was found. Antimuscarinic treatment has lower cure rates in women with symptomatic detrusor overactivity complaining of incontinence at orgasm or in patients with detrusor overactivity following provocative maneuvers (Serati et al., 2009b).

SURGERY AND PELVIC PROLAPSE

Urologic surgery, such as simple or radical cystectomy, prolapse, and incontinence surgery, may variably impact a woman's SF (Azar et al., 2008; Pauls, 2010; Jha et al., 2012a; Doumouchtsis and Chrysanthopoulou, 2013; Maher et al., 2013). In this context, SD may arise due to nerve or vessel damage and/or an alteration of vaginal anatomy. To this aim, there is a growing interest in preserving the neurovascular bundles in female patients submitted to oncologic pelvic surgery (Carter et al., 2013). Literature on incontinence surgery is not without controversy; indeed, some reports suggest a

deterioration of SF (Mazouni et al., 2004; Tunuguntla and Gousse, 2006; Dalpiaz et al., 2008), some an equivocal effect (Maaita et al., 2002; Yeni et al., 2003; Elzevier et al., 2004; Glavind and Tetsche, 2004; Rogers et al., 2004; Shah et al., 2005; Marszalek et al., 2007; Berthier et al., 2008; Sentilhes et al., 2008), whereas others show a postoperative improvement (Ghezzi et al., 2006; Jha et al., 2007, 2008). Whatever the effect may be, the potential impact on sexual functioning should be discussed both pre- and postoperatively with the patient and her partner (Pace and Vicentini, 2008).

Pelvic organ prolapse (POP) is a very common disorder, observed in 38–75% of women attending an outpatient clinic for gynecologic care (Bekker et al., 2009). Women with prolapse may present with a wide range of LUTS: SUI, urgency, frequency, and urinary incontinence have been reported in 40%, 34%, 29%, and 30% of women with POP, respectively (Grody, 1998; Swift et al., 2005). Understanding the relationship between POP and pelvic floor symptoms is a crucial step in the management of patients (Maher et al., 2013; Jeppson and Sung, 2014; van der Ploeg et al., 2014). POP-related symptoms are largely subjective in nature (De Boer et al., 2011), and contradictory results have been reported regarding the association of POP with LUTS and FSD (Ellerkmann et al., 2001; Burrows et al., 2004; Ghetti et al., 2005; Ghoniem et al., 2008; Broekhuis et al., 2010; Salvatore et al., 2011). The lifetime risk of undergoing surgery for prolapse has been reported to be 11% by the age of 80 and approximately one-third of these women undergo repeated surgeries (Olsen et al., 1997; Gutman et al., 2008). Overall, a success in terms of surgical outcome has usually been described as "an improvement in anatomical support." However, pelvic reconstructive surgery has been shown to not always provide functional improvement and patient satisfaction. Cetinkaya et al. (2013) carried out a study to evaluate the relationship between POP staging and clinical findings, LUTS, FSD, and QoL using validated questionnaires. The authors found that LUTS seemed to be more prominent in patients with advanced prolapse, for whom associated QoL was also worse. SF did not seem to be adversely affected by POP stages measured by the total score of the PISQ-12 in the same cohort (Cetinkaya et al., 2013).

As a whole, the effect of POP on SF is controversial. Decreased SF was demonstrated in women with POP compared with unaffected women (Cetinkaya et al., 2013). However, Lukacz et al. (2007) have demonstrated that, although women with pelvic floor disorders were less likely to be sexually active, they were found to be equally as sexually active when data were controlled for confounders such as age, menopausal status, and sexual desire. These factors were shown to be the only significant contributors to a decreased SF (Novi et al., 2005). Similarly, Burrows et al. (2004) had previously reported measures of SF which did not significantly differ between women with or women without POP. Interestingly, Roos and colleagues (2014) observed a relatively small cohort of women in whom significant improvement was seen following pelvic floor surgery for PISQ total score ($P = 0.003$) as well as physical ($P < 0.001$) and partner-related ($P = 0.002$) domains, but not for the behavioral/emotive domain ($P = 0.220$). The analysis of qualitative data showed that improvement in SF was a result of cure of POP and SUI symptoms. Deterioration of SF was due to dyspareunia, fear of causing damage to the surgical result, new symptoms, and a disappointing result of surgery. The authors concluded that their qualitative data showed that PISQ may be a limited tool in the assessment of SF after pelvic floor surgery as it does not assess most surgery-specific negative effects on SF (Roos et al., 2014).

MECHANISMS AND ETIOLOGY OF COMORBID FSD AND LOWER URINARY TRACT SYMPTOMS

The reasons for the clinical correlation which has been observed among LUTS, urinary incontinence, and FSD are not completely clear from the pathophysiologic standpoint. Women complaining of urinary incontinence certainly may be fearful of having urine leakage during sexual intimacy, and of the consequent potential distress of their sexual partner. In this context, the anxiety created by previous urinary incontinence episodes during sexual activity and the potential for future urinary incontinence can affect all aspects of female sexual arousal. Furthermore, it has been suggested that LUTS-related depression and embarrassment can affect women's sexual desire and their satisfaction from sexual activity. Likewise, fear of urinary incontinence throughout sexual activity can prevent women from achieving orgasm, because of the rhythmic and uncontrollable muscle contractions which usually occur at the pelvic floor level throughout the orgasmic phase and that may be related to wet OAB. Further potential aspects to be considered are related to the hormonal milieu – i.e., estrogen and androgen levels – since many of these women are postmenopausal (Lukacz et al., 2007; Cohen et al., 2008).

In some cases, a single underlying cause (e.g., vulvovaginal atrophy, gynecologic surgery, pregnancy/parturition) may predispose a woman to both sexual and urinary problems (Handa et al., 2004; Knoepp et al., 2010). However, there are few data to support a direct causative mechanism linking most FSD and either LUTS and/or urinary incontinence . A number of more specific potential pathologic reasons have been identified in

women with neurologic disorders (Bronner et al., 2010; Bronner, 2011; Rosenbaum et al., 2014).Therefore, for instance, SD and decreased sexual satisfaction are common in the poststroke population and are related to physical, psychosocial, and relational factors (Rosenbaum et al., 2014). Likewise, SD is frequent (40–74%) among women with MS, reflecting neurologic dysfunction, psychologic factors, depression, side-effects of medications, and physical manifestations of the disease, such as fatigue and muscle weakness (Bronner et al., 2010).

MANAGEMENT OF WOMEN SUFFERING FROM FSD AND URINARY SYMPTOMS

As stated earlier, women complaining of LUTS should be investigated for comorbid FSD, and vice versa; this is possible via a comprehensive sexual and medical history and by completing dedicated psychometric tools. When combined complaints are diagnosed, therapy for urinary disorders may have a positive effect on SF by mitigating distressing symptoms (Wehbe et al., 2010b); however, treatment-related side-effects or complications may attenuate SF gains or even worsen SF as a whole (Barber et al., 2005; Moore, 2010). Careful patient counseling and documentation of baseline SF are required before any therapy for LUTS and urinary incontinence . The first step is that of conservative measures: education and advice may yield SF benefits in nearly every setting. Timed voiding, education of both the patient and her partner on the benignity of exposure to sterile urine, fluid avoidance, and/or voiding immediately prior to sexual activity, and the use of sexual lubricants may help SF in many urinary syndromes (Wehbe et al., 2010b). The next step consists of medical and surgical therapy of the different types of LUTS and urinary incontinence. This, however, must go alongside proper education and counseling of female patients, who may benefit from treatment of urologic problems in sexual terms, although sometimes the treatments themselves can lead to a deterioration in terms of sexual QoL.

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Section 4

Clinical syndromes

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 11

Sexual dysfunction in patients with peripheral nervous system lesions

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INTRODUCTION

Sexual excitement and satisfaction are components of a fulfilled life. This chapter covers sexual dysfunction (SD) in patients with disorders of the peripheral nervous system (PNS). The prevalence and clinical characteristics of SDs associated with disorders of the PNS will be described.

The main function of the PNS is communication between the central nervous system (CNS) and peripheral effector organs (i.e., skeletal and smooth muscle, sensory receptors and glands). Likewise, in sexual response PNS transmits sensory information from sensory receptors to the CNS, and motor activity from the CNS to genital organs. Thus, the somatic and/or visceral erotic sensations inducing sexual behavior, or the autonomic and/or somatic genital responses (or both) are compromised by a significant deficit of PNS ability to transmit signals.

Lesions may affect all the PNS constituents or, for anatomic or pathophysiologic reasons, only some. All different types of PNS involvement – either somatic motor, autonomic, or sensory – may cause some SD. In practice, the relative contribution of lesions of the individual constituents to dysfunction is difficult to determine in the individual patient, unless the lesion is obvious (of significant extent), and its occurrence is chronologically related to the onset of SD. To the clinician, somatic motor and, particularly, sensory deficits in the lower sacral segments are accessible for assessment. By contrast, autonomic function is not directly testable clinically. While, for instance, the significant association of erectile dysfunction (ED) with deficient sensory innervation of glans penis can be demonstrated (Bleustein et al., 2002), there is no direct test of the relevant parasympathetic nerves to permit such a study in patients, or to substantiate a working diagnosis of autonomic neuropathy of nervi erigentes in an individual patient. Thus, such diagnosis is made by inference, supported by association with other abnormalities pointing to ANS involvement.

The apparently clear division between the CNS and PNS often becomes fuzzy in practice, either due to the functional anatomic overlap (i.e., bodies of both α-motor neurons of the voluntary system – the lower motor neurons, and motor neurons of the involuntary (autonomic) system – the autonomic preganglionic neurons, are functionally part of the PNS, although they are situated within the spinal cord) or due to the fact that lesions may affect both PNS and CNS, although possibly to different degrees (e.g., combined spinal cord and cauda equina lesion in L1 vertebral fracture).

Another problem is the frequent lack of a direct and clear correlation between a particular nervous system involvement (as judged by neurologic criteria) and the resulting SD in the individual patient. For instance, the relative importance of a (mild) neurogenic ("neurologic") versus a (minor) vascular or endocrinologic abnormality in a depressed patient is difficult to determine with our present means of diagnosis. In sexual disorders, particularly ED, "organic" causes are often associated with a psychogenic component of performance anxiety.

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THE PERIPHERAL NERVOUS SYSTEM

The PNS functions via a series of reflex arc circuits with afferent and efferent arms controlled by the CNS. An understanding of the many PNS disorders requires an understanding of the complexities of the macro- and microanatomy of peripheral nerves, as well as their molecular biology, immunology, and pathophysiology (Kanda, 2013).

The pathophysiologic mechanisms that result in peripheral neuropathies are almost as diverse as the number of peripheral nerve diagnoses. However, at a microscopic level the patterns of damage are few. Axonal degeneration occurs distal to a site of nerve transection (which may be physical, inflammatory, or vascular; as well as focal, multifocal, or diffuse). Axonal degeneration can also occur as a distal dying-back phenomenon, especially in toxic and metabolic neuropathies (i.e., axonal polyneuropathies). In many inflammatory neuropathies, segmental demyelination occurs, which may result in conduction failure but not necessarily subsequent axonal degeneration (i.e., demyelinative polyneuropathies). Remyelination (with thin myelin, short internodes, and "onion bulbs") may occur, restoring more or less adequate clinical nerve function. Axonal regeneration occurs less consistently and over distances of centimeters only (Berry et al., 1995).

THE PERIPHERAL NERVOUS SYSTEM AND SEXUAL FUNCTION

The origin of sexual excitement is the result of many factors. Sexual ideation and whole-body sensory stimuli are important, but the primary erotic stimuli are mainly derived from the genitals themselves. In addition to this role of sensation in producing the individual's awareness of sexual excitement, the afferents also elicit phasic and tonic reflex responses, which induce and help maintain the genital responses (i.e., assuring penile erection and rigidity to allow vaginal penetration), and maintain erection throughout intercourse to bring about ejaculation. The vagina needs to be lubricated to allow painless erectile penetration and intercourse ending in ejaculation, which delivers sperm to the uterine cervix.

The part of the penis and of the clitoris known as the glans has a high receptor density: up to 80–90% of the nerve endings are free in the most superficial layer of mucosa. Histologic studies in the glans penis have shown mainly free nerve endings responding to deep pressure and pain (Halata and Munger, 1986), and a high density of fine-touch mechanoreceptors (corpuscular-type endings) beneath the mucosal layer in the transitional area from the external to the internal surface (i.e., ridged band) and the frenulum of the foreskin. The receptors are of two types: slowly adapting distally and rapidly adapting proximally, with afferent C and A-δ fibers. Surrounding the cavernous bodies are large nerve endings that resemble onions, with thick lamellae and a central nerve fiber connected to thick, myelinated nerve fibers. These nerve endings respond to deep pressure and vigorous movement. Receptors close to the cavernous bodies are influenced by the amount of engorgement of cavernous tissues so that touch may be experienced simply as touch or as a sexual stimulus depending on the degree of engorgement (Taylor et al., 1996).

The clitoris is the most densely innervated area of the skin, with an innervation density approximately twice that of the male dorsal penile nerve, so that clitoral sensory thresholds are lower than that of the glans penis. The clitoris contains three different types of nerve endings: free endings that mediate response to pain, submucosal fibers that respond to pressure and movement, and onion bulbs that are involved in sensing pressure and vigorous movement. These latter two types of nerve endings are localized in close proximity to cavernous tissue and are thereby stimulated during the phase of vascular engorgement (Yang et al., 2006).

The afferent fibers from the penis and clitoris form the nervi dorsales (penis or clitoris), which join the pudendal nerves and ultimately reach the dorsal nerve roots S2 and S3, and to a minor degree S1 and S4 (Deletis et al., 1992), and finally the respective sacral spinal cord segments. The afferents from the root of the penis and from the anterior part of the scrotum join the ilioinguinal nerve. Genital afferents synapse in the spinal cord via interneurons with both somatic and autonomic motor neurons; those afferents destined for supraspinal structures travel in the anterolateral funiculus (Berry et al., 1995). "Erotically colored" sensations from the genital region are conveyed by the spinothalamic pathways (Beric and Light, 1993).

Somatic sensory afferents deliver information on tactile sexual stimuli that, after synapsing in the sacral spinal cord, induce local sexual responses (i.e., erectile and glandular responses). The sensory fibers from the penis and clitoris form the afferent limb of a phasic and a tonic reflex response of the perineal and pelvic floor muscles. The phasic response is routinely elicited clinically by squeezing the glans and is called the bulbocavernosus reflex. The ensuing contraction of the perineal muscles (ischiocavernosus, bulbospongiosus, external anal sphincter) may be observed or palpated (Podnar, 2011). Vibratory stimulation evokes a tonic reflex involving sustained contraction of the pelvic floor musculature. Electromyographic (EMG) recording of the pelvic floor muscles in women during vibratory clitoral stimulation shows intermittent activity associated with contractions on a background of continuous activity (Gillan and Brindley, 1979).

The ischiocavernosus and bulbospongiosus muscles surround the vaginal introitus and insert on the dorsal surface of the crura penis and clitoris, forming an anatomic sling. During muscle contraction, the dorsal vein of the penis and of the clitoris is compressed and facilitates engorgement of the cavernous tissue with blood. The sacral reflexes are also integrated in the orgasmic behavioral response; ejaculation in males involves repetitive perineal muscle contractions, which eject semen. It can be recorded as bursts of EMG activity. The sensation of orgasm, however, is not fully dependent on pelvic muscle contractions. Men report that orgasmic sensation began before and lasted longer than bursts of EMG activity in the perineal muscles (Gerstenberg et al., 1990). The female orgasmic response is accompanied by rhythmic contractions of the pelvic floor muscles, the uterus, fallopian tubes, and paraurethral glands. Concomitantly, expulsions from the paraurethral glands through the urethra may occur (so-called female ejaculation) (Whipple, 2000).

The lower motor neurons innervating the perineal muscles (ischiocavernosus, bulbospongiosus, striated external sphincters) lie in the anterior horns of the sacral segments 1–3 and form the so-called Onuf's nucleus (Pullen et al., 1997). Likewise, the preganglionic parasympathetic neurons controlling the smooth muscle of the corpora cavernosa reside in the intermediolateral horns of the same sacral segments of the spinal cord. By contrast, the preganglionic sympathetic neurons lie in the intermediolateral horns of the thoracolumbar segments T10–L2 of the spinal cord (Berry et al., 1995).

The somatic motor axons originating from the anterior horns S1–3 travel within the pudendal nerve to the perineal muscles and the external urethral and anal sphincter muscles. Motor innervation of the pelvic floor muscles is conveyed by the levator ani nerve. The axons of the preganglionic parasympathetic neurons run a long distance within the pelvic nerves to the ganglia (pelvic plexus) (Berry et al., 1995). The main neurotransmitter for the preganglionic and postganglionic parasympathetic fibers is acetylcholine (ACh) (Andersson and Wein, 2004). The axons of the preganglionic sympathetic neurons synapse in one of the nearby paravertebral ganglia of the sympathetic chain. Some fibers pass through the paravertebral ganglia and synapse with one of the prevertebral or collateral ganglia on the aorta or internal iliac vessels, such as the inferior mesenteric ganglia, then continue inferiorly as the hypogastric nerves. Some fibers pass through both the pre- and paravertebral ganglia and synapse with the end organ (Berry et al., 1995). The main neurotransmitter for preganglionic sympathetic fibers is ACh, and for the postganglionic sympathetic fibers is norepinephrine (Andersson and Wein, 2004).

Erection is initiated by activity of the sacral parasympathetic efferents, traveling through the pelvic plexus and cavernosal nerves. Continued sacral parasympathetic activity is needed to maintain the erection (Andersson, 2011).

In women, parasympathetic activity causes clitoral erection, engorgement of the labia, and vaginal lubrication. Increased vaginal blood flow, lubrication, and erection of cavernous tissue in the clitoris and around the outer part of the vagina are the female homologues of the male erectile response; indeed, lubrication occurs during rapid-eye-movement sleep in women as in men. The response is dependent on intact innervation and a normal estrogen level (Puppo, 2013).

In the periphery, the main proerectile transmitter is nitric oxide, which is colocalized with vasoactive intestinal peptide and ACh. By contrast, the main antierectile neurotransmitter is norepinephrine (see Chapter 2). The erection mechanisms that occur in men also operate in women, including nitrous oxide and cyclic guanosine monophosphate (cGMP)-mediated vascular events (Andersson, 2011).

Genital responses can still occur in men and women after lesions of the sacral spinal cord, cauda equina, and pelvic nerves. This is due to the "alternative" proerectile pathway mediated through the hypogastric nerves. This explains the so-called psychogenic erections of paraplegics with lesions below thoracolumbar segments (i.e., conus medullaris or cauda equina lesions) (Benevento and Sipski, 2002). Similarly, women with sacral spinal cord lesion and an ability to perceive pinprick in the T12–L2 dermatomes may retain the capacity for psychogenic genital vasocongestion (Sipski et al., 1997). In women with complete spinal cord injuries above the sacral segments, such a response is as a rule obtained only by manual genital stimulation. Thus, the reflex – "psychogenic" dichotomy of the genital sexual response – can be seen in either gender.

Ejaculation is effected by integrated sympathetic outflow from T11 to L2 segments traveling through the sympathetic chain and hypogastric plexus, and along the pelvic and pudendal nerves, as well as by outflow from somatic efferents traveling through the pudendal nerves. Although the predominant neural effector of the male accessory sexual organs is sympathetic (adrenergic and purinergic), the secretion of seminal fluid is under parasympathetic control. Sympathetic activity causes smooth-muscle contraction in the seminal vesicles, vas deferens, and prostate to deliver seminal fluid to the posterior urethra; in the bladder neck to prevent retrograde ejaculation; and in the corpora cavernosa to cause detumescence. The latter "antierectile" activity is inhibited during erection through spinal coordination of reflex action (Giuliano, 2011).

Knowledge of the topographic anatomy is particularly important to achieve preservation of the peripheral nerves related to sexual (and bladder and bowel) function during abdominal and pelvic surgery. In the pelvis and abdomen, autonomic structures related to genital innervation are situated in the retroperitoneal space. The superior hypogastric plexus is located anterior to the aortic bifurcation at the level of the fifth lumbar vertebral body and anterior to the sacral promontory between the common iliac arteries. It divides caudally into the right and left hypogastric nerves. Within the pelvis, these nerves become the inferior hypogastric (pelvic) plexus, which is joined on each side by the pelvic nerves. In males, the inferior hypogastric (pelvic) plexus is lateral to the rectum, seminal vesicle, prostate, and the posterior part of the urinary bladder. The lesser and greater cavernosal nerves that originate from the anterior part of the inferior hypogastric (pelvic) plexus are joined by fibers from the pudendal nerves, and pass below the pubic arch. In females, the inferior hypogastric plexus gives off uterine nerves, branches for the vagina and cervix, and connections with the paracervical plexus (Berry et al., 1995). Awareness of the anatomy, careful surgical technique, and specific intraoperative "mapping" and "monitoring" procedures are needed to preserve neural structures relevant for sexual function (Rodi and Vodušek, 2008).

CONSEQUENCES OF PNS LESIONS ON SEXUAL FUNCTION

The normal sexual response has traditionally been conceptualized as consisting of several distinct phases, including desire, excitation, and orgasm (Lue et al., 2004), but is nowadays seen as a circular model of overlapping phases of variable order (see Chapter 2). The phases of genital response still serve to structure the relevant observational, neuroanatomic, physiologic, and clinical issues related to SD in both genders.

Any lesion involving innervation of genital organs may cause SD. In addition, SD may be caused by lesions of other neural structures more generally involved in control of sensation, motor and autonomic function (e.g., loss of fine motor control of fingers, pain, and dysesthesiae, incontinence) There are generally fewer reports on female than on male SD, particularly in PNS disease. However, based on considerations of the homologous nature of neurologic control of sexual responses, it is reasonable to assume that the same lesions affecting male sexual response also adversely affect women.

It is well recognized that frequency of SD progressively increases with age. In the Massachusetts Male Aging Study complete ED increased from 5% at age 40 to 15% at age 70, and partial ED from 29% to 71%, respectively (Feldman et al., 1994). In general, older men need more time to achieve a complete erection and have more difficulty in sustaining erection to complete sexual intercourse. Similarly, even some asymptomatic elderly subjects have non-elicitable ankle jerks and asymptomatic postural hypotension (6% and 10%, respectively in one study of subjects of age >65 years (Alvarez and Idiaquez, 1991)). The most common explanation for non-elicitable ankle jerks is subclinical age-related axonal polyneuropathy. By contrast, postural hypotension is supposed to be mainly due to vascular pathology (Smith and Fasler, 1983). Although is difficult to establish the reason for SD in the elderly, PNS changes does not seem to be crucial. Changes in sexual function that occur with age in otherwise normal subjects reflect age-related decline in testosterone and other androgen hormone levels, endothelial dysfunction in subjects with risk factors for cardiovascular disease (e.g., hyperlipidemia, hypertension, glucose intolerance, obesity, raised C-reactive protein levels), renal and liver insufficiency, anxiety, and depression (Camacho and Reyes-Ortiz, 2005; Wylie and Kenney, 2010). Furthermore, many elderly subjects take medications that negatively affect sexual function, such as antihypertensives (e.g., beta-blockers, clonidine), antidepressants (e.g., selective serotonin reuptake inhibitors, tricyclic antidepressants), neuroleptics and lipid-lowering agents (Camacho and Reyes-Ortiz, 2005; Wylie and Kenney, 2010).

SD may occur as the presenting symptom of a developing PNS disease and may occur without other disturbances of the ANS (e.g., ED in amyloid neuropathy) or as an isolated phenomenon after local nerve injury (e.g., painful clitoral dysesthesia after a pudendal nerve lesion). Particular lesions may cause a specific SD, limited to a part of the genital response (e.g., isolated ejaculation failure in lesions of the hypogastric plexus). However, more often the lesion is complex or less well defined, or the consequences go beyond what can be expected from the affected anatomy.

SEXUAL DYSFUNCTION IN PATIENTS WITH PERIPHERAL NEUROLOGIC DISEASE

SD in PNS involvement is commonly conceptualized as a consequence of compromised neural control of genital organs. Possible indirect effects of PNS (such as pain and compromised mobility) are less well characterized and are probably similar to other chronic diseases. The "specific" neurogenic contribution to SD is often difficult to ascertain in the individual patient; in populations of patients, it has to be ascertained against the background of valid control groups. SD, such as lack of libido

(in both sexes), ED and disturbances of ejaculation (in men), and deficient lubrication, dyspareunia, and problems with orgasm (in women) is not uncommon in the general population, and increases with aging (Addis et al., 2006). In populations of patients with disorders of the PNS, the prevalence of SD is reportedly higher, although there have been few comparative studies.

While desire and arousal depend primarily upon the higher brain centers, they also depend on the overall "capability" of the subject to act as a sexual being. This is probably why desire may be affected in patients with pure PNS lesions such as residual deficits after a cauda equina lesion (Podnar et al., 2002). This type of SD after a PNS lesion might be called "indirect" neurogenic, although all of the consequences of the PNS lesion on the relevant CNS regions (and hormonal homeostasis) are not yet explored.

By contrast, the peripheral pathways mediate the genital response. They convey efferent and afferent activity to pelvic parasympathetic, sympathetic, and somatic innervated structures; if these structures are damaged, the "final common pathway" to effectors of the sexual response is defective, and the sexual response is "directly" abolished (Giuliano, 2011).

CAUDA EQUINA AND CONUS MEDULLARIS LESIONS

Disorders and lesions of the cauda equina are characterized by motor and sensory symptoms (particularly weakness and sensory loss) in the lower limbs, buttocks, and perineum, usually accompanied by abnormalities of the bladder, bowel, and sexual function, of various degrees. This pattern of symptoms and signs is called the cauda equina syndrome (CES) (Gitelman et al., 2008). For a diagnosis of CES, one or more of the following must be present: (1) bladder and/or bowel dysfunction; (2) reduced sensation in the saddle area; and (3) SD. Neurologic deficit in the lower limbs (motor/sensory loss, reflex change) may or may not be present (Fraser et al., 2009).

As the axons within the roots comprising cauda equina extend into the spinal cord, dysfunctions caused by lesions of spinal cord segments (the conus) or the cauda equina are similar (Podnar et al., 2006). Due to the difficulties in distinguishing the localization of the lesion by means of imaging and inference from the mechanism of the noxae, and in distinguishing the clinical conus and CES, the CES is used as a clinical term defined by the typical combination of deficits. It is, therefore, not inferring certainty that it is necessarily the cauda equina that is the anatomic site of the lesion responsible for the syndrome. As such, CES is also commonly reported in the literature.

A study at a national referral uro-neurophysiologic unit found for CES an annual incidence rate of 3.4 per million and a prevalence rate of 8.9 per 100 000 population (Podnar, 2007). No "PNS neurogenic" SD would be expected in "trivial" spinal or disc disease without damage of the nervous structures, or in a patient with lumbar or sacral monoradiculopathy. However, a higher prevalence of ED (but not premature ejaculation) has been reported after lumbar disc herniation (Yazici et al., 2013).

Acute cauda equina syndrome

Lower-back pain, sacral sensory loss, and urinary symptoms (typically retention) are the most frequent presenting features of CES (Jalloh and Minhas, 2007). Motor and sensory involvement of lower extremities is variable. Acute CES may be difficult to recognize as only a minority of patients (19%) present with the "classic" clinical picture (Jalloh and Minhas, 2007). The clinical picture is due to a sudden or rapid occurrence of a mechanical or ischemic lesion of the PNS structures of the sacral segments S2–4, causing tissue irritation and destruction. The disruption of sexual function would not be appreciated in the short term unless it appears as "positive" symptoms (see below).

Chronic CES

Chronic CES is diagnosed in patients with slow or even insidious onset of symptoms, and in patients with residual deficits after an acute CES. The typical example for the former is a slowly growing expansive lesion of the cauda equina or the conus (see Chapter 4 for further discussion of this topic). In such patients the cause of the lesion is of primary concern.

A particular clinical picture of chronic CES arises through degenerative disc disease and osteoarthritis of the spine contributing to the lumbar spinal stenosis. The symptoms are a combination of intermittent neurogenic claudication and chronic radicular symptoms. The hallmark symptom of intermittent neurogenic claudication (known also as cauda equina claudication, or pseudoclaudication) (Haswell et al., 2008) consists of various combinations of low-back, buttock, leg, and uro-anogenital pain and paresthesias, paresis, and uro-anogenital symptoms brought on or exacerbated by walking, and characteristically by standing erect. Walking on a slightly down-going surface makes problems worse. Symptoms are relieved by 5–10 minutes of rest in a seated position, which contrasts with the brief rest upright of less than a minute required to relieve vascular claudication. Patients often adopt a slightly bent-forward posture on walking and standing – the position in which the spinal canal space is at its maximum (Storm et al., 2002).

The chronic radicular symptoms are similar to those of acute radiculopathy, but often less severe. The symptoms and signs of chronic CES depend on the spinal roots involved, and the extent of the lesion (Haswell et al., 2008). Involvement of lower sacral nerve roots by any process can lead to "positive" as well as "negative" symptoms. As an example of positive symptoms in the sexual domain some men with lumbar spinal canal stenosis obtain unwanted short-lasting erections unaccompanied by any erotic sensations after walking a short distance as they sit down (Laha et al., 1979; Hopkins et al., 1987). Erections were also described after kneeling for half an hour or so, and the authors had a patient who obtained an erection when reaching up to top shelves at home, or – embarrassingly – in stores. Men with lumbar spinal stenosis may even present with intermittent priapism, months later followed by leg weakness, numbness, and pain provoked by stance or walk, and relieved by sitting or lying down. These symptoms may completely resolve after decompressive lumbar laminectomy (Rojas et al., 2007). Intermittent symptoms in women may involve sensory phenomena in the vulva, and urinary symptoms. There are no reports of "sexual" irritative symptoms in women with spinal stenosis.

In patients with "stable" chronic CES, which is a consequence of some past disorder or trauma, SD causes significant frustration. In men, ED is the major problem, and can vary from complete inability to obtain an erection, to inability to sustain adequate erection, to complete sexual activity. A complete lesion of the cauda equina damages the parasympathetic erectile pathways to the penis, but approximately one-fourth of men are still able to achieve a psychogenic erection. As explained above, this response is probably mediated by the sympathetic erectile pathway traveling in the hypogastric plexus. Since complete bilateral loss of neural function is rare, some kind of sexual gratification is usually possible in these patients. Ejaculation may be delayed or absent, although occasionally premature ejaculation is reported. Bilateral damage to all S2–5 roots results in dribbling ejaculation, since seminal emission is preserved, but bulbo- and ischiocavernosus muscles are paretic. In such a patient reflex erection is not possible but psychogenic erection mechanisms are still active. Ejaculation may also be painful. Orgasmic dysfunction was the most common SD in men with CES, and was associated with, and probably caused by, impaired genital sensation (Podnar et al., 2002).

A common problem for the patient of either gender with chronic CES is diminished saddle sensation, which includes impairment of genital sensation. Unfortunately, sensory symptoms recover poorly because in cauda equina lesions, the central sensory axons between the dorsal root ganglia and the spinal cord are damaged. Unlike regrowth of peripheral axons, no such regrowth of the central axons into the spinal cord occurs; cutting the dorsal roots at the conus (i.e., proximal to the dorsal root ganglia) rather than peripherally produces a permanent deafferentation.

Impaired genital sensation reduces the desire for, and some of the most rewarding features of, sexual activity. Genital sensory loss is often accompanied by paresthesias and dysesthesias, and pain syndromes are commonly reported as disruptive for sexual function, particularly if patients suffer from coital pain.

Women with CES report diminished vaginal lubrication in response to psychogenic and genital stimulation. They also report loss of erotic sensation, dyspareunia, loss of lubrication, loss of sensation during vaginal intercourse, difficulties in achieving orgasm, and changes in the feeling of orgasm (Sipski et al., 2001).

Unilateral cauda equina damage results in ipsilateral genital anesthesia. However, sexual function is usually not impaired, because the innervation of the unimpaired side is sufficient for normal genital reflex responses.

Some patients with a history of CES of different causes and variable severity, and with residual neurologic symptoms, report normal sexual function. In the authors' population of CES patients, there were 15% such patients (Podnar et al., 2002). In a population of patients after spinal decompression due to CES caused by lumbar disc herniation, a recent review reported micturition dysfunction in 43% (range 13–90%), defecation dysfunction in 50% (range 10–90%) and SD in 44% (range 10–77%) of patients (Korse et al., 2013). In patients with pure lumbar spinal stenosis prevalence of ED was higher compared to population-based standard data. Furthermore, although decompressive surgery significantly decreased severe preoperative back and leg pain, it was, for unknown reasons, associated with a significant increase of ED (Gempt et al., 2010). A recent prospective study revealed similar findings in a population of patients with fracture-unrelated lumbar spine disease (mainly disc herniations) requiring surgical decompression. Despite significant improvement in back and leg pain, disability index, and neurogenic symptoms at 2 years, erectile function remained unchanged; preoperatively 38% of patients reported ED (Siddiqui et al., 2013). Similarly, selective endovascular embolization of the spinal dural arteriovenous fistula may dramatically improve leg weakness and voiding difficulty, but cause deterioration of SD (Shin et al., 2011).

Spinal dural arteriovenous fistulas are a rare pathologic entity with a diverse and often misleading clinical presentation. Failure to recognize and treat them by surgical or endovascular occlusion in a timely fashion can result in irreversible neurologic disability, including

myelopathy, lower-extremity weakness and bowel, bladder, and SD (Marcus et al., 2013).

Increase in use of regional anesthesia resulted in a higher frequency of neurologic deficit and arachnoiditis that may appear as transient nerve root irritation, CES, and later as radiculitis, clumped nerve roots, fibrosis, scarring dural sac deformities, pachymeningitis, pseudomeningocele, and syringomyelia. Arachnoiditis may be caused by infections, blood in the intrathecal space, trauma, as well as surgical interventions on the spine, and other iatrogenic lesions (e.g., myelograms mostly from oil-based dyes, intrathecal corticosteroids) (Aldrete, 2003).

Intraspinal tumors in the region of L1 and below may cause CES, but CES may also only appear as a consequence of surgical removal of tumor in that region (Ohtonari et al., 2009).

CES is a rare complication of ankylosing spondylitis. In a small series of nine patients with ankylosing spondylitis and dural sac dilation, eight developed CES 10–51 years after onset of disease. Presenting symptoms were sensory in six, urinary in four, and pain in four. The symptoms worsened progressively, and ED was reported by three cases. Magnetic resonance imaging showed, among other abnormalities, nerve root tethering with adhesion to the dura mater and vertebrae (Ea et al., 2010).

Spinal malformations

Any type of dysraphism may be associated with neurologic symptoms that may include sexual disturbances, but data from large patient populations are lacking. The most important malformation giving rise to SD is meningomyelocele. Depending upon the degree of malformation, there is a more or less pronounced loss of sexual functions. Some boys have no genital sensation at all, some can have erections only, and some can have both erections and emissions. Loss of genital sensations is the major complaint in girls (Dorner, 1977; Sawyer and Roberts, 1999).

Now that individuals with dysraphism live well into adulthood, ED has become recognized as an associated medical disorder. In general, adult males with dysraphism have normal sexual desires and an interest in addressing these issues with healthcare providers, although sexual education and access to intimacy are delayed compared to the general population. In spite of 75% of men achieving erections, maintaining erections is a problem. Many of these men show marked improvement with sildenafil (Palmer et al., 2000). Further investigation into sexuality, sex education, intimacy, and treatments for ED and infertility in this population is needed (Bong and Rovner, 2007).

ED may occur in patients with Arnold–Chiari malformations; the onset of sexual symptoms is generally after the development of other neurologic disturbances. Precocious, early, and accelerated puberty in male patients was reported in Arnold–Chiari malformation type I, suggesting the need to carry out brain imaging in such boys (Stagi et al., 2004).

VIRAL CAUDA EQUINA SYNDROMES

Although cytomegalovirus, herpes zoster (a varicella-zoster virus infection), and genital herpes simplex infections cause lower urinary tract symptoms, there are no reports on significant SD.

SACRAL PLEXUS AND PUDENDAL NERVE LESIONS

Lesions of the sacral plexus and pudendal nerves can be caused by pelvic fractures, hip surgery, malignant infiltration, local radiotherapy (Vock et al., 1988), and by the use of orthopedic traction tables (Amarenco et al., 2001). Sacral plexus lesions are usually unilateral and do not result in significant SD, unless the sensory symptoms are disruptive.

Trauma may cause pudendal nerve injury, leading to loss of penile sensation, dysesthesias, pain syndromes, and dribbling ejaculation due to perineal muscle denervation. In one study, 22% of long-distance cyclists had penile sensory symptoms, and 13% had ED with symptoms that persisted for up to 8 months (Andersen and Bovim, 1997). Pudendal nerve lesion induced by bicycling may also cause ejaculatory dysfunction (Leibovitch and Mor, 2005). Ejaculatory dysfunction can be readily explained by denervation of perineal muscles (e.g., ishiocavernosus, bulbospongiosus) that can be demonstrated by EMG.

Pudendal neuralgia is considered a syndrome, with pudendal nerve entrapment as one of the possible etiologies (Stav et al., 2009). The leading symptom is pain, although SD has also been reported. Unfortunately, clinical neurophysiologic tests are of little help in the diagnosis, which remains clinical (Lefaucheur et al., 2007).

Iatrogenic pelvic plexus lesions will be discussed separately.

PERIPHERAL NEUROPATHIES

There are many causes of polyneuropathy, but relatively few of them cause prominent SD (Table 11.1). As a general rule, SD is encountered particularly in patients with polyneuropathies involving autonomic nerve fibers, and in patients with focal neuropathies of the pelvic nerves.

SD (and, particularly, ED) in patients with polyneuropathy have traditionally been linked to this “obvious” neurogenic factor in the pathogenesis of the dysfunction. There are studies substantiating this claim,

Table 11.1

Peripheral neuropathies causing sexual dysfunction

Focal neuropathies/radiculopathies
Cauda equina lesions
Sacral plexus and pudendal nerve lesions
Focal pelvic nerve lesions
Generalized neuropathies
Metabolic/nutritional
Diabetes mellitus
Alcohol, chemotherapeutics
Uremia
Hepatic disease
Vitamin B_1 and B_{12} deficiencies
Hereditary
Charcot–Marie–Tooth disease
Hereditary sensory autonomic neuropathies
Transthyretin amyloid polyneuropathy
Immune-mediated
Guillain–Barré syndrome
Pandysautonomia
Pure cholinergic dysautonomia
Paraneoplastic autonomic neuropathy
Lambert–Eaton myasthenic syndrome
Infectious
HIV-associated polyneuropathy
Tabes dorsalis
Neoplastic
AL amyloid polyneuropathy

HIV, human immunodeficiency virus; AL, amyloid light-chain.

demonstrating, for instance, the significant association of ED with deficient sensory innervation of the glans penis (irrespective of etiology) (Bleustein et al., 2002). The contribution of the autonomic nerves controlling erection is difficult to determine, because specific tests for these nerves are lacking. In many polyneuropathies, there are other possible relevant pathogenetic factors for SD linked to the underlying cause of polyneuropathy, which may contribute to dysfunction in their own right. A case in point, by no means isolated, is diabetes mellitus (DM) and diabetic neuropathy. While this chapter discusses SD in different patient populations with PNS involvement, other potential pathogenetic factors need to be acknowledged, particularly as we lack diagnostic tools to evaluate the proportional contribution of factors to what ends up as SD in a particular patient population. In this context, it is important to be aware that ED (even in a patient with polyneuropathy) is primarily an important risk factor for cardiovascular disease and death. Therefore ED in an individual patient should give rise to clarification of whether cardiovascular risks have been adequately managed (Banks et al., 2013).

Autonomic neuropathy

Autonomic neuropathies comprise a wide spectrum of syndromes and diseases caused by hereditary or acquired diseases (see Table 12.1 in Chapter 12). Autonomic dysfunction may manifest with various clinical presentations, including SD (Freeman, 2005). Polyneuropathy is thus considered an important "risk factor" for SD – particularly polyneuropathies with prominent affection of the ANS (McDougall and McLeod, 1996). In 341 consecutive patients with ED, neurophysiologic evaluation revealed the presence of polyneuropathy in 38% of diabetic cases and in a further 10% of other patients (Vardi et al., 1996).

The most common genetic disorders presenting with autonomic dysfunction include familial amyloid polyneuropathy, hereditary sensory autonomic neuropathies (HSAN), Fabry's disease, and porphyrias (Low et al., 2003; Freeman, 2005). In familial amyloid polyneuropathy ED is common (Andrade, 2009).

In porphyric neuropathy autonomic function studies have demonstrated abnormalities of both sympathetic and parasympathetic nerves (Laiwah et al., 1985), although it seems that SD was reported so far in only a single patient (with acute intermittent porphyria). The patient had sensory neuropathy, and also reported lower-extremity numbness, paresthesias, constipation, and urinary retention. Vitamin B_6 and glucose therapy initiated resolution of symptoms (Goren and Chen, 1991). A recent comprehensive review of porphyric neuropathies does not include ED or SD in the clinical picture (Shin-Yi Lin et al., 2013).

Fabry's disease patients have symptoms and signs compatible with autonomic dysfunction that are considered to be due to impairment of the PNS. However, scores in the male SD domain of the Autonomic Symptom Profile were comparable between 15 Fabry patients (most were treated with enzyme replacement therapy) and 15 age-matched controls (Biegstraaten et al., 2010).

Primary autonomic neuropathies (also known as idiopathic) are acquired disorders that include pandysautonomia, pure cholinergic dysautonomia, Holmes–Adie syndrome, Ross syndrome, idiopathic distal small-fiber neuropathy, and (acquired) amyloid neuropathy. SD has been described in pandysautonomia and pure cholinergic dysautonomia (Kirby et al., 1985) and in amyloid neuropathy (see below).

There are several identifiable causes of secondary acquired autonomic neuropathies, in which SD (particularly ED) has been described. These are metabolic disorders (DM, hepatic disease, and uremia – see below), vitamin deficiencies (B_1, and B_{12}), toxins and prescription medications (alcohol, chemotherapeutics), infectious diseases (human immunodeficiency virus (HIV),

botulism, diphtheria, tabes dorsalis) and autoimmune conditions (paraneoplastic autonomic neuropathy, plasma cell dyscrasia (Takatsuki and Sanada, 1983), Lambert–Eaton myasthenic syndrome, Guillain–Barré syndrome (GBS)) (Hahn, 1998; Low et al., 2003; Vinik et al., 2003). It is likely that the condition of acute distal autonomic neuropathy is a form of GBS. It may affect the pelvic plexus and its associated nerves (sympathetic and parasympathetic), resulting in SD (Koike et al., 2013).

Several of the secondary autonomic neuropathies are discussed separately below.

Diabetes mellitus

The prevalence of ED in DM has been reported as 50% and attributed – in addition to damage of nerves essential for erection – to elevated advanced glycation end products, impaired nitric oxide synthesis, increased endothelin B receptor-binding sites, increased oxygen free radicals, upregulated RhoA / Rho-kinase pathway, and impaired cGMP-dependent protein kinase 1 (Thorve et al., 2011).

Traditionally, ED, and the other "typical" SD in diabetic men, retrograde ejaculation, have been attributed particularly to neuropathy, although nowadays additional pathogenetic factors for ED are recognized. DM is the most common cause of polyneuropathy in developed countries. The neuropathy is often asymptomatic or manifests with minor symptoms. Most occur in the course of the disease. Diabetic autonomic neuropathy is a frequent accompaniment of severe distal symmetric sensory neuropathy (Powers, 2011), but may be the dominant peripheral nerve involvement. The prevalence of neuropathy in 3250 randomly selected insulin-dependent diabetic patients from 31 European centers was 28% with no significant geographic differences. Neuropathy was correlated with age, duration of disease, quality of metabolic control, height, retinopathy, cigarette smoking, high-density lipoprotein cholesterol, elevated diastolic blood pressure, a history of severe ketoacidosis, microalbuminemia, and vascular disease (Tesfaye et al., 1996).

A correlation between SD and the occurrence of peripheral neuropathy has been reported since early studies (Jensen, 1981). Diabetic neuropathy is by far the commonest polyneuropathy to be associated with bowel, bladder, and SD; peripheral neuropathy is an independent predictor for ED in DM (Romeo et al., 2000; Wessells et al., 2011). Morphologic alterations have been demonstrated in unmyelinated nerve fibers of the penis (Faerman et al., 1973). A preferential involvement of unmyelinated sensory fibers resulting in neuropathic pain and gastroparesis was reported in diabetic patients with ED (Wellmer et al., 1999). The vibration perception threshold was also reported to be diminished in diabetic men and correlated with the severity of ED (Amano et al., 2011). In sleep laboratory studies, fewer sleep-related erections, shorter tumescence time, and diminished penile circumference increase and lower penile rigidity were recorded in men with diabetic polyneuropathy than in non-diabetics (Hirshkowitz et al., 1990). Measurement of bulbocavernosus and urethroanal reflex latencies as well as penile evoked potentials has been reported as more abnormal in diabetic males with ED than in non-diabetic males with ED and diabetic males without ED (Bemelmans et al., 1994). A significant difference in the sural neurogram was also found between a diabetic and control group of men with ED (Wellmer et al., 1999). Neurophysiologic testing of pudendal nerve function did not prove to be more sensitive in diagnosing neuropathy in diabetics with ED than limb nerve conduction studies (Vodusek et al., 1993). It is still suggested that the neurogenic component of ED in diabetic men can be revealed by measuring the R-R ratio on Valsalva maneuver, the bulbocavernosus reflex, and the sensory neurography of the dorsal penile nerve (Hamdan and Al-Matubsi, 2009). Other authors suggest quantitative sensory testing, for instance, the measurement of vibration perception threshold (Amano et al., 2011). However, some studies found no correlation of SD with polyneuropathy, as defined by pathologic nerve conduction studies, including testing the sympathetic skin response (SSR) (Zgur et al., 1993). Cardiovascular reflex tests of the sympathetic nervous system could not differentiate between diabetic men with and without ED (Quadri et al., 1989). The sensitivity and specificity of all these tests in diabetic men with ED have not been formally reported. Since the result of neurophysiologic testing does not alter patient management, extensive testing is nowadays neither recommended nor practiced.

Typically, a prevalence of ED of 50% is reported in diabetic men (Thorve et al., 2011). In an Italian cohort of 1503 newly diagnosed type 2 diabetics (mean age 59 years), 43% reported ED, and only 7% neuropathy. Comorbidities were arterial hypertension (55%) and coronary heart disease (8%) (Corona et al., 2013). Other studies report an even larger prevalence of ED. Among 455 male diabetic patients 82% had ED (28% severe ED) (Chuang et al., 2012). A large US epidemiologic study even defined ED as an observable marker for DM in men up to 65 years of age. In that study the prevalence of diabetics in the whole population with ED was 20% (Sun et al., 2006). It has been reported that glycemic control is independently and inversely correlated with ED (Awad et al., 2010), as is albuminuria (Chuang et al., 2012).

ED in diabetic men usually begins insidiously with a progressive decline in erection rigidity and duration, to

the point where penetration and intercourse become impossible. Despite the lack of erection, ejaculation and orgasm may occur on sexual stimulation, indicating the particular susceptibility of the erectile mechanisms in this disorder. The severity of ED depends on age, duration of DM, number of DM complications and the vibration perception threshold (Amano et al., 2011). Among 455 male diabetics albuminuria, retinopathy, neuropathy, insulin therapy, calcium-channel blockers, and higher level of HbA1c correlated with severe ED (Chuang et al., 2012).

As indicated, the prevalence of ED in cohorts of diabetic men is generally reported as higher than that of neuropathy, indicating that, in addition to damage of nerves essential for erection, there are other important pathogenetic factors contributing to ED: vascular, elevated advanced glycation end products, impaired nitric oxide synthesis, increased endothelin B receptor binding sites, increased oxygen free radicals, upregulated RhoA / Rho-kinase pathway, and impaired cGMP-dependent protein kinase 1 (Thorve et al., 2011). The above-mentioned metabolic defects block the vasodilator action of released nitric oxide in corporeal tissue and are probably the cause of the relatively poor response to sildenafil in diabetic men with ED. In the long-term management of both neuropathy and ED, good glycemic control has always been stressed. Indeed, a period of intensive glycemic therapy significantly reduced the prevalence of ED 10 years later in men with non-proliferative retinopathy or microalbuminuria, but not in those without microvascular complications (Wessells et al., 2011).

A higher prevalence of hypogonadism has been reported in men with DM as compared to non-diabetic controls with ED (Corona et al., 2004). By contrast, another study found levels of testosterone, prolactin, follicle-stimulating hormone, luteinizing hormone, and thyroid-stimulating hormone of diabetic patients no different from levels in the control group (Hamdan and Al-Matubsi, 2009).

DM in men is indeed significantly associated with all aspects of SD, as also sexual desire, ejaculatory function, and sexual satisfaction were affected in a cohort of 2115 men between 40 and 79 years of age (Burke et al., 2007). In men with long-standing DM type 1 the prevalence of particular SD was as follows: ED 34%, orgasmic dysfunction 20%, and decreased libido 55% (Penson et al., 2009). ED is much more frequent than ejaculatory difficulties. The latter usually involves retrograde ejaculation rather than total lack of ejaculation. Retrograde ejaculation in diabetic patients is a result of internal bladder sphincter paresis (Hershlag et al., 1991). However, a systematic and focused search for this symptom has given figures as high as 14% (unpublished observation). SD is significantly associated with lower Diabetes Quality of Life questionnaire scores (Jacobson et al., 2013).

Sexual function in women with DM has been the object of more research in recent years. Loss of libido has been reported (Newman and Bertelson, 1986), but also deficits of desire, lubrication, orgasmic capacity, sexual satisfaction, and a negative impact on the relationship with the sexual partner as compared to matched control women (in type 2, but not type 1 diabetic women) (Schreiner-Engel et al., 1987). In a study consisting of a structured interview, Hulter et al. (1998) found that 26% of 42 women with insulin-dependent DM had decreased sexual desire, 22% had decreased vaginal lubrication, and 10% had decreased capacity to acquire orgasm. Several of the women reported more than one dysfunction. Taken together the figure for SD was 40%. Among age-matched controls without DM or neurologic disease only 7% of women reported SD. More studies are beginning to appear, confirming a negative impact of DM on female sexuality. Scores for the sexual drive, arousal, vaginal lubrication, orgasm, and overall satisfaction domains were all lower in the 50 married diabetic women compared with those of 40 non-diabetic controls ($P < 0.05$). Duration of DM and age correlated negatively with all domains of sexual function (Fatemi and Taghavi, 2009).

From the PNS perspective, it is relevant to consider the neuropathic element in female SD due to DM. A postmortem study of tissue samples from 17 diabetic women showed evidence of both clitoral nerve degeneration and changes in clitoral blood vessels. A non-diabetic control group did not show any signs of neuropathy or vascular damage (Zrustova et al., 1978). In other studies, diabetic patients had significantly higher vibration perception thresholds in the hands and in the clitoris than controls (Enzlin et al., 2002). A number of autonomic and sensory (i.e., neuropathic) symptoms, such as reduced foot perspiration, increased gustatory perspiration, and impaired subjective vulvar sensibility, were noted more often by women with insulin-dependent DM than by controls (Hulter et al., 1998).

Only a few studies have dealt with lubrication, the most important female counterpart to penile erection. Tyrer et al. (1983) found that in insulin-dependent diabetic women vaginal lubrication was often inadequate or required more prolonged stimulation compared to controls. Significantly decreased lubrication was reported in women with DM compared to controls, which would be expected as a consequence of disturbed physiologic mechanisms in DM, particularly neuropathy. No association between SD and age, body mass index, duration of DM, HbA(1c), use of medication, menopausal status, or microvascular complications

was found (Enzlin et al., 2002). Another study did not find a significant relationship between sexual function and body mass index, glycemic control (i.e., fasting plasma glucose and glycosylated hemoglobin) (Fatemi and Taghavi, 2009). While DM is an independent predictor of orgasmic dysfunction, depressive symptoms, individual perception of sexual needs, and partner-related factors were reported as stronger predictors of female SDs in same patients (Nowosielski et al., 2010). Thus, importantly, the impact of psychologic factors, especially depression, needs to be acknowledged (Esposito et al., 2010; Giraldi and Kristensen, 2010). Depression is of course a significant predictor for SD in both women with DM and control subjects (Enzlin et al., 2002).

Chronic renal failure

In clinical practice, little attention is given to sexual problems of patients with end-stage renal disease, and one of the earlier studies indicated that ED in patients with renal failure is no more frequent than in a group of "non-neuropathic" chronic patients (with rheumatoid arthritis) (Toorians et al., 1997). In other studies, a high prevalence of SD has been reported. The prevalence of ED among 75 hemodialysis patients in upper Egypt was significantly higher (83%) compared to 945 controls (30%) (Ali et al., 2005). A multinational cross-sectional study found that most men on hemodialysis experience ED and are untreated. In men on hemodialysis 83% reported ED, 47% of them severe ED. The prevalence of ED was highest (94%) in unmarried and unemployed or retired men with depressive symptoms (Vecchio et al., 2012). Male patients on hemodialysis have a similar prevalence of ED as patients on peritoneal dialysis (Toorians et al., 1997).

ED has been attributed to uremic neuropathy, tissue lesions related to chronic renal failure, endocrine disorders, and drugs. Up to 60% of patients with renal failure, uremia, and dialysis have a subclinical neuropathy. Symptoms and signs are of a length-dependent sensory axonal neuropathy occasionally with pain and prominent itching. Recovery from renal failure or renal transplantation may improve or reverse the neuropathy. There is a tendency for pre-existent ED to improve after transplantation (El-Bahnasawy et al., 2004; Shamsa et al., 2005), but other factors (drugs) may subsequently appear to cause SD (Kleinclauss et al., 2005).

In double-blind, placebo-controlled studies in patients receiving dialysis or renal transplants, sildenafil significantly improved erectile function as assessed by the International Index of Erectile Function (IIEF), and 75–85% of patients reported improved erectile function on Global Assessment Questions. Only about 1% of patients undergoing dialysis or with renal transplants who received sildenafil in clinical studies discontinued therapy because of adverse events. Similar results have been published for vardenafil. Sildenafil and vardenafil appear to be efficacious and well tolerated in patients receiving renal dialysis or transplant (Lasaponara et al., 2013). However, in one study, only 4% of men with ED due to renal failure were receiving pharmacologic treatment (Vecchio et al., 2012).

Men on hemodialysis or peritoneal dialysis have higher prevalence of loss of sexual interest, hypoactive sexual desire disorder, sexual aversion disorder, and inhibited male orgasm than men with kidney transplantation or rheumatoid arthritis (Toorians et al., 1997).

In women on hemodialysis or peritoneal dialysis loss of sexual interest, subjectively ascribed to fatigue, was reported. Transplanted female patients suffered less from hypoactive sexual desire disorder than the renal failure or rheumatoid arthritis group. Genital responses during psychophysiologic assessment had no relationship to the duration of renal replacement treatment, biochemical/endocrine variables, or the presence/absence of neuropathy (Toorians et al., 1997). In another study, female SD was found in 80 of 85 peritoneal dialysis patients, in all 32 hemodialysis patients, and in 22 of 48 married age-matched controls. A significant negative correlation was found between total Female Sexual Function Index score and age, Beck Depression Index score, and mental–physical component score of quality of life in peritoneal dialysis and hemodialysis patients. The rates of depression were 75% in peritoneal dialysis, 44% in hemodialysis, and 4% in control subjects (Yazici et al., 2009).

The hormonal profile and the Female Sexual Function Index results improved significantly after transplantation. In a study of 58 women with chronic renal failure who received kidney transplantation, successful transplantation significantly improved the patient's sex life; 74% of patients had menstrual disturbances during dialysis, as opposed to 45% after transplantation. Forty-one percent of patients had an active sex life during dialysis and 88% did after transplantation (Filocamo et al., 2009).

Alcoholism

In most western countries the lifetime risk for alcohol dependence is 10–15% in men and 5–8% in women (Hasin et al., 2007). Alcohol leads to a multiorgan disease state, and to neurologic disorders affecting the brain, brainstem, cerebellum, and the peripheral nerves. Traditionally, ED has been seen as one of the clinical manifestations of polyneuropathy, which is the most common chronic complication in alcoholics, affecting 5–15% of them (Schuckit, 2011). Polyneuropathy is a result of thiamine deficiency and/or a direct toxic effect

of ethanol and acetaldehyde (Mellion et al., 2012). Alcoholic polyneuropathy usually presents as a gradual development of distal symmetric, sensory, and motor symptoms. Axonal degeneration and segmental demyelination are the main features (Messing and Greenberg, 1989), although non-myelinated fibers are also involved. A loss of sympathetic and parasympathetic nerve fibers as well as ganglion neurons has been observed (Windebank, 1993). Symptoms of autonomic neuropathy in the absence of alcoholic hepatopathy have been demonstrated in 74% of alcoholics; at least one autonomic test was abnormal in 62% and two of three neurocardiologic test results for autonomic neuropathy were abnormal in 26% of detoxified chronic alcoholics. The pattern of autonomic involvement was mainly parasympathetic; in 10 of 18 patients its sole clinical expression was ED. Autonomic neuropathy did not correlate with peripheral neuropathy, nor with any parameter reflecting the amount of alcohol intake (Ravaglia et al., 2004).

Vascular factors are probably also responsible for the onset of ED in alcoholics; 43% of alcoholics had penile vascular impairment on ultrasonography (Fabra and Porst, 1999). Vascular and endocrine ED were more frequent in 80 men with alcohol dependence as compared to 40 men without alcohol dependence, and the presentation of sexual disorder was complicated due to an increase in the number of accompanying syndromes. In addition to ED, atrophy of testicles, low serum level of testosterone, and impaired spermatogenesis have been reported (Taniguchi and Kaneko, 1997). As alcohol dependence progresses the pathogenetic factors causing ED accumulate (Krupnov et al., 2011).

Generally, long-term and excessive intake of ethanol is associated with SD. In a study performed in Hong Kong on 816 subjects aged 31–60 years, alcohol drinkers who consumed three or more standard drinks a week were more likely (odds ratio 2.27) to report ED compared with never drinkers after adjusting for age and cigarette smoking (Lee et al., 2010). In a Turkish study 70% of participants had a mild, and 4% a moderate, ED. With a multivariate analysis, predictors of ED in chronic alcohol-dependent men were age, age of onset of alcohol consumption, duration of alcoholism, and cigarette use (Dissiz and Oskay, 2011).

Alcohol use was among the most important factors associated with low sexual activity in urban Chinese women (odds ratio 2.7), more probably due to psychosocial than to medical reasons (Lianjun et al., 2011). Likewise, partner's alcohol abuse and ED were inversely correlated with sexual function in a cohort of 179 sexually active 40–65-year-old Spanish women (Perez-Lopez et al., 2012). However, there is currently no study evaluating the direct effect of alcohol on female sexual function.

Guillain–Barré syndrome and chronic inflammatory demyelinating polyneuropathy

GBS includes a combination of acute autoimmune demyelinating and axonal polyneuropathies. Clinically it is characterized by a largely symmetric ascending motor paralysis with or without obvious sensory and autonomic disturbances. Autonomic features may be present in up to 50% of patients, and include labile blood pressure, extremity anhidrosis, paralytic ileus, and lower urinary tract dysfunction. Guillain himself mentioned erectile and ejaculatory dysfunction during recovery in a few GBS patients (Guillain, 1938). However, due to the acute nature of GBS, opportunity to judge SD is limited. In a retrospective series of 179 patients, only two typical GBS patients were unable to sustain erections. One of them had other autonomic abnormalities, and the other did not (Ropper, 1992). In a study including 396 men more than 3 years after acute GBS, Burk and Weiss (1998) reported a significant increase in ED compared to age-matched controls. Severity of ED was related to severity of the residual disability.

By contrast, men with pure pandysautonomia and its sensory variants, probably a type of GBS, frequently have impotence both at the peak of illness and later, associated with persistent signs of autonomic dysfunction. The patient described by Young and colleagues (1975) had poor erectile function, retrograde ejaculation, and atonic dartos muscle early in the illness, all improving as the disease receded. In similar cases impotence has generally paralleled micturition difficulty and cholinergic deficits (Okada et al., 1975). A few reports comment that women with pandysautonomia may be capable of orgasm (Andersen et al., 1972).

Although autonomic dysfunction is often pronounced in GBS, it is typically mild in chronic inflammatory demyelinative polyradiculoneuropathy (CIDP). Likewise, SD is also only very rarely reported in patients with CIDP, and may or may not be associated with urinary and fecal incontinence and additional signs or symptoms of autonomic dysfunction. ED in such patients may return together with muscle strength and improved continence after intravenous immunoglobulin treatment (Bussemaker et al., 2007).

HIV-associated sexual dysfunction

Expectations of both patients and physicians alike have changed significantly over the past decade and a half, due to improved antiviral treatment. Men living with HIV expect now to lead a normal sex life. This may be jeopardized by SD associated with their disease. Counseling and treatment may be especially important

in male acquired immunodeficiency syndrome (AIDS) patients with ED, since the use of condoms often precipitates their ED, and men are therefore unwilling to use protection.

The early onset of ED in HIV-infected men could be considered a peculiar clinical hallmark of HIV (Zona et al., 2012). In a study of 1361 gay men (236 of whom were HIV-positive), in those 40–59 years of age a significant trend was found towards greater prevalence of ED with progressive HIV infection relative to age-matched HIV-negative men. Only HIV infection with AIDS, but not HIV infection without AIDS, was associated with greater odds of ED in a logistic regression model controlling for other variables (Shindel et al., 2011). In persons infected with HIV, peripheral nerve disorders are common and may be accompanied by dysautonomia. Slowed sural and dorsal penile sensory conduction velocities were taken as suggestive that neuropathy is important in the genesis of ED in HIV-positive men (Ali et al., 1994). Hypogonadism is also more common among men infected with HIV compared to age-matched men within the general population (Crum et al., 2005). In a cross-sectional, observational, controlled study on 444 HIV-infected men and 71 HIV-uninfected men, the prevalence of mild, moderate, and severe ED was higher in HIV-infected men than in HIV-uninfected men of all age. In multivariable logistic regression analysis, HIV infection remains the strongest predictor of ED, followed by hypogonadism, after adjusting for age and body mass index (Zona et al., 2012). Disease-related factors are not only of "organic" nature; in 158 men with HIV (mean age 46 years, 96% on antiretroviral therapy, 91% with undetectable viral load, and mean CD4 count 534 cells/mL), ED was present in 67% of patients. In addition to age, ED was related to anxiety (Perez et al., 2013).

In 668 HIV-infected men, in addition to 33% with moderate or severe ED, 24% also reported moderate to severe impairment of sexual desire. Loss of libido was most consistently associated with older age and depression (Asboe et al., 2007).

Treatment of AIDS may have a deleterious effect on erectile function. In a cross-sectional, observational study of 90 patients (mean age 42 ± 8 years, CD4 cell count of 465 cells/μL, and 72% with undetectable viral load) 53% of patients had ED. On multivariate logistic regression analysis there was an association between the patients' age (odds ratio 2.2 per decade) and greater duration of exposure to protease inhibitor (odds ratio 1.6 per year) on various SD domains ($P < 0.05$) (Moreno-Perez et al., 2010). Another study of ED and antiretroviral drugs in patients with AIDS did not reveal an association (Wang et al., 2013).

A significant relationship between male patients with AIDS complaining of delayed ejaculation and peripheral neuropathy has been reported (Richardson et al., 2006). But in another study, HIV infection with or without AIDS was not significantly associated with premature ejaculation (Shindel et al., 2011).

Women with HIV were less likely to report heterosexual activity in the previous 6 months (65% HIV-positive, 76% HIV-negative) in a multisite, longitudinal study following the natural history of HIV infection among women in the USA and comparing 561 HIV-negative with 2040 HIV-positive women (Wilson et al., 1999). Women with HIV reported greater sexual problems than did those without HIV, and those with CD4 cell count <200 cells/μL had lower Female Sexual Function Index scores, compared to those with CD4 of 200 cells/μL or higher (Wilson et al., 2010). No study reporting the effect of HIV infection on SD itself has yet been published.

Amyloid neuropathy

Amyloidosis refers to diseases caused by the extracellular deposition of insoluble polymeric protein fibrils in tissues and organs. Amyloid fibrils share a common pleated sheet structural conformation that confers unique staining properties. Amyloid diseases are defined by the biochemical nature of the protein in the fibril deposits. The accepted nomenclature is "AX," where A indicates amyloidosis and X represents the protein in the fibril. In AL the amyloid is composed of immunoglobulin light chains; the disease is also called primary systemic amyloidosis. AF groups the familial amyloidoses, most commonly due to abnormal transthyretin, the transport protein for thyroid hormone and retinol-binding protein.

Small-fiber neuropathy is seen in AL and transthyretin amyloidosis, but not in other amyloidoses. Deposition of amyloid was found in afferent somatic nerves, and in the detrusor (Ito et al., 2006; Andrade, 2009). SD has been reported in both.

Acquired amyloid neuropathy

The incidence of AL is 5.1–12.8 per million. It occurs predominantly in later life; two-thirds of cases occur between the ages of 50 and 70. In AL the constituent amyloid protein is derived from a clonal B-cell disorder producing monoclonal immunoglobulin light chains secondary to multiple myeloma, malignant lymphoma, or Waldenström's macroglobulinemia, or to a non-malignant immunocyte dyscrasia. Amyloid develops in approximately 15% of patients with myeloma and less frequently in other malignant monoclonal disorders.

AL may present with non-specific symptoms such as malaise, fatigue, and weight loss, or with system-specific symptoms, the most common being nephrotic syndrome, congestive cardiomyopathy, peripheral neuropathy

(sometimes with autonomic involvement), and hepatomegaly. Patients with neuropathy present with an acquired, length-dependent sensory loss with prominent small-fiber involvement. Pain is often burning, especially nocturnally, or lancinating. Autonomic involvement, including distal-limb anhidrosis, orthostatic hypotension, difficulty in voiding urine, ED, and ejaculatory difficulty tends to be early. On examination, nerves may be thickened, pain and temperature are selectively involved, and autonomic involvement is often evident (including pupillary involvement).

Transthyretin-related familial amyloid polyneuropathy

Over 100 mutations causing transthyretin amyloidoses have been identified, leading to destabilization of the physiologic transthyretin tetramer. The disease is most commonly caused by a point mutation within the transthyretin gene, and is inherited in an autosomal-dominant fashion. Those that involve peripheral nerves are called familial amyloidotic polyneuropathy and are further classified on the basis of the specific mutation in the transthyretin gene. Transthyretin-related familial amyloid polyneuropathy is a fatal disorder characterized by extracellular deposition of abnormal fibrils derived from misfolded, normally soluble transthyretin molecules. There are regions in Portugal and northern Sweden with large clusters of patients, but patient populations with independent mutations are spread around the world. The main clinical feature of transthyretin familial amyloidotic polyneuropathy is progressive sensorimotor and autonomic neuropathy. In the beginning, this polyneuropathy predominantly involves small unmyelinated nerve fibers, resulting in dissociated sensory loss disproportionately affecting sensation of pain and temperature.

Autonomic neuropathy typically accompanies sensory deficits early in the disease course. The symptoms include orthostatic hypotension, constipation alternating with diarrhea, ED, anhydrosis, and urinary retention or incontinence. Later, involvement of motor fibers causes rapidly progressive weakness and gait disturbances. Onset of symptoms is bimodal, with one peak at age 33 years (early onset) and another distinct peak in the sixth decade of life (late onset). The course of transthyretin familial amyloidotic polyneuropathy is uniformly progressive and fatal. Death occurs an average of 11 years after the onset of symptoms in Portuguese patients, and 7 years in late-onset Japanese patients. Common causes include cachexia, cardiac failure, arrhythmia, and secondary infections (Andrade, 2009).

In men with familial amyloidotic polyneuropathy the first complaint can be SD. Pudendal evoked potentials, and bulbocavernosus reflex abnormalities were reported to have a statistically significant correlation with clinical and EMG scores. Abnormal SSRs in the feet preceded other clinical or EMG abnormalities (Alves et al., 1997).

In non-menopausal women with a sexual partner, those with familial amyloidotic polyneuropathy had four times greater risk for disorders of desire, arousal, orgasm disorders, and sexual dissatisfaction reported by a questionnaire compared to control women. Risk of SD correlated with disease severity (Oliveira-e-Silva et al., 2013).

The standard therapy for AL in patients who are in a clinical condition good enough to tolerate this intervention is liver transplantation. This stops progression of neuropathy by removing the main source of mutant transthyretin. Recently, orally administered medication tafamidis meglumine has been approved by European authorities for the treatment of familial amyloid polyneuropathy (Hund, 2012).

A case report of a man with familial amyloidotic polyneuropathy, whose ED did not improve after liver transplantation, suggests that sildenafil citrate is an effective and safe treatment of ED in this condition (Obayashi et al., 2000).

Other hereditary peripheral neuropathies

Inherited neuropathies can be divided into those in which the neuropathy is the sole or primary part of the disease and those in which the neuropathy is part of a more widespread neurologic or multisystem disorder (these will not be further discussed). The first group includes Charcot–Marie–Tooth (CMT) disease, which is the most common inherited neuropathy, affecting approximately 1/2500 in the Caucasian population, and usually presents with a length-dependent sensorimotor neuropathy. At least 43 causative gene defects have been identified with genetic mapping in CMT (Braathen et al., 2011). This group also includes familial amyloid polyneuropathy, a disease in which neuropathy (often including autonomic neuropathy) is the cardinal feature, although other systems can be involved (e.g., heart).

CMT disease is a group of clinically and genetically heterogeneous neuropathies. They are also referred to as hereditary motor and sensory neuropathies, although CMT is now the more commonly used term. CMT is characterized clinically by distal muscle wasting and weakness, reduced reflexes, impaired distal sensation, and variable foot deformity. Neurophysiologically, CMT is characterized by a motor and sensory neuropathy. There is a wide variation in the age of onset and the severity of CMT, depending to a large extent on the underlying genetic defect. Certain forms of CMT and HSAN are very difficult to distinguish clinically. Therefore, the same phenotypes may be caused by different

genes and the same gene may cause different phenotypes.

Erectile and ejaculation problems have been observed in patients with CMT (Bird et al., 1994), Refsum's disease (Lundberg, personal communication), and HSAN I–IV (Obayashi et al., 2000). It does not seem to be the involvement of the somatic nerves (pudendal nerves) that is causing ED in CMT (Vodusek and Zidar, 1987).

It seems that, at least in women with CMT, social aspects are very important in sexual functioning, as overall sexual problems were more prominent in younger women with milder clinical involvement. By contrast, women with more severe CMT symptoms reported more pain during intercourse. Age of onset and type of CMT (demyelinating vs axonal) were not associated with differences in sexual functioning. Almost 30% of women with CMT did not engage in sexual intercourse with a partner (Gargiulo et al., 2013).

Other polyneuropathies

Small-fiber neuropathies are an increasingly recognized and symptomatically troublesome group of disorders with diverse causation. The list of causes of small-fiber neuropathies is increasing (see Table 12.1 in Chapter 12), but 50% or more small-fiber neuropathies have no identifiable cause. In idiopathic small-fiber neuropathy significant autonomic disturbances are uncommon, and if present, mostly mild. The relationship to SD is not clarified.

The recently described restless genital syndrome is characterized by unwanted, unpleasant genital sensations, restless legs, and/or overactive bladder, most commonly in women. Genital sensory testing was reported to reveal static mechanical hyperesthesia in the pudendal area, conceptualized as neuropathy of the dorsal nerve of the clitoris (Waldinger et al., 2011).

FOCAL PELVIC NERVE LESIONS

SD can occur from damage to genital innervation anywhere in its course in the pelvis. Fractures of the pelvic girdle and missile injuries can cause damage to these nerves at any or several sites. Pelvic fracture, especially when urethral injury has occurred, is associated with lesions of the neurovascular bundles and SD.

ED has also been reported after injection of sclerosing agents to treat hemorrhoids and overactive bladder, obviously due to inadvertent lesion of pelvic plexus (Bullock, 1997).

SD may follow involvement of autonomic nerves within the abdominal cavity and the pelvis. The sympathetic thoracolumbar fibers may be injured by retroperitoneal lymph node dissections. Pelvic plexus and cavernosal nerves may be injured by abdominoperineal resection for carcinoma, hysterectomy, radical prostatectomy, or sphincterotomy, thus significantly impairing the quality of life in patients after otherwise successful surgery. The pathophysiology of the problem is essentially related to the disruption of the nerves during the procedure, although a vascular impairment may also be implicated. Depending on the location and severity of these nerve injuries, this may result in temporary or permanent erectile and ejaculation dysfunction in the male and loss of lubrication and genital engorgement in the female, also inducing genital pain syndromes. In the female, total hysterectomy for cancer may not be just about nerve injury, but about sacrificing the faculty of pregnancy and sexual intercourse.

The manifestations and mechanisms of dysfunction may vary with the specific type of surgery performed, and the underlying condition, which may have caused some pre-existent pretreatment SD which may have been unnoticed, particularly if minor. Validated questionnaires to assess preoperative baseline SD and postoperative outcomes have become available and their use in clinical practice should be promoted.

Surgeons are increasingly aware of the need to preserve relevant neural tissue even during radical surgery and have developed "nerve-sparing" operations (Klotz, 2004). Nerve-sparing surgery enables the recovery and/or maintenance of sexual function in a significant proportion of patients and it is now also adopted for women.

Major pelvic urologic surgery comprises radical prostatectomy and radical cystectomy in the male patient and radical cystectomy in the female. Postsurgical SD has been reported with a high prevalence in both sexes and is becoming increasingly important in the patient's view as a result of improved cancer prognosis, refinements in surgical technique, and increased awareness of quality-of-life aspects that involve sexual satisfaction.

Prostatic surgery

ED assessed prospectively with nocturnal tumescence studies before and after transurethral prostatectomy showed that ED occurred in none of the 40 men studied (Soderdahl et al., 1996); such surgery has been reported, nevertheless, to occasionally cause ED. Retrograde ejaculation, however, is not uncommon following transurethral prostatectomy, but is usually accepted by patients as a minor problem.

The prospects are quite different for patients undergoing treatment for prostate cancer. The two standard treatments for this are radiotherapy or radical prostatectomy; the latter involves removal of the prostatic capsule, to which the corporeal nerves are intimately bound. A meta-analysis following these treatments has

shown that the chances of developing ED after these two types of treatment were 30% and 60%, respectively (Robinson et al., 1997).

"Nerve-sparing" surgical techniques involve identifying and preserving the nerves to the corpora cavernosa. These travel outside and behind the prostatic capsule in the lateral pelvic fascia until nearer the apex of the prostate, where they lie just lateral to the urethra. It is at this point that they are particularly vulnerable to surgery. They then pass behind the penile artery and dorsal penile nerve to enter the corpora on each side.

In a group of patients after laparoscopic radical prostatectomy the median baseline IIEF-5 score of 22 changed to 13 at 24 months after surgery. At that time, 35% of 150 patients with unilateral nerve-sparing surgery and 68% of 436 patients with bilateral nerve-sparing surgery reported sufficient erectile function for intercourse (Cathala et al., 2012).

Laparoscopic radical prostatectomy with bilateral nerve preservation preserved potency in 85% of preoperatively potent men at 24 months. However, only 27% returned to their baseline sexual function. Number of nerves spared and age were independent predictors of a return to baseline function (Levinson et al., 2011).

Cavernous nerve sparing during radical prostatectomy is not associated with worse cancer outcomes in appropriately selected patients. Unfavorable clinical factors, prostate biopsy characteristics, and poor baseline erectile function predict less cavernous nerve-sparing surgery (Stember et al., 2013).

Cavernous nerve preservation during laparoscopic radical prostatectomy is not an all-or-none phenomenon. Partial nerve preservation may lead to an incremental improvement in the return of sexual function. Other independently predictive variables were patient age at surgery, months since surgery, and preoperative Sexual Health Inventory for Men (Levinson et al., 2008).

During robot-assisted radical prostatectomy, avoidance of thermal injury produced nearly a fivefold improvement in early return of sexual function; otherwise dysfunction due to thermal injury largely recovered 2 years after the intervention. Authors caution, however, about an uncritical increase in nerve volume preservation at the expense of positive surgical margins (Ahlering et al., 2008). Preservation of just one nerve, in the majority of patients, results in similar potency recovery to that with two nerves preserved. Crossover innervation of the one nerve may be the underlying mechanism.

Abdominoperineal resection

The last 20 years have seen enormous strides forward in the treatment of rectal cancer, with the development of improved surgical technique, tumor staging, histopathologic audit, and multidisciplinary team management, with an emphasis on improving survival and reducing local recurrence rates. Having improved oncologic treatment, quality of life must not be forgotten (Fisher and Daniels, 2006).

In the best hands, permanent impotence occurs in less than 2% of patients following restorative proctocolectomy and at a similarly low rate after proctocolectomy and ileostomy; isolated ejaculatory dysfunction is a minor problem postoperation for benign disease. However, more than half of patients treated for rectal cancer experience a deterioration in sexual function, consisting of ejaculatory problems and impotence in men and vaginal dryness and dyspareunia in women (Lange and van de Velde, 2011). Around one-third of women aged 50–70 years report lack of sexual desire after treatment for rectal cancer; overall, SD is in the order of 60% (Panjari et al., 2012).

Abdominoperineal resection affects the sexual life of men much more than (low) anterior resection for treatment of rectosigmoid carcinoma; two of nine and 12 of 17 men were sexually active after surgery, respectively. Patients report complete or incomplete ED, anorgasmia, and retrograde ejaculation (Havenga and Welvaart, 1991). In Africa anorectal carcinoma seems to be particularly common in young adult men (mean age was 27 years in one study). In the same study 31% of men had complete and 12% partial SD after surgery (Aghaji and Obiekwe, 1991).

The concept of total mesorectal excision in rectal cancer treatment has led to a substantial improvement in autonomic nerve preservation. In addition, use of laparoscopy has allowed favorable results with regard to sexual function (Nagpal and Bennett, 2013). During mesorectal excision surgery, the hypogastric and cavernous nerves could not always be identified, particularly in previously operated patients. In such patients a nerve-stimulating device may help to localize and protect autonomic nerves. The hypogastric nerves were successfully identified during surgery in six of seven patients, and cavernous nerves in four of five patients with otherwise unrecognized nerves using a commercial nerve-stimulating device (CaverMap). After proctectomy, CaverMap successfully confirmed the preservation of both hypogastric and cavernous nerves in 93% of patients. There were no adverse events related to use of the device (da Silva et al., 2005).

Although intraoperative neuromonitoring significantly improved urinary and anorectal functional outcome, in rectal cancer patients only a trend towards a lower rate of SD was shown (Kneist et al., 2013).

Radical resections for rectal cancer with or without extended systematic lymph node dissection decrease

sexual function to a similar degree, and even a permanent colostomy significantly decreased IIEF scores; this finding reveals the importance of other than physiologic factors in determining male SD after abdominoperineal resection (Col et al., 2006).

Hysterectomy

In a study measuring vaginal blood flow during sexual arousal using photoplethysmography, radical hysterectomy was associated with disturbed vaginal blood flow, probably related to denervation of the vagina (Maas et al., 2004). Transection of the uterosacral ligaments disrupts the major part of the hypogastric nerve in the conventional procedure, but only the medial branches of the hypogastric nerve are disrupted in nerve-sparing surgery. Similarly, division of the cardinal ligaments in the conventional procedure severed the anterior part of the inferior hypogastric plexus, which was preserved after the nerve-sparing procedure. Dissection of the vesicouterine ligament disrupted only small nerves on the medial border of the inferior hypogastric plexus in both techniques (Maas et al., 2005). In women with early-stage cervical cancer newer, modified radical hysterectomy results in significantly better sexual function (including vaginal functioning, sexual activity, and sexual enjoyment) in comparison to classic radical hysterectomy (Plotti et al., 2012).

It has to be acknowledged that sexuality may actually improve after hysterectomy, probably due to removal of health problems which led to the indication for surgery in the first place (dysfunctional uterine bleeding). The complex contribution of psychologic and anatomic factors to changes in sexual function following hysterectomy is still a matter of research (Maas et al., 2003).

Radiation therapy

The pelvis is a relatively confined space that contains the bladder, prostate, uterus, and rectosigmoid portions of the large intestine that are in close proximity to the autonomic and somatic nerves which innervate them. External-beam radiation therapy designated for any one particular organ will therefore inevitably result in simultaneous radiation exposure to other vital structures, including blood vessels and peripheral nerves. Animal studies have revealed the threshold dose for peripheral neuropathy following radiation therapy is only 15–20 Gy, well below the normal dose utilized for most pelvic malignancies (Johnstone et al., 1995). Numerous studies have demonstrated pelvic organ dysfunction after radiation therapy (Nguyen et al., 1998; Litwin et al., 2000), which may potentiate negative effects of chemotherapy, and vice versa (Keime-Guibert et al., 1998).

PNS cell death may occur months to years after radiation therapy due to slow reproductive cycles of glial and Schwann cells. Indirectly, nerve damage may be induced by involvement of vascular endothelium and obliteration of neural blood supply. Radiation-induced perineural fibrosis may also result in compression and ischemia of peripheral nerves (Sindelar et al., 1986). Although SD after radiation therapy is mainly attributed to nerve damage, direct radiation damage to microvascular, epithelial, and muscular tissue may also contribute.

Following prostate cancer treatment with both radiotherapy and brachytherapy, sexual function declines progressively; the onset of occurrence of ED is 12–18 months after both treatments. The pathophysiologic pathways by which radiotherapy and brachytherapy cause ED are multifactorial, as patient comorbidities, arterial damage, exposure of neurovascular bundle to high levels of radiation, and radiation dose received by the corpora cavernosa at the crurae of the penis may be important in the etiology of ED (Droupy, 2010).

The advent of widespread prostate-specific antigen screening has resulted in a larger number of younger, potent men being diagnosed with early-stage, organ-confined prostate cancer amenable to definitive surgery. Intensity-modulated radiation therapy is becoming more widespread because it allows dose escalation with increased sparing of the surrounding normal tissue. Despite the high dose (mean dose 70 Gy) to the prostate bed and nerves, postoperative intensity-modulated radiation therapy had no negative effect on erectile function for the patients who remained potent after nerve-sparing prostatectomy; all patients potent postoperatively remained potent after radiation therapy (Bastasch et al., 2002).

Radiotherapy for low rectal cancer probably has a role in the development of sexual, but not urinary, dysfunction (Lange and van de Velde, 2011).

INVESTIGATIONS OF THE PATIENT WITH SEXUAL DYSFUNCTION SUSPECTED TO BE DUE TO A PNS LESION

Patients with SD and suspected or known PNS involvement deserve a careful history to assess all possible causative agents. Whether the involvement of PNS requires any additional diagnostics is a matter to be solved in the individual patient. Sexual function as such is as a rule not tested, unless ED is suspected to be vasculogenic.

On the other hand, particularly in males with ED or suspected retrograde ejaculation without an obvious cause, polyneuropathy with ANS involvement should be ruled out. To support a diagnosis of polyneuropathy, peripheral nerve conduction studies, often supplemented by needle EMG examination of distal-limb muscles, are as a rule performed, and distinguish the

demyelinating from the axonal type of polyneuropathy. However, these studies evaluate (only) the large-diameter nerve fibers that are less relevant in SD. To support a diagnosis of autonomic polyneuropathy, clinical evaluation of the ANS should be performed. Symptoms of orthostatic hypotension, lower urinary tract dysfunction, upper gastrointestinal tract dysfunction (e.g., abdominal bloating), dry eyes, dry mouth, and sweating abnormalities are all indicators of autonomic dysfunction.

The examination of the ANS is, however, rather restricted. Sluggish pupillary responses to light, very dry hands and feet, resting tachycardia, a failure of the heart rate to increase or the arterial pressure to adapt on changing from the lying to standing position are features of ANS dysfunction. A drop of at least 20 mmHg systolic or 10 mmHg diastolic pressure is evidence of sympathetic vasoconstrictor abnormality. Apart from clinical tests, there are laboratory tests of autonomic functions, including the thermoregulatory sweat test, quantitative sudomotor axon reflex test, the SSR, and neurocardiovascular testing (Santiago et al., 2000; Low et al., 2003). Other means of diagnosing thin nerve fiber pathology (quantitative sensory testing for temperature sensation, and biopsy) are available. Testing for thin nerve fiber involvement in the individual patient is often not deemed necessary or practical, and the diagnostics in an individual patient suspected of having thin fiber neuropathy goes straight to establishing (or ruling out) possible etiologies, limited as a rule to those which would be plausible in the individual patient. The search is often limited to DM, although in the particular epidemiologic setting it might also be amyloid polyneuropathy.

A different problem is establishing the direct link of a particular neurologic condition in an individual patient and SD. A straightforward diagnosis of a neurogenic SD may be made in the case of a clear new neuropathic condition with a concomitant onset of a plausible SD, such as a loss of propulsive ejaculation in a man who made a prolonged bicycle tour and suffered bilateral compressive pudendal neuropathy with accompanying bilateral perineal muscle paresis and penile paresthesias. In this and similar cases of localized PNS involvement, a more detailed definition of the lesion in the lower sacral segments is possible. The recommended methods are quantitative concentric needle EMG of the external anal sphincter and recording the bulbocavernosus reflex (Vodušek et al., 2009). Such diagnostics allow better delineation of lesions due to cauda equina involvement (Podnar et al., 2002). It must be stressed that this test correlates with the PNS lesion and not directly with SD, although the latter might be "neurogenic." Only a weak correlation has been established between external anal sphincter EMG and SD in cauda equina patients (Podnar et al., 2002).

In research, clinical neurophysiologic testing has been instrumental in revealing group associations of PNS involvement and SD (e.g., bulbocavernosus reflex testing, pudendal somatosensory evoked potentials), but tests have not proven to be generally relevant for the diagnosis of individual patients with SD. One of the problems is the absence of an established test of parasympathetic innervation of the penile smooth muscle. The smooth-muscle (penile) EMG, which is the only direct test of penile smooth muscle and its innervation, is for the moment restricted to the research laboratory (Giuliano and Rowland, 2013).

The only established test of autonomic fibers in the uroanogenital region is the SSR. On noxious stimulation (such as a sudden noise, electric pulse) a potential shift can be recorded with surface electrodes not only from the skin of the palms and the soles, but also from perineal skin and the penis (Daffertshofer et al., 1994). The SSR is a reflex which consists of myelinated sensory fibers, a complex central integrative mechanism and a sympathetic efferent limb with postganglionic non-myelinated C-fibers. Recording from the perineal skin assesses sympathetic nerve function within the thoracolumbar cord (Rodic et al., 2000). Quantitative thermal threshold sensory testing assesses the function of small-diameter nerve fibers and has been recommended in diagnosing neurogenic ED. Not the genital region, however, but distal parts of the lower limbs should be tested, where the earliest signs of neuropathy would be expected (Ali et al., 1989). Investigations to support a diagnosis of neurogenic SD in an individual patient have been popular in the past (Lundberg et al., 2000). However, it should be critically acknowledged that for a patient with SD (mainly ED was investigated), no clinical neurophysiologic test would consistently aid in assessment (Giuliano and Rowland, 2013), or change treatment. The present role of further investigations of a patient with SD and PNS involvement is limited to those clinical situations with a need for substantiating the diagnosis of the PNS lesion, and to medicolegal issues. Concerning the diagnosis of "neurogenic" SD, it is appropriate to make a diagnosis ("possible" or "probable" neurogenic SD) on clinical grounds, and treat appropriately, without extensive testing.

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 12

Lower urinary tract dysfunction in patients with peripheral nervous system lesions

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INTRODUCTION

The ominous urinary symptoms related to cauda equina lesions represent the paradigmatic syndrome of lower urinary tract dysfunction (LUTD) due to a peripheral nervous system (PNS) lesion. However, there are many others, and they can be equally incapacitating.

This chapter covers LUTD due to lesions of the PNS. The prevalence and clinical characteristics of LUTD associated with disorders of the PNS will be described, with some reference to urodynamic and electrodiagnostic findings. When appropriate, this chapter will also describe management. Since lower urinary tract (LUT) and sexual dysfunction in patients with PNS disorders are covered in separate chapters, some structural and textual overlap between the texts is not only unavoidable but even intended. Our goal is to present chapters which are equally informative if read individually.

Lesions may affect all the PNS constituents or only some, depending on anatomic and other reasons. All types of PNS involvement – either motor somatic, autonomic, or sensory – may cause some LUTD. Furthermore, in particular PNS disorders, different and sometimes typical patterns of LUTD may emerge. In practice, the relative contribution of lesions of the individual constituents of neural control to dysfunction is difficult to determine in the individual patient, unless the lesion is isolated and severe. An even more troubling problem is the lack of a direct and clear correlation between a particular nervous system involvement (as judged by neurologic criteria), and the resulting LUTD in individual patients. Thus, the relative importance of a mild neurogenic ("neurologic") versus a minor structural or other ("urologic") abnormality in an individual patient is difficult to determine with our present means of diagnosis. This can be exemplified by the problem of residual urine in a diabetic patient with voiding difficulty and an enlarged prostate.

Experienced clinicians know that the apparently obvious division between the central nervous system (CNS) and PNS often becomes blurred in practice. This may be due to the functional anatomic overlap (i.e., bodies of both α motor neurons of the voluntary system – the lower motor neurons, and motor neurons of the involuntary/autonomic/system – the autonomic preganglionic neurons – are functionally part of the PNS, although they lie within the spinal cord). Alternatively, it can be due to the fact that particular causative agents in patients may affect both PNS and CNS, although often to different degrees.

ANATOMIC PRIMER

The main function of the PNS is communication between the CNS and peripheral effector organs (i.e., sensory receptors, skeletal and smooth muscle, and glands). A comprehensive review of LUT neural control is provided in Chapter 5.

The lower motor neurons innervating the external (striated) urethral sphincter muscle (EUS) and the external (striated) anal sphincter muscle (EAS) lie in the anterior horns of the sacral segments 1–3 (the Onuf's nucleus) (Pullen et al., 1997). The preganglionic parasympathetic neurons controlling the smooth muscle of the detrusor are located in the intermediolateral horns of the same sacral segments of the spinal cord.

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The preganglionic sympathetic neurons lie in the intermediolateral horns of the thoracolumbar segments of the spinal cord at T10–L2 (Berry et al., 1995).

The axons originating from Onuf's nucleus travel within the pudendal nerve to the EUS. Acetylcholine (ACh) is the neurotransmitter at the skeletal muscle endplate. The axons of the preganglionic parasympathetic neurons run a long distance within the pelvic nerves to the ganglia (pelvic plexus), which are located close to the bladder. ACh is the main neurotransmitter not only in preganglionic (acting on nicotinic receptors), but also in postganglionic parasympathetic fibers (acting on muscarinic receptors) (Andersson and Wein, 2004). Activation of the parasympathetic system results in bladder contraction during voiding. During the storage phase, parasympathetic activity is countered by the sympathetic system. The axons of the preganglionic sympathetic neurons intermingle with somatic efferents from spinal nerves and synapse in one of the nearby paravertebral ganglia of the sympathetic chain. Some fibers pass through the paravertebral ganglia and synapse with one of the prevertebral or collateral ganglia on the aorta or internal iliac vessels, such as the inferior mesenteric ganglia, then continue inferiorly as the hypogastric nerves. Some fibers pass through both pre- and paravertebral ganglia and synapse with the end organ (Berry et al., 1995). The main neurotransmitter for preganglionic sympathetic fibers is ACh (acting on nicotinic receptors), and for postganglionic sympathetic fibers it is norepinephrine (acting on α- and β-adrenergic receptors) (Andersson and Wein, 2004).

The inner surface of the bladder is covered by a specialized mucosa (urothelium). The afferent nerve fibers lie beneath the urothelial lining, with some nerve ends extending into the urothelium. Two types of afferent nerve fiber have been described: (1) myelinated Aδ fibers that respond to normal bladder distension and are the main afferent nerve during physiologic micturition; and (2) unmyelinated C fibers that respond to chemical irritation or cold. They are silent under physiologic conditions, but become active during pathologic conditions (Fowler et al., 2008). These afferent fibers travel within the pelvic, hypogastric, and pudendal nerves. Bodies of these afferent neurons lie within the dorsal root ganglia and enter the spinal cord in the same segments as the respective efferents they traveled with (Berry et al., 1995).

PHYSIOLOGIC PRIMER

During the storage phase, the bladder and the internal urethral sphincter are predominantly activated by the sympathetic nervous system. Activation of the sympathetic nervous system leads to contraction of smooth muscles in the bladder base and proximal urethra via activation of α-adrenergic receptors (the α1A subtype) and relaxation of the detrusor via activation of β-adrenergic receptors (β2 and β3 subtypes). Overall, sympathetic nervous system activation provides urinary accommodation and inhibition of the micturition reflex (Andersson and Wein, 2004; Fowler et al., 2008). The EUS is continuously active during the storage phase due to tonically firing motor units.

The voiding phase is initiated voluntarily from the prefrontal cerebral cortex. The voiding process begins with relaxation of the EUS, followed by activation of parasympathetic activity that leads to contraction of the detrusor muscle (mediated via muscarinic receptors, M2 and M3, as predominant subtypes, in the bladder) and relaxation of the smooth muscles in the bladder base and proximal urethra (mediated by the release of nitric oxide) (Andersson and Wein, 2004; Fowler et al., 2008).

CONSEQUENCES OF PNS LESIONS ON LUT FUNCTION

Destructive lesions of the nerves to the bladder are followed by a silent, painless distension of the bladder (i.e., detrusor atonia) (Pavlakis et al., 1983). Urinary retention is the resulting symptom and difficulty eliminating urine is the most common primary dysfunction in symptomatic peripheral neuropathic lesions. If bladder retention is complete, the accompanying incontinence is of the "overflow" type, although in the case of a denervated EUS the patient may also suffer from stress incontinence. Continuous incontinence is the consequence of severe EUS denervation, particularly in women.

The sensory dimension of the bladder dysfunction has been less attended to by clinical research, although it is indispensable for appropriate LUT function, and an important complaint of patients. In partial lesions, sensory symptoms may predominate, with dysesthetic sensations attributed to bladder or urethra.

Apart from the above "logical" functional consequences of lesions of LUT peripheral innervation, other urodynamic features have been observed in patients with presumed isolated PNS involvement (for instance, in Guillain–Barré syndrome (GBS)): detrusor overactivity, both with and without sphincter dyssynergia. Pelvic nerve irritation was suggested as the underlying mechanism (Fowler, 1999; Podnar et al., 2006).

LUTD in an individual disease may be affected not only by the PNS lesion caused by the disease, but possibly by some additional disease-specific factors (affecting muscle and mucosa).

CAUDA EQUINA AND CONUS MEDULLARIS LESIONS

Opening of the dura covering the lumbar cistern below L1 reveals the multiple, tightly packed pale thin roots,

which look like a horse's tail, i.e., the cauda equina. Due to differential growth, at birth the spinal cord ends, with the conus medullaris, opposite the third lumbar vertebra, and a few months later it ends at the adult level at about the lower edge of the first lumbar vertebra. The continuation of the spinal cord is a strand of connective tissue, the filum terminale. Spinal roots of lumbar and sacral spinal cord segments (anterior roots conveying somatic and autonomic motor function, and posterior roots conveying sensory information) thus "exit/enter" the spinal cord at the level of (Th12) L1. As a consequence, moving down the lumbosacral spinal cord, the dorsal and ventral roots increasingly "elongate." The main destinations for these roots are the lumbar and sacral plexuses. Nerves from these plexuses provide motor and sensory innervation of the lower limbs and pelvic organs (Berry et al., 1995).

Disorders and lesions of the cauda equina are characterized by motor and sensory symptoms (particularly weakness and sensory loss) in the lower limbs, buttocks, and perineum, as a rule accompanied by abnormalities of bladder, bowel, and sexual function, of various degrees. This pattern of symptoms and signs is called cauda equina syndrome (CES) (Gitelman et al., 2008).

Animal studies have demonstrated a greater resistance of small- compared to large-diameter nerve fibers to acute compression, and equal susceptibility of large-diameter motor and sensory fibers (Fowler et al., 1972). This explains why some patients with "typical" sensory loss have largely preserved pelvic organ function, as parasympathetic fibers within cauda equina are thinner than somatosensory afferent fibers. (Some patients, however, have, paradoxically, an "opposite" constellation of deficits).

As the axons within the roots comprising cauda equina extend into the spinal cord, dysfunctions caused by lesions of respective spinal cord segments (the conus), or the cauda equina, are similar (Podnar et al., 2006). Due to the impossibility of distinguishing with any certainty the clinical pictures of conus and CES, the CES is used as a rule as a clinical term defined by the typical combination of deficits.

Causes of cauda equina damage and their epidemiology

A national referral uro-neurophysiologic unit study has reported a CES annual incidence rate of 3.4 per million and a prevalence rate of 8.9 per 100 000 population (Podnar, 2007a). Cauda equina involvement was most common in men in their 40s, while conus medullaris lesions were more common in younger men (in their 20s and 30s). Spinal fracture was the main etiology in men younger than 40 years, disc herniations in middle-aged patients (40–60 years), and iatrogenic lesions (i.e., spinal stenosis surgery) in older patients (>60 years) (Podnar, 2007a).

Disc material may prolapse centrally, causing compression of some or all of the lower lumbosacral roots within the spinal canal. Compression of the cauda equina occurs in approximately 0.12% of all herniated lumbar discs (Podnar, 2007a), and in approximately 2% of operated herniated lumbar discs (Gitelman et al., 2008).

It should be stressed that no neurogenic LUTD would be expected in "trivial" spinal or disc disease without lesion of nervous structures, or in a patient with lumbar or sacral monoradiculopathy. (The most common lumbosacral monoradiculopathy is L5, caused by a L4/L5 disc herniation.) However, as heavy opiate medication may be necessary to control pain, constipation and impaired bladder emptying (even urinary retention) may occur as side-effects of treatment in such patients (Holzer, 2012).

The second most common cause of CES is spinal fracture, which most often occurs at L1 and T12 vertebra level (Podnar, 2007a). This is an area of great mechanic stress due to transition from a rigid thoracic to a mobile lumbar spinal column. As a result, flexion-distraction and burst fractures are likely to occur in this region, causing damage to the adjacent conus medullaris containing somatic motor and autonomic parasympathetic neurons in the ventral and intermediolateral gray-matter horns, and sensory input and interneurons in the dorsal horns (Berry et al., 1995). Such injuries in principle result in a combination of upper and lower motor neuron deficits, although, due to the lower motor neuron lesion, the upper motor neuron lesion may be masked. In the fracture scenario, concomitant lesions of conus and roots are probable. Severe injuries to the lower spine, as in high-velocity impacts in motor vehicle accidents or falls from a great height, will often injure the cauda equina. Stabbings, gunshot and shrapnel wounds are other causes of such an injury. These patients usually have many other associated injuries.

CES may be iatrogenic, a complication of lumbar disc or spinal stenosis surgery. Accidental tearing of the dura is also associated with damage to the cauda equina, and a cerebrospinal fluid (CSF) leak may be an indicator of problems during surgery. It appears that, in patients with spinal stenosis who have only a partial laminectomy, there may be insufficient space to accommodate postoperative edema, with a resulting risk of cauda equina compression (Jensen, 2004). CES occurring after surgery for severe spinal stenosis (anteroposterior diameter <10 mm) most often occurs in patients older than 65 years, and may be related to applied surgical technique (Podnar, 2010).

Congenital or acquired stenosis of the lumbar spinal canal can produce symptoms of neurogenic claudication

(i.e.; pain paresthesia and weakness in buttocks and legs during standing and walking relieved by a few minutes of sitting). The main structural abnormality is narrowing of the spinal canal, although there are often associated stenoses of individual nerve root foramina. These changes are usually due to a combination of developmental stenosis and superimposed spondylosis (Singh et al., 2005). Other causes include severe spondylosis without congenital narrowing, Paget's disease, achondroplasia, and fluorosis.

The most common infective cause of CES in developing countries is tuberculosis (i.e., Pott's disease, a tuberculous infection of the spine) (Moon, 1997). Tuberculous meningitis also causes radiculomyelopathy with spinal meningeal enhancement, lumbosacral arachnoiditis, myelitis, CSF loculations, and cord atrophy (Gupta et al., 2013).

CES is also a recognized complication of long-standing ankylosing spondylitis, which characteristically causes dorsal arachnoid diverticula and bony erosions. The pathogenesis of the neural deficit in connection to these changes is not clear (Bartleson et al., 1983). If ankylosing spondylitis causes lumbar spinal stenosis, marked LUT and bowel dysfunction is the rule (Bartleson et al., 1983); urinary incontinence is a common presenting symptom (Hassan, 1976).

Although very rare, CES has been described following various forms of spinal anesthesia (Aldrete, 2003). One survey has found the incidence of permanent damage to nerves or the spinal cord to be 1 in 100 000 following central neuraxial block (Cordato et al., 2004). Injection of wrong drugs or preservatives (Aldrete, 2003) or of higher than the recommended dosage of high-density lidocaine are among the possible causes (Prick et al., 2003). Spinal stenosis is a recognized risk factor. An increasingly recognized syndrome is that of transient radicular irritation (also called transient neurologic syndrome; LUTD has so far not been described with this syndrome) (Schneider et al., 1993).

Although spinal arachnoiditis can develop anywhere, the lumbosacral meninges are most commonly affected (Esses and Morley, 1983). The arachnoid becomes thickened, scarred, and adherent to the pia and dura, obliterating meningeal blood vessels. Although the spinal cord may also be affected, more commonly single or multiple roots within the cauda equina are involved. Oil-based contrast agents injected intrathecally for myelography used to be the commonest cause. However, currently used water-soluble contrast agents are safer. Lumbar spinal surgery, epidural anesthesia, intrathecal injections, and infection have also been implicated to cause spinal arachnoiditis. LUTD seems to appear only in advanced cases.

Spinal tumors, such as an ependymoma or schwannoma, can cause external compression to the cauda equina or conus medullaris, and occasionally spinal cord astrocytomas grow in the region of the conus medullaris (Bagley and Gokaslan, 2004). Direct metastases to the conus medullaris are rare. Rarely, spinal tumors, particularly ependymomas, bleed, causing an acute episode of severe headache and neck stiffness followed by increased back pain and sciatica, possibly with sensory, motor and autonomic (including LUT) symptoms. More common causes are vertebral metastases (most commonly from breast, lung, and prostate cancer), primary bone tumors (e.g., chordoma), or multiple myeloma, usually presenting with severe back pain followed by other symptoms (Hammack, 2012). Meningeal carcinomatosis is a rare cause of CES suspected in the patient with a known malignancy (usually of the breast or lung) (Clarke, 2012).

Congenital malformations of the distal spinal cord often involve the conus and/or cauda equina. Such malformations constitute part of a larger group of congenital neurologic disorders, collectively termed spinal dysraphism. Myelomeningocele is the most frequent and important of these. The tethered-cord syndrome can present in patients with known spinal dysraphism (usually myelomeningocele), usually already operated on, or in patients without known dysraphism. This disorder consists of conus medullaris and cauda equina dysfunction, the exact pathophysiology of tethering being a matter of discussion (Michelson and Ashwal, 2004).

Arteriovenous malformations in the thoracic region can present with a clinical picture of CES, presumably for hemodynamic reasons (Aminoff et al., 1974).

Occasionally, the exact cause of CES remains elusive.

Clinical picture

Acute CES (motor and sensory symptoms)

Acute large central lumbosacral disc herniations produce the dramatic CES of bilateral sacral, buttock, perineal and posterior leg pain, tingling, and numbness in some or all the described areas, and LUTD, with variable motor and sensory involvement of lower extremities. Worsening of back pain prior to the development of the syndrome is usual, but may be absent. Lower-back pain, sacral sensory loss, and urinary symptoms are the most robust presenting features of CES (Jalloh and Minhas, 2007). CES has been classified as "complete" if associated with urinary retention, and "incomplete" if other urinary symptoms (e.g., straining, loss of bladder sensation) are present (Gitelman et al., 2008). Examination may show weakness in the muscles innervated by sacral (S1 and S2) myotomes: ankle plantar flexion for gastrocnemius; knee flexion for hamstrings; and hip extension for gluteals. Variable sensory loss extends from the soles of the feet to the perianal region. The

pattern of sensory loss characteristic for CES is restricted to the inner proximal thigh, lower buttocks, and perineal area, producing so-called "saddle anesthesia." There is a patulous anal sphincter, and the anal and bulbocavernosus reflexes are lost (Podnar, 2008). Only a minority of patients (19%), however, present with the "classic" clinical picture described above. Therefore acute CES may be difficult to recognize (Jalloh and Minhas, 2007).

Disc herniation may affect the root population in different patterns; asymmetry of involvement is the rule. Smaller central herniations produce a more limited syndrome of mainly perianal anesthesia and LUTD, although the opposite clinical picture, sparing the centrally lying S3–5 roots, is sometimes observed (Lafuente et al., 1985). Hemi-CES has been described (Barthels and de Vries, 1996). Indeed, in our clinical experience, mild cases of cauda equina lesions, with subtle or subclinical motor and sensory symptoms stemming from somatic innervation, and unrecognized at the acute traumatic event (e.g., vertebral fractures) can be diagnosed by demonstrating straightforward electromyogram (EMG) abnormalities in muscles of S2–4 myotomes. This explains the prolonged acute retention (attributed to pain) and the occasionally persisting mild LUT symptoms.

The anterior spinal artery syndrome may affect the conus medullaris, manifesting itself by an acute or subacute onset of pain and LUTD (also accompanied by anorectal and sexual dysfunction) with perineal sensory loss limited to pain and temperature perception (Herkes et al., 1989). In all patients with severe postoperative pain and new numbness in the perianal region, a postoperative hematoma should be suspected (Podnar, 2010).

Chronic CES (motor and sensory symptoms)

Chronic degenerative disc disease and osteoarthritis of the spine contribute to narrowing of the central canal and/or spinal nerve root foramina, known as lumbar spinal stenosis. The symptoms may consist of intermittent neurogenic claudication and radicular symptoms. The hallmark symptom is intermittent neurogenic claudication, known also as cauda equina claudication, or pseudoclaudication (Haswell et al., 2008). It consists of various combinations of low-back, buttock, leg, and anogenital pain and paresthesias, with or without paresis or uro-ano-genital symptoms brought on or exacerbated by walking, and characteristically by standing erect. Walking on a slightly down-going surface makes problems worse. Symptoms are relieved by 5–10 minutes of rest in a seated position, in contrast to the brief upright rest of less than a minute required to relieve typical vascular claudication in the lower limbs. Patients often adopt a slightly bent-forward posture on walking and standing, this being the position in which the spinal canal space is at its maximum (Storm et al., 2002). This also explains why, in contrast to severe incapacitation for walking, bicycling is as a rule not a problem. The chronic radicular symptoms are similar to those of acute radiculopathy, but often less severe. Persisting leg weakness is infrequent as the predominant symptom of spinal stenosis. Physical examination is normal in about half of the patients. The others have varying degrees of motor and sensory abnormalities attributable to involvement of one or more lumbar and/or sacral roots (Storm et al., 2002). Of course, eliciting the unique feature of the intermittent neurogenic claudication syndrome by exercise that may unmask or worsen the neurologic signs is not practical in a busy outpatient clinic.

The symptoms of the spinal dural arteriovenous fistulas are remarkably similar to those of spinal stenosis. On clinical examination these patients often have a combination of upper and lower motor neuron signs (Jellema et al., 2006). Failure to recognize and treat the spinal dural arteriovenous fistulas in a timely fashion can result in irreversible neurologic disability, including myelopathy, lower-extremity weakness and bowel, bladder, and sexual dysfunction (Marcus et al., 2013).

Central disc herniation may mimic tumors of the conus medullaris or cauda equina. Back pain and radicular sensory symptoms may be absent, and the presenting complaints are often perineal pain or paresthesias, LUTD, and erectile dysfunction in men. As with the acute condition, the symptoms and signs of chronic CES depend on the spinal roots involved (Haswell et al., 2008).

A long history of chronic back pain with or without sciatica, with slow progression to numbness and LUT symptoms, is typical for a neoplasm in the lumbosacral spinal canal (Lavy et al., 2009). The main symptom is pain, variably located in the low back, sacrum, buttock, or perineum, that may worsen with recumbence and is particularly severe during the night. As a rule, pain is not relapsing and remitting. Symptoms of nerve root compression (paresthesias, lower-limb paresis, LUT symptoms) often develop months or even years later. Bowel and sexual symptoms (erectile dysfunction in men) are less commonly reported. There are no particular characteristic features on physical examination. Lumbar scoliosis or lordosis may be present; straight-leg raising is often abnormal. Deficits due to (lower sacral) root lesions vary from none to widespread. A high index of suspicion and imaging studies are essential for early diagnosis (Bagley and Gokaslan, 2004). Occasionally, LUT disturbances are the first and only symptom and no somatic sensory or motor deficits can be found; a tumor is discovered when back pain and radicular symptoms appear.

Cauda equina tumors can also present with intermittent neurogenic claudication syndrome (see above). Some patients with tumor have progressive painless weakness of the legs similar to generalized peripheral neuropathy or neuronopathy.

Vertebral metastases, primary bone tumors (e.g., chordoma), or multiple myeloma can cause foraminal compression of nerve root(s), gradual compression of the conus medullaris or cauda equina, collapse of a vertebra acutely compressing the cauda equina, and invasion of the spinal nerves or the lumbosacral plexus outside the foramina. The initial symptom is usually low-back pain, followed by other symptoms (Bagley and Gokaslan, 2004; Hammack, 2012).

Meningeal carcinomatosis presents with the triad of headache, cranial neuropathies, and lumbosacral radiculopathies. Early in its course, the predominant features are usually low-back pain radiating into the legs, leg weakness and numbness, and LUTD. Neurologic deficits in the lower limbs are variable. The diagnosis should be suspected in a patient with a known malignancy (usually of the breast or lung) (Clarke, 2012).

Back pain and an insidious onset of neurologic symptoms is also seen with tuberculous infection of the spine (Moon, 1997). An intramedullary spinal tuberculoma can also mimic a conus neoplasm.

The tethered-cord syndrome usually presents in childhood with sensorimotor symptoms and signs, commonly in both legs, LUTD, and skeletal abnormalities, such as scoliosis or foot deformity. The indicators of the dysraphic state may be myelomeningocele, subcutaneous lipomas, or a sacral hairy patch (Michelson and Ashwal, 2004). The tethered-cord syndrome in adults is less well recognized. Some of these patients have had lifelong neurologic and/or skeletal deformities before new symptoms appear; others are normal until symptoms and signs develop in adulthood. These late presentations can occur even in the elderly, and are easily confused with spinal stenosis. Patients with this syndrome characteristically have pain localized to the anal, perineal, and gluteal areas, sometimes radiating diffusely down the legs; radicular-type pain is uncommon. Leg weakness is usually present, with several myotomes involved bilaterally. Upper motor neuron signs, such as extensor plantar responses, may be present (Klekamp, 2011).

Arachnoiditis manifests as constant low-back pain, usually radiating into both legs, and motor and sensory symptoms in the legs. The symptoms may begin within days of the damage to the arachnoid or there may be a delay of many years. Examination usually shows involvement of more than one lumbar or sacral nerve root, and the motor deficit ranges from being mild to paraplegia (Esses and Morley, 1983).

LUT dysfunction in CES

Sudden urinary retention is considered the most important clinical feature heralding the onset of CES (DeLong et al., 2008). Retention of urine may result in "overflow" incontinence. Incontinence may, however, be the presenting symptom. Although constipation may also occur in acute CES, this and other anorectal and also sexual symptoms often take much longer to become apparent to patients and physicians (Kostuik, 2004).

On urodynamics, lesions of the lower sacral cord or cauda equina lesions typically produce an underactive detrusor and urinary retention with loss of bladder sensation. By contrast, insensitive bladder with poor compliance and detrusor overactivity can also occur (Hattori et al., 1992; Podnar et al., 2006). Although the occurrence of detrusor overactivity is counterintuitive in a lower motor neuron lesion, there are several potential explanations. Following loss of parasympathetic innervation it has been shown in cats that preganglionic sympathetic nerves reinnervate the parasympathetic ganglion cells, as demonstrated by bladder contraction induced by hypogastric nerve stimulation (de Groat and Kawatani, 1989). In patients with thoracolumbar fractures (the level of the conus medullaris), overactive bladder might be also due to an upper motor neuron lesion (Pavlakis et al., 1983; Podnar et al., 2006). Irritation of the lower sacral roots (as a "positive symptom" of the nerve lesion) has also been postulated; some patients with spinal stenosis report urgency as a symptom in neurogenic claudication. Intrinsic activity of the detrusor smooth muscle driven by urothelial-mediated reflexes – a consequence of decentralization of the parasympathetic ganglia situated within the bladder wall – may also contribute (Hellstrom et al., 1986a; Fowler, 1999).

LUT symptoms persist in many patients after an acute cauda equina lesion. They reportedly interfere with daily life in 88% of men and 92% of women with chronic CES (Podnar et al., 2006). Symptoms of disturbed bladder emptying were reported by 95% of men and 92% of women, and urinary incontinence by 56% and 71% respectively. Urgency and frequency occur in 40% of men and 56% of women. However, on cystometry, subjective reports were supported by the finding of detrusor overactivity in only 21% of men, and no women, although reduced bladder capacity was found in 9% of men and 15% of women (Podnar et al., 2006).

In about 10% of patients with long-standing CES there is significant pelvic organ dysfunction without uro-ano-genital sensory loss (Podnar, 2007b). The mechanism of preserved touch and pinprick sensation in these patients, in spite of significant motor fiber damage to the same segments, is not clear.

Urinary symptoms were present in one-third of patients with tuberculous meningitis, and 70% had urodynamic abnormalities: detrusor hyporeflexia/areflexia in 43%, detrusor overactivity in 20%, reduced bladder sensation in 24%, increased postvoid residuals in 24%, and detrusor sphincter dyssynergia in 12% of patients. A significant association was found between urodynamic abnormalities and tuberculous lumbosacral arachnoiditis and myeloradiculopathy (Gupta et al., 2013).

Although bladder dysfunction is considered an uncommon symptom of lumbar spinal stenosis, it may be prominent in individual patients. In a series of 100 women with a mean age of 58 years who had urinary retention, severe spinal canal stenosis was the fourth most common cause. The subgroup so affected consisted of elderly women, with a mean age of 71 years (Yamamoto et al., 2005). Intermittent "irritative" symptoms of urgency or feeling of bladder (or rectal) "fullness" and incontinence have also been reported.

Investigations – acute CES

Acute CES is one of the few emergency conditions that affect the PNS. A high level of suspicion is essential in every patient with back pain, uro-ano-genital sensory symptoms and urinary symptoms (Bell et al., 2007; Jalloh and Minhas, 2007). Careful clinical neurologic examination is necessary in such patients, and includes motor, sensory, and reflex testing of lower limbs, plus assessment of anal tone, perianal touch and pinprick, the anal reflex, and in men also the bulbocavernosus (penilo-cavernosus) reflex (Kostuik, 2004; Podnar, 2007a; Lavy et al., 2009). Measurement of postvoid residual urine volume may be considered if there are symptoms of voiding difficulty. This is achieved by catheterization or ultrasonography.

Urinary retention in combination with sensory symptoms (tingling and/or sensory loss) in lower sacral segments and back pain (i.e., clinical abnormalities compatible with CES) should lead to urgent imaging of the lumbosacral spine, preferably emergency magnetic resonance imaging (MRI) (Bell et al., 2007; Gitelman et al., 2008; Lavy et al., 2009). A high false-positive rate (45%) was obtained for suspected CES requiring MRI by resident neurosurgeons, probably due to the wish to err on the side of caution (Bell et al., 2007). Cases with and without abnormal imaging are often clinically almost indistinguishable (Rooney et al., 2009).

Investigations – chronic CES

In the patient with long-standing (possibly slowly worsening) LUTD the reasoning and investigations are similar, but without the same urgency. If the patient is not an individual with residual deficits after known acute CES in the past, the underlying cause (e.g., spinal stenosis, arachnoiditis, neoplasm, tethered-cord syndrome) is sought by imaging, and, if imaging is inconclusive, lumbar puncture.

Urologic investigations are valuable because they might support a clinical impression of LUTD and assist in planning management. Measurements of postvoid residual urine, uro-flow studies as well as filling and emptying cystometry all give valuable information about the underlying pathophysiology of the LUTD (Hellstrom et al., 1986a; Podnar et al., 2006).

If available, sacral electrodiagnostic studies (anal sphincter EMG and penilo- / clitoro-cavernosus reflex measurements), support the clinical suspicion of lower motor neuron involvement in the lower sacral segments (denervation and reinnervation in perineal and pelvic floor muscles), and of an abnormal lower sacral reflex arc (Podnar, 2006). Motor nerve conduction studies of the peroneal and tibial nerve demonstrate reduced amplitudes of compound motor action potentials if there is axon loss in the spinal nerve roots (L5 and S1) innervating them. Standard EMG studies of the lower-limb muscles are useful to determine the extent of damage to segments. Needle EMG studies show chronic neurogenic changes in leg muscles in a pattern reflecting involvement of nerve roots L2–S2. Finding such abnormalities in proximal muscles, such as the glutei, helps to differentiate patients with chronic CES from a chronic axonal polyneuropathy (the latter producing much greater distal than proximal muscle abnormalities). Paraspinal muscle denervation localizes the abnormalities to the roots rather than plexus or a more distal site, when normal lower-limb sensory nerve action potentials are also expected (the spinal ganglia and the distal axons of the primary sensory neurons are spared in cauda equina lesions).

Management of acute CES

In acute CES, insertion of a urinary catheter is needed to check for urinary retention and to drain the bladder during the upcoming procedures. The adage that the "sun should not set" on an acute CES is still valid; a surgical intervention as early as possible – preferably within 24 hours – is highly desirable, although often not achieved for various reasons. Better outcomes of CES have been demonstrated with early (<48 hours after onset of urinary symptoms) compared to late intervention (Shapiro, 1993; Kennedy et al., 1999).

Urgent imaging and surgical evacuation of hematoma may prevent permanent damage in cases of spinal subarachnoid hemorrhage or postoperative hematoma. Delays in CES diagnosis and decompression are among the most common causes of legal complications and

litigation in all spinal disorders (Kostuik, 2004; Lavy et al., 2009).

The techniques of surgical management are beyond the scope of this *Handbook*.

Further management of LUTD after treating acute CES depends on the type and severity of bladder dysfunction. In general, men are more prone to voiding problems and women to urinary incontinence. Incomplete bladder emptying is common (Podnar et al., 2006) and the postmicturition residual volume should be checked. If this exceeds 100 mL or a third of bladder capacity, patients should be taught clean intermittent self-catheterization (CIS). Patients with mild lesions may only need a few days or weeks of CIS. Due to the accompanying EUS weakness, many patients learn to void by straining (Hellstrom et al., 1986a).

Management of chronic CES

Management decisions in spinal stenosis are complicated by several factors. The natural history of the disorder is poorly understood, as are indicators of prognosis. The patients are often elderly and have complex medical problems. The correlation between the imaging abnormalities and symptoms is generally not good. In most patients, the course is relatively benign. Conservative treatments are widely mentioned in the literature, but there is a paucity of critical evaluations regarding specific methods and their outcomes. A useful generalization is that surgery becomes a valid option once symptoms are seen as significantly bothersome to the patient, and a meta-analysis has shown benefits for certain surgical approaches over conservative treatment (Jacobs et al., 2013). Following lumbar decompression surgery postvoid residual urine, maximum cystometric capacity and maximum flow rate significantly improved. However, there was no significant improvement in voided volume, bladder compliance, maximum detrusor pressure, or upper urinary tract damage (Cong et al., 2010).

In tethered-cord syndrome, surgical intervention is often effective in relieving pain and some of the motor and sensory deficits. Some improvement of LUTD is possible (Hellstrom et al., 1986b). Patients with dysraphism and LUTD should be under the long-term care of a urologist since they are at risk of developing upper urinary tract dilatation and serious impairment of renal function (Veenboer et al., 2013).

VIRAL CAUDA EQUINA SYNDROMES

Cytomegalovirus (CMV)

CES due to CMV is a dramatic and serious infectious disorder occurring in patients with acquired immune deficiency syndrome (AIDS) (Anders and Goebel, 1999). Low-back pain and urinary disturbances are early symptoms, followed by asymmetric leg weakness and sensory loss that extends into the saddle area. This usually rapidly advances to a flaccid paraplegia with bladder and bowel incontinence. The CSF shows abnormalities indicative of acute infection, and polymerase chain reaction (PCR) is positive for CMV. There is usually also evidence of CMV infection in other organs. Antiviral agents effective against CMV may arrest the course, or partially reverse it, so early diagnosis is important (Quartier et al., 1996).

Lymphomatous meningitis and syphilis are other disorders producing a similar syndrome in patients with AIDS.

Infections by the herpesviruses

LUTD is caused mainly by varicella-zoster and less often by anogenital herpes simplex (type 2).

Herpes zoster is a varicella-zoster virus infection manifested by circumscribed painful vesicular eruption of the skin and mucous membranes. Infections occur sporadically in healthy subjects with previous exposure to varicella (chickenpox), or in the immunocompromised. Urinary retention afflicts 3.5% of patients with active herpes zoster infection, and is most common with involvement of the sacral dorsal root ganglia (Broseta et al., 1993). The urinary retention typically presents concurrently with, or within a few days following, the onset of the rash (Cohen et al., 1993). It is thought to be due to a sensory neuronopathy from inflammatory reaction in the dorsal nerve root ganglia (Erol et al., 2009). A parasympathetic motor neuropathy may also contribute to the urinary retention. Urodynamic testing in the acute phase typically reveals detrusor underactivity with decreased sensation of bladder filling that resolves in 4–8 weeks (Chen et al., 2002). Cystoscopy may reveal mucosal eruptions ipsilateral to the side of skin involvement (Ray and Wise, 1970). Management of zoster-induced urinary retention consists of simple analgesics, antiviral medications, and CIS for a period of 4–8 weeks. Patients should be reassured that the voiding dysfunction is transient and full return to normal detrusor behavior is expected (Chen et al., 2002). Postherpetic neuralgia in the lower sacral segments may occur, but the incidence is not known.

Genital herpes simplex infections are often seen in sexually active young adults. In less than 1% of cases it causes a neurologic syndrome consisting of urinary retention, constipation, and sacral pain or numbness (Greenstein et al., 1988). Spontaneous recovery occurs as a rule, though treatment with antiviral agents may hasten the recovery. Urinary retention may be due to severe

dysuria caused by direct contact of urine with the blistering urethral mucosa (Clason et al., 1982). Urodynamic abnormalities described in patients with LUT symptoms and genitourinary herpes simplex include detrusor underactivity with impaired or absent sensation of bladder fullness. These changes are fully reversible, often within 4–8 weeks. The pathogenesis of the neurogenic retention with herpes simplex virus (HSV) is localized lumbosacral meningomyelitis, with involvement of sacral nerve roots, or the pelvic nerves (Yamanishi et al., 1998). The diagnosis is based on the history, characteristic rash, raised level of anti-HSV immunoglobulin M titers and PCR testing. Herpetic genital ulcers may be associated with local neurologic deficits, such as a lax anal sphincter, weak or absent bulbocavernosus reflexes, and some sensory loss in the lower sacral dermatomes. Treatment is directed towards effective bladder drainage by CIS for about 4–8 weeks. Any superimposed urine infection should be treated, but prophylactic antibiotics are not necessary. The patient should be reassured that the bladder dysfunction is temporary and reversible. Systemic antiviral therapy may be indicated in some patients to shorten the course of skin lesions. Postherpetic neuralgia is a rare complication (Haanpaa and Paavonen, 2004).

SACRAL PLEXUS AND PUDENDAL NERVE LESIONS

Rarely, complicated vaginal delivery causes a severe sacral plexus lesion (Feasby et al., 1992) with obvious severe sensory and motor deficits in lower sacral segments, which, however, are occasionally not associated with LUT dysfunction. The uneventful vaginal delivery may cause some mechanic and neurogenic pelvic floor and sphincter muscle lesions. These neurogenic lesions are as a rule mild (Mallet et al., 1993) and not associated with gross structural damage to nervous structures. It is commonly assumed that lesions associated with vaginal delivery are relevant in the pathogenesis of stress urinary incontinence and pelvic organ prolapse in women, but direct damage to the striated muscles and fibroelastic supporting tissues of the pelvic floor is probably more important than the lesions of nerves as such. In the EAS muscle neurogenic changes are minimal after uncomplicated deliveries (Podnar et al., 2000).

Evaluation includes history, neurologic examination of motor, sensory and reflex function in lower sacral segments (particularly pelvic floor muscle assessment), and imaging. Electrodiagnostic testing is recommended only in women with complicated deliveries and suspected significant nerve lesion (Vodušek et al., 2009).

Other lesions of the sacral plexus and pudendal nerves can be caused by pelvic fractures, hip surgery, malignant infiltration, local radiotherapy (Vock et al., 1988), and by the use of orthopedic traction tables (Amarenco et al., 2001). They are usually unilateral. Pudendal nerve lesions may be induced by bicycling and symptoms include sensory loss and dysesthesias, also affecting the urethra (Leibovitch and Mor, 2005).

Pudendal neuralgia is considered a syndrome, with pudendal entrapment as one of the possible etiologies (Stav et al., 2009). The leading symptom is pain, but LUT symptoms are also reported by some patients. Unfortunately, clinical neurophysiologic tests are of little help in the diagnosis, which remains clinical (Lefaucheur et al., 2007). Iatrogenic pelvic plexus lesions will be discussed separately.

PERIPHERAL NEUROPATHIES

Polyneuropathies involving autonomic nerve fibers, and focal neuropathies of the pelvic nerves, are the most frequent cause of LUT symptoms. There are many causes of polyneuropathy, but relatively few of them cause prominent bladder dysfunction (Burakgazi et al., 2012) (Table 12.1). In patients with LUTD, but without "urologic" pathology, polyneuropathy should be among the suspected neurogenic causes. The diagnosis of peripheral nerve disease is straightforward by history and examination. The causal link to LUTD is strengthened if other symptoms of autonomic nervous system (ANS) involvement are present. The clinical evaluation of the ANS should be an integral part of the appraisal

Table 12.1

Polyneuropathies affecting autonomic nerve fibers and causing lower urinary tract dysfunction (LUTD)

Autonomic neuropathies
Primary autonomic neuropathies
Transthyretin amyloid polyneuropathy
AL amyloid polyneuropathy
Hereditary sensory autonomic neuropathies
Fabry's disease
Porphyrias
Secondary autonomic neuropathies
Diabetes mellitus
Alcohol, chemotherapeutics
Guillain–Barré syndrome
Paraneoplastic autonomic neuropathy
Lambert–Eaton myasthenic syndrome
HIV-associated polyneuropathy
Tabes dorsalis
Neurosarcoidosis

AL, amyloid light-chain; HIV, human immunodeficiency virus.

of a patient with polyneuropathy. Symptoms of orthostatic hypotension, LUTD, upper gastrointestinal tract dysfunction (e.g., abdominal bloating), dry eyes, dry mouth, and sweating abnormalities are all indicators of autonomic dysfunction. The possibilities of examining ANS clinically are rather limited. Sluggish pupillary responses to light, very dry hands and feet, resting tachycardia, a failure of the heart rate to increase or the arterial pressure to adapt on changing from the lying to standing position are features of ANS dysfunction. A drop of at least 20 mmHg systolic or 10 mmHg diastolic pressure is evidence of sympathetic vasoconstrictor abnormality.

Focal pelvic nerve injury in the pelvis should be suspected or diagnosed in a patient with LUTD after pelvic or prostatic surgery. The neurologic examination is seldom helpful in these patients.

Investigations

Investigations can be considered to detect or confirm polyneuropathy, to test ANS function, and to test the function and nerve supply of the bladder and EUS.

Peripheral nerve conduction studies, often supplemented by needle EMG examination of distal limb muscles, supports a diagnosis of polyneuropathy and distinguishes the demyelinating from the axonal type. The involvement of somatic nerve fibers in the lower sacral segments can be demonstrated by needle EMG of the EAS muscle (and other striated muscles of the perineum and pelvic floor) and by testing of sacral reflex responses. However, even in patients with proven polyneuropathy and LUTD, the electrophysiologic abnormalities in lower-limb nerves are more pronounced (easier to demonstrate) than the abnormalities of the pudendal nerve function. All mentioned studies evaluate only the large-diameter nerve fibers that are less relevant in LUTD. There is no routine electrophysiologic test for bladder smooth muscle and its innervation. Thermal thresholds assess the function of small-diameter nerve fibers.

Autonomic tests may be performed to demonstrate involvement of the ANS. If abnormalities are found, it is inferred that the bladder may be similarly affected. The potential pitfalls are evident, as bladder autonomic innervation itself is not tested. Tests include the thermoregulatory sweat test, quantitative sudomotor axon reflex test, sympathetic skin response test, and quantitative sensory testing Santiago et al., 2000; Low et al., 2003). A skin biopsy with a quantification of pilomotor nerves may also be performed to evaluate involvement of thin autonomic nerve fibers.

Assessment of LUT should include history and determination of residual urine as a minimum.

Urodynamic tests will reveal bladder sensory and motor function. Pressure–flow cystometry directly reveals the function of bladder afferents, but any lesion of autonomic (motor) fibers can only be inferred.

In summary, laboratory testing of the neurogenic causation of bladder dysfunction in the context of polyneuropathy provides mostly indirect proof, requires particular expertise, and has significant limitations. It is often more appropriate to make the neurologic diagnosis on clinical grounds, as treatment of LUT dysfunction would only in rare exceptions rely on the diagnosis of the neurologic lesion. LUT dysfunction, of course, needs to be appropriately assessed to allow for rational management (see Chapters 9 and 26).

Treatment

The approach to treatment is no different from that of other neurologic causes of LUTD. Particular care should be taken with the insensitive underactive bladder due to the danger of hyperdilatation with consequent damage to the detrusor.

Autonomic neuropathy

Autonomic neuropathies comprise a wide spectrum of syndromes and diseases caused by hereditary or acquired diseases (Table 12.1). Autonomic dysfunction may manifest with various clinical presentations, including bladder dysfunction (Freeman, 2005).

The most common genetic disorders presenting with autonomic dysfunction include familial amyloid polyneuropathy, hereditary sensory autonomic neuropathies, Fabry's disease, and porphyrias (Low et al., 2003; Freeman, 2005). The acquired autonomic neuropathies are more prevalent than the inherited ones. Commonly they are classified into primary and secondary, although the classification is not consistent. Primary autonomic neuropathies are idiopathic and autonomic dysfunction is part of the disease process. In the secondary autonomic neuropathies, autonomic neuropathy is not a defining feature of the underlying disease process (McDougall and McLeod, 1996; Freeman, 2005).

Primary autonomic neuropathies with LUT involvement include pure pandysautonomia and pure cholinergic dysautonomia (Kirby et al., 1985). Neuronopathy in the autonomic ganglia is considered a common pathology in these autonomic neuropathies. There is a correlation between the autoimmune abnormality and the type and severity of autonomic pathology. Nicotinic ACh receptors (nAChRs), particularly the α3 and the β4 subunits, are necessary for normal bladder function (De Biasi et al., 2000). Bladder dysfunction may be associated with neuronal nAChR antibodies (De Biasi et al., 2000). Animals immunized with the recombinant α3

subunit develop profound gastrointestinal hypomotility, dilated pupils with impaired light response, and grossly distended bladder. The severity parallels the serum levels of ganglionic nAChR autoantibody, as observed also in patients with idiopathic and paraneoplastic autoimmune autonomic neuropathy (Vernino et al., 2000). Pure pandysautonomia is mainly an idiopathic autoimmune disorder caused by immunoglobulin G vs α3 subunit of ACh receptor. Postganglionic cholinergic dysautonomia also most probably has an autoimmune pathogenesis, with the postulated antibodies acting highly specifically on unknown structures of the cholinergic postganglionic autonomic neurons. It is likely that the condition of acute distal autonomic neuropathy is a form of GBS and may affect the pelvic plexus and its associated nerves (sympathetic and parasympathetic), resulting in LUTD. In addition, clinically significant autonomic neuropathy may be associated with pre-existing immunologic diseases such as paraneoplastic syndrome and Sjögren's syndrome. An overlap with autoimmune autonomic ganglionopathy has been suggested in these settings (Koike et al., 2013).

There are several identifiable causes of secondary acquired autonomic neuropathies, including metabolic disorders (diabetes mellitus (DM), hepatic disease, and uremia), vitamin deficiencies (B_{12}), toxins and prescription medications (alcohol, chemotherapeutics), infectious diseases (tetanus, human immunodeficiency virus (HIV), botulism) and autoimmune conditions (Lambert–Eaton myasthenic syndrome, GBS) (Hahn, 1998; Low et al., 2003; Vinik et al., 2003). Some of the secondary autonomic neuropathies, such as associated with DM, GBS, and HIV, are discussed separately below.

Diabetic neuropathy

The two main forms of DM are type 1 and type 2. Type 1 is due to an autoimmune destruction of the pancreatic Langerhans islet beta cells, leading to insulin deficiency. Type 2 is a heterogeneous disease that typically occurs at an older age and is characterized by increased glucose production, insulin resistance, and impaired insulin secretion (Powers, 2011). The two types affect men and women almost evenly, and seem to be susceptible to similar complications. Polyuria is linked to the clinical picture of the metabolic disturbance, but LUTD is also present in a significant proportion of patients. This is often thought to be linked to the peripheral neuropathy, but actually, diabetic LUTD and neuropathy are distinct clinical entities and as such need to be researched and discussed separately. LUTD has been reported as the most common complication of diabetes (prevalence 80%), and is more frequent than neuropathy (60%) (Daneshgari et al., 2009).

DM is the most common cause of peripheral neuropathy worldwide. Neuropathy is present in 5% of patients in their 20s and 44% in their 70s. Similarly, it increases with duration of disease: 21% with duration <5 years and in 37% of those with duration >10 years (Young et al., 1993). Diabetic peripheral neuropathy can be separated into several clinical syndromes. The most frequent is distal symmetric polyneuropathy, with different relative involvement of particular nerve fiber populations and of variable severity; severe neuropathy is relatively uncommon.

The pathogenesis of diabetic neuropathy is not fully clarified; proposed pathogeneses include altered metabolism of glucose, ischemia, superoxide-induced free-radical formation, and impaired axonal transport (Pasnoor et al., 2013). Diabetic autonomic neuropathy is a frequent accompaniment of more severe diabetic polyneuropathy (Powers, 2011), but may also be the dominant feature of the disease. It can be restricted to certain organs or functions, or may be widespread, involving most or all of the peripheral ANS. In diabetic autonomic neuropathy neuronal degeneration as well as neurons with vacuoles and granular deposits are found. There is a loss of myelinated nerve fibers in the vagus and splanchnic nerves, as well as neuronal loss in the spinal cord intermediolateral columns. Alterations such as beading, thickening, and fragmentation of postganglionic sympathetic axons adjacent to the bladder have been demonstrated (Schmidt, 2002), as well as reduced density of acetylcholinesterase-positive staining nerves in the bladder wall (Van Poppel et al., 1988).

Up to 57% of diabetics will complain of urinary symptoms, although very careful questioning is often needed to elicit LUT symptoms (Frimodt-Moller, 1980; Ueda et al., 1997). The prevalence of diabetic cystopathy with detrusor underactivity is estimated to be 43–87% in insulin-dependent diabetics with no sex or age differences (Frimodt-Moller, 1980; Gomez et al., 2011). Diabetic cystopathy (the term used initially for LUTD in diabetics) has been described on its own right, meaning "involvement of the LUT by diabetic neuropathy," and describing a clinical picture of decreased bladder sensation, increased bladder capacity, and impaired detrusor contractility (Frimodt-Moller, 1980).

LUT symptoms in diabetics often begin with diminished sensation of bladder filling, resulting in decreased frequency of voiding. Patients complain of difficulty in voiding and a poor stream, accompanied by incomplete emptying of the bladder. Chronic retention often leads to repeated urinary infections. Although urinary infections are traditionally thought to result from increased postvoid residuals, altered expression of adherence receptors for bacteria on surface of urothelial cells may also take part (Daneshgari et al., 2009). Patients with reduced

detrusor contractility may void by abdominal straining (Niakan et al., 1986). Postvoid dribbling may also occur, mimicking bladder neck obstruction. Urinary tract infections may lead to detrusor fibrosis, further worsening LUT function. Onset of diabetic LUTD is in most patients insidious and often not recognized until it has reached an advanced stage.

Some studies show that nocturia and urinary frequency are the most common LUT symptoms in diabetics complaining of LUTD, and that detrusor instability is actually more common that detrusor underactivity (Kaplan et al., 1995; Hill et al., 2008). LUTD in DM may therefore also manifest as bladder overactivity and urge urinary incontinence.

Pathogenesis of LUTD in diabetes has been explained by impaired sensation of bladder fullness, leading to overstretching of detrusor muscle with resulting reduced contractility (Kaplan et al., 1995; Mitsui et al., 1999; Bansal et al., 2011; Gomez et al., 2011). In this hypothesis of diabetic cystopathy pathogenesis, there are also delayed micturition reflexes due to diminished bladder sensation with increases in bladder capacity (Kaplan et al., 1995; Vinik et al., 2003; Yoshimura et al., 2005). However, some authors reported that bladder overactivity might be actually more common than diminished contractility (Kaplan et al., 1995; Yamaguchi et al., 2007). Therefore, apart from the view that diabetic LUTD is usually understood as a consequence of diabetic autonomic neuropathy, the known cerebrovascular involvement in diabetes has also been implicated as a cause of diabetic LUTD (Ueda et al., 1997; Yamaguchi et al., 2007).

The alternative pathogenesis of diabetic LUTD postulates that, in early diabetes, hyperglycemia induces osmotic polyuria which leads to bladder hypertrophy and remodeling, causing bladder overactivity. According to this hypothesis, decompensation of bladder tissue with resulting detrusor hypoactivity occurs only later due to accumulation of oxidative stress products of prolonged hyperglycemia (Daneshgari et al., 2009). Furthermore, in addition to CNS and PNS tissue damage, animal models suggest the implication of changes in the detrusor muscle and urothelium (Yoshimura et al., 2005; Hill et al., 2008; Daneshgari et al., 2009).

Diagnosis

The diagnosis of neurogenic LUTD in diabetes is established by a history of neurologic symptoms, neurologic examination, evaluation of LUT function, and ruling out other causative agents. Reduced bladder sensory function is reflected in the frequency–volume chart by either infrequent voiding of large volumes or frequent voiding of small volumes.

Examination may show a diminished superficial and deep sensation in the lower limbs and, less commonly, in the perianal region. Knee and particularly ankle jerks are often depressed or absent. EAS tone may be reduced, with no response to cough and voluntary contraction. The anal and the bulbocavernosus reflex are often absent.

Diabetic neuropathy can be demonstrated by nerve conduction studies, as is characterized by axonal degeneration, demyelination, and nerve fiber loss. Abnormal nerve conduction in the lower limbs of diabetic patients correlates with LUTD (Mitsui et al., 1999). Needle EMG is usually normal, but may occasionally demonstrate sphincter denervation. The latency of the bulbocavernosus reflex is delayed only in patients with advanced diabetic polyneuropathy. However, this reflex investigation only assesses conduction in thick somatic, but not in autonomic, fibers and is indeed less sensitive to diagnose neuropathy, as are the routine nerve conduction studies in limbs (Vodušek et al., 2009). A correlation between diabetic cystopathy and abnormal sympathetic skin response has been reported, although differences between small subgroups of patients with and without response did not reach statistical significance in cystometric parameters (Ueda et al., 1997). Both sensory and motor diabetic cystopathy correlated with abnormal motor and sensory nerve conduction studies, but only motor diabetic cystopathy appears to correlate with abnormal sympathetic skin responses (Bansal et al., 2011).

Diabetic LUTD is a heterogeneous and unpredictable condition, and urodynamic evaluation has been proposed as essential to reveal the underlining pathophysiology and enable the optimal treatment strategy (Kaplan et al., 1995). The urodynamic of the "classic" hyposensitive underactive poorly contracting detrusor with the desire to void at a large volume may not be the most common finding in asymptomatic diabetic patients. Kaplan et al. (1995) reported detrusor overactivity in 55% of symptomatic patients, and underactive or accontractile detrusor in only 33%. In another study, detrusor underactivity was demonstrated in 79%, increased postvoid residual in 65%, detrusor overactivity in 39%, impaired first sensation in 23%, increased bladder capacity in 25%, and bladder outlet obstruction in 29% of the men (Bansal et al., 2011).

A pressure–flow study has been recommended for all diabetics with LUTD (Kaplan et al., 1995; Vinik et al., 2003). Others recommend a urodynamic study for all type 2 DM patients 8–9 years after diagnosis (Kebapci et al., 2007).

As a minimum, diabetic patients with recurrent urinary tract infections, pyelonephritis, incontinence, or palpable bladder should be tested for renal function and residual urine. Age should be taken into account, since elderly diabetic patients more often have concomitant disorders (Hunter and Moore, 2003). Urodynamic

testing is always indicated before surgical treatment (Bansal et al., 2011).

Management

Optimal glycemic control should be achieved because hyperglycemia and diabetic nephropathy lead to increased urine output, thus to increased mean voided volume and facilitation of incontinence. The management of LUT symptoms in DM depends on the degree of bother, its impact on quality of life, and considering the risk for recurring UTI.

Diabetic patients with reduced bladder sensation and infrequent voiding should practice timed voiding every 2–4 hours. CIS is often needed to achieve bladder emptying and reduce the risk of UTI with potential deterioration of renal function. The optimal CIS frequency may vary from one to four times daily depending on the individual's needs (Wagg and Malone-Lee, 1998). There is no effective medication currently available to assist with bladder emptying in diabetic cystopathy. In patients with outlet obstruction from prostatic enlargement, α-blockers may be helpful (Hunter and Moore, 2003).

Alcoholic polyneuropathy

In western countries the lifetime risk for alcohol dependence is 10–15% in men and 5–8% in women (Hasin et al., 2007); in several other countries it is probably larger. Alcohol-related neurologic disorders affect the brain, brainstem, cerebellum, and peripheral nerves, polyneuropathy being the most common (Messing and Greenberg, 1989), affecting 5–15% of alcoholics (Schuckit, 2011). Women may be more susceptible to alcoholic polyneuropathy than men.

Polyneuropathy is a result of thiamine deficiency and/or a direct toxic effect of ethanol and acetaldehyde (Mellion et al., 2012). The half-life of thiamine is only about 14 days, therefore a continuous intake of food is vital to prevent lack of this important vitamin. Alcoholic polyneuropathy usually presents as a gradual development of distal symmetric, sensory, and motor symptoms. Axonal degeneration and segmental demyelination are the main features (Messing and Greenberg, 1989), but non-myelinated fibers are also involved. A loss of sympathetic and parasympathetic nerve fibers as well as ganglion neurons has been observed (Windebank, 1993). References to LUTD in alcoholics are sparse; urinary retention has been described (Tjandra and Janknegt, 1997; Yuan et al., 2002).

Guillain–Barré syndrome

GBS consists of a group of acute autoimmune demyelinating and axonal polyneuropathies. Clinically it is characterized by a largely symmetric ascending motor paralysis accompanied in most patients by sensory disorders and often also by autonomic disturbances. Although complete recovery is common, GBS may leave patients severely disabled (Hahn, 1998). Autonomic features may be present in up to 50% of patients, and include labile blood pressure, extremity anhidrosis, paralytic ileus, and LUTD. Hesitancy, poor and prolonged flow, urinary retention, urgency, nocturnal frequency, and urge incontinence have all been described, because both storage and voiding can be affected (de Jager and Sluiter, 1991). In the general GBS population, LUTD was reported in about 25% of patients, more often in patients with severe weakness (Sakakibara et al., 1997; Naphade et al., 2012). LUTD typically presents after the onset of weakness (Sakakibara et al., 1997; Naphade et al., 2012), with no correlation to sensory deficit, and to antibody titer against neuronal nAChRs (Sakakibara et al., 2009). Correlation of LUTD and severity of motor involvement was confirmed in a series of 63 intubated patients where 75% developed micturition problems (de Jager and Sluiter, 1991).

Urodynamic studies are often (60%) abnormal, even in patients with no LUT symptoms (Naphade et al., 2012). Detrusor underactivity and impaired bladder sensation with large postvoid residuals have been described as common (Sakakibara et al., 2009; Naphade et al., 2012). Detrusor overactivity, both with (Naphade et al., 2012) and without detrusor sphincter dyssynergia (Sakakibara et al., 2009), has also been reported. As these paradoxic findings were seen in the absence of clinical evidence of spinal cord involvement, overactivity was attributed to pelvic nerve irritation or involvement of spinal cord inhibitory interneurons (as has been proposed for the explanation of exaggerated myotatic reflexes noted in some patients with axonal GBS). Urodynamic parameters improve approximately 6–8 weeks after the onset of weakness (Naphade et al., 2012).

In GBS patients with a higher Hughes motor grade, older age, and defecation dysfunction, checking postvoid residual by ultrasonography is recommended (Sakakibara et al., 2009). To prevent bladder overdistension injury, CIS or indwelling urethral catheter is recommended for detrusor hypoactivity or detrusor overactivity with detrusor-sphincter dyssynergia. Prolonged CIS is occasionally needed for patients with slow and/or poor recovery (Sakakibara et al., 2009). Symptoms improve gradually with the neurologic signs; this may take months.

Chronic inflammatory demyelinating polyneuropathy

By contrast to GBS, autonomic dysfunction seems to be less common in chronic inflammatory demyelinating

polyneuropathy (CIDP). LUTD has varied from only 2% (Prineas and McLeod, 1976) to 25% (Sakakibara et al., 1998), so the true prevalence needs to be determined by validated questionnaires in further studies. LUTD in the form of voiding difficulty and urgency was more common in patients with severe weakness (Sakakibara et al., 1998). The description of a patient with severe constipation, voiding difficulty, and urinary urgency associated with greatly enlarged nerve roots filling the lumbosacral spinal canal alerts the clinician to this additional possibility of "mechanic" effect of LUT innervation in CIDP (Ishii et al., 2005).

Urodynamic findings were reported in only four CIDP patients with LUT symptoms: disturbed bladder sensation was found in two, bladder underactivity in one, and detrusor overactivity in two patients (without CNS involvement!). In one patient EMG showed neurogenic motor unit potential changes in the EAS muscle (Sakakibara et al., 1998).

HIV-associated neuropathy

Voiding dysfunction in AIDS patients may be related to encephalitis, cerebral toxoplasmosis, meningitis, tumors, myelitis, polyradiculoneuritis, and peripheral neuropathy (Helweg-Larsen et al., 1986). Approximately 9–16% patient with AIDS have PNS dysfunction (Snider et al., 1983; Levy et al., 1985). However, the overall prevalence of bladder dysfunction in HIV patients, and in patients with HIV-related peripheral neuropathy, is not known. In a series of 39 HIV-positive patients with voiding symptoms of straining, urinary retention, frequency, and urgency, urodynamic examination revealed signs of overactive bladder and/or detrusor sphincter dyssynergia in 56%, hypoactive bladder or other presumably "peripheral deficits" in 13%, isolated urethral hypertonia in 10%, and a hypersensitive bladder or no urodynamic abnormalities in the remainder. Urgency without UTI was treated with antimuscarinic medications, and poor bladder emptying by CIS (Hermieu et al., 1996).

Neurosarcoidosis

In neurosarcoidosis, neurogenic damage can occur at any site within the neuraxis. The proportion of PNS involvement ranges from 25% to 67% (Said and Lacroix, 2005). The pathologic findings in peripheral nerves are scattered perineural changes and sarcoid granuloma infiltration between nerve fibers, resulting in involvement of all nerve types (Said and Lacroix, 2005). The type of neuropathy is most consistent with a multifocal axonal degeneration. In one series six out of 17 neurosarcoidosis patients reported voiding difficulties (Koffman et al., 1999).

Amyloid neuropathy

Amyloidosis is a term for diseases caused by the extracellular deposition of insoluble polymeric protein fibrils in tissues and organs. Amyloid fibrils share a common pleated-sheet structural conformation that confers unique staining properties. Amyloid diseases are defined by the biochemical nature of the protein in the fibril deposits. The accepted nomenclature is "AX," where A indicates amyloidosis and X represents the protein in the fibril. AL is amyloid composed of Ig light chains, also called a primary systemic amyloidosis. It arises from a clonal B-cell disorder, usually myeloma. AF groups the familial amyloidoses, most commonly due to abnormal transthyretin, the transport protein for thyroid hormone and retinol-binding protein. Over 40 mutations causing transthyretin amyloidoses have been identified, with autonomic involvement occurring in about half. Small-fiber neuropathy is seen in AL and transthyretin amyloidosis, but not in other amyloidoses. LUTD has been reported in both. Deposition of amyloid was found in afferent somatic nerves, and in the detrusor (Ito et al., 2006; Andrade, 2009).

Symptoms of LUTD were reported in four patients with amyloid neuropathy (two with AL, two with transthyretin amyloidosis). They had impaired bladder sensation and voiding difficulties due to detrusor weakness. In two patients, cholinesterase inhibition caused urge incontinence, indicating denervation supersensitivity, probably due to degeneration of postganglionic cholinergic neurons (Ito et al., 2006; Andrade, 2009). In transthyretin amyloid neuropathy patients the initial LUT symptoms appeared on average within 3 years of disease onset, commonly as voiding difficulties and stress incontinence. On cystometry, diminished bladder sensation, poor detrusor contractility (78%), open bladder neck with paradoxical closure on attempt to void, nonrelaxing external sphincter (52%), and even detrusor sphincter dyssynergia (38%) were detected (Andrade, 2009). LUTD was the most common autonomic dysfunction in a Japanese patient cohort, as 92% of patients were affected: 86% of patients showed difficulty in urination, 38% had urinary incontinence, and 19% urinary frequency. Filling cystometry demonstrated reduced bladder sensation in 38%, low-compliance bladder in 43%, and detrusor overactivity in 14% of patients. First desire to void, strong desire to void, and postvoided residual urine were increased in patients as compared to control subjects. An incompetent urethral closure mechanism was demonstrated in 71% of patients (Wada et al., 2006).

Many patients with transthyretin amyloid neuropathy are completely unaware of LUTD in spite of severely abnormal cystometric findings (Andrade, 2009), which points to the need for urologic surveillance after

appearance of the first symptoms of disease. In management, scheduled CIS is recommended in order to avoid bladder overdistension. Alpha-adrenergic blocking agents can exacerbate the postural hypotension which is common in these patients (Ito et al., 2006). Milnacipran, a serotonin–norepinephrine reuptake inhibitor, lacks muscarinic receptor-blocking property, and has been therefore suggested in the treatment of incontinence due to sphincter deficiency combined with detrusor overactivity (Thor, 2003; Ito et al., 2006).

Porphyric polyneuropathy

The porphyrias are hereditary disorders affecting hepatic heme metabolism. The four types with neurologic manifestations are acute intermittent porphyria, variegate porphyria, hereditary coproporphyria, and 5-aminolevulinic acid dehydratase deficiency. Pathologically, the peripheral nerves show degeneration of the axons with secondary demyelination. Hypotheses on pathogenesis include toxicity of porphyrin precursors and deficiency of heme synthesis.

The acute attacks are often precipitated by intake of different drugs and alcohol. Starvation, infections, and fever may also provoke attacks (Lin et al., 2013). Autonomic function studies show abnormalities of both sympathetic and parasympathetic nerves (Laiwah et al., 1985). The most common LUT manifestation is urinary retention. In two female patients with porphyria and acute urinary retention cystoscopy was normal (Redeker, 1956).

Other hereditary peripheral neuropathies

Hereditary peripheral neuropathies are genetically and phenotypically heterogeneous disorders, Charcot–Marie–Tooth (CMT) disease being the most common. At least 43 causative gene defects have been identified by genetic mapping (Braathen et al., 2011).

LUT involvement is generally regarded as rare in hereditary peripheral neuropathy. LUT symptoms were, however, significantly more common in a cohort of 58 CMT patients compared to a control group. Symptoms were particularly frequent in female CMT patients (Krhut et al., 2014).

Autonomic disturbance, including LUTD, was reported as one of the major clinical signs associated with CMT secondary to the myelin-associated protein zero gene mutation in codon 124 (Stojkovic et al., 2003). In a study of four-generation Japanese CMT pedigree (with proximal dominant form), all affected members showed LUTD (Miura et al., 2008). These findings suggest that autonomic dysfunction should be evaluated and included in the diagnostic approach and care of CMT patients.

FOCAL PELVIC NERVE LESIONS

Bladder dysfunction can occur from damage to its innervation anywhere in the pelvis. Fractures of the pelvic girdle and missile injuries can cause damage to these nerves at any or several sites. Most injuries to these nerves are, however, iatrogenic.

Extensive pelvic surgery, such as abdominoperineal resection for rectal cancer, radical hysterectomy, and aortoiliac surgery, are all likely to damage the pelvic autonomic innervation of the bladder and result in LUTD. The manifestations and mechanisms of dysfunction vary with the specific type of surgery performed, and the preoperative pathology. In general, neurologic injury is usually implicated as the cause for postoperative LUTD, although anatomic derangements of the bladder, urethra, or sphincter may have occurred. Injuries due to neural traction during surgery can cause neuropraxic or axonal lesions of nerve fibers; the first only cause transient dysfunction.

The typical complication of surgical injury to parasympathetic nerves in the pelvis is difficult voiding, Valsalva voiding, incomplete bladder emptying, and large urinary residual urine. Other types of LUTD may occur, as injury may affect primarily sympathetic fibers and manifest as either α- or β-adrenergic denervation: β-adrenergic denervation may result in poor bladder compliance and occasional detrusor overactivity (Yalla and Andriole, 1984), and α-adrenergic denervation typically manifests as bladder neck incompetence.

Expanding knowledge of pelvic neuroanatomy and improved surgical expertise, in recent years, have led to a decrease in these complications.

Abdominoperineal resection

The extent of pelvic dissection during abdominoperineal resection relates directly to the degree of subsequent LUTD (Hojo et al., 1991). These patients complain of incontinence, retention, or both (Blaivas and Barbalias, 1983). Radical rectal excision via abdominoperineal resection is associated with postoperative voiding dysfunction. Bladder neck incompetence, impaired compliance, detrusor underactivity, and diminished proprioception have been observed 2 weeks to 4 months after surgery on videourodynamics, suggesting combined parasympathethic and sympathetic denervation. Additionally, totally incontinent patients manifested absent reflex EUS activity. Within 4 months 75% of incontinent patients regained passive continence. This corresponded to restored urethral closure pressure in the membranous urethra with return of the EUS reflex activity. The presence of bladder neck incompetence, indicative of persistent sympathetic innervation, was

variable in delayed evaluations, while parasympathetic denervation persisted, manifested in a large cystometric capacity and detrusor underactivity (Yalla and Andriole, 1984).

LUT morbidity after abdominoperineal resection may be largely avoided by preservation of autonomic innervation, which allowed 88% of patients to void spontaneously within 10 days of surgery, as opposed to 78% of patients who remained in urinary retention by 2 months postoperatively after complete resection of the pelvic autonomic nerves (Hojo et al., 1991). During perineal dissection surgeons should dissect cautiously near the ischial tuberosity, where the terminal branches of the pudendal nerve may be injured as they exit Alcock's canal. Preservation of the vagina protects autonomic fibers as they travel to the urethra (Hollabaugh et al., 2000).

In patients with low rectal cancer, surgical nerve damage is the main cause of urinary dysfunction, occurring in one-third of patients (Lange and van de Velde, 2011).

Intraoperative neuromonitoring has significantly improved urinary functional outcome in rectal cancer patients matched for gender, tumor site and stage, neoadjuvant radiotherapy and type of surgery; newly developed urinary dysfunction was six times less frequent, and postoperative residual urine volume was significantly lower (Kneist et al., 2013).

Hysterectomy

Even simple hysterectomy may be associated with postoperative LUTD. Urodynamic studies in 126 women with LUT symptoms after hysterectomy revealed an urodynamic abnormality in 86%: 47% had detrusor overactivity, 37% urethral obstruction, and 25% stress incontinence (Parys et al., 1990).

Radical hysterectomy, like abdominoperineal resection, is associated with significant postoperative LUTD (Parys et al., 1990). The reason is close anatomic proximity between the pelvic plexus and resected uterosacral and cardinal ligaments, which carry autonomic nerve fibers that innervate the bladder and urethra (Tong and Huo, 1991). Nearly all patients with LUTD after radical hysterectomy suffered parasympathetic denervation (Yalla and Andriole, 1984), and up to 50% have additional sympathetic denervation, the extent of which probably corresponds to the extent of dissection of the cardinal ligaments (Forney, 1980).

Nerve-sparing hysterectomy prevents these complications but is still followed by reduced voiding pressures at maximal flow compared to preoperative measurements (Todo et al., 2006).

Techniques for the identification and preservation of the pelvic nerves during type III radical hysterectomy include the sequential approach to parametrial resection, direct visualization of the main nerve trunks at all sites during parametrial resection, and the avoidance of direct manipulation and unnecessary dissection of the nerves. A thorough understanding of anatomy and adequate surgical skills are always vital components of successful nerve-sparing radical hysterectomy (Charoenkwan, 2010).

One study has shown that, in patients with cervical carcinoma, laparoscopic nerve-sparing radical hysterectomy along with pelvic lymphadenectomy is feasible in a high percentage of patients. The authors point out that nerve sparing is easier done laparoscopically. The median return time for normal bladder function was 2 days and maximal catheterization time was 2 weeks. The mean residual urine volume was <50 mL. Urodynamic studies performed at 3 weeks after the operation showed no impairment of maximum flow rate (maximal flow rate: 20 ± 2 mL) (Puntambekar et al., 2010).

Other studies suggest that intraoperative electric nerve stimulation of the cardinal ligaments to identify the location of the detrusor branches of the pelvic nerve may be a useful adjunct to nerve-sparing procedures (Kuwabara et al., 2000). Electric stimulation of the roots of the pelvic splanchnic nerves and the posterior and dorsal regions of the vesicouterine ligaments is performed with simultaneous bladder cystometry. In all patients who demonstrated an increase in intravesical pressure, detrusor contractility was preserved, and there were no subjective complaints of postoperative voiding difficulties, whereas the other patients voided either by Valsalva or CIS, and detrusor underactivity was demonstrated in them (Katahira et al., 2005).

Prostatectomy

Following transurethral prostatectomy for benign prostatic hypertrophy, urinary retention or incontinence may occur immediately postoperatively. It improves as a rule within weeks; long-term LUTD incidence is less than 1% (Rassweiler et al., 2006).

Micturition abnormalities are more common following radical prostatectomy, with a reported incidence of incontinence between 7 and 17% depending on definition of incontinence (Sacco et al., 2006). Urodynamic studies have shown that in most affected patients this is due to direct damage to the intrinsic urethral sphincter (Bruschini et al., 2011). A proportion of patients have, however, concomitant detrusor dysfunction (overactivity, impaired compliance) (Porena et al., 2007). In men undergoing radical prostatectomy, pre- and postoperative bladder biopsies in the superficial trigone demonstrated decreased nerve fiber density that increased over time (John et al., 2001). Patients with persistent

incontinence had less than half the amount of nerve fiber regeneration compared to continent patients at 6 months postoperatively. Urinary incontinence was associated with trigonal denervation, a high sensory threshold, and a low maximal urethral closure pressure. Wide dissection around the prostate, bladder base, and seminal vesicles was thought to lead to disruption of bladder and proximal urethral innervation, leading to incontinence (John et al., 2001).

Robotic-assisted laparoscopic radical prostatectomy has enabled enhanced, magnified three-dimensional vision and more precise identification and preservation of pelvic nerves. In a study of 154 consecutive patients who underwent nerve-sparing robotic-assisted laparoscopic radical prostatectomy, 97% of patients had complete urinary control at 1 year after surgery, 29% being continent at the time of catheter removal (usually 7 days postoperatively). Most regained complete continence by 1 month postoperatively. These results suggest that enhanced attention to nerve preservation at the time of radical prostatectomy may result in improved outcomes in terms of LUT function (Kaul et al., 2006).

Radiation therapy

The pelvis is a relatively confined space that contains the bladder, prostate or uterus, and rectosigmoid portions of the large intestine that are in close proximity to the autonomic and somatic nerves, which innervate them. External-beam radiation therapy designated for any one particular organ will therefore inevitably result in simultaneous radiation exposure to other vital structures, including blood vessels and peripheral nerves. Animal studies have revealed that the threshold dose for peripheral neuropathy following radiation therapy is only 15–20 Gy, well below the usual dose utilized for most pelvic malignancies (Johnstone et al., 1995). Nerve cell death may occur months to years after radiation therapy due to the slow reproductive cycles of glial and Schwann cells. Nerve damage may also be induced by involvement of vascular endothelium and obliteration of neural blood supply. Radiation-induced perineural fibrosis may result in compression and ischemia of peripheral nerves (Sindelar et al., 1986).

Numerous studies have demonstrated LUTD after radiation therapy (Nguyen et al., 1998; Litwin et al., 2000). Although LUTD after radiation therapy is mainly attributed to nerve damage, direct radiation damage to microvascular, epithelial, and muscular components of the bladder and urethra may also contribute. Radiotherapy increases the negative effects of chemotherapy, and vice versa (Keime-Guibert et al., 1998).

Radiation therapy for prostate cancer resulted in a gradual decline in LUT function and an increase in urinary symptoms up to 1 year posttherapy; symptom severity was similar to those after radical prostatectomy (Litwin et al., 2000). LUTD have been reported after pelvic radiation therapy for the treatment of prostate, bladder, rectal, cervical, and uterine cancers (Tait et al., 1997; Hanfmann et al., 1998; Litwin et al., 2000). Urgency/frequency and urge incontinence were reported. A decrease in micturitional volumes to 70% of pre-radiation therapy for prostate cancer was noted by 6 weeks after therapy (Hanfmann et al., 1998).

Urodynamic testing of 104 patients who received pelvic irradiation for cervical carcinoma demonstrated *de novo* urge incontinence related to detrusor overactivity concomitant with poor compliance and diminished cystometric capacity in 60% of patients. Maximal urethral closure pressures were initially unchanged, but the risk for stress urinary incontinence increased over time and was significant 6 years posttherapy (Behr et al., 1990).

Due to the anatomic apposition of the pelvic viscera and their innervating nerves it is likely that peripheral nerve exposure and subsequent injury will occur with any treatment modality implemented in the pelvis, although attempts to limit radiation exposure to bystander tissues with new therapeutic approaches have shown some success (Tait et al., 1997).

Radiotherapy for low rectal cancer seems not to affect urinary function (Lange and van de Velde, 2011).

Managing the patient with LUT dysfunction related to pelvic nerve injury

The time course and completeness of recovery of LUTD after pelvic surgery are not predictable; LUTD may resolve during the early postoperative period (weeks to several months), or stabilize and persist postoperatively.

Urodynamic evaluation has proven invaluable for the proper assessment of patients complaining about postoperative or postradiation LUTD. Postoperative urodynamic testing, preferably videourodynamics, has been suggested by the third or fourth week after surgery (Norris and Staskin, 1996). Concentric needle EMG of perineal / pelvic floor muscles determines the presence or absence of recent denervation, thus diagnosing or excluding a pudendal nerve or levator ani nerve lesion. Sacral reflex responses test the integrity of the sacral reflex arc (Vodušek et al., 2009).

Treatment of LUTD after pelvic surgery or radiotherapy should be directed by the urodynamic findings. For the patient in urinary retention, CIS is the treatment of choice. A period of 24 months should pass before considering any definitive surgical intervention in the patient with sphincteric incontinence or poor compliance (Sacco et al., 2006).

CONCLUSION

PNS disorders are an important cause of LUTD. LUT symptoms may be a guide to the diagnosis of processes localized in the lumbosacral spinal canal (as in CES), and in the pelvis. LUTD caused by PNS involvement causes typically bladder and sphincter hypoactivity with poor emptying, and incontinence, but also bladder overactivity. LUTD due to PNS involvement is rarely a medical and surgical emergency (as in acute CES). More prevalently, it is a chronic condition needing appropriate detection (which may still be neglected), appropriate assessment, and management with follow-up, as it presents a health hazard due to possible recurrent urinary infections and upper urinary tract complications. Not to be neglected, LUTD also significantly affects the quality of life of patients.

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 13

Sexual dysfunction in patients with spinal cord lesions

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Each year, 21–83 per million inhabitants in North America and 8–131 per million inhabitants in Europe are affected by a spinal cord injury (Furlan et al., 2013). The lesions can be complete or incomplete and result in paralysis and loss of sensation or allow various degrees of recovery, both motor and sensory. Sexual dysfunction can therefore vary as a consequence of spinal cord lesion (SCL), but when individuals require active rehabilitation, sexual dysfunction usually accompanies the condition and requires treatment. Many aspects of sexuality can be disrupted following a SCL, both physical and psychologic. It can alter an individual's sexual self-esteem and body image, interfere with positioning and mobility during sexual activity, introduce unexpected problems with incontinence and spasticity, and inhibit sexual pleasure through pain and side-effects of medication (Kreuter et al., 2011; Biering-Sørensen et al., 2012; Hess and Hough, 2012). All of these aspects require individuals to reinvent their sexuality and develop new grounds for intimacy.

Aside from these many aspects, sexual function is further affected by SCL and described as one of the most important factors for quality of life (Anderson et al., 2007a, b, c). For men, this can translate into concerns with erectile function, which is essential for intercourse, ejaculation, which is necessary for fertility, and climax, which allows one to reach the utmost experience of sexual pleasure. For women, this can translate into concerns with vaginal lubrication and genital congestion, which may no longer be perceived; vaginal infections, which may go unnoticed (especially with local irritation); orgasm, which may be lost; and fertility and pregnancy, which is often feared. All of these concerns must be addressed during rehabilitation, through educational courses (as often offered today), or individual counseling to help individuals adapt to their new sexual life.

This chapter describes the impact of SCL on various phases of men's and women's sexual responses and on various aspects of sexuality. Treatments are described in terms of what is currently available and what is specific to (or can be adapted to) the SCL population. Because men's and women's sexual function have specific aspects that are not necessarily common to both genders, sexual function in men and women with SCL are presented separately. However, because sexual adjustment goes beyond the primary impact of SCL on men's and women's genital function, sexual counseling is covered in a closing section common to both genders. Throughout the chapter, attempts are made to integrate neurophysiologic knowledge, findings from the literature on SCL, and clinical experience in sexual rehabilitation.

MEN WITH SCL

Normal sexual function and remaining sexual potential

Remaining physical potential is a key aspect to rehabilitation, and sexual function is no exception to the rule. Remaining sexual capacity despite the lesion should not be overlooked even when treatments are available (e.g., phosphodiesterase (PDE5) inhibitors), and treatment options should be associated with the individual's natural potential in order to maximize their effectiveness and facilitate sexual adjustment.

Understanding the individual's remaining potential requires an understanding of men's and women's natural responses. In men, this includes erection, which comprises tumescence and rigidity, ejaculation, comprising emission and expulsion, and climax. In women, it includes erection of the clitoris, congestion of the clitoro-urethro-vaginal complex, vaginal lubrication,

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and climax. All of these responses involve an interplay between spinal reflexes and the brain, which explains how remaining sexual function in individuals with SCL can vary as a function of the lesion level and its completeness (Bors and Comarr, 1960; Comarr, 1970; Chapelle et al., 1980; Courtois et al., 1993b), and how successful sources of stimulation must rely on preserved neural pathways.

Normal sexual function

As described in previous chapters, erection is primarily a reflex, receiving excitatory and inhibitory influences from the brain (Andersson, 2011; Giuliano, 2011; Tajkarimi and Burnett, 2011; Courtois et al., 2013a). It comprises a vascular and a muscular process, the first (most important) being responsible for penile tumescence (but sometimes insufficient to provide satisfying erection in men with SCL) and the second maximizing penile rigidity. The reflex mediation of erection is governed by the sacral segments S2–4 of the spinal cord (Giuliano and Rampin 2000, 2004; Andersson, 2011; Giuliano, 2011; Tajkarimi and Burnett, 2011; Courtois et al., 2013a). Sensory fibers from the dorsal penile nerve (sensory branch of the pudendal nerve) synapse in the spinal cord with efferent fibers of the pelvic nerve, triggering vasodilation, which is responsible for penile tumescence, and with the perineal nerve (motor branch of the pudendal nerve) triggering sporadic contractions of the bulbospongiosus and ischiocavernosus muscles maximizing penile rigidity (Karacan et al., 1983, 1987; Lavoisier et al., 1986, 1988a, b; Claes et al., 1996; Lue, 2000).

Although erection is primarily a reflex, it can also be triggered by psychogenic stimulation, derived from visual, auditory, olfactory, somesthetic and verbal stimulation, perceived or recalled, and by sexual fantasies. Such stimulation from the higher centers either feed into the sacral pathway to mediate psychogenic erection, or runs through the spinal thoracolumbar (TL) pathway from T11, T12, L1 and L2, exiting the spinal cord through the splanchnic nerves and running down the paravertebral sympathetic chain and inferior hypogastric nerve, feeding into the pelvic plexus (Courtois et al., 1993a; Giuliano et al., 1996, 1997; Yaïci et al., 2002; Rampin and Giuliano, 2004).

Ejaculation is composed of two phases, emission and expulsion. Emission involves smooth-muscle contractions from the internal reproductive organs and creates the semen (crucial for fertility), whereas expulsion is characterized by rhythmic contractions of perineal muscles (in particular the bulbospongiosus, ischiocavernosus, and anal muscles) accompanied by signs of autonomic discharge (e.g., flushing, shivering, red skin spots and the like) (Rampin and Giuliano, 2004; Giuliano and Clément, 2005a, b; Courtois et al., 2011a, 2013a; Giuliano, 2011).

The neural mechanism governing emission is controlled by the TL segments, where preganglionic sympathetic fibers synapse in the peripheral celiac or mesenteric ganglia with the hypogastric nerve innervating the internal reproductive organs. Expulsion is mediated by the sacral segments (described above for reflex erection), where the perineal nerve stimulates the contractions of the bulbocavernosus and ischiocavernosus muscles, forcing the expulsion of the semen forward towards the urethra (although retrograde ejaculation can occur in SCL: see later). The sequence of events from erection to emission to ejaculation is coordinated by the spinal generator of ejaculation, located in the lumbar segments L3 and L4, and regulating the pacing of events (Truitt and Coolen, 2002; Truitt et al., 2003; Borgdorff et al., 2008, 2009; Carro-Juárez and Rodríguez-Manzo, 2008).

Erection potential following SCL

Based on the innervation of male sexual organs, erectile potential following SCL can be affected by the level and completeness of the lesion (Bors and Comarr, 1960; Comarr, 1970; Chapelle et al., 1980; Courtois et al., 1993b, 1999; Biering-Sørensen and Sønksen, 2001; DeForge et al., 2006; Elliot, 2006; Everaert et al., 2010). As a general rule, higher lesions preserve better reflex activity and greater sexual potential (in particular through multisegmental reflexes), while lower lesions impair reflex activity and maintain only psychogenic potential, which however lacks the muscular components to maximize sexual function.

Figure 13.1 illustrates the remaining sexual function according to various lesion levels. Higher lesions to the cervical or thoracic spinal segments maintain all reflexes below the lesion, including multisegmental reflexes. Reflex erections are therefore possible. In contrast, psychogenic erection is generally lost (except for incomplete lesions).

Studies support this neurologic prognosis, as observations as early as 1948, and throughout the 1960s and later (Munro et al., 1948; Talbot, 1949, 1955; Bors and Comarr, 1960; Comarr, 1970; Courtois et al., 1993b, 1999; Everaert et al., 2010) consistently report the maintenance of reflex erection in these men, while clinical observations consistently confirm the appearance of reflex erections upon genital manipulation (e.g., when catheterized).

Lesions to the TL spinal segments (Fig. 13.1) also maintain reflex erection. Psychogenic erection may or may not be preserved, the literature being parsimonious on this topic (Comarr, 1970; Courtois et al., 1993b, 1995;

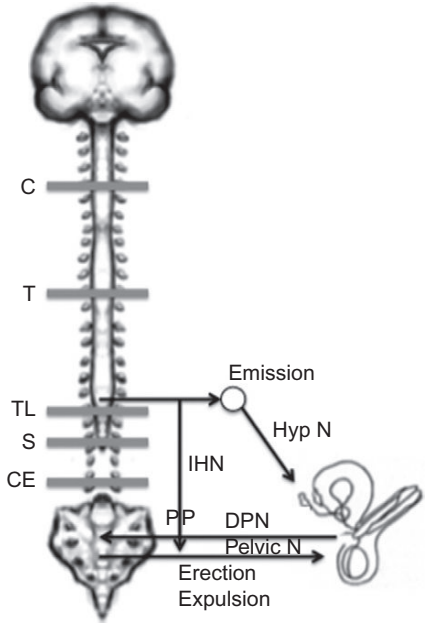

Fig. 13.1. Innervation of the male genitals and impact of various spinal cord lesions on sexual function. Lesions to cervical (C) or thoracic (T) segments (above T10) of the spinal cord can maintain reflexogenic erection to genital stimulation, but not psychogenic erections, and can achieve both emission and ejaculation, although at higher threshold; Lesions to cervical (C) segments of the spinal cord can maintain reflexogenic erection to genital stimulation and ejaculation, although at higher threshold; lesions to thoracolumbar (TL)segments of the spinal cord can maintain reflexogenic erection to genital stimulation, but not psychogenic erections; emission (and hence following expulsion) is generally lost, although lesions to the last thoracic segments (T11, T12) may spare the first lumbar segments (L1, L2). Lesions to sacral (S) segments of the spinal cord or cauda equina (CE) can maintain psychogenic but not reflexogenic erection and are often associated with premature ejaculation. DPN, dorsal penile nerve; IHN, inferior hypogastric nerve; Hyp N, hypogastric nerve; PP, pelvic plexus.

Everaert et al., 2010), but clinical experience suggests little psychogenic potential for men with these lesion levels (Courtois et al., 2009b, 2013a; Everaert et al., 2010).

Lesions to lower sacral segments (Fig. 13.1) impair reflex activity and abolish reflex erection. Psychogenic erection however is possible and typically preserved (Bors and Comarr, 1960; Comarr, 1970; Courtois et al., 1993b, 1995, 1999; Everaert et al., 2010).

Lesions to the cauda equina present a special case, aside from the fact that they are lower motor neuron (LMN) lesions. The extent of the damage can vary largely (as high as T12–L1 spinal root) or narrowly (lumbar fracture). The neurologic damage is also often incomplete given the nature of the cauda equina as peripheral nerves rather than spinal segments, and some recovery or plasticity may be expected (i.e., peripheral nerves). Special attention is therefore required to assess remaining sexual function. The literature unfortunately bends to blend these lesions into the general group of lumbosacral lesions and generally indicates poor sexual function (Comarr, 1970).

Ejaculation potential following SCL

Ejaculation potential following SCL is similarly affected by the level and completeness of the lesion (Bors and Comarr, 1960; Comarr, 1970; Chapelle et al., 1980; Courtois et al., 1993b, 1999; Biering-Sørensen and Sønksen, 2001; DeForge et al., 2006; Elliot, 2006; Everaert et al., 2010). Higher lesions to the cervical or thoracic spinal segments maintain all reflexes below the lesion, including multisegmental reflexes. Reflex ejaculation is therefore possible.

Studies support this neurologic prognosis, as observations as early as 1948, and throughout the 1960s and later show some ejaculation potential (Munro et al., 1948; Talbot, 1949, 1955; Bors and Comarr, 1960; Comarr, 1970; Courtois et al., 1993b, 1995, 1999; Everaert et al., 2010). Although ejaculation is possible through preservation of the multisegmental reflex, the literature indicates that the natural occurrence of ejaculation is rather infrequent (DeForge et al., 2005; Courtois et al., 2008a; Chéhensse et al., 2013). Earlier studies have shown that ejaculation was relatively rare (5–15%) in men with SCL when using natural stimulation (e.g., masturbation, intercourse) (Munro et al., 1948; Bors and Comarr, 1960; Comarr, 1970), but later studies on vibrostimulation (Brindley, 1981a; Szasz and Carpenter, 1989; Sønksen et al., 1994; Brackett et al., 1998, 2010a; Brackett, 1999) indicated that using stronger stimulation parameters, especially of higher amplitude (Sønksen et al., 1994, 1996; Ohl et al., 1996; Fode et al., 2012), significantly increased the success rate for ejaculation. The combination of natural and vibrostimulation in men with higher lesions further increases the potential for men with higher lesions to over 90% (Brackett and Lynne, 2000; Courtois et al., 2008a, b). It is noteworthy that ejaculation in men with SCL can go, and often does go, unnoticed as a result of retrograde ejaculation, which can result from bladder sphincter dyssynergia (typical in men with higher lesions) or opening of the bladder neck (lower lesions) (Chen et al., 1999; Sipski et al., 2006; Courtois et al., 2009b, 2013b). The assessment of remaining sexual function in men with SCL therefore requires paying attention to retrograde ejaculation in addition to anterograde ejaculation in order to conclude on true ejaculation potential.

While lesions to the TL spinal segments (Fig. 13.1) maintain reflex erection, the spinal connections between the sacral and TL pathways are generally lost, leading to

anejaculation (except for incomplete lesions or lesions at T11–12, which may spare some lumbar fibers) (Comarr, 1970; Courtois et al., 1993b, 1995; Everaert et al., 2010).

Lesions to lower sacral segments (Fig. 13.1) impair reflex activity (Bors and Comarr, 1960; Comarr, 1970; Courtois et al., 1993b, 1995, 1999; Everaert et al., 2010). Reflex ejaculation is therefore lost, but psychogenic ejaculation, often referred to as dribbling ejaculation, is reported (Kuhr et al., 1995; Courtois et al., 2013c). These dribbling ejaculations, which are often indistinctly associated with lumbosacral lesions in the literature (hence failing to distinguish epiconus, conus, or cauda equina lesions), are also described as extremely premature (e.g., upon a mere sexual thought), a condition which appears following SCL in men who otherwise controlled their ejaculation prior to injury.

As mentioned before, lesions to the cauda equina present a special case where the extent of the damage can largely vary. Special attention is therefore required to assess remaining sexual function.

Orgasm in men with SCL

Studies on men (and women: see below) with SCL show that they can experience orgasm even despite complete lesions to the spinal cord (Sipski et al., 2006; Dahlberg et al., 2007; Tas et al., 2007; Alexander and Rosen, 2008; Cardoso et al., 2009). Sipski et al. (2006) showed that 64% of men with SCL and Dahlberg et al. (2007) showed that 65% of men with SCL report orgasm. Orgasm is most often associated with ejaculation, although sometimes to a weaker extent than before the injury (Dahlberg et al., 2007; Cardoso et al., 2009). It can also be perceived in the absence of ejaculation, suggesting that "dry orgasm" or orgasm during retrograde ejaculation can also occur in men with SCL (Sipski et al., 2006). Courtois et al. (2008a, b) further showed that ejaculation in men with SCL is not only accompanied by significant increases in systolic blood pressure (SBP) (and tachycardia), but with significant sensations, including cardiovascular (e.g., tachycardia), autonomic (flushing, shivering) and muscular sensations (Courtois et al., 2008a, b). The responses resemble those recorded during orgasm in able-bodied individuals (Masters and Johnson, 1966; Littler et al., 1974; Nemec et al., 1976; Bohlen et al., 1980, 1982, 1984; Carmichael et al., 1994; Kruger et al., 1998) and resemble the symptoms of autonomic hyperreflexia (AHR) in individuals with SCL (especially those with lesions above T6) (Campagnolo and Merli, 2002; Krassioukov, 2004; Alexander et al., 2009; Krassioukov et al., 2009; Prévinaire et al., 2010, 2012; Bauman et al., 2012; Weaver et al., 2012). The findings led Courtois et al. (2011b) to suggest that the normal phenomenon of orgasm corresponds to a non-pathologic analog of AHR. In able-bodied people, AHR quickly returns to baseline due to supraspinal inhibition, leaving the individual with a pleasurable experience of climax. In individuals with SCL, AHR remains because of the lesion and can vary along a continuum ranging from mild (SBP increases <30 mmHg) to moderate (SBP increases <60 mmHg) to severe symptoms (SBP increases >60 mmHg). While mild to moderate AHR lies within the normal range of hypertension in able-bodied men and women (Masters and Johnson, 1966; Littler et al., 1974; Nemec et al., 1976; Bohlen et al., 1984; Pollock and Schmidt, 1995; Exton et al., 1999) and is often associated with a pleasurable experience in individuals with SCL, severe (or sustained) AHR is considered a clinical concern (Teasell et al., 2000; McBride et al., 2003; Thumbikat and Tophill, 2003; Elliot and Krassioukov, 2005; Sheel et al., 2005; Ekland et al., 2008) and may require treatment (Courtois et al., 2012).

Management of sexual dysfunction in men with SCL

Sexual potential following SCL tends to be inversely proportional to the lesion level: higher lesions are associated with better erectile and ejaculatory potential than lower lesions (because of remaining reflexes), and lower lesions present more frequent and more severe sexual dysfunction. While the lesion level is generally associated with sexual potential (Everaert et al., 2010), surprisingly, sexual assessment is seldom reported following SCL, and treatment options are generally offered on a trial-and-error basis.

Assessment of sexual potential

Assessment of sexual potential in men with SCL should start with an evaluation of perineal reflexes, including the bulbocavernosus and anal reflex, mediated by the sacral segments, also mediating reflex erection, and the cremasteric reflex, mediated by the TL segments, also mediating emission and psychogenic erection. The bulbocavernosus reflex is initiated by pressure applied on the glans penis triggering a reflex contraction of the bulbospongiosus muscle located underneath the scrotum or recorded during rectal touch. The reflex can be visually observed, manually palpated, or recorded from electromyography. Clinical assessment is usually based on a three-point scale (absent $=0$, doubtful $=1$, present $=2$). The anal reflex is initiated by pinprick stimulation of the anal margin (left and right) triggering a reflex contraction of the anal sphincter, which can also be scored on a three-point scale. The cremasteric reflex is initiated by gentle stroking of the inner thigh (left and right) triggering elevation of the ipsilateral testicle. The

neurologic examination can also include anal testing assessing the presence of voluntary contraction of the anal sphincter during rectal touch.

While these reflexes assess the integrity of the sacral and TL segments innervating the genitals, they can guide exploration of remaining sexual function in men with SCL using reflexogenic or psychogenic stimulation. Men with positive sacral reflexes should thereby be encouraged to use direct genital stimulation (e.g., masturbation, intercourse, oral sex, and the like) to achieve erection. Upon positive cremasteric reflex, they should be encouraged to attempt ejaculation, or to explore possible retrograde ejaculation, or attempt vibrostimulation if natural ejaculation is absent (Courtois et al., 2009b, 2013b; Everaert et al., 2010). Men with negative sacral reflexes but positive cremasteric reflex should be encouraged to use psychogenic stimulation (e.g., visual, auditory, olfactory, or verbal stimulation, fantasies or memories of positive sexual experiences) to achieve erection and ejaculation (Courtois et al., 2009b, 2013b; Everaert et al., 2010).

In all cases, sexual exploration should be emphasized and attempts accompanied by counseling. If there are negative results, treatment options can be offered.

Treatment options for men with SCL

Treatment options for erectile dysfunction (ED) range from PDE5 inhibitors to intracavernous injections (ICI), vacuum devices, penile rings, and penile prostheses, which cover most (if not all) needs (Rahimi-Movaghar and Vaccaro, 2012). Ideally, these treatments are adjusted to the patient's sexual potential with accompanying counseling.

As for other conditions, the first lines of treatment for ED in men with SCL are PDE5 inhibitors. In this domain, men with SCL are no exception to the rule, but assessing their initial sexual potential and adjusting treatment accordingly may be advisable to prevent frustration. As mentioned before, men with higher lesions usually maintain reflex erections, which can be of good quality, but which can also be described as unstable or unpredictable clinically (Courtois et al., 1995, 2009b, 2013b). Given the good quality of the initial erection, PDE5 inhibitors usually give good results clinically, especially for men with higher lesions. Men with lower lesions however often have erections of poor quality, so that PDE5 inhibitors often remain insufficient to compensate for the neurologically based ED. ICI or a combination of treatments (see below) may be offered as interesting and more successful choices (McMahon et al., 1999; Gutierrez et al., 2005; Nandipati et al., 2006; Yang et al., 2011; Rahimi-Movaghar and Vaccaro, 2012).

PDE5 inhibitors

Among PDE5 inhibitors, sildenafil (Viagra) comes in three formats: 25 mg, 50 mg, and 100 mg. Its delay of action is 30–60 minutes and its half-life is 3–5 hours (Boolell et al., 1996; Goldstein and Berman, 1998). The efficacy of sildenafil has been repeatedly demonstrated in men with SCL (Derry et al., 1998; Giuliano et al., 1999; Maytom et al., 1999; Hultling et al., 2000; Schmid et al., 2000; Gans et al., 2001; Sanchez Ramos et al., 2001; Derry et al., 2002; Del Popolo et al., 2004; Barbara-Bataller and Mendez Suarez, 2006; Soler et al., 2007a; Ergin et al., 2008). Clinically, it is not always patients' first choice because of complaints about its restricted duration, which limits the spontaneity of sexual activities (Courtois et al., 2009b, 2013b).

Tadalafil comes in two formats: 10 mg and 20 mg, and in daily doses of 2.5 mg or 5 mg. Its delay of action is 45–60 minutes and it has a half-life of 17–24 hours or longer (Eardley and Cartledge, 2002; Porst, 2002). The efficacy of tadalafil has been demonstrated in men with SCL (Giuliano et al., 2007; Lombardi et al., 2009). Clinically, its perceived advantage is its longer duration of action, which allows spontaneous sexual activities. Some patients, however, complain of erections in non-sexual contexts (e.g., urinary drainage), which they find disturbing (Courtois et al., 2009b, 2013b). Daily use of tadalafil may be considered, but for men with lower spinal lesions (e.g., conus terminalis or cauda equina lesions) presenting severe ED, the daily dosage may not reach the maximal dose of other formats (e.g., maximal daily dosages do not add up to the available 20 mg format) and the regular format (e.g., 20 mg) may remain insufficient for severe ED. Combination treatments or alternatives (e.g., ICI) may then be considered (Courtois et al., 2009b, 2013b).

Vardenafil (Levitra, Staxyn) comes in three formats: 5 mg, 10 mg and 20 mg. It responds within 15–60 minutes, with a half-life of 4–5 hours (Porst et al., 2001; Hellstrom et al., 2002; Pryor, 2002). Because of its similar characteristics to sildenafil, it is less often used, but its effectiveness is similar to the other compounds and has been demonstrated in men with SCL (Giuliano et al., 2006, 2008; Kimoto et al., 2006).

All PDE5 inhibitors have few and similar side-effects. These include dyspepsia and headache, and to a lesser extent, myalgia, flushing, low-back pain, and rhinitis. The choice of treatment is usually left to the patient after explaining the mode of action, advantages, and disadvantages of each product. Few contraindications are known for PDE5 inhibitors, except the concomitant use of nitrates. In this context, special attention must be paid to nitrol paste, clinically used in rehabilitation centers for episodes of AHR.

Given the natural remaining function of men with SCL, the effectiveness of PDE5 inhibitors or other ED treatment is optimal when residual reflexogenic or psychogenic stimulation is used (Courtois et al., 1995, 2009b, 2013b). When PDE5 are ineffective, especially in men with lower lesions and/or severe ED, ICI, the second line of treatment for ED in men with SCL, are usually offered.

Intracavernous injections

ICI are powerful drugs directly injected (and metabolized) into the penile cavities to produce erection. Previously used as a common treatment for ED in men with SCL (before PDE5 inhibitors) (Sidi et al., 1987; Yarkony et al., 1995; Zaslau et al., 1999), the powerful effect of ICI is also accompanied with increased risks of priapism (Halsted et al., 1986), leading some states and countries to discontinue their use.

The very first product attempted in ICI is phentolamine (Szasz et al., 1987), followed by papaverine (Virag, 1982; Brindley, 1983, 1986; Virag et al., 1991), and prostaglandins (Hirsch et al., 1994; Tang et al., 1995), all of which trigger erection without the need for sexual stimulation (Bereta et al., 1986; Earle et al., 1992). ICI became popular treatments of ED in men with SCL following self-injection programs (Zorgniotti and Lefleur, 1985; Bodner et al., 1987, 1992; Kapoor et al., 1993). When unsuccessful, bimixtures (papaverine phentolamine) or trimixtures (Chao and Clowers, 1994; Valdevenito and Melman, 1994), combining papaverine (vasodilation effect), prostaglandins (endogenous molecule), and possibly phentolamine (smooth-muscle relaxant) are used to maximize the effect of each drug while minimizing their side-effects. Self-injections start with minimal dosages (often unsuccessful), followed by small increments (0.1 mL steps) until a satisfying dose is found.

Although less used today (as PDE5 inhibitors are used), ICI remain a treatment for severe ED, especially for men with lower lesions (conus terminalis or cauda equina). The risk of priapism is explained and defined as a sustained erection (still rigid) of 3 hours or more (Dietzen and Lloyd, 1992), where increased risks of anoxia and necrosis develop (Hashmat et al., 1990). Early procedures consist of applying an ice pack (or attempting ejaculation for those who can) to facilitate vasoconstriction. If unsuccessful, patients are advised to go to the emergency room, where blood is aspirated to relieve pressure on the penile cavities and facilitate blood drainage. If still unsuccessful (despite two or three attempts), injection of an adrenergic drug such as ephedrine may be considered to avoid further risks of ED.

Aside from priapism, explained to patients, other minor side-effects include bruising at the site of the injection and sometimes fibrosis (Hu et al., 1987; Larsen et al., 1987; Corriere et al., 1988; Fuchs and Brawer, 1989), which can lead to scar tissue formation resembling (but not being) Peyronie's disease. Fibrosis usually disappears upon temporary cessation of treatment. Patients are advised to alternate the side of injection to reduce these risks.

Few formal contraindications are found for ICI. Attention however should be paid to the use of anticoagulants in men with SCL, which may increase the risk of bruising and hemorrhage (limited by pressure on the injection site), although no formal contraindication exists.

Other treatment options include intraurethral medications, vacuum device, and penile rings, all of which have demonstrated effectiveness but are seldom satisfying in sexual rehabilitation. In more severe cases of ED, penile prostheses can offer successful alternatives.

Intraurethral medication

Intraurethral medication was expected to be well accepted among men with SCL (and ED) as they were already using a catheter for urinary drainage. The procedure involves inserting a tablet of prostaglandins into the fossa navicularis and rubbing the glans penis until the product is dissolved and absorbed through the urethral walls. Although giving significant results (Bodner et al., 1999; Shokeir et al., 1999; Guay et al., 2000), the product was disappointing (Fulgham et al., 1998; Mulhall et al., 2001). Perhaps catheterization and possible scar tissue formation explain the poor results. A new product with a prostaglandin gel (Vitaros) has been announced, but has not yet demonstrated its clinical superiority in the SCL population.

Vacuum device and penile rings

The vacuum device (e.g., Erect Aid) (Lloyd et al., 1989; El-Bahrawy et al., 1995; Denil et al., 1996) and penile rings are aids that can be found in regular sex shops. They are usually proposed in severe cases of ED or in men who have retracted penis (often observed following injury). The procedure involves inserting the penis into a cylinder, applying negative pressure with the pump (manually or battery-assisted), aspirating the blood into the penile cavities, and sliding the penile ring (previously inserted around the cylinder) at the base of the penis to maintain erection.

While the vacuum device appears useful to distend the penile tissue and maintain malleability of the penis (particularly after urethral or penile surgery), it is not commonly used or well accepted by men with SCL

(Biering-Sørensen et al., 2012). The ring should not be left in place more than 20–30 minutes. There is no formal indication, although the use of anticoagulants may warrant caution (Rivas and Chancellor, 1994).

Penile rings associated with the vacuum device are available independently, in various formats and thickness. The advantage of the constrictive ring associated with the vacuum device is its larger thickness and associated "ears" that help when removing the band (e.g., for a tetraplegic man). The rings can be clinically useful for men with SCL who can achieve, but not sustain, erection (i.e., unstable erections are common in men with higher SCL), or those who want to optimize rehabilitation procedures such as the bulbocavernosus reflex or tilting (see later), which have been found to improve sexual function in men with SCL (Courtois et al., 2013b).

Penile prostheses

When all other treatments fail, penile prostheses may be proposed for severe ED (Golji, 1979; Green and Sloan, 1986; Iwatsubo et al., 1986; Zermann et al., 2006; Trost et al., 2013). Penile prostheses are considered as a last alternative because they destroy the internal penile tissues. Penile prostheses come in various formats, semirigid and inflatable, in two- or three-piece equipment (Light and Scott, 1981; Rossier and Fam, 1984; Kim et al., 2008; Trost et al., 2013). Semirigid prostheses are not recommended for men with SCL because of the lack of sensation (hence unperceived infections), the sitting position (hence friction), and the occasional spasms (hence traumas) that can cause irritation and infections, and, in severe cases, perforation (Collins and Hackler, 1988; Kabalin and Kessler, 1988; Zermann et al., 2006).

Inflatable prostheses are preferred and provide a natural appearance combined with better protection against internal friction. In both two-piece and three-piece equipment, the cylinders are inserted in the penile cavities and the pump in the scrotum, while the reservoir in the three-piece equipment is inserted in the abdominal cavity. These inflatable penile prostheses give successful results, but are irreversible procedures. They may also be difficult to manage for tetraplegic men lacking manual dexterity.

Ejaculation dysfunction

Treatment options for ejaculation dysfunction in men with SCL are covered in another chapter 25. While treatment may be considered for fertility (Brackett et al., 2010b), many men with SCL also consult to achieve sexual pleasure and orgasm. Treatment available includes vibrostimulation, which can come from commercial massagers or the Ferticare device (specifically designed for men with SCL) (Brackett et al., 1998, 2010a; Fode et al., 2012). They can be used alone or in sandwich to maximize their effect (Brackett et al., 2010a). Commercial vibrators are considered for their lower cost, but may be less effective than the Ferticare device, which has been shown to significantly improve ejaculation in men with SCL compared to commercial vibrators (Brackett, 1999). Among commercial devices, massagers appear to be clinically more successful than regular sex toy vibrators, which are of lower amplitude.

Other treatments available for anejaculation involve oral midodrine combined with vibrostimulation (Staerman et al., 2001; Soler et al., 2007b, 2008; Courtois et al., 2008a, b, 2009a), which can be used at home for sexual pleasure, or fertility (e.g., home insemination program with intravaginal insertion following Ferticare use). Electroejaculation (Brindley, 1981b; Seager and Halstead, 1993; Ohl et al., 2001) and other assistive procedures in contrast are only used in fertility clinics (Sarkar, 2007; Fode et al., 2012).

Retrograde ejaculation is another dysfunction commonly observed in men with SCL and should not be overlooked during rehabilitation (Fode et al., 2012). Ejaculation tests provided in rehabilitation may be ideal to assess both ejaculation potential and the risk of (severe) autonomic dysreflexia (AD), which may then involve preventive medication (Courtois et al., 2012) and the purchase of a home pressure cuff. Urinary samples after negative ejaculation tests are encouraged to rule out retrograde ejaculation (as opposed to anejaculation), which may not prevent climactic sensations in men with SCL (Sipski et al., 2006).

Premature ejaculation is a third problem that may be observed in men with lower lesions (conus terminalis, cauda equina). The complaint is such that a mere sexual thought can trigger ejaculation or ejaculation can occur spontaneously (e.g., "wet pants" upon spontaneous ejaculation) (Meirowsky and Scheibert, 1950; Bors and Comarr, 1960; Comarr, 1970; Larsen and Hejgaard, 1984; Kuhr et al., 1995; Courtois et al., 2010). This type of ejaculation is often dribbling (Comarr, 1970; Courtois et al., 2010) and is perceived as lacking climactic sensations (Kuhr et al., 1995; Courtois et al., 2010) (i.e., perceived as seminal incontinence). Treatments include antidepressive drugs, especially selective serotonin reuptake inhibitors (known for their side-effects on ejaculation) (Kara et al., 1996; Montejo-González et al., 1997; Waldinger et al., 1997; Haensel et al., 1998; McMahon, 1998). Dapoxetine, a short-acting selective serotonin reuptake inhibitor that has been newly developed (Pryor et al., 2006; Buvat et al., 2009), could be used, but data on men with SCL are not available. Given the premature ejaculation and its impact on erectile function (refractory period), ED treatments with ICI or combining PDE5 inhibitors may be considered.

WOMEN WITH SCL

Women's sexual potential and satisfaction are related to a wider range of variables than genital function alone (Basson, 2002; Basson et al., 2004). Variables such as the quality of the relationship, emotional closeness with the partner (Mah and Binik, 2002, 2005; King et al., 2011), sexual desire (Kaplan, 1974), sexual self-esteem, and body image are among the many factors that contribute to sexual satisfaction in women (Cramp et al., 2013). The loss of sensation, difficulty sustaining sexual positions, spasticity, pain, and concerns with urinary (and other) incontinence add to the burden of SCL and limit the types and frequency of sexual activities that women are willing to engage in (Forsythe and Horsewell, 2006; Kreuter et al., 2011; Cramp et al., 2013). Despite these limitations, women with SCL continue to be sexually active and perceive sexuality as a top priority for quality of life (Harrison et al., 1995; Lysberg and Severinsson, 2003; Ferreiro-Velasco et al., 2005; Singh and Sharma, 2005; Anderson et al., 2007c; Kreuter et al., 2008, 2011; Lombardi et al., 2010; Biering-Sørensen et al., 2012; Cramp et al., 2013).

Genital responses are important aspects of sexual function and, as for men, arousal and orgasm in women with SCL are possible even despite complete spinal lesions. Recent findings from functional imagery in able-bodied women further reveal that the clitoris is a more complex structure than the sole glans, which supports the notion that clitoral versus vaginal versus cervical orgasm are possible, and suggests that various sources of stimulation and stimulation sites may trigger sexual responses in women with SCL. Sexual rehabilitation can therefore gain knowledge from the neurophysiology of the female sexual response and combine remaining sexual function with psychosocial and other rehabilitation variables to provide better sexual adjustment consistent with a holistic approach (Kreuter et al., 2011).

Normal sexual function and remaining sexual potential in women with SCL

Normal sexual function in women is described in Chapter 2. Briefly, earlier studies by Masters and Johnson (1966) have subdivided the female sexual response into four phases: arousal, plateau (characterized by an orgasmic platform), orgasm, and resolution. Kaplan (1974) later reviewed Masters and Johnson's (1966) model and added an initial phase of desire, necessarily involved in normal sexual functioning.

The arousal phase of women's sexual response is characterized by genital changes, including erection of the clitoris, vulvar congestion, and vaginal lubrication. Erection of the clitoris results from vasodilation of the clitoral and vaginal arteries, which distends the vaginal epithelium and triggers a pressure gradient along with increased permeability, responsible for vaginal lubrication (Giuliano et al., 2002; Cuzin, 2012). Congestion of the vaginal epithelium further smoothens the vaginal wall, which loses its irregularities and distends the vaginal canal. Combined with contraction of the uterine ligaments at full arousal (i.e., plateau phase), pulling the uterus upward and clearing the vaginal cul-de-sac, the resulting elongation of the vagina can allow deeper and painless thrusts during intercourse. Secretions of Bartholin's glands complete the phase of sexual arousal and produce mucus to line the vaginal canal and vulvar entry, preventing irritation or lesions during intercourse.

The plateau phase and its orgasmic platform are primarily characterized by maximal congestion of the external third of the vagina (Masters and Johnson, 1966). This outer congestion, initially described by Masters and Johnson and characterizing the orgasmic platform, appears to correspond to the recent findings on the G spot (Grafenberg, 1950), identified on the anterolateral aspect of the vagina (Gravina et al., 2008; Battaglia et al., 2010; Caruso et al., 2011; Buisson and Jannini, 2013). These recent findings indicate that the clitoris is composed of a glans, prolonged by two vestibular bulbs surrounding the urethral opening and vagina, and two crura running more laterally (Buisson et al., 2008; O'Connell et al., 2008; Foldès and Buisson, 2009; Caruso et al., 2011). The urethral opening is surrounded by erectile tissue forming a urethrovaginal space (Gravina et al., 2008; Battaglia et al., 2010; Caruso et al., 2011), the thickness of which varies between women and positively correlates with vaginal orgasm (Gravina et al., 2008).

These experimental findings suggest that a clitoro-urethro-vaginal complex is located on the anterolateral aspect of the external third of the vagina, and supports the existence of the G spot as an anatomophysiologic location (rather than a neurologic unit) (Buisson et al., 2008; Foldès and Buisson, 2009; Jannini et al., 2010; Buisson and Jannini, 2013). The findings further suggest that clitoral and vaginal stimulation may be relatively independent sources of stimulation to trigger orgasm: external stimulation of the clitoral glans triggers a different pattern of results from internal vaginal stimulation during functional imagery (Buisson and Jannini, 2013). Adding to these reports is cervical stimulation, which can trigger orgasm in women with SCL and able-bodied women (Whipple and Komisaruk, 2002; Komisaruk et al., 2004), all of which indicating that clitoral, vaginal, and cervix stimulation may trigger sexual responses and orgasm, which may benefit women with SCL with various lesion levels.

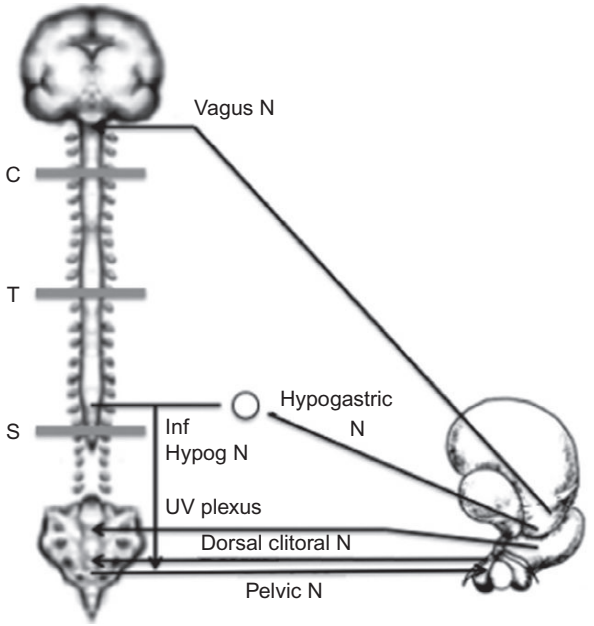

Fig. 13.2. Innervation of the female genitals and impact of some spinal cord lesions on sexual function. Lesions to cervical (C) or thoracic (T) segments (above T10) of the spinal cord maintain erection of the clitoris, vaginal congestion, and vaginal lubrication to direct genital stimulation, but not psychogenic responses; incomplete lesions to these C or T levels can maintain vaginal responses as a function of preserved pinprick sensations in the T11–L2 dermatomes. Lesions to sacral (S) segments of the spinal cord maintain genital responses to psychogenic stimulation but not to genital stimulation. Inf Hypog N, inferior hypogastric nerve; UV plexus, uterovaginal plexus.

The differential responses from clitoral, vaginal, and cervix stimulation are further supported by the innervation of the female genitals (Fig. 13.2), and by recent functional magnetic resonance imagery (fMRI). Recent fMRI during self-stimulation of the clitoris, vagina, and cervix has shown that each site activates distinct (although adjacent) areas of the sensory cortex (Komisaruk et al., 2011). Neurologic pathways innervating the female genitals have also been described as involving at least three (Rees et al., 2007) and perhaps four (Whipple and Komisaruk, 2002; Komisaruk et al., 2004) sets of afferents (with some overlapping distribution): (1) the dorsal clitoral (pudendal) nerve, innervating the clitoris and external labia; (2) the pelvic nerve and inferior hypogastric nerve, feeding into the uterovaginal plexus, innervating the vagina and cervix; (3) the hypogastric nerves, innervating the cervix and uterus (Nadelhaft and McKenna, 1987; McKenna, 2000; Giuliano et al., 2002; Hubscher, 2006; Rees et al., 2007); and (4) the vagus nerve, possibly innervating the cervix and upper vagina (Whipple and Komisaruk, 2002; Komisaruk et al., 2004). These afferent fibers and their corresponding efferent pathways convey sexual responses (erection, congestion, lubrication) through reflexes mediated by the sacral segments S2–4 of the spinal cord. They can also mediate psychogenic responses through TL pathways running through the paravertebral inferior hypogastric nerve and feeding into the uterovaginal plexus or the hypogastric nerves innervating the cervix and uterus.

Taken together, these findings suggest that clitoral, vaginal, or cervical (uterine) responses could be differentially maintained in women with SCL (although studies have not formally compared the three stimulation sites). Studies on women with SCL generally support these hypotheses and indicate that sexual responses are possible following clitoral, vaginal, and cervical stimulation (Sipski et al., 1995a, 2001; Whipple et al., 1996; Whipple and Komisaruk, 2002; Komisaruk et al., 2004).

Sexual arousal in women with SCL

Remaining sexual function in women following SCL suggests differential maintenance of reflexogenic and psychogenic lubrication depending on the lesion level. Bérard (1989) first interviewed a group of women with SCL and found that higher lesions were generally associated with reflexogenic lubrication and lower lesions with psychogenic lubrication (Bérard, 1989). Sipski et al. (1995b), using more sophisticated (i.e., more elaborate) designs, demonstrated that women with complete lesions above T6 did not respond to audiovisual stimulation with significant increases in vaginal pulse amplitude (VPA) unless manual stimulation was added to stimulation, demonstrating reflex mediation of sexual responses in women with higher lesions. Women with incomplete lesions in contrast responded to audiovisual stimulation, but as a function of preserved pinprick sensations in the T11–L2 dermatomes (Sipski et al., 1997). Women with little or no pinprick sensation in the T11–L2 dermatomes showed no change in VPA during audiovisual stimulation, while those with moderate sensations in the T11–L2 dermatomes showed significant increases in VPA, and those with high levels of sensations in the T11–L2 dermatomes had the most significant results (Sipski et al., 1997). These findings together support TL mediation of psychogenic responses in women with incomplete SCL.

Orgasm in women with SCL

Studies on orgasm also indicate that women with SCL can reach climax with clitoral or vaginal or cervical stimulation despite even complete lesions to the spinal cord (Sipski et al., 1995a, 2001; Whipple and Komisaruk, 2002; Komisaruk et al., 2004; Alexander and Rosen,

2008). Sipski et al. (1995a) indicated that 52% of women with SCL achieved orgasm with clitoral stimulation (manual or personal vibrator), and the resulting orgasm was accompanied with significant increases in blood pressure, thereby supporting subjective reports. The authors (Sipski et al., 2001) then compared women with upper motor neuron (UMN) and LMN lesions and found that 59% of the first group achieved orgasm compared with 17% in the second group. Arousal levels again measured with VPA significantly increased during audiovisual stimulation for women with incomplete lesions, again as a function of moderate to high sensations in the T11–L2 dermatomes. Sipski et al. (2005) then compared the effect of manual and vibrostimulation (Ferticare) of the clitoris in women with complete and incomplete UMN and LMN lesions, and found that VPA in all cases significantly increased compared to baseline. VPA changes however did not significantly differ between vibrostimulation and manual stimulation, or differ between UMN and LMN lesions (whether complete or incomplete). These findings altogether suggest that women with SCL are capable of orgasm, through reflex pathways involving clitoral stimulation (manual or vibrostimulation), and that psychogenic arousal can be mediated by TL innervation in particular in women with incomplete SCL.

Whipple and Komisaruk (2002) and Komisaruk et al. (2004) further showed that women with SCL could also achieve orgasm with vaginal or cervical stimulation, again with significant increases in cardiovascular measures supporting the subjective reports. After showing through magnetic resonance imaging (MRI) that their participant's lesions were complete, the authors demonstrated with fMRI that the subjects reporting orgasm also showed activity in the brainstem solitary nucleus despite their lesion.

Altogether, these findings confirm that sexual arousal and orgasm are possible for women with SCL, and that they can be achieved with genital reflex stimulation, including clitoral, vaginal, or cervical stimulation, or psychogenic stimulation mediated by the TL pathway. When the resulting responses are not satisfying, treatments have been attempted to improve sexual function.

Management of sexual dysfunction in women with SCL

As for men, sexual assessment in women with SCL is seldom reported clinically. Since research suggests that the lesion level may differentially affect vaginal lubrication, assessment should equally start with an evaluation of perineal reflexes, followed by exploration of remaining sexual potential to reflexogenic or psychogenic stimulation.

Assessment of sexual potential

As for men, assessment of sexual potential in women with SCL should start with an evaluation of perineal reflexes, including the bulbocavernosus and anal reflex, and an evaluation of prinprick sensation in the TL dermatomes (Sipski et al., 1995a, 2001). Neurologic examination should also include anal testing and the sensations perceived during rectal touch. More recently, we introduced a therapeutic approach to further evaluate the perceptual threshold of women with SCL to light touch (Semmes-Weinstein monofilaments), pressure (vulvogesiometers; Pukall et al., 2007), vibration (Vibralgic) and pain (needle), as applied on the clitoris, internal margin of labia minora, vaginal margin, and anal margin (Courtois et al., 2011b). The results show that these evaluations benefit women with SCL who can better identify their genital sensations, and recreate a mental image of their vulva post-SCL. This assessment also helps to reframe the sensations characterizing sexual arousal and orgasm despite the SCL (Courtois et al., 2011b).

Assessment of reflexes and perineal sensitivity can further guide women with SCL to explore their remaining sexual potential to psychogenic or reflexogenic stimulation. Similarly to men, women with positive sacral reflexes may be encouraged to use direct genital stimulation to achieve vaginal lubrication, and women with additional positive TL dermatomes to explore orgasm with manual or vibrostimulation (Courtois et al., 2009b, 2013b). Women with negative sacral reflexes but positive TL dermatome reflex may be encouraged to use psychogenic stimulation (e.g., visual, auditory, olfactory, or verbal stimulation, fantasies or memories of positive sexual experiences) to achieve sexual responsiveness (Courtois et al., 2009b, 2013b).

Treatment options for women with SCL

Treatment options for women in general and for women with SCL in particular are rather limited. Studies on PDE5 inhibitors provided contradictory results and are therefore uncommon treatments for women with SCL. A vacuum device equivalent to the men's vacuum has been designed but not directly tested on women with SCL. Recent developments have been attempted to offer a guided approach, with perineal sensitivity assessment, coaching with vibrostimulation and midodrine, and help identifying the sensations that characterize sexual arousal and orgasm following SCL (Courtois et al., 2011b, 2013d).

PDE5 inhibitors

Studies on PDE5 inhibitors in women have not been conclusive. Although animal findings (Vemulapalli and Kurowski, 2000; Kim et al., 2003; Gragasin et al.,

2004) and data from human cadaveric tissues (both clitoral and vaginal) (D'Amati et al., 2002; Uckert et al., 2005) have shown significant effects of sildenafil, clinical studies remain inconclusive, with some findings showing positive results (Laan et al., 2002; Berman et al., 2003; Caruso et al., 2003), and others negative or controversial effects (Rosen, 2002; Rosen and McKenna, 2002; Munarriz et al., 2003a; Dasgupta et al., 2004; Mayer et al., 2005). The discrepancy between results from women and men may stem from the methodology: women were asked about their overall sexual function and satisfaction, while men can visually inspect erection in response to PDE5 treatment. Women may therefore possibly show improved genital congestion (as demonstrated by animal findings and cadaveric tissues) but the congestion may not change overall psychosexual satisfaction (Basson et al., 2002; Basson and Brotto, 2003; Dasgupta et al., 2004).

Sipski et al. (2000b) nevertheless investigated the effect of sildenafil on VPA in women with SCL submitted to audiovisual stimulation and genital stimulation and found only borderline results, without clear significant effects compared to placebo ($P < 0.07$). Later findings in a larger group of women with SCL (Alexander et al., 2011) from several countries across North America, Europe, and Africa maintained the non-significant difference between the drug and placebo on various questionnaires (but there were no physiologic measures).

Eros clitoral therapy device

Another treatment designed for women is the Eros clitoral therapy device (CTD), a vacuum device designed to improve sexual responsiveness and orgasm in women with sexual disorders (Goldstein and Berman, 1998; Billups et al., 2001; Wilson et al., 2001; Munarriz et al., 2003b). Similar to men's Erect Aid device, the Eros CTD consists of placing a flexible cap on the clitoris and applying negative pressure through a battery-assisted pump, to fill the clitoral sinusoidal spaces. The device has been shown to significantly improve sexual sensations in able-bodied women, to increase vaginal lubrication, enhance orgasm, and maximize overall sexual satisfaction (Wilson et al., 2001). Empirical data on women with SCL however are lacking. Clinical observations suggest that women with SCL use the device to prepare the genitals for optimal congestion, thereby facilitating orgasm, but reach orgasm through other sources of stimulation.

Recent developments

More recently, we developed a therapeutic approach combining perineal sensory assessment, coaching with vibrostimulation and midodrine, and providing cognitive reframing to better identify the sensations that characterize sexual arousal and orgasm following SCL (Courtois et al., 2011b). The rationale was that men with SCL are accompanied during ejaculation tests, are more systematically offered vibrostimulation (in particular with the Ferticare device) and when negative combined with midodrine, and have visual feedback from ejaculation when positive tests occur. Sensory assessment was designed to give feedback on remaining function and explored sensations of light touch, pressure, vibration, and pain on the clitoris, internal margin of labia minora, vaginal margin, and anal margin (Courtois et al., 2011b). Stimulation was demonstrated with the investigator first, using an inclined mirror to properly place the vibrator and observed body responses (e.g., shivers, spasms), followed by self-stimulation as the women were left alone. The use of an inclined mirror was designed as coaching and feedback but was also motivated by Sipski et al.'s findings (2000a, 2004) in women with SCL, showing that visual feedback (positive or negative) influences women's perception of sexual arousal. Each test (whether positive or negative) was completed with questionnaire administration on the body sensations perceived during vibrostimulation (adapted from Courtois et al. (2011b) on SCL men) to give sensory feedback from positive and negative tests (to differentiate sexual arousal from possible climax). The results from 53 women with SCL, among which 36 completed the protocol (five ongoing), were encouraging, showing that 78% reached orgasm (in the laboratory or subsequently at home), and significantly more sensations were perceived at orgasm compared to sexual stimulation (Courtois et al., 2011b). Interestingly, the comparison between cardiovascular measures from these women with SCL at orgasm and our previous data from men with SCL at ejaculation showed very similar results (Courtois et al., 2008a, b).

Sexual counseling

Sexual rehabilitation cannot be restricted to remaining sexual function and treatment, and must be integrated in a holistic approach including other aspects of sexuality and of SCL (Lombardi et al., 2008; Kreuter et al., 2011). As for other physical disabilities or chronic diseases, sexual concerns in individuals with SCL may be classified under three broad categories (Lombardi et al., 2010): (1) concerns with the primary consequences of the spinal lesion (largely covered in other sections of this chapter); (2) concerns with the secondary consequences of the SCL, including the impact of injury on other bodily functions (e.g., spasticity, incontinence) and side-effects of medication; and (3) concerns with the tertiary consequences of the lesion, including social and professional relationships, couple's relationships and psychologic

well-being, affecting sexual self-confidence, self-esteem, and overall feeling of self-worth.

Secondary consequences of SCL

Many secondary consequences of SCL can be dealt with by providing tips and strategies to compensate for other consequences of SCL. Developing heightened body sensations, becoming more sensuous, increasing satisfaction with stimulation of the nipples, earlobes, and inner thighs are successful strategies for men and women with SCL to reach sexual satisfaction (Kreuter et al., 2011; Hess and Hough, 2012). Becoming more open to sexual fantasies (Kreuter et al., 2011; Hess and Hough, 2012), including memories of previous sexual activities (preinjury) (Kreuter et al., 2011), engaging in more frequent activities such as kissing, hugging, and caressing (Kreuter et al., 2011; Hess and Hough, 2012), getting involved in longer foreplay and stronger stimulation in particular on the clitoris are described by women with SCL as means of achieving sexual gratification (Kreuter et al., 2011). Oral genital stimulation, use of sex toys with assistive devices (e.g., straps for vibrators, dildos) or substitution systems (Borisoff et al., 2010) to facilitate stimulation, to increase one's pleasure or that of the partner, and observing the partner's satisfaction are other means to increase sexual adjustment (Hess and Hough, 2012).

Sexual positions can be improved and their repertoire enlarged by using adapted devices (e.g., intimate rider), which facilitate motion, or pillows and large cushions which provide better body support during intercourse (e.g., pillow beneath the hips, large cushion to lean forward) (e.g., YouTube videos by Mitchell Tepper, sex educator). Adapting positions can relieve pressure or prevent fatigue from dominant positions (e.g., side positions). Engaging in sexual activities in the wheelchair (arms removed) can facilitate movement, improve stimulation, and decrease spasticity (Hess and Hough, 2012).

Other tips and strategies can involve training with the bulbocavernosus reflex (100 pressures applied daily on the glans penis, triggering reflex contractions of the bulbospongiosus and ischiocavernosus muscles) (Courtois et al., 2011b), which has been found to improve tumescence and rigidity. Tilting (or standing with support for individuals with incomplete lesions) can facilitate ejaculation and limit the drastic increases in blood pressure during ejaculation (Courtois et al., 2013c). For women, using water-based lubricants (or products adapted for condoms and sex toys) can compensate for poor vaginal lubrication, which may go unnoticed, and help to prevent friction and irritation that may arise from intercourse and degenerate in mycosis (which can also go unnoticed) (Hess and Hough, 2012).

Problems with spasticity, often described as limiting sexual positions, can be dealt with by adding passive stretching and smooth-muscle massages during foreplay (Hess and Hough, 2012). Women should be advised that menstruation (and urinary infection) could increase spasticity. Although sexual stimulation itself can increase spasms, ejaculation and orgasm are known to dramatically decrease spasticity for several hours to a few days (Halstead et al., 1993; Sonksen et al., 2001; Courtois et al., 2004; Laessøe et al., 2004; Alaca et al., 2005; Biering-Sørensen et al., 2005). Spasms and mild signs of AD should not be taken as necessary signs of pathology, as mild to moderate hypertension (>40 to 60 mmHg) along with muscular spasms are normal signs of sexual arousal. While severe or persistent AD must necessarily be controlled and treated, mild to moderate AD may be reinterpreted as cognitive arousal and climax.

Prescriptions of antispastic medication such as oral baclofen or intrathecal baclofen pump help to control daily spasms but can decrease sexual responsiveness (Denys et al., 1998; Hess and Hough, 2012). Revision of dosages should be considered whenever possible. Other medications, such as painkillers, muscular relaxants, antidepressant drugs, and sleeping pills, are all known to have negative side-effects on sexual function. Revising drug prescriptions (use and dosage) regularly should be discussed with the patient to facilitate sexual adjustment (Hess and Hough, 2012).

Comorbidities should not be overlooked as possible causes of sexual dysfunctions, as SCL is not always the unique cause of the dysfunction. Cardiovascular conditions such as diabetes, hyperlipidemia, and metabolic syndrome (Lombardi et al., 2010) are known causes of sexual dysfunction (ED, decreased genital responsiveness in women, delayed orgasm) and develop in sedentary people with SCL. Related pathologies, such as bladder and bowel function, may negatively affect sexual function (e.g., increasing spasticity), and pressure ulcers correlate with poor satisfaction (Biering-Sørensen et al., 2012). Although not directly investigated, recovery from spinal or other surgeries (e.g., skin grafts for skin ulcers), fatigue from physiotherapy and general rehabilitation, and continuous pain are all possible contributors to sexual dysfunction.

The state of spinal shock and its four stages of recovery (Ditunno et al., 2004) does not last only a few hours to a few days, but recovers over the first 3 months, and more subtly over up to 18 months following injury (Ditunno et al., 2004). Its impact on sexual function may reduce erectile capacity (reflex returned but not optimal), ejaculatory potential (multisegmental reflex required), or delay (prevent) orgasm.

Following sexual activities, care should be taken to prevent negative consequences. The skin should be

inspected for redness, irritation, and indurations, all of which can degenerate into skin ulcers. Pre-existing pressure sores should be inspected (by self or partner or other, visually or with a mirror) and specific positions avoided until healed (Hess and Hough, 2012).

Tertiary consequences of SCL

Tertiary consequences of SCL must be addressed during sexual counseling not only during active rehabilitation but also, and perhaps more importantly, after hospital discharge when psychosexual and psychosocial concerns may become more acute. Major depression, anxiety, alcohol and drug abuse (Lombardi et al., 2010) may have been controlled during rehabilitation, but may re-emerge after hospital discharge, especially when new stressors appear. A couple's relationship may change, regular habits may be disrupted, and sex roles shaken (Hess and Hough, 2012). Relying on external aids for sexual function may not have only positive effects and may be associated with psychologic distress, associated with poorer sexual satisfaction (Biering-Sørensen et al., 2012). Men appear particularly vulnerable as they are less satisfied with their sexual life than women for up to 10–45 years postinjury (Biering-Sørensen et al., 2012).

Poor social skills and limited social contact may precipitate isolation and depression. Individuals with SCL should be encouraged to engage in social activities, make themselves available, and live an outgoing life to improve their self-esteem and feel empowered (Hess and Hough, 2012). Maintaining regular physical activities improves psychologic well-being, and participation in social clubs, leisure, web chats, or web dating can increase opportunities for contact and reduce isolation.

Readiness for sexuality

The readiness for sexual activity following SCL is often a subject of debate. Some consider that it is better to wait for the individual to be ready before discussing sexuality matters, while others believe that sexual issues should be addressed during rehabilitation (Hess and Hough, 2012). Several studies have shown that patients complain of poor (or lack of) sexual information during rehabilitation, and data suggest that patients wait for professionals to address the issue of sexuality. Data in the 2000s indicate that up to 61% (Kreuter et al., 2008) and 77% (Ferreiro-Velasco et al., 2005) of women with SCL complain of not having received information on sexuality during their rehabilitation. While many centers offer educational courses to patients, books and websites are also available to provide much information. The guide on sexuality and reproductive health in adults with spinal cord injury (Consortium for Spinal Cord Medicine, 2010), the article on sexual health following spinal cord injury (Abramson et al., 2008), the manual PleasureABLE (Naphtali et al., 2010), websites from spinal cord injury organizations (e.g., www.sci-u.ca; www.luciebruneau.qc.ca/fr/main_nav/programmes/multi-clienteles/pcs/parents-plus/), internet videos on equipment (intimate rider, vacuum), and on positioning (YouTube videos on sexual positions for men and women with spinal cord injury from Mitchell Tepper) are all helpful guides for men and women with SCL.

CONCLUSION

Individuals with SCL continue to have active sexual lives, and consider sexuality as one of their priorities for quality of life. Sexual treatment should be offered to overcome dysfunction but should be integrated with the individual's remaining sexual potential, in accordance with any rehabilitation philosophy. Sexual dysfunctions are not the only aspects of sexuality, and sexual adjustment must be considered in a holistic approach to sexual health (Kreuter et al., 2011), where the primary, secondary, and tertiary consequences of the SCL are discussed and assessed. Readiness for sexuality should not be a prerequisite to give sexual information, and information can be provided through various means, including hospital seminars (for patients), individual sexual counseling (for those interested), clinical guides from spinal cord injury organizations (documented information), and websites and internet videos, all of which provide a functional package for individuals with SCL to successfully adjust to their new sexual life.

ACKNOWLEDGMENTS

The authors wish to thank Thomas Lefebvre for drawing the figures.

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 14

Dysfunction of lower urinary tract in patients with spinal cord injury

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"One who has a dislocation in the vertebral column of the back of his neck and he is unaware of his legs and his arms and his urine dribbles: [this is] a medical condition that cannot be healed." Dating from the 17th century BC, the Edwin Smith papyrus is a unique treatise containing the oldest known descriptions of signs and symptoms of injuries of the spinal column and spinal cord (Breasted, 1930). At this time, the chain of events often associated with spinal cord injury (SCI) was already well known; namely, urinary retention followed by overflow incontinence. Later on, in the 19th century and at the beginning of the 20th century, many efforts were made to manage the bladder of patients with SCI in order to preserve the upper urinary tract.

To treat these disturbances, different methods were tried (intermittent catheterization, suprapubic catheter or tidal drainage) (Curling, 1833; Munro and Hahn, 1935; Bumpus et al., 1947; Pearman and England, 1976). However, most were not able to avoid pyelonephritis and urosepsis. In 1947, Sir Ludwig Guttmann sought to reduce the incidence of infection by resorting to intermittent catheterization using a non-touch technique (Guttmann, 1949), and the overall infection rate dropped markedly. Only 62% of patients discharged left the rehabilitation unit with sterile urine. However, it should not be forgotten that Munro, on the other side of the ocean, resorted to the same concept and obtained the same results (Munro and Hahn, 1935) and Jack Lapides, who is considered to be one of the fathers of clean intermittent self-catheterization (CISC) (Lapides et al., 1972). Over the last 60 years, many techniques have evolved, such as the use of anticholinergic drugs to control detrusor overactivity, the development of neuromodulation, and the introduction of botulinum toxin treatment for detrusor and sphincter overactivity.

INCIDENCE, MORTALITY, AND MORBIDITY

Disturbances of micturition are, in fact, very common after SCI. Reports from the Model Spinal Cord Injury Systems of Care show that approximately 81% of SCI patients have some degree of impaired bladder function 1 year after injury (Breasted, 1930; Stover et al., 1995). During the acute phase, impaired voiding is present in all patients with complete and motor complete lesion (American Spinal Injury Association (ASIA) Impairment Scale (AIS) A and B). Moreover, Patki et al. (2006b) reported that, in a group of mobile patients with incomplete spinal lesion, a voiding dysfunction was present in 100%, 82%, and 41% of patients with motor incomplete lesions AIS C, D, and E, respectively.

The amazing development in neurogenic bladder management has allowed a dramatic change in morbidity and mortality of patients with SCI patients. Until 1969 up to 75% of deaths after SCI were due to renal failure and/or urosepsis (Tribe and Silver, 1969; Whiteneck et al., 1992; Soden et al., 2000), while at present, mortality from the same cause is around 2.3% (Devivo et al., 1989, 1993). In spite of this enormous improvement, it should be pointed out that the standardized mortality ratio due to urinary system diseases is still 22.8 in SCI patients and even more (172.3) due to septicemia, mainly secondary to urinary tract-related infections (Soden

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et al., 2000). According to these data, it seems evident that good knowledge of lower urinary tract dysfunction (LUTD) in SCI is mandatory for clinicians confronted with this disease. It should not be forgotten that neurologic bladder control is an important determinant in quality of life after SCI, and that better control of urinary symptoms, mainly incontinence, can improve it significantly (Ku, 2006).

PATHOPHYSIOLOGY: SPINAL CORD INJURIES

The range of bladder symptoms caused by neurologic lesions is wide and determined by whether the lesion primarily affects the supraspinal control, the pontine–sacral neural circuit, or the sacral nerves, and whether these lesions are predominantly motor or sensory, or both. Deep comprehension of bladder neurophysiology is mandatory to understand LUTD in SCI (see Chapter 5).

Although several classifications of neurogenic LUTD have been proposed in the literature, the most commonly utilized are those developed by Madersbacher (1990b).

According to this classification, four types of neurologic bladder are recognized (Fig. 14.1):

1. detrusor hyperreflexia in combination with a hyperreflexive (spastic) sphincter
2. detrusor hyporeflexia in combination with a hyperreflexive (spastic) sphincter
3. detrusor hyporeflexia (areflexia) in combination with a hyporeflexive (flaccid) sphincter
4. detrusor hyperreflexia in combination with sphincter hypo-normoreflexia.

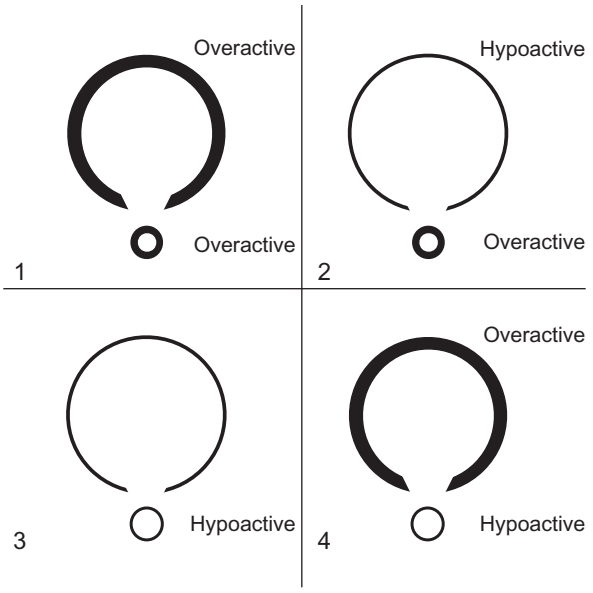

Fig. 14.1. Madersbacher classification system. (Adapted from Madersbacher, 1990b, Stöhrer et al., 2009.)

Type 1 dysfunction is the most frequently seen in supraconal SCI; type 2 can be observed in conal lesions, and type 3 in cauda equina lesions. Type 4 is typically seen in suprapontine lesions.

In the next section, the underlying physiopathology of these subtypes of neurologic LUTD will be assessed in detail.

The bladder in "spinal shock"

After an acute SCI above the sacral micturition center and usually during the first 2 weeks to 3 months after injury, the central synapses between the afferent and efferent arms of the micturition reflex will be rendered inactive. This phase is called "spinal shock." The exact neurophysiologic mechanism of spinal shock remains unclear and its correct definition is also controversial (Ditunno et al., 2004). Most likely, intramedullary facilitation or total depression of interneuronal activity and release of inhibitory neurotransmitters are the main determinants of this phenomenon: the detrusor muscle is paralyzed (an acontractile, areflexic detrusor), and there is no conscious awareness of bladder fullness (Rossier et al., 1979, 1980). In this phase, the bladder neck has been found to be closed or barely open. There is a marked activity of the external urethal sphincter, whereas the bladder is hypotonic and inactive (Rossier, 1974; Rossier and Fam, 1979; Rossier et al., 1979). After a variable period of time (from a few days to 12 weeks), reflex activity under the neurologic lesional level reappears, usually with a caudocranial pattern. It is important to underline that the only reflex activity that is preserved or returns almost immediately after the spinal shock is the anal and the bulbocavernosus reflex. Urinary retention and overflow incontinence occur and urinary tract infections (UTIs) resulting from large residual urine may lead to pyelonephritis and urosepsis.

Upper motor neuron lesions

Suprasacral neurogenic detrusor overactivity

Reflex bladder function generally occurs in humans after suprasacral cord injury within weeks or months after injury. Bladder sensation may be somewhat preserved (in incomplete lesions) but voluntary inhibition of the micturition reflex arc is lost. The initial retention of urine will be followed by neurogenic detrusor overactivity, resulting in a small, hyperreflexic bladder. Dyssynergic contraction of the external sphincter, increased guarding reflex, and impaired detrusor contraction result in inefficient voiding. Overall, reorganization of the central nervous system leads to a high voiding pressure, residual urine in the bladder, and incontinence. These subsequently might induce recurrent UTI, stone formation, hydronephrosis, and finally renal failure

(McGuire and Savastano, 1983). In incomplete suprasacral lesion, synergistic relaxation of the external sphincter may be preserved. Balanced voiding may occur but urgency and urge incontinence usually persist.

Detrusor sphincter dyssynergia

Detrusor sphincter dyssynergia (DSD) frequently correlates with completeness of the SCI (Siroky and Krane, 1982; Schurch et al., 2004) and is responsible for the bladder outlet obstruction. The diagnosis of DSD is made by urodynamic testing, and is characterized by the presence of an elevated electromyographic activity on the urethral/anal sphincter during detrusor contraction, in the absence of Valsalva and Credé maneuvers (De et al., 2005; Spettel et al., 2011), see Table 14.3. DSD was classified in the 1980s by Blaivas et al. into three types: (1) type I: concomitant increase in both detrusor pressure and sphincter electromyogram activity; (2) type II: sporadic contractions of the external urethral sphincter throughout the detrusor contraction; and (3) type III: crescendo–decrescendo pattern of sphincter contraction which results in urethral obstruction throughout the entire detrusor contraction (Blaivas et al., 1981). More recently, this classification has been simplified by Weld et al. (2000) into two types:continuous or intermittent DSD. Patients with continuous sphincter activity during the voiding phase are at higher risk for upper urinary tract lesions, since the obstruction is persistent during the urine outflow (Schurch et al., 1994; Mahfouz and Corcos, 2011). Concomitant uncoordinated bladder and bladder neck contractions result in bladder neck functional obstruction (i.e., bladder neck dyssynergia) and reinforce bladder outlet obstruction (Schurch et al., 1994).

Lower motor neuron lesion

As opposed to lesions above the the sacral micturition center at S1–4, SCI to the sacral micturition center determines a loss of parasympathetic control of the bladder detrusor and a somatic denervation of the external urethral sphincter, with associated loss of some afferent pathways. In a complete lesion, conscious awareness of bladder fullness will be lost and the micturition reflex is absent. Some pain sensation may be preserved due to the hypogastric (sympathetic) nerve remaining intact. Urinary retention and stress incontinence are the milestones of the lower motor neuron bladder (see Table 14.3).

Bladder

Lower motor neuron lesions induce detrusor acontractility, resulting in non-voiding or incomplete voiding. Dramatic changes also appear in the detrusor muscle fibers so that bladder compliance may be altered. This is a very common finding in patients with myelodysplasia (McGuire et al., 1981), whereas in adult patients with SCI bladder compliance usually remains preserved, if patients are correctly managed with intermittent catheterization (Gajewski et al., 1992).

Urethra and external urinary sphincter

The most common finding after lower motor neuron lesion is an incompetence of the urinary sphincter with a significant reduction of the maximal urethral pressure that induces stress or overflow incontinence (Gajewski et al., 1992). However, in some patients, some muscle tone can be present and it is not rare to observe a paradoxic obstruction of the external urethral sphincter that may be due to a secondary fibrotic degeneration of the muscle (Bauer et al., 1977) or to bladder neck dyssynergia (Awad and Downie, 1977).

Bladder neck and proximal urethra

In contrast to healthy subjects, in patients with lower motor neuron bladder, the bladder neck typically remains open even during the filling phase, although the origin of this modification is unclear and has been attributed to either rheologic modifications of detrusor muscle or autonomous contractions (McGuire and Wagner, 1977; Gajewski et al., 1992). This modification increases overflow and stress incontinence.

Correlation between neurologic findings and urodynamic patterns

Correlation between clinical neurologic findings and urodynamic pattern is strong in SCI patients, even if not direct. Weld and Dmochowski (2000a) found that, in a population of 243 patients with SCI, suprasacral lesions were associated with detrusor hyperreflexia and/or DSD in 94.9%, and sacral lesions with detrusor areflexia in 85.7% of cases. These results have been replicated by other authors (Schurch et al., 2004; Agrawal and Joshi, 2013). Even if this roughly corresponds to the classic differentiation in upper and lower motor neuron bladder, it should be kept in mind that the completeness or incompleteness of the lesion and the possible association of multiple injury levels can complicate the picture, so much so that a urodynamic evaluation is mandatory in order to correctly assess and classify LUTD in SCI patients (Stöhrer et al., 2009).

CLINICAL EXAMINATION

In patients with SCI, the neurologic assessment is based on the International Standard for the Neurologic Classification of Spinal Cord Injury, formerly the ASIA standards (American Spinal Injury Association, 2011; Kirshblum et al., 2011).

Milestones of this examination are the determination of the neurologic level for light touch, pinprick sensation, strength of key muscles, and the neurologic rectal examination.

Sensory level is defined as the most caudal normally innervated dermatome for both modalities. The normal dermatome level is located immediately above the first dermatome level with impaired or absent light touch or pinprick sensation.

Motor level is defined as the most caudal normally innervated myotome. It is the most caudal key muscle with a grade of at least 3, when the key muscle above is graded 5. For levels C1–3, T2–12, and S2–5, the motor level is the same as the sensory level.

If at S4-S5 level there is no pinprick or light touch sensation, the sensitivity to deep anal pressure should be assessed and noted.

With these elements, a spinal lesion can be graded as motor and sensory complete, or motor only complete, or sensory and motor incomplete (AIS grade A, B, C, and D). If both motor and sensory functions are normal, the lesion is graded E (Table 14.1).

It is very important also to test sacral reflexes, such as the anal wink reflex (left and right), the bulbocavernous reflex, and, in men, the cremasteric reflex.

NEUROUROLOGIC INVESTIGATIONS

The neurourologic investigations will aim to identify the bladder at risk for the upper urinary tract. After recovery from spinal shock and then annually, a complete assessment is usually proposed, including videourodynamics, ultrasound scan, and renal function measurement. A closer reassessment is mandatory if any neurologic or urologic change happens, as well as during pregnancy. Usually the patient fills in a 3-day bladder diary and symptom questionnaire before the investigative tests (Stöhrer et al., 2002). It is recommended to assess bowel and sexual function as well at that time (Table 14.2).

Flowmetry

Free flowmetry is obtained by urinating into a funnel device that measures the urinary flow rate. Pathologic findings are low flow rate, low volume, and intermittent flow. Along with a postvoid residual urine measurement, this non-invasive screening test provides information on a possible obstruction or pathologic detrusor contraction. Its use in SCI patients is limited to patients with an incomplete lesion who can void.

Videourodynamics

Urodynamics study explores vesicosphincteric function during the bladder filling and voiding phase, using filling cystometry and pressure–flow study, respectively. Urodynamics study is mandatory in understanding bladder dysfunction, as symptoms alone are not reliable in SCI patients (Wyndaele, 1997). The investigation consists

Table 14.1

American Spinal Injury Association (ASIA) Impairment Scale (AIS)

Grade	Status	Description
A	Complete	No sensory or motor function is preserved in the sacral segment S4–5
B	Sensory incomplete	Sensory, but not motor, function is preserved below the neurologic level and includes the sacral segments S4–5 (light touch or pinprick at S4–5 or deep anal pressure) and no motor function is preserved more than three levels below the motor level on either side of the body
C	Motor incomplete	Motor function is preserved below the neurologic level,* and more than half of key muscle functions below the neurologic level of injury (NLI) have a muscle grade <3 (grades 0–2)
D	Motor incomplete	Motor function is preserved below the neurologic level,* and at least half (half or more) of key muscle functions below the NLI have a muscle grade >3
E	Normal	If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments, and the patient had prior deficits, then the AIS grade is E. Someone without an initial spinal cord injury does not receive an AIS grade

Reproduced from American Spinal Injury Association (2011).

*For an individual to receive a grade of C or D, i.e., motor incomplete status, he or she must have either voluntary anal sphincter contraction or sacral sensory sparing with sparing of motor function more than three levels below the motor level for that side of the body. The International Standards at this time allow even non-key muscle function more than three levels below the motor level to be used to determine motor incomplete status (AIS B versus C).

Note: When assessing the extent of motor sparing below the level for distinguishing between AIS B and C, the motor level on each side is used, whereas to differentiate between AIS C and D (based on proportion of key muscle functions with strength grade 3 or greater) the neurologic level of injury is used.

ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury.

Table 14.2

Recommendations for urodynamics in patients with neurogenic bladder

Before urodynamics	Bladder diary 2–3 days
	Uroflowmetry when void
	Postvoid residual
During urodynamics	Simultaneous intravesical and abdominal pressure measurement
	Use of video
	Slow filling rate
	Filling cystometry followed by pressure–flow study
	Provocative tests and uroneurophysiologic tests are elective procedures

Modified from Abrams et al. (2010) and Stöhrer et al. (2009).

Table 14.3

Main urodynamic findings in patients with spinal cord injury

Lesion	Usual clinical finding	Usual urodynamic finding
Supraconal lesion		
Complete	Reflex incontinence Reflex voiding	Detrusor overactivity Detrusor-sphincter dyssynergia
Incomplete	Urge incontinence Reflex voiding	Detrusor overactivity Detrusor-sphincter dyssynergia
Conal lesion		
Complete	No voiding Overflow incontinence Stress incontinence	Detrusor acontractility Incompetent urethral closure
Incomplete	Stress incontinence Voluntary voiding using straining	Detrusor hypocontractility Incompetent urethral closure
Mixed lesion		
Complete Incomplete	All possible symptoms	All possible findings (combining 1+2)

of inserting pressure catheters into the bladder and the rectum to measure respectively the abdominal pressure and therefore the subtracted detrusor pressure, the true bladder pressure (Figs 14.2 and 14.3).

Cystometry

The bladder is filled slowly with contrast media, and fluoroscopic images (video) of the urinary tract are taken.

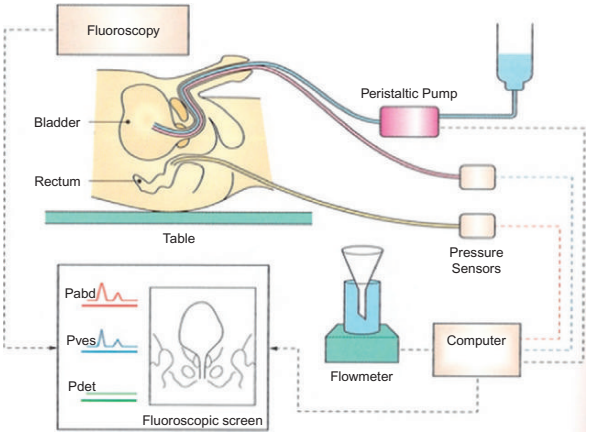

Fig. 14.2. Simplified scheme of a standard urodynamic set-up (cystomanometry). Pabd, abdominal pressure; Pves, bladder pressure; Pdet, detrusor pressure. (Reproduced from Chapple et al., 2009.)

The patient is asked to describe any sense of bladder filling or need to void. Urine leakage is investigated, sometimes with provocative tests such as coughing or tapping on the suprapubic area. This phase allows recording of bladder sensitivity, capacity, and compliance as well as urethral and detrusor activity during filling.

Pressure–flow study

During voiding or attempt to void, fluoroscopic images are taken to investigate the bladder neck and urethra, looking for signs of DSD. The presence and amplitude of detrusor contractions are recorded.

Vesicoureteric reflux, kidney and bladder stones can be identified during the videourodynamics. In patients with autonomic dysreflexia blood pressure measurement during urodynamics is emphasized. A complete report of urodynamic findings is provided by the International Continence Society (Abrams et al., 2003). Possible urodynamic findings in SCI patients are listed in Table 14.2.

Additional urodynamic tests

Some provocative tests aim to discriminate between different neurogenic bladder patterns (Chancellor et al., 1998; Riedl et al., 2000; Al-Hayek and Abrams, 2010). During the iced-water test cooled water is rapidly infused into the bladder and detrusor activity is recorded by cystometry. Uninhibited detrusor contraction will appear in patients with upper motor neuron lesion (Fig. 14.4). During the bethanechol test, detrusor activity is recorded by cystometry after administrating betanechol 5 mg subcutaneously. Detrusor contraction of more

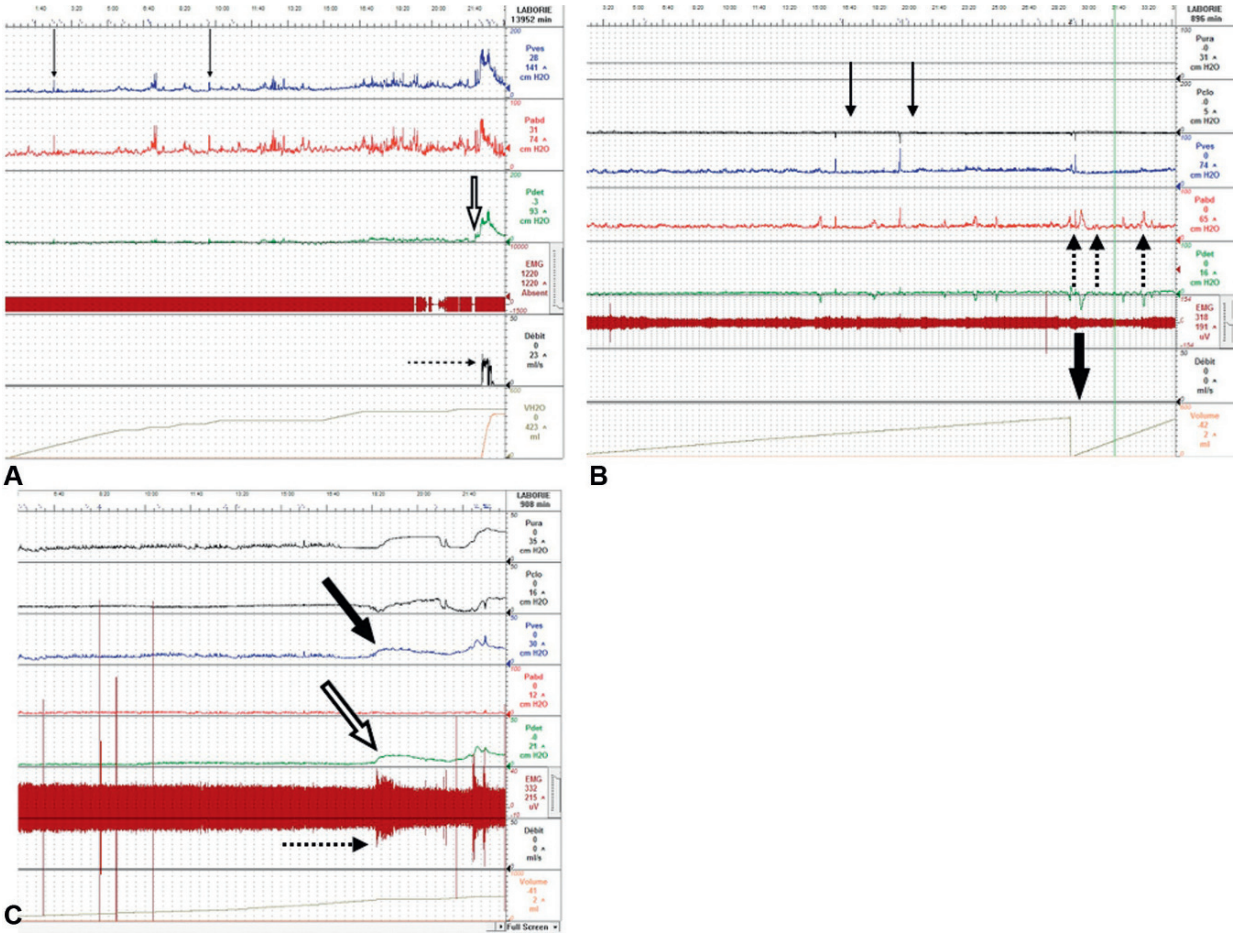

Fig. 14.3. Samples of urodynamic findings.

(**A**) Normal micturition pattern. B3 (severe urge) at 423 ml. Vertical thin lines: volontary cough. Vertical white filled arrow: end of filling phase and start of micturition, with a debimetry showing a normal, «bell-shaped», pattern (horizontal dashed line). Please note that the EMG was not recorded.

(**B**) Areflexic, acontractile lower motor neuron bladder. No filling sensation at the end of filling phase, 520 ml (vertical white filled arrow). From several unsuccessful micturition attempts are realized (vertical dotted arrows, showing the increase in abdominal pressure). Solid black arrow shows that no urinary flow is detected.

(**C**) Detrusor sphincter dyssynergia. While the ladder fills, a neurogenic detrusor overactivity is detected (solid black arrow). At this time the detrusor contracts (white solid arrow) with a marked concomitant activation of the sphincter (horizontal dotted line), consistent with detrusor sphincter dyssynergia. No micturition is shown at uroflowmetry.

than 25 cm H_2O indicates a detrusor denervation hypersensitivity and muscular integrity of an acontractile detrusor.

At the present time, no specific reports exist about the optimal frequency and techniques of follow-up urodynamics in patients with neurogenic LUTD. A possible recommendation is to perform the first examination as soon as possible after the end of the spinal shock phase. It is then advisable to perform another urodynamic study at 6 months and 12 months after the injury (Abrams et al., 2008). An annual examination is preferable in SCI patients with cervical and thoracic injury for the first 5 years, deferring it to one every 2 years after attaining a low-pressure reservoir with continence and complete emptying. In case of lumbar injury, urodynamics are done annually for the first 2 years and once every 2 years thereafter (Patki et al., 2006b), since bladder dysfunction can change over time without clinical signs of deterioration. Maximal attention should be paid to patients with incomplete suppression of detrusor overactivity and to those who empty their bladder by reflex voiding (Nosseir et al., 2007).

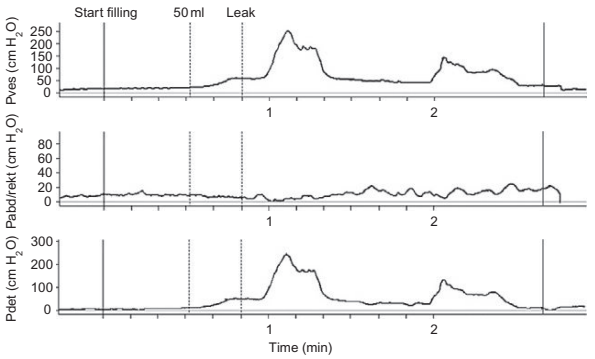

Fig. 14.4. Cystometry chart during the iced-water test showed a strong involuntary contraction of the bladder up to a pressure of 240 cm H_2O after 1 minute. Pves, vesical pressure; Pabd/rekt, abdominal pressure; Pdet, detrusor pressure. (Reproduced from Boy et al., 2005.)

The prophylactic use of antibiotics in patients with SCI having urodynamics is not recommended as routine and potential benefits have to be weighed against risks (Foon et al., 2012).

Specific uroneurophysiologic tests

Different neurophysiologic tests may be of use as part of the neurologic clinical assessment of the SCI patient. In the management of neurogenic bladder there are only two tests commonly used: electromyographic activity of pelvic floor, urethral, anal sphincter, and pudendal nerve conduction studies. The former is used commonly with surface electrode during urodynamics and to help diagnose DSD (Blaivas et al., 1981); the latter assess conus medullaris integrity and have a prognostic value (Curt et al., 1997). Recording the sympathetic skin responses from the perineal skin has proven to be useful for assessing sympathetic dysfunction. This impairment is associated with bladder neck incompetence in patients with autonomic disorders due to lesions of the thoracolumbar spinal cord. Whereas urodynamic testing remains mandatory for evaluating the functional aspect of voiding disorders in spinal cord-injured patients, the sympathetic skin response partially assesses the neurogenic origin of such disorders. (Borodic et al., 1992; Rodic et al., 2000).

Ultrasound scan

Urinary tract ultrasound scan should be performed routinely to identify urinary tract complications such as hydronephrosis and stones (Cameron et al., 2012). Postvoid residual measurement is used to follow bladder emptying in patients who can void. Further imaging, such as computed tomography (CT) scan or isotopic renography, may be necessary for patients with recurrent UTIs or impaired renal function. For the diagnosis of stone, CT scan has a better specificity and sensibility than ultrasound (Tins et al., 2005). Its use is mandatory before any surgical approach of the lower or upper urinary tract in SCI patients (Fig. 14.5).

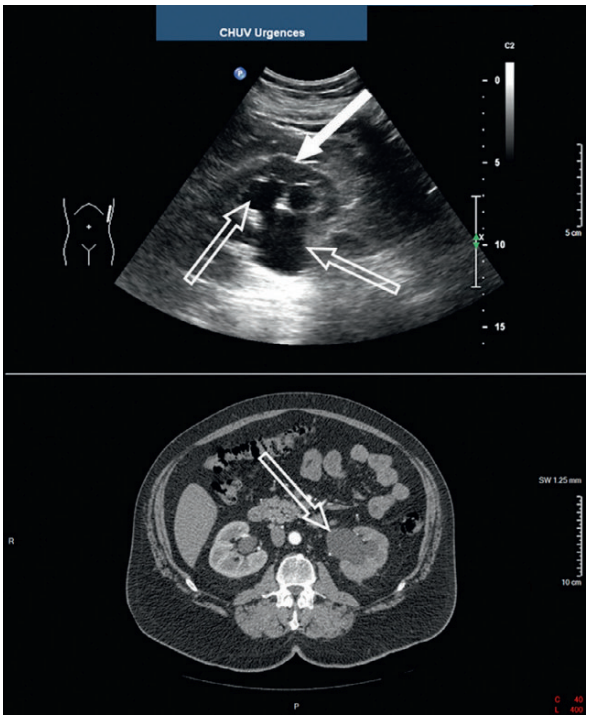

Fig. 14.5. Echographic (top) and contrast-enhanced computed tomography scan (bottom) of a left-kidney hydronephrosis in a patient with spinal cord injury. White solid arrow, left-kidney parenchyma; white open arrow, dilated renal pelvis.

Renal function

Creatinine clearance is preferred to creatinine measurement due to muscular atrophy in SCI patient but creatinine alone is a good test for individual follow-up (MacDiarmid et al., 2000). Other techniques may be proposed, such as isotopic renography and cystatine C measurement (Erlandsen et al., 2012).

COMPLICATIONS

Renal failure

The incidence of renal failure in SCI patients has dramatically decreased since intermittent self-catheterization has been generally adopted in clinical practice (Strauss et al., 2006). While renal failure was affecting 50% of SCI patients in their 50s, this risk is now estimated to

be low, with only a 3.5-time risk of dialysis compared to the general population (Lawrenson et al., 2001). Neurogenic bladders with presence of high-amplitude detrusor overactivity, DSD, low bladder compliance, and straining to void are considered to be at higher risk, and will require thorough follow-up and management. Among bladder management indwelling urethral and suprapubic catheters are associated with a higher incidence of renal failure (Weld and Dmochowski, 2000b) as well as Credé maneuver (Chang et al., 2000). Other risk factors include amyloidosis, lithiasis, and pyelonephritis.

Vesicoureteric reflux

Vesicoureteric reflux is a consequence of high bladder pressure in SCI patients. It is a risk factor for upper UTIs, stones, and renal function alteration.

Urinary infections

Asymptomatic bacteriuria is common in SCI patients, especially in those who use CISC, and should not be checked systematically or treated. If treated, bacteriuria would recur, with the risk of bacterial stains showing increased antimicrobial resistance (Waites et al., 1993). Symptomatic urinary infections should be treated with antibiotic therapy following an antibiogram (Grabe et al., 2013). Even if a single randomized controlled study shows that 14 days of antibiotic therapy offers a higher microbiologic cure rate than a 3-day course in patients with SCI (Dow et al., 2004), at the present time, the optimal duration of treatment is uncertain (Pannek, 2011). Bladder management, including the CISC technique, should be reassessed in case of recurrent infections. The presence of stones should be excluded by CT scan or by cystoscopy.

Stones

Upper and lower urinary tract stones are more frequent in SCI patients (Bartel et al., 2014), especially during the first year after injury, probably due to immobilization hypercalciuria (Chen et al., 2000). In SCI survivors there is a higher incidence of "infection" stones (struvite and carboxyapatite) than in the general population (DeVivo et al., 1984), but this tends to change with the increase of "metabolic" stones, due to better general management and survival of SCI patients (Matlaga et al., 2006). Long-term risk factors are mainly indwelling urethral and suprapubic catheter as well as bladder augmentation and non-continent diversion (Chartier-Kastler et al., 2002; Ord et al., 2003). The lifetime risk for urinary bladder stones in the general population is 12% for men and 6% for women, with an age-standardised annual incidence of 0.36–1.22/1000 person-years (Chen et al., 2000; Curhan, 2007), whereas in SCI survivors the incidence is 8/1000 person-years (Chen et al., 2000). The cumulative proportion of patients with SCI who had renal stones was 38% in a study with 45 years' follow-up (which is the longest at this time) (Hansen et al., 2007). Risk factors are hypercalcemia, UTIs, vesicoureteric reflux, indwelling catheter, urinary diversion, and enterocystoplasty (Ku et al., 2006). Screening of urinary tract stones, especially in patients with a high level of injury who may not feel renal colic, is important to prevent further complications, such as infection and renal failure (Gupta et al., 1994; Vaidyanathan et al., 2000).

Bladder cancer

Bladder cancer, in particular squamous cell carcinoma, is more frequent in SCI patients (Hess et al., 2003). Even if bladder cancer incidence significantly varies among authors (from 0.11% to 10% of the SCI population) (Welk et al., 2013), recent data show that the incidence is probably 0.1–2.4% (or an age-standardized incidence rate of 19–77/100 000 persons-year) (Groah et al., 2002a). This is higher than in the general population, where the incidence is 0.02% and age-standardized incidence is 16/100 000 (Canadian Cancer Society's Steering Committee on Cancer Statistics, 2012). Moreover, patients with SCI develop bladder cancer earlier than the general population. The mean age at time of diagnosis was 48–61 years for people with SCI (Subramonian et al., 2004) compared to 60–70 years in the general poulation (Silverman et al., 1992), and cancers are more agressive, with a specific mortality that is 71-fold higher than that in the general population (Groah et al., 2002a). This may be due to chronic inflammation, especially in those with indwelling catheter (West et al., 1999; Groah et al., 2002b). Follow-up by cystoscopy and biopsy is recommended (Groah et al., 2002b; Stöhrer et al., 2009).

THERAPY

Conservative treatment of neurogenic bladder in SCI patients

In SCI patients the goals of treatment of LUTD are:

- to achieve full continence, which is essential to improve social participation and quality of life
- to regularly and fully empty the bladder to reduce the risk of developing lower UTIs and stones
- to maintain or enhance bladder volume, while maintaining low bladder pressure
- to reduce the risk of damaging the high urinary tract, thus preventing chronic renal failure.

To achieve these goals, there are different treatment strategies that can be utilized alone or in combination:

1. Conservative methods, which include:
   (a) triggered reflex voiding
   (b) Credé and Valsalva maneuvers
   (c) drainage systems (CISC, permanent catetherization, external drainage systems)
   (d) drugs (systemic, intradetrusorial, intravesical)
   (e) physical modalities (electric stimulation)
2. Surgical methods.

Conservative methods

Triggered reflex voiding

This method of voiding consists of triggering uninhibited reflex detrusor muscle contractions to start bladder voiding, usually by suprapubic tapping or by scratching the skin of the inner thigh. In order to achieve this, the sacral micturition reflex must be intact, e.g., an upper motor neuron lesion. However, as DSD is a very common finding in these patients, triggered reflex voiding carries the risk of developing high bladder pressures and vesicorenal reflux. Therefore, it is mandatory to check bladder pressure voiding (which must be below 40 cm H_2O) by urodynamic testing (McGuire and Savastano, 1983). Moreover, in patients with SCI lesions above T6, triggered reflex voiding may carry the risk of autonomic dysreflexia. As reflex bladder contractions are involuntary, nearly all patients who use triggered reflex voiding will require an external collecting device. Even if this method is no longer considered as a first-line treatment in SCI patients, it can be considered in male patients who have neurogenic bladder resistant to anticholinergics, or in tetraplegic male patients unable to perform CISC, mainly after sphincterotomy, as long as the patient can be equipped with a condom catheter. However, these recommendations are based on experts' consensus and not on scientific evidence (Consortium for Spinal Cord Medicine, 2006).

Credé and Valsalva maneuvers

Other methods of voiding are the Credé and Valsalva maneuvers, by which intra-abdominal pressure is raised, thus facilitating urine outflow. It is contraindicated in patients who have a bladder outlet obstruction, and therefore can be considered only for patients with an underactive detrusor muscle associated with an incompetent sphincter (e.g., lower motor neuron lesion or after bladder neck incision).

However, complications are common with these voiding techniques, such as epididymoorchitis, prolapse, and hemorrhoids. Silent upper urinary tract reflux is also not uncommon and careful monitoring is strongly recommended if the patient opts for this emptying method (Giannantoni et al., 1998; Chang et al., 2000). As a consequence, both techniques are currently usually discouraged (Consortium for Spinal Cord Medicine, 2006).

Drainage systems

Even if this may be considered a simple but possibly quite invasive solution, drainage aids are the mainstay of LUTD management in SCI and include:

1. intermittent catheterization
2. permanent catheterization (indwelling or suprapubic drainage)
3. external drainage system (condoms).

Intermittent catheterization. For more than 60 years, intermittent catheterization has been the method of choice to empty the bladder, achieve continence, and maintain a normal bladder volume and detrusor compliance in SCI patients. This method greatly reduces the incidence of renal failure, urinary reflux, stone formation, urothelial cancer, and probably UTIs compared to other indwelling catheterization (Weld and Dmochowski, 2000b; Groah et al., 2002b; Ord et al., 2003). Ruz et al. (2000) found, in patients with SCI, that the number of UTIs/100 person-days was 2.72 for indwelling catheterization in males and only 0.41 for intermittent catheterization. As early as 1947, intermittent catheterization during spinal shock was strongly advocated by Sir Ludwig Guttmann, who first published in 1949. He was an energetic supporter of a no-touch, sterile technique to reduce the risk of UTIs (Guttmann and Frankel, 1966). Some years later, Lapides et al. (1972) published a paper, which is still considered a milestone in neurourology, defending the use of CISC. The conceptual basis of his work was that a healthy urothelium is more resistant to infections than a sick one. Accordingly, bladder distension with increased intravesical pressure may create an ischemic environment, which fosters infections. Lapides' concept was that frequency was more important than sterility. CISC is nowadays the method of choice to empty the bladder in all types of neurogenic bladder and, independently from spinal shock, as soon as detrusor overactivity is under control.

There is nowadays enough evidence to say that sterile intermittent catheterization is not superior to the clean technique in reducing UTI risk, both in the rehabilitation setting (Moore et al., 2006) and at home (Moore et al., 2007). Pathogenesis and strategies needed to reduce the risk of UTI are still not completely understood and clearly need more research, as pointed out in a comprehensive review on CISC and UTIs (Wyndaele et al., 2012). It should be considered that, even if CISC is the modality of choice for many SCI patients and it carries

the lowest risk of long-term renal complications, it has some risk of urethral complications (mainly lesions, abrasions, and hemorrhage, with an incidence of 19%) with further development of infections (urethritis or epididymoorchitis, with an incidence of 28.5%) (Groah et al., 2002a). Moreover, in male patients, these complications can also hamper fertility (Ku, 2006). If CISC is chosen as bladder management, urodynamic evaluations are warranted to ensure that filling is achieved at low pressure and that no vesicorenal refluxes are present, and an early adequate management of high pressure detrusor overactivity is mandatory.

To summarize, at present CISC is considered as the technique of choice in the management of bladder voiding after SCI. It can be utilized early, during the phase of spinal shock and throughout the patient's life, for every patient who is willing to learn the technique, has enough motor control of the hand (or has a caregiver willing to perform clean intermittent catheterization for the patient) (Giannantoni et al., 1998; Consortium for Spinal Cord Medicine, 2006).

Permanent catheterization. Permanent catheterization, mainly with a urethral indwelling catheter, is usually used for acute bladder management immediately after SCI. Even if it is possible with this method to both continuously monitor urine output and avoid bladder overfilling and dissention, permanent catheterization should be discontinued as soon as possible. Indeed, the utilization of an indwelling catheter is burdened by frequent complications (urethritis, urethral erosions, stones, infections, bladder cancer) (Weld and Dmochowski, 2000b; Welk et al., 2013). Katsumi et al. (2010) published a retrospective study in which patients with SCI and indwelling catheter were followed for several years (indwelling urethral catheter group: 133 patients for 23.4 years; suprapubic catheter group: 46 patients for 14.3 years). The rate of complications was not statistically different between the two groups (UTI 93% and 98%; urosepsis 15% and 11%; bladder stone 38% and 41% in the indwelling urethral and suprapubic catheter group, respectively). The number of urethral strictures and fistulas, scrotal abscess, and epididymitis was higher in patients with urethral catheters but the difference between the two groups was not statistically significant (Katsumi et al., 2010). The use of silver alloy-coated catheters or nitrofurazone-impregnated catheters has not significantly reduced the risk of UTI (at least in the short term), even if the cost of these devices is higher than standard catheters (Lam et al., 2014). Suprapubic catheterization requires a minimal surgical act, with the risk of bleeding and of lesions to adjacent organs. The main advantage usually claimed is a reduction in complication rates, such as urethral lesions, erosions, and infections (Weld and Dmochowski, 2000b). However, evidence supporting these advantages is very limited, and some clinicians have encountered frequent complications even with these devices with long-term use (Katsumi et al., 2010; Hunter et al., 2013). Although Nwadiaro et al. (2007) published that suprapubic catheterization carries a lower risk of infections and subsequent mortality in SCI patients as compared to indwelling catheterization (65% vs 14%), a recent review found that suprapubic catheterization is associated with a similar risk of upper urinary tract damage and stone formation (Hunter et al., 2013).

Permanent catheterization (both indwelling and suprapubic) carries the risk of rapidly diminishing bladder compliance, with subsequent development of a small, hypocompliant bladder, followed by vesicorenal reflux. Also the risk of bladder stone formation by permanent catheterization as compared to CISC is increased. Some authors (Weld and Dmochowski, 2000b; Ord et al., 2003) found that the risk ratio is 10.5 for suprapubic catheters and 12.8 for indwelling urethral catheters (Ord et al., 2003). Therefore, indwelling catheterization as long-term management of LUTD in SCI patients should be considered only in older and more compromised subjects, in those who are not compliant with intermittent catheterization or in those who refuse surgery.

External drainage systems. External drainage systems (condom catheters) may be proposed in male patients with neurogenic bladder. Drawbacks with the long-term use of these appliances are bacteriuria, cutaneous erosions, UTIs, and penile retraction. Bladder pressure should be maintained low to avoid high urinary tract damage, and cutaneous hygiene should be as stringent as possible.

Drugs

Pharmacologic treatments are aimed to act on the detrusor muscle or on the bladder neck/sphincter.

Since the detrusor muscle is activated by the action of acetylcholine on M_3 muscarinic receptors and detrusor overactivity is the most frequent finding in supraconal lesions, the main pharmacologic tools are antimuscarinic drugs.

There are several effective antimuscarinic drugs, including oxybutinin, tolterodine, and trospium chloride.

Despite their extensive clinical use, there are relatively few good randomized, double-blind, placebo-controlled trials looking at the efficacy of antimuscarinic drugs in detrusor overactivity in SCI patients (Stöhrer et al., 1991, 1999; O'Leary et al., 2003; Ethans et al., 2004; Hortsmann et al., 2006). The majority of studies

published with these medications included patients with neurogenic detrusor overactivity from a different origin, even if the majority of patients had SCI. It should be noted that, in these studies, urodynamic parameters (such as maximum cystometric bladder capacity, maximal detrusor contraction, and bladder capacity) have been taken into account, whereas clinical outcomes (such as incontinence episodes, number of voids per day, or quality of life) are only rarely reported.

Propiverine (Stöhrer et al., 1999), oxybutinin (O'Leary et al., 2003), and trospium chloride (Stöhrer et al., 1991) have been shown to be effective in improving maximum cystometric bladder capacity and in reducing the number of voids per day.

Propiverine, at a dose of 15 mg three times a day, has been shown to be more effective than placebo in a randomized controlled trial on a population of 124 patients with SCI, in increasing bladder capacity (by 72 mL vs 35 mL under placebo) and maximal cystometric capacity (by 104 mL, in comparison with a decrease with placebo), in reducing maximal detrusor contractions (by 27 ± 32 cm H_2O), and in improving clinical symptoms (63.3% of the patients reported "improved" symptoms in comparison with 22.6% under placebo) (Stöhrer et al., 1999).

In a randomized controlled trial on 61 patients with SCI, trospium chloride, at a dose of 20 mg twice a day, has been shown to be more effective than placebo in improving maximal cystometric capacity and in reducing maximal detrusor pressure, with a low rate of side-effects that did not differ between placebo and active treatment group (Stöhrer et al., 1991). This study did not report data regarding incontinence or other urinary symptoms.

In a randomized controlled trial conducted on a small population of SCI survivors (10 patients), an extended-release form of oxybutinin, at a dose of 10 mg/day (progressively increased to 30 mg/day), has been shown to improve maximal cystometric capacity and to reduce the mean number of voids per day by concomitant reduction of the number of incontinence episodes per week (O'Leary et al., 2003).

Stöhrer and colleagues (2007) compared the efficacy and side-effects of propiverine (15 mg three times per day) with oxybutinin (5 mg three times a day) in a randomized controlled trial conducted on a population of 131 patients with SCI. They showed that both drugs were effective, with no significant difference between them in improving maximal cystometric capacity, in decreasing maximal detrusor pressure, and in improving bladder compliance. The propiverine group reported fewer side-effects than those treated with oxybutinin. They also found a decrease of 1.3 incontinence episodes following oxybutinin compared with a decrease of 1.6 episodes following propiverine.

However, in clinical practice, it is common for patients to need a combination of antimuscarinic drugs or a regimen of progressively increased doses, beyond the recommended upper limits. To evaluate the efficacy of this strategy of treatment and its safety, Amend and colleagues (2008) conducted a study on 27 patients with SCI, who were formerly and unsuccessfully treated with a single anticholinergic drug. Patients were divided into three groups: one received 8 mg tolterodine and 15–30 mg oxybutinin; another group received 90 mg trospium chloride and 4–8 mg tolterodine; the third group received 30 mg oxybutinin and trospium chloride (45–90 mg). Data showed that there was no significant difference between groups (either in efficacy or in side-effects) in decreasing the number of incontinence episodes and improving bladder capacity, as well as detrusor compliance. Treatment was considered successful in 85% of patients independently of which group they were assigned to.

In summary, in all these trials antimuscarinic drugs were shown to be effective at reducing urine leakage between catheterizations and in improving urodynamic parameters (such as reflex volume, amplitudes of detrusor contractions, and bladder capacity) as compared to placebo (Stöhrer et al., 1991, 2007, 2013; Ethans et al., 2004). Therefore, all antimuscarinic agents are the primary treatment for urinary incontinence and the prevention of high voiding pressure in SCI patients. However, even if effective, the side-effects of these medications (dry mouth, constipation, and blurred vision, among others) frequently limit their use in the clinical setting (Stöhrer et al., 2007; Amend et al., 2008). Active controlled studies reported a higher frequency of side-effects for oxybutynin 5 mg three times per day compared to trospium chloride 20 mg twice per day (23% of patients reporting dry mouth vs 4%), with a lower discontinuation rate for trospium chloride (6% vs 16%) (Madersbacher et al., 1995).

Trospium chloride is a quaternary ammonium compound that does not pass the blood–brain barrier; therefore, it is less prone to develop cognitive side-effects. It is recommended in older patients or in those with cognitive impairment, but other side-effects, like dry mouth, remain. Increasing the dose or combination therapy can be offered to maximize efficacy but patient compliance with long-term utilization of multiple drugs can be a serious issue and caution is recommended in SCI patients with cardiac arrhythmias, especially with the combination of these medications.

Transdermal administration of oxybutinin could have been an alternative to oral medication, with the same positive effect and less dry mouth (Kennelly et al., 2009), but one-third of patients in this study had to stop this medication due to cutaneous eruption.

Other drugs that have been utilized to reduce detrusor overactivity in SCI patients are vanilloids, capsaicin, and resiniferatoxin (Chancellor and de Groat, 1999). The rationale for their use is that the vanilloid receptor TRPV1 plays a role in detrusor contraction, and is essential for purinergic signaling (Birder et al., 2002). In SCI patients with detrusor overactivity, TRPV1 is overexpressed, and the use of one of its agonists, such as capsaicin, can inactivate C-fiber conduction and reduce bladder overactivity (see Chapter 5). Resiniferatoxin, which is 1000 times stronger than capsaicin, can also be used. Intravesical instillations of resiniferatoxin and capsaicin have been utilized to reduce detrusor overactivity in SCI patients, with significant urodynamic improvements (de Sèze et al., 2004; Shin et al., 2006). The main advantage of resiniferatoxin is that it seems to have fewer side-effects (e.g., pain, hematuria), than capsaicin, which is now abandoned, even if the side-effects observed may have been provoked by the alcoholic solvent concentration rather than the drug itself (de Sèze et al., 2004). However, the relatively short duration of the effects of resiniferatoxin and the instability of the solution have also led to its limited clinical use.

Anticholinergic drugs such as atropine and nociceptin/orphanin FQ have also been utilized intravesically to treat neurogenic detrusor overactivity (Lazzeri et al., 2006; Fader et al., 2007), but currently their use is limited to clinical trials, with the exception of oxybutinin.

Drugs that have been utilized to improve bladder obstruction due to overactivity of the bladder neck and the external sphincter are alpha-adrenergic antagonists, such as moxisylyte, terazosin, or tamsulosin (Costa et al., 1993; Linsenmeyer et al., 2002; Abrams et al., 2003). As example, in the study of Abrams and colleagues, long-term tamsulosin treatment (0.4 and 0.8 mg once daily) was shown to be effective and well tolerated in patients with neurogenic LUTD in improving bladder storage and emptying, and decreasing symptoms of autonomic dysreflexia. However, is important to note that all these studies showed a reduced arterial pressure in SCI patients, which is a dose-dependent effect. Therefore, these drugs should be utilized cautiously in SCI patients with orthostatic hypotension or in tetraplegic patients with acquired hypotension.

Finally, there is also some experience with the utilization of alpha-adrenergic agonists and beta-adrenergic agonists to increase resistance in patients with an incompetent sphincter, with some beneficial effect, even if the evidence is weak in patients with neurogenic bladder and side-effects have usually limited the clinical use of these drugs (Alhasso et al., 2005).

Botulinum toxin. The first use of botulinum toxin type A (BoNT-A) to treat neurogenic detrusor overactivity in SCI patients was published in 2000 by Schurch et al. (2000a, b). After this non-placebo-controlled trial, the same authors published a rigorous, randomized, placebo-controlled trial that confirmed the significant effect of botulinum toxin on continence and urodynamic parameters (e.g., maximum cystometric capacity, bladder compliance, and maximum detrusor pressure). Improvements were maintained for up to 6 months (Schurch et al., 2005). The authors found, in the groups treated with BoNT-A 200 and 300 IU, a reduction in incontinence episodes of nearly 50% and a mean improvement in maximum cystometric capacity of 186.1 and 215.8 mL, and a reduction in maximum detrusor pressure of 66.3 and 52.9 cm H_2O (in the 300 and 200 IU groups respectively). These three parameters did not change significantly in the placebo group.

After these pivotal studies, other well-conducted randomized controlled studies were published (Ehren et al., 2007; Schurch et al., 2007; Cruz et al., 2011; Ginsberg et al., 2012; Sussman et al., 2013), which all came to the conclusion that, at present, BoNT-A is a cornerstone in the treatment of neurogenic detrusor overactivity in patients with SCI (Mehta et al., 2013). After intramuscular injection in the detrusor muscle (done under cystoscopy) BoNT-A mainly acts by inhibiting the release of acetylcholine at the presynaptic junction. Along with this primary action, some authors have proposed that BoNT-A may inhibit the release of various neurotransmitters, like adenosine triphosphate, substance P, and calcitonin gene-related peptide (Apostolidis et al., 2006). Even if detrusor overactivity is the most frequent indication for BoNT-A treatment in SCI patients, it may also be utilized to treat DSD, using a transperineal or a cystoscopic approach (Schurch et al., 1996; de Sèze et al., 2002; Kuo, 2003). In the treatment of DSD, the mean dose of onabotulinumtoxinA usually varies between 50 and 100 IU (Schurch et al., 1996; de Sèze et al., 2002; Gallien et al., 2005).

To treat neurogenic detrusor overactivity, doses commonly administered are between 200 and 300 IU of onabotulinumtoxinA (Botox) (Schurch et al., 2005; Cruz et al., 2011; Ginsberg et al., 2012) or 500–1000 IU of abobotulinumtoxinA (Dysport) (Del Popolo et al., 2008; Grise et al., 2010). Reimbursement is accepted in almost all countries for dosage up to 200 units of onabotulinumtoxinA (Botox). The effect of one injection session lasts on average 9 months (Schurch et al., 2005; Cruz et al., 2011; Herschorn et al., 2011). Repeated injections up to five times show similar results as after the first injection (Reitz et al., 2007), without ultrastructural detrusor changes before and after BoNT-A treatment (Haferkamp et al., 2004).

Beside its therapeutic effect, it seems that BoNT-A treatment can reduce costs and resource use for patients

with neurogenic detrusor overactivity (Kalsi et al., 2006; Wefer et al., 2010; Carlson et al., 2013).

The main side-effect seems to be a high incidence of UTI (21–32%) (Schurch et al., 2005; Cruz et al., 2011), keeping in mind that the definition of UTI was only bacteriologic (Cruz et al., 2011). Therefore, the clinical relevance of these UTIs remains to be proven. Hyposthenia secondary to BoNT-A injection is rare, and seems to occur more frequently in patients treated with abobotulinumtoxinA compared to onabotulinumtoxinA (2.6% vs 0.5%) (Mangera et al., 2011).

Even if detrusor overactivity is the most frequent indication for BoNT-A treatment in SCI patients, it may also be utilized to treat DSD, using a transperineal or cystoscopic approach (Schurch et al., 1996; de Sèze et al., 2002; Kuo, 2003), aiming to decrease postvoid residual volume and improve voiding. Usually only patients who have light neurogenic disorders or who do not want to catheterize will be candidates for this treatment. The mean dose of onabotulinumtoxinA usually varies between 50 and 100 IU (Schurch et al., 1996; de Sèze et al., 2002; Gallien et al., 2005). In all these studies, botulinum toxin injections were proved to improve DSD as well as voiding, even if the change in postvoid residual volume did not show a significant difference against placebo (Gallien et al., 2005).

Physical modalities (electric stimulation)

Electrical stimulation has been utilized for years in the treatment of LUTD. Several techniques have been utilized, such as anogenital electric stimulation, transcutaneous electric stimulation, and percutaneous posterior tibial nerve stimulation. However, in this section we will focus on techniques that have been utilized in patients with SCI:

1. intravesical stimulation (IVES)
2. neuromodulation
3. sacral root stimulation (SRS) combined with sacral root deafferentation (SRD)

Intravesical stimulation. Even if it has been in use since the 19th century (the first report was produced by Saxtorph, a Danish surgeon in 1878) (Madersbacher, 1990a), IVES treatment is still controversial, with little evidence concerning its efficacy. Its main mechanism is to elicit detrusor muscle contraction by electric stimulation, making this treatment a possible option for patients with partial lower motor neuron bladder. IVES has also been utilized to improve bladder sensation in incomplete SCI patients. However, at present, only a few, uncontrolled studies focusing on this topic have been published (Madersbacher et al., 1982; Lombardi et al., 2013).

Neuromodulation. Vodusek et al. showed, in 1986, that an overactive detrusor muscle could be inhibited by stimulation of the pudendal nerve. Similar results have been obtained later in patients with SCI by other authors, who pointed out that some carry-over effect can also be achieved (Wheeler et al., 1992; Previnaire et al., 1996). Magnetic (Sheriff et al., 1996) or electric stimulation (Chartier-Kastler et al., 2001) of the sacral roots S2–4 probably has the same effect as stimulation of the pudendal nerve. However, the main problem with this treatment is that, even if it is effective in the short term, its application as long-term use is more difficult.

In 2010 Sievert et al. published a small controlled study on the early application of bilateral sacral neuromodulation in patients with complete SCI above T12. Up to 39 months after implantation, none of the patients treated with neuromodulation developed an overactive bladder. Further studies are required to confirm these data.

Sacral root stimulation combined with sacral root deafferentation. The electric stimulation of the sacral roots to improve bladder control in patients with SCI was developed by Brindley in 1969; he published his first results in 1982. By this method, bladder emptying is achiev by electrical stimulation of the anterior sacral roots (SRS). However, to obtain a low filling bladder pressure, electrode stimulation has to be preceded by posterior root rhizotomy (SRD) of S2–4. After SRD, the bladder becomes areflexic, allowing a greater capacity and low bladder filling pressures. The most utilized electrostimulation system (known as the Finetech–Brindley system) consists of an implanted stimulator with a receiver that can be controlled by an external transmitter device. By varying patterns of stimulation it is possible for the patient to control bladder and bowel function. Despite its drawbacks of altered male sexual function due to SRD, global satisfaction with SRS combined with SRD is generally high (Creasey et al., 2001; Martens et al., 2011). Kirkham et al. (2002) proposed the application of SRS without dorsal rhizotomy, using an electrosystem able to stimulate both anterior and posterior roots. Increased bladder capacity could be observed in 60% of patients; however, incomplete voiding remained due to persisting DSD. In the same vein and more recently, Possover (2009) introduced a new technique in patients with SCI, utilizing a laparoscopic placement of neural electrodes on both dorsal and ventral sacral nerves as well as the pudendal nerves (laparoscopic implantation of neuroprosthesis: LION procedure) aiming to improve voiding and bladder filling. The procedure was reported as minimally invasive, with a small complication rate. In his small case series (eight patients), bladder emptying was complete up to

27-month follow-up. However, long-term follow-up has not yet been published and the results have not yet been replicated by other groups. As a consequence, further investigations are needed.

Summary

CISC of the bladder is so far the gold standard to void a neurogenic overactive bladder in SCI. In selected patients reflex triggered voiding can be utilized, but the upper urinary tract must be kept safe with low bladder pressure. In many patients with supraconal spinal lesions, detrusor muscle overactivity limits maximum bladder volume and therefore continence, even with a careful intermittent catheterization plan. In this case, antimuscarinic drugs are the first choice to reduce detrusor overactivity, and in turn to protect the kidneys and achieve continence. When antimuscarinic drugs are not effective or not tolerated, BoNT-A is a good alternative to control neurogenic detrusor overactivity.

In refractory patients, SRS may be utilized to control detrusor overactivity. However, to obtain satisfying control of bladder overactivity, SRD is usually necessary, with secondary loss of reflex erections and ejaculation in males. Newer techniques (anterior and posterior stimulation, LION procedure) may reduce these problems but further studies are needed.

In patients with lower motor neuron bladder, intermittent catheterization is usually the better choice, even if, in some patients with low outflow resistance, voiding by Credé and Valsalva maneuvers can be also be used.

When conservative treatment fails or the risk of deterioration of the urinary tract is high, surgery is taken into consideration.

SURGICAL MANAGEMENT

Surgical therapy is indicated when adequate bladder management is not achieved with other measures and in cases when renal failure develops. The aim of any surgical management is to preserve the upper urinary tract and improve quality of life. It should cater to the patient's desire to be treated, as well as the patient's cognitive and mobility abilities. Patients with supraconal lesion and reflex bladder may require surgery due to refractory detrusor overactivity and loss of bladder capacity and patients with conal lesion and areflexic bladder may require surgery due to stress incontinence. In some other conditions, surgical intervention should definitely be considered, including tetraplegia, decreased ability to catheterize, e.g., due to aging or obesity, difficulties with undressing (spasticity, limitations at the upper limbs), and in the case of bladder cancer.

Enterocystoplasty

Bladder augmentation enterocystoplasty is a standard treatment option for patients with neurogenic bladder, low bladder compliance, and preserved renal function (Chartier-Kastler et al., 2000). Usually an ileal segment is detubulated and applied to the opened bladder, or after supratrigonal excision of the bladder (Karsenty et al., 2008; Gobeaux et al., 2012). However, other segments (colon or stomach) can be utilized. The rationale for this technique is that, by increasing the radius of the bladder, pressure is lowered with unchanging wall tension (following Laplace's law). The patient will have to catheterize either through the urethra or through an abdominal stoma to empty the bladder because the intestinal segment used to augment the bladder has only passive elastic properties.

The most frequent complication of enterocystoplasty is the accumulation of mucus production from the intestinal mucosa, requiring bladder washing. The most severe complication is perforation, which may have fatal consequences. Chartier-Kastler et al. (2000) reported, in a group of 17 patients with SCI followed up to 10.5 years, complete continence under CISC in 88.5% and, as a long-term complication, a patient who had recurrent pyelonephritis. In females, since no effective external collecting device exists, additional stress incontinence surgery may be offered at the same time, such as an artificial urinary sphincter (Khoury et al., 1992) or a urethral sling and colposuspension (see later). Current evidence strongly suggests that enterocystoplasty improves bladder capacity and compliance (Singh and Thomas, 1995; Chartier-Kastler et al., 2000), with an improvement in quality of life (Khastgir et al., 2003).

Urinary diversion

Urinary diversion is a surgical procedure in which urine is no longer drained into the bladder but into a reservoir that is made for urine storage. This allow the replacement of a non-functional bladder, for example in patients with spina bifida or bladder malformation, after a radical cystectomy for bladder cancer, or in some SCI patients with a refractory overactive bladder.

Urinary diversions have been made by surgeons for more than 150 years, with the first procedure described being ureteroproctostomy by Simon in 1851, although it was in 1950 that Eugene M. Bricker made the first neobladder with an ileal loop. In this procedure the ureters are resected from the bladder and an anastomosis is created with a detached section of ileum. At present, there are different techniques (Koch pouch, Indiana pouch, orthotopic diversion, and others) that have evolved from Bricker's intervention.

Currently, urinary diversion falls into two categories:

1. continent diversions
2. non-continent diversions.

Continent diversions

In continent diversions the neobladder, made from a detubularized ileal segment, is connected to the abdominal wall by a small abdominal stoma, which can be created using an ileal conduit (using the Mitrofanoff procedure (Sylora et al., 1997) or other procedure such as Yang–Monti modified technique (Casale, 1999)). Neobladder emptying is performed by regular CISC through a stoma, which can be hidden in the umbilicus. This technique is recommended in people with tetraplegia and difficulties in performing CISC and mainly in female patients (Chartier-Kastler et al., 2002; Karsenty et al., 2008), or in patients who have severe urethral erosions and incontinence (Colli and Lloyd, 2011). People with kidney failure or limited liver function are usually not considered good candidates for continent diversions, due to potential problems with reabsorption of urea through the ileal wall. At present, data on patient satisfaction, continence, and neobladder functioning are encouraging (Sylora et al., 1997; Chartier-Kastler et al., 2002; Karsenty et al., 2008). However, the procedure can be complicated by infections (pyocystitis and pyonephritis) and both reservoir and new-onset upper tract stones (32% and 22.5% of patients respectively) (Chen and Kuo, 2009). Moreover, the long-term safety (especially with respect to malignancies) is still unknown.

Non-continent diversions

This is the most widely known procedure. The neobladder is connected to the abdominal wall through a small stoma, permitting urine output, that is collected into a bag and regularly emptied by the patient or caregiver. The main indications for non-continent bladder diversion are: (1) a neurologic bladder associated with complications that prevent restoration of an adequate bladder; (2) SCI patients without sufficient upper-limb skills to provide clean self-catheterization; (3) patients showing lower urinary complications secondary to indwelling catheters (urethral destruction, mainly in females, and urethrocutaneous fistulas); and (4) hydronephrosis secondary to vesicoureteral reflux or a thickened bladder wall.

According to the literature, continence rate and patient satisfaction are high (Chartier-Kastler et al., 2002; Kato et al., 2002), even if the procedure is accompanied by some complications (36% of patients in the study by Chartier-Kastler et al. had one or more postoperative complication, mainly infectious, but also intestinal obstruction due to adhesions and strictures and stone disease).

Bladder diversion techniques are often carried out with cystectomy due to the risk of recurrent infection, pyocystitis, or bladder cancer.

Artificial urethral sphincter

In 1946, Frederic Foley proposed the implantation of an artificial sphincter, which was an inflatable cuff put around the urethra. After the development of different models, in 1983, the first completely implantable system with a deactivation button was introduced (AMS 800). This technique has been developed to treat stress incontinence, but it has also been utilized in patients with SCI. The technique should be somewhat modified in male SCI patients, since voiding the bladder by CISC can induce urethral erosions. Morevover, in these cases, the cuff will usually be placed at the periprostatic urethra because of the prolonged sitting position in a wheelchair that creates the risk of overpressure on the cuff and subsequent decubitus.

The implantation of an artificial sphincter in patients with SCI has been proved to significantly improve continence in nearly all patients at short-term follow-up and in more than an half in the longer term (Patki et al., 2006a; Bersch et al., 2009; Chartier Kastler et al., 2011). Main risks are infection and malfunctioning of the device. In patients with myelomeningocele and poorly compliant bladder, the implantation of a sphincter prothesis is usually associated with enterocystoplasty. In patients with neurogenic stress urinary incontinence who are not willing to undergo or unsuitable for this invasive surgery, a periurethral balloon device placed in the perineal area might be an alternative (Mehnert et al., 2012).

Transurethral sphincterotomy

Transurethral sphincterotomy is a common surgical method to treat DSD. It is usually indicated in tetraplegic male patients with SCI and DSD, in association with condom catheters and in patients unwilling or unable to perform intermittent catheterization. This procedure reduces urinary outflow resistance with the objective of reducing intravesical pressure. Improvement in bladder emptying and stabilization of the upper urinary tract has been shown in 70–90% of treated SCI patients (Wein et al., 1976; Perkash, 2007).

Different techniques exist, but the most commonly utilized and described in the literature is the transurethral approach, inserting an endoscope in front of the veru montanum and descending it through the sphincter to the bulbar urethra. The sphincter may be cut by a diathermy electrode or laser. Laser sphincterotomy seems

to be burdened with fewer complications (Noll et al., 1995; Perkash, 1996) and is at present the recommended technique. Bladder leak point pressure greater than 40 cm H_2O seems to be a useful parameter in predicting sphincterotomy success or surgical outcome (Vapnek et al., 1994; Juma et al., 1995). Moreover, in the long term, the reoperation rate is around 30% (Juma et al., 1995).

Several studies have evaluated the efficacy of urethral stent placement instead of sphincterotomy (Abdill et al., 1994; Chancellor et al., 1995; Mehta and Tophill, 2006; Seoane-Rodriguez et al., 2007; Abdul-Rahman et al., 2010). The main finding of these studies (which are case series or retrospective studies) is that stent placement might be an effective short-term technique in reducing voiding pressure, postvoid residual volume, autonomic dysreflexia, and UTIs. However, the overall life duration of a stent is relatively short (usually 2 years), due to deformation, migration, and incrustation of the device (Mehta and Tophill, 2006).

To answer the question of whether a urethral stent placement is a valid alternative to endoscopic transurethral sphincterotomy, Chancellor et al. (1999) conducted a randomized study in 57 patients with SCI. The two techniques were equally effective at reducing maximal bladder pressure and postvoid volume as well as in improving quality of life and patient satisfaction. In the long term, the need to replace the stent was present in 19% of cases and for repeated transurethral sphincterotomy was 8% (Chancellor et al., 1999).

CONCLUSION

Better understanding and management of LUTD in SCI patients have led to a dramatic change in survival and quality of life for these patients.

Both evaluation and treatment should be carried out in specialized institutions with physicians who are trained in spinal cord medicine.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Gabrielle Cissé-Gerelle, MD, for her advice and editing.

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 15

Lower urinary tract dysfunction in patients with brain lesions

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INTRODUCTION

In brain lesions, lower urinary tract dysfunction (LUTD) may be an integrated part of the neurologic syndrome (i.e., a neurogenic LUTD, most often urinary incontinence [UI]), or it may be due to other conditions. LUTD may also be a consequence of associated deficits; in particular motor and cognitive dysfunction may lead to UI, which in this case is called "functional." Both neurogenic and functional UI may be combined. Patients themselves, however, rarely link the LUT symptoms to the neurologic disorder.

The spectrum of brain diseases includes multiple etiologies, but for most, after the initial impact of disease onset, unless there is complete restitution of function, there is the burden of a residual impairment and chronicity of symptoms, often including LUTD. Therefore, regardless of the nature of the disorder, it is important to identify the symptoms and complications that can lead to further health impairment and poorer quality of life (Vodusek, 2004; Fowler et al., 2008; Birder and Drake, 2009; Fowler and Griffiths, 2010).

In this chapter, LUTD in patients with brain diseases is addressed in the context of particular diseases, and then the importance of the localization of lesions is discussed to some extent separately. It should be remembered that inasmuch as LUTD is a direct consequence of a brain lesion, it is because of the particular location of that lesion. Description of the brain neural control of the LUT, a functional pairing of the bladder and the sphincter, can be found in previous chapters. Much of that knowledge is based on data recently acquired by functional neuroimaging; but prior to the advent of these powerful techniques, our knowledge of the association of the cortical and deep brain areas in the control of LUT relied on carefully observed clinical cases: patients presenting with specific symptoms of LUTD, who had been found to have lesions at particular brain sites. Initially the lesion studies were based on observations made in life correlated with postmortem or surgical specimens, but with increasingly better means of imaging it becomes possible to correlate symptoms with smaller, more discrete abnormalities.

As a new insight, effects of diffuse brain lesions have recently emerged as a significant factor to produce overactive bladder (OAB) in the elderly.

The chapter concludes with a short discussion of appropriate management of LUTD in brain diseases.

BRAIN DISEASES AND LUTD

Among brain diseases, stroke and brain tumor are best localized, and have been interesting to researchers also because of the possibility of learning more about brain control of LUT. Several reports on LUT involvement in stroke and space-occupying brain lesions have been published. In contrast, epidemiology and pathophysiology studies of LUTD in other brain diseases are limited, apart from those obviously associated with LUTD (normal-pressure hydrocephalus: NPH). Overall, urodynamic studies in patients with brain diseases and LUTD are few, and have been performed in small patient groups, which are often heterogeneous as to the exact localization of the lesion, and other variables.

STROKE

LUTD in stroke may be a consequence of direct involvement of neural structures which are part of the brain neural control of LUT. As will be discussed later, the consequence is in most events the OAB syndrome (urgency and frequency of micturition, and urge UI)

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(Abrams et al., 2002). Furthermore, there often is a functional component (immobility and loss of initiative/cognition) (Brocklehurst et al., 1985).

Incidence of LUTD

Stroke, a major form of cerebrovascular disease, is a common brain disease that preferentially affects the elderly. Not only hemiplegia but also LUTD significantly affects quality of life in poststroke patients (Itoh et al., 2013). With the exception of UI, reports on the frequency of LUT symptoms in patients with stroke have been scarce. Sakakibara et al. (1996a) reported on the bladder symptoms of 72 patients who had been admitted with an acute hemispheric stroke to the neurology department. When assessed at 3 months, 53% were found to have significant LUT symptoms. The commonest problem was nocturnal urinary frequency (36%), then urge UI (29%) and difficulty in voiding (25%); urinary retention was seen in 6%. Brittain et al. (2000) reported an incidence of poststroke LUT symptoms of 64% (in 423 subjects) that was higher than in a control normal population (32%). The major urinary symptoms were: nocturia (49%), UI (33%), urgency (19%), frequency (15%), straining (3.5%), and pain (2.5%). More recently, among 1248 stroke patients, Williams et al. (2012) found that 83.6% of survivors reported one or more abnormal LUT symptoms at 3 months: nocturia was the most frequent (79.1%), followed by UI (43.5%; urge type 37.0%, stress type 20.6%) and urinary frequency (17.5%).

Thomas et al. (2005) reported UI in 40–60% of patients admitted to hospital after a stroke, with 25% still having problems on hospital discharge, and approximately 15% remaining incontinent at 1 year. Amelioration of UI in 25–45% of the patients may reflect amelioration of both functional component (mobility, initiative, and cognition) as well as the OAB component in this commonest brain disease. More recently, Kuptniratsaikul et al. (2009) noted bladder/bowel dysfunction in 31.5% among 327 poststroke patients who started rehabilitation.

Stroke characteristics and LUTD

Studies reporting on stroke localization and LUTD stress the effect on the frontal lobe, and there are no clear reports of bladder dysfunction as a consequence of a single/focal deficit in the parietal, temporal, or occipital lobe. Findings in patients supported the idea that lesions of the anteromedial frontal lobe, its descending pathways, and the basal ganglia are mainly responsible for bladder dysfunction in stroke patients.

Khan et al. (1981, 1990) reported on 33 poststroke patients with LUT symptoms; the majority of patients had frontal cortex and/or internal capsular lesions. Bogousslavsky and Regli (1990) noted UI in 22% (six of 23 cases) of anterior cerebral artery infarction affecting the frontal lobe. Subsequently, Sakakibara et al. (1996a), analyzing 72 poststroke patients irrespective of the presence of LUT symptoms, found a significant correlation between the occurrence of a urinary disturbance and hemiparesis ($P < 0.05$) and a negative correlation with hemianopia ($P < 0.05$): brain imaging techniques confirmed a more anterior location of brain lesions in the former group (Fig. 15.1). More recently, Woessner et al. (2012) reported a urinary-incontinent patient whose stroke was localized in the cortical motor area of the bladder/sphincter.

Considering LUT neural control one expects LUTD also in brainstem infarcts. An analysis of LUT symptoms

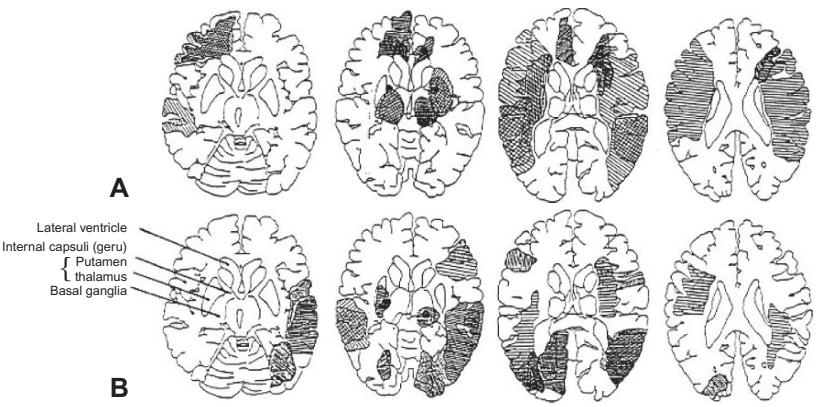

Fig. 15.1. (**A**) Lesions on brain computed tomography (CT) or magnetic resonance imaging (MRI) in patients with micturitional disturbance. Most patients had lesions of the anterior and medial surface of the frontal lobe, anterior edge of the paraventricular white matter, genu of the internal capsule, large lesion of the putamen, and large lesion of the thalamus adjacent to or including the genu of the internal capsule. (**B**) Lesions on brain CT or MRI in patients without disturbance of micturition. Most patients had lesions of the occipital, temporal, or parietal lobe, posterior lateral surface of the frontal lobe, crus posterius of the internal capsule, and small lesion of the putamen or thalamus. (Reproduced from Sakakibara et al., 1996a.)

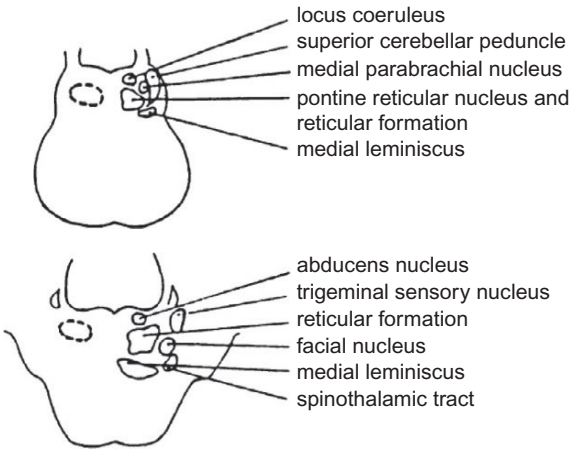

Fig. 15.2. Sites of brainstem lesion responsible for voiding disturbance within the dashed circle on the left and the organization of neural structures at this level shown on the right. (Reproduced from Sakakibara et al., 1996a.)

of 39 patients who had had brainstem stroke showed that it was dorsally situated lesions (Fig. 15.2) that resulted in disturbance of micturition (Sakakibara et al., 1996b). Forty-nine percent of all patients had LUT symptoms: there was nocturnal urinary frequency and voiding difficulty in 28%, urinary retention in 21%, and UI in 8%. The problems were more common in those following hemorrhage, possibly because the damage was usually bilateral. Magnetic resonance scanning showed that the lesions responsible were in the pontine reticular nucleus and the reticular formation, adjacent to the medial parabrachial nucleus and the locus coeruleus. A correlation was found between LUT symptoms and sensory disturbance, abnormal eye movement, and incoordination. Lateral medullary infarction (Wallenberg syndrome) has recently been reported to produce voiding difficulty and detrusor sphincter dyssynergia (DSD) (Tokushige et al., 2012). In Naganuma's case (Naganuma et al., 2005) the lesion seemed to extend to basal medulla and produced hemiparesis. Brainstem stroke cases suggest that the relevant region for LUT control is located in the dorsolateral pons, including the pontine reticular nucleus and the reticular formation, adjacent to the medial parabrachial nucleus and the locus coeruleus. More recently, Yum et al. (2013) analyzed 30 brainstem infarction cases. They found LUT symptoms in 70% of patients, comprising 46.7% storage disorder and 23.3% emptying disorder. In their series of patients, emptying disorder was more common in medullary lesions (55.6%) than pontine lesions (9.5%). Storage disorder was found only in pontine lesions (61.9%).

There are few reports on LUTD related to specific other brain areas than hemispheres or brainstem. Cerebellar stroke (Nardulli et al., 1992) has been reported to cause LUTD (detrusor overactivity (DO)).

Sakakibara et al. (1996a) reported a correlation with lesion size and LUT symptoms ($P < 0.05$); a large middle cerebral artery infarction very often involved the frontal lobe.

Kumrala et al. (2002) noted UI in 13% (2/16) of right and 33% (10/30) of left anterior cerebral artery infarctions. We (Sakakibara et al., 1996a), however, did not see a clear relationship between stroke laterality and LUT symptoms. Similar findings were reported by others (Kim et al., 2010). In contrast, Ersoz et al. (2005) divided their poststroke patients with LUTD into infarction and hemorrhage. The infarction group had larger bladder capacity (250.3 mL) and larger postvoid residual urine (PVR) volume (136.1 mL) than the hemorrhage group (194.9 mL, 29.5 mL, respectively), indicating a more severe bladder dysfunction. Han et al. (2010) found that the infarction group had more DO but less detrusor underactivity (70.7%, 29.3%, respectively) than the hemorrhage group (34.65%, 65.4%, respectively).

Urodynamic analysis

Khan et al. (1981, 1990) demonstrated detrusor (bladder) overactivity (DO) in 79% of 33 poststroke patients with LUT symptoms. None of them had DSD on voiding. DO is a urodynamic observation characterized by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked (Abrams et al., 2002). The mechanism of DO seems not to be uniform; certainly DO has been described in patients with different locations of lesions in the central nervous system, but is also seen in patients without (obvious) neurologic involvement. It is postulated that the micturition reflex is under tonic (mainly inhibitory) influences (Fowler et al., 2008; Birder and Drake, 2009) from the central cholinergic pathway (Masuda et al., 2009) and the fronto-nigro-striatal, dopamine D1-GABAergic direct pathway (Sakakibara et al., 2012b). Furthermore, it is postulated that in patients with brain lesions DO is an exaggerated spino-bulbo-spinal micturition reflex; the pontine micturition center (PMC) normally promotes micturition, and without inhibition, DO develops (Fowler et al., 2008; Birder and Drake, 2009; Fowler and Griffiths, 2010) (Fig. 15.3). The exaggerated micturition reflex is abolished after chemical lesioning of the PMC in stroke rats.

Consequent urodynamic studies showed a more varied picture: in 19 poststroke UI patients Gelber et al. (1993) reported DO in 37%, underactive detrusor in 21%, and DSD in 5%. In a urodynamic study of 27 symptomatic stroke patients (Kong et al., 1994) DO

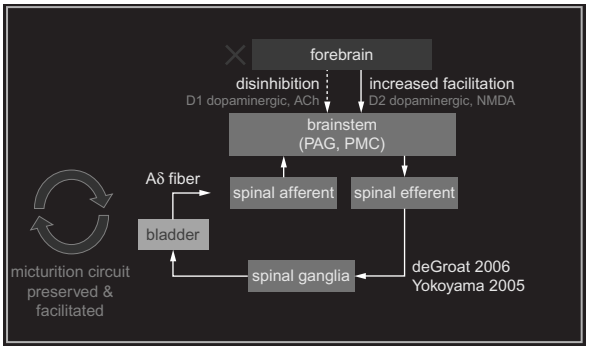

Fig. 15.3. Detrusor overactivity after forebrain lesion. ACh, acetylcholine; NMDA, *N*-methyl-D-aspartic acid; PAG, periaqueductal gray; PMC, pontine micturition center. (Modified from Fowler et al., 2008.)

was seen in 40.7% and detrusor areflexia in 3.7%. Similarly, a study of 38 symptomatic stroke men by Nitti et al. (1996) showed DO in 82% and outlet obstruction in 63%. Our study of 22 symptomatic stroke patients (Sakakibara et al., 1996a) showed DO in 68%, DSD in 14%, and uninhibited sphincter relaxation (involuntary relaxation of sphincter particularly with DO) in 36%. Patients with urinary retention (noted in 4% at the acute phase) had acontractile detrusor and an unrelaxing sphincter. The urodynamic findings in these patients changed from acontractile detrusor to normal or DO. Urinary retention in such patients can be referred to as "brain shock" phase, akin to the "spinal shock" phase of spinal cord injury. More recently, in 57 poststroke patients, Natsume (2008) also found detrusor underactivity in 35% of men and 43% of women; most of them had so-called detrusor hyperactivity with impaired contraction (DHIC). In contrast to the pathophysiology of DO, little is known about the pathophysiology of "brain shock" and DHIC (Yamamoto et al., 2006). Within the brain, it is known that there are both micturition-inhibiting and micturition-promoting areas. The latter include A10 ventral tegmental area mesolimbic dopaminergic pathway, and D2-subthalamic indirect pathway, in addition to the glutamatergic PMC adjacent to the locus coeruleus and sacral cholinergic preganglionic cells (Sakakibara et al., 2012b). These pathways may be involved in many brain diseases affecting the frontal lobe.

Gupta et al. (2009) found DO in 90% and DSD in 27.5% in their 40 patients with poststroke UI. Urodynamics in 11 symptomatic patients with brainstem lesions showed DO in eight (73%), low-compliance detrusor in one (9%), acontractile detrusor in three (27%), nonrelaxing sphincter on voiding in five (45%), and uninhibited sphincter relaxation in three (27%). Three asymptomatic patients had normal findings (Sakakibara et al., 1996a).

No statistically significant correlation could be demonstrated between any particular lesion site and urodynamic findings (Yoo et al., 2010).

Stroke prognosis, UI, mobility, and cognition

Studies have shown that early UI following a stroke is a specific indicator of poor prognosis. Wade and Langton Hewer (1985) analyzed the symptoms of 532 patients seen within 7 days of their stroke and found that the presence of UI appeared to be a more powerful prognostic indicator for poor survival and eventual functional dependence than was a depressed level of consciousness. Barer and Mitchell (1989) and Barer (1989) also reported that the outcome was better in those who remained or became dry. More recently, Rotar et al. (2011) demonstrated that poststroke UI is a predictor of greater mortality not only at the end of the first week, but also at 6 months and 12 months after stroke.

Gelber et al. (1993) found that poststroke UI was associated with large infarcts, aphasia, cognitive impairment, and functional disability. Nyberg and Gustafson (1997) noted a strong link between easy fall and UI. More recently, van Kuijk et al. (2001) reported that, among 143 poststroke patients, activities of daily living (modified Barthel index) and discharge rate to their own home are negatively related with UI. Landi et al. (2006) reported that, among 355 poststroke patients, functional (mobility and activities of daily living) decline is related to UI. Pettersen and Wyller (2006), among 355 poststroke patients, noted a relation between UI and poor mobility. Paolucci et al. (2001) and Daviet et al. (2004) reported that not only immobility and dementia but also unilateral spatial neglect (mostly due to right hemispheric lesion) strongly correlate with UI after stroke. It seems likely that UI is a strong predicting factor for poor prognosis of stroke for a number of reasons: (1) the same lesion might cause neurogenic bladder dysfunction (neurogenic UI), motor or cognitive impairment (functional UI, or combined UI); (2) falls, gait difficulty, and cognitive decline are all marked in severe, bilateral brain lesions; and (3) UI may secondarily cause psychologic depression and also generally interfere with rehabilitation and quality of life.

UI and white-matter lesions in the elderly

UI is a major concern in geriatric populations, which have grown rapidly in recent decades. In addition, the incidence of urinary frequency/urgency (OAB), with or without UI, is high in the general population over 40 years old (Milsom et al., 2001; Stewart et al., 2003; Homma et al., 2005), and it increases significantly with age. It is widely acknowledged that urinary frequency and poor bladder control have a negative impact on

quality of life (Irwin et al., 2005), that LUTD in elderly persons adds to their caregivers' burden, and that LUTD is an important factor leading to institutionalization. The mechanisms underlying OAB and UI in the frail elderly are multifactorial; the factors may include age-related changes in the bladder itself (Irwin et al., 2005) or central nervous system changes innervating the bladder (Resnick, 1995).

Atherosclerosis and subsequent ischemia of the bladder occur in patients with pelvic peripheral vascular disease (Resnick, 1995). Bladder ischemia and reperfusion injure the nerves, leading to smooth-muscle damage and impaired contractility as well as DO (Brading and Symes, 2003; Radu et al., 2011; Giuliano et al., 2013).

Atherosclerosis is a systemic condition which also affects cerebral arteries supplying the brain. Cerebral WMD is a common chronic bilateral ischemic brain disease in the elderly. WMD progresses insidiously, and the likelihood of WMD increases significantly with age. It has been proposed that WMD is the pathoanatomic substrate in the brain etiology of OAB. Thus, it is proposed that WMD leads to three different geriatric syndromes: vascular dementia, vascular parkinsonism, and "vascular incontinence" (Sakakibara et al., 2012a, b).

WMD as the brain etiology of elderly OAB

A body of work examined ultrastructural details of the bladder muscle and its innervation in the elderly in an attempt to identify specific morphologic features which correlate with DO, detrusor hypocontractility, and the disorder DIHC (Elbadawi et al., 1997). The findings indicated that the problem of UI in the frail elderly is age-related changes in the bladder itself. In contrast, a recent view has emerged that there may also be a cerebral vascular component in the pathogenesis of vascular incontinence (Sakakibara et al., 2012a, b). We (Sakakibara et al., 1999) have investigated 63 subjects (mean age 73 years) with varying degrees of cerebral WMD or leukoaraiosis (Fig. 15.4). Magnetic resonance imaging (MRI)-defined WMD was graded on a scale of 0–4. The prevalence of nighttime urinary frequency in cases of grade 1 WMD was 60%; grade 2, 58%; grade 3, 93%; and grade 4, 91%, respectively giving an overall prevalence of nighttime urinary frequency of around 75%, which was a more common and earlier feature than UI (40%). Of particular importance was the fact that OAB was not always accompanied by gait disorder or dementia (grade 1 WMD), so that it appeared that OAB might be the first clinical manifestation of the WMD observed (Sakakibara et al., 1999).

Urodynamic findings in WMD

DO is the major underlying pathophysiology of vascular incontinence. The incidence of DO in WMD cases is reported as 70–91% of patients (Sakakibara et al., 1993, 1999), and is more common than following hemispheric stroke (Sakakibara et al., 1996a). In our study (Sakakibara et al., 1999), urodynamic studies were performed in 33 subjects. We found that subjects with grade 1–4 WMD had DO significantly more commonly (82%) than those with grade 0 WMD (9%) ($P < 0.05$). Postmicturition residuals, low compliance, DSD, and uninhibited sphincter relaxation were also more common in grade 1–4 WMD than in grade 0 WMD, though not significantly so.

Geriatric syndromes and WMD

Recent population-based MRI studies suggest that the incidence of moderate WMD (periventricular WMD grade >4/9 and subcortical white-matter volume >1.5 mL) is approximately 10% (7.6–24%) in the general population of individuals over 55 years of age (van Dijk et al., 2004), comparable to that of OAB at 10–16% (Milsom et al., 2001; Stewart et al., 2003; Homma et al., 2005). WMD can develop into three different geriatric syndromes: (1) vascular dementia: usually mildly reduced Mini-Mental State Examination (MMSE) score with low score on the Frontal Assessment Battery (FAB) (Haruta et al., 2013) (Fig. 15.5); hallucinations and delusions are rare; sometimes stepwise deterioration is observed (Wade and Hachinski, 1986); in most advanced stages, emotional incontinence may occur; (2) vascular parkinsonism: gait disorder or easy falls; slow, short-stepped gait, often with wide-based gait, usually lacking apparent tremor and rigidity in the hands (Rektor et al., 2006). Vascular parkinsonism is otherwise called lower-body parkinsonism, and the gait disturbance may manifest as frontal gait apraxia; it sometimes presents with frontal release signs (palmomental, snout, or grasping); in advanced stages, dysphagia and aspiration pneumonia may occur; and (3) "vascular incontinence": urinary frequency/urgency with or without UI) (Sakakibara et al., 1999; Kuchel et al., 2009; Tadic et al., 2010). These three syndromes can present in any combination, but clinically, urinary and gait disorders are more prominent than dementia, and usually precede dementia.

Cortical WMD in MRI looks diffuse. However, within the brain, detailed pathology studies confirmed that the frontal lobe is most severely affected (Hentschel et al., 2007). This is in line with the reports that MRI volumetry showed frontal-lobe atrophy (Mok et al., 2011), where glucose metabolism was most severely reduced (Tullberg et al., 2004). Corresponding to this, brain perfusion was most severely reduced in the frontal lobe of subjects with WMD (Hanyu et al., 2004), a finding that remains to be fully explained.

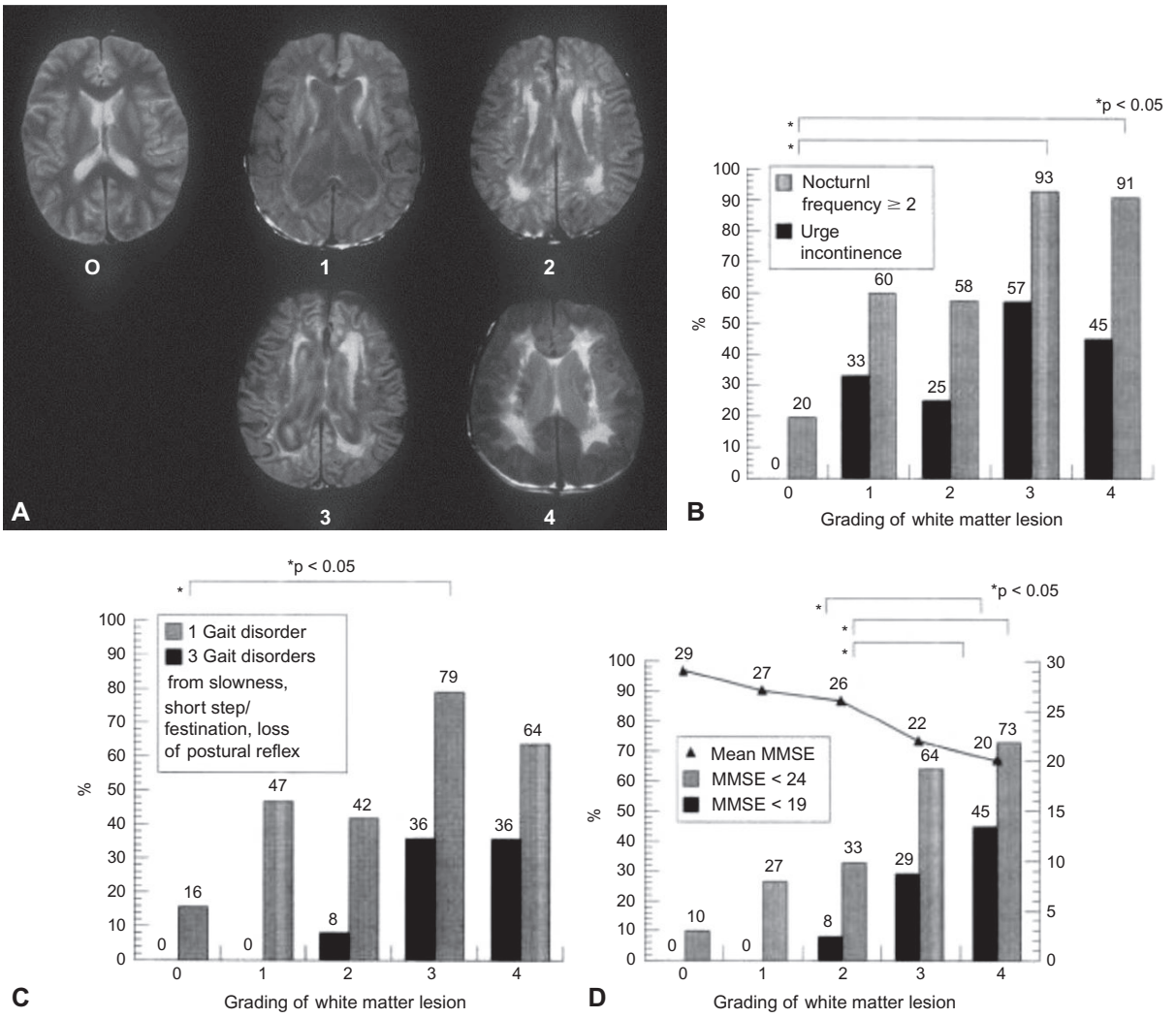

Fig. 15.4. Cerebral white-matter disease and urinary dysfunction. (**A**) Schematic presentation of the grading of white-matter lesions on magnetic resonance imaging (MRI). Grade 0, none; grade 1, punctate foci with high signal intensity in the white matter immediately at the top of the frontal horns of the lateral ventricles; grade 2, white-matter lesions seen elsewhere but confined to the immediate subependymal region of the ventricles; grade 3, periventricular as well as separate, discrete, deep white-matter foci of signal abnormality; and grade 4, discrete white-matter foci that had become large and coalescent. (**B**) Urinary dysfunction and white-matter lesions on MRI. (**C**) Cognitive disorder and white-matter lesions on MRI. MMSE, Mini-Mental State Examination. (**D**) Gait disorder and white-matter lesions on MRI. (Reproduced from Sakakibara et al., 1999.)

More recently, Kuchel et al. (2009) and Tadic et al. (2010) showed a significant relationship between OAB/UI with WMD. Tadic et al. (2010) studied 25 older women (age 71.5 ± 7.5 years) with urgency UI, and they reported that brain responses to bladder filling during self-reported urgency were most prominent in the frontal regions. Regional activations became more prominent with increased global WMD (Fig. 15.6). Looking at the fiber tracts, the main effects of activations and deactivations were superimposed on anterior thalamic radiation and superior longitudinal fasciculus (Tadic et al., 2010). These results indicated that WMD, particularly the anterior portion, is clearly related to OAB in cognitively intact, elderly persons.

It is widely accepted that OAB occurs in otherwise healthy elderly individuals. A recent survey was carried out to look at the relationship between DO and higher brain function in 40 WMD patients with OAB (age 60–89 years) (Haruta et al., 2013). In that study, DO was independent of general cognitive status (the mean MMSE score or any of its subdomains). In contrast, the presence of DO was significantly associated with the inhibitory control subdomain in the FAB test ($P < 0.01$). This finding is in agreement with the fact that brain perfusion was most severely reduced in the frontal lobe of subjects with WMD (Hanyu et al., 2004), as mentioned above. What exactly this finding means is a matter of debate. One explanation might be that the bladder is

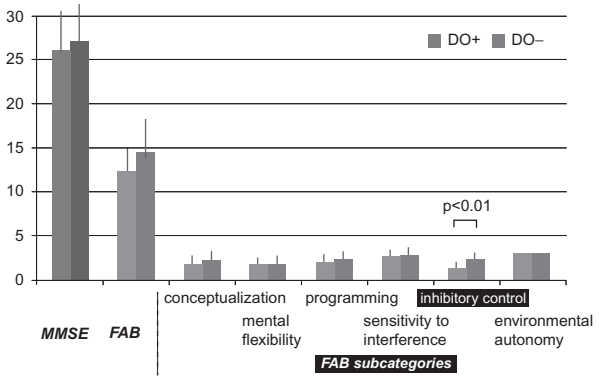

Fig. 15.5. Relationship between detrusor overactivity (DO) and two cognitive tasks in patients with white-matter disease. MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery. There was no significant relationship between DO and the total MMSE or FAB score (left). The analysis of the relationship between DO and the six subcategories of FAB (right) revealed a significant relationship between DO and the inhibitory control task ($P < 0.01$). (Reproduced from Haruta et al., 2013.)

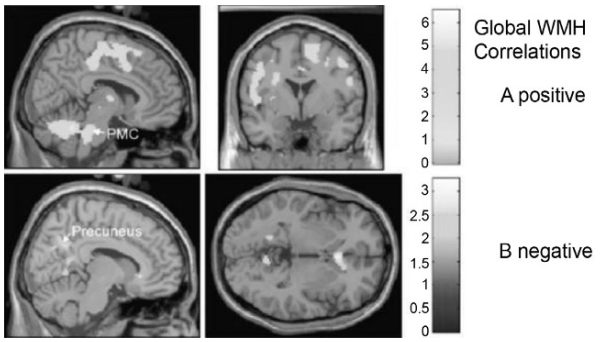

Fig. 15.6. Cerebral white-matter disease (WMH) and urinary dysfunction. Regional activations (e.g., medial/superior frontal gyrus adjacent to dorsal anterior cingulate gyrus, cerebellum, and pontine micturition center (PMC)) are positively correlated with global white-matter change (**A**), whereas some regional activations (e.g., precuneus) have negative correlations (**B**). Scale of global WMH indicates intensity of preexisting WMH. (Reproduced from Tadic et al., 2010.)

under general inhibitory control concerning decision making (Sakagami et al., 2006) and emotion (Declerck et al., 2006) by the prefrontal cortex. In patients with WMD, this neural network might be impaired, leading to both frontal cortex-related behavior changes and DO.

UI, WMD, and Alzheimer's disease

Both age-related WMD (also called vascular dementia) and Alzheimer's disease (AD) are common causes of elderly dementia, and are known to be independent risks for OAB/UI. A recent survey (Takahashi et al., 2012) was carried out among 49 mild/moderate dementia patients

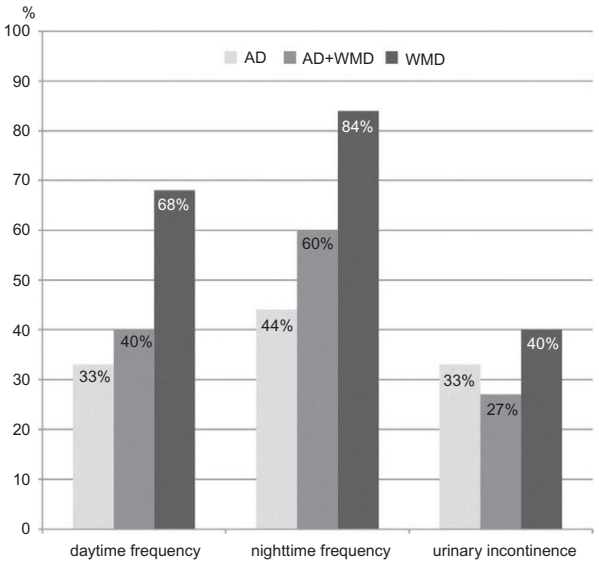

Fig. 15.7. Lower urinary tract symptoms in Alzheimer's disease (AD) and white-matter disease (WMD). (Reproduced from Takahashi et al., 2012.)

irrespective of OAB (mean age, 76 years), including AD alone in nine, AD+WMD in 15, and WMD alone in 25. OAB was most common in WMD alone (Fig. 15.7). Therefore, WMD is a more significant contributor to OAB and UI than AD in elderly dementia patients. It should be mentioned that, in WMD, LUTD occurs independently from dementia. The pathologic mechanisms for LUTD in AD and WMD remain obscure. However, a single-photon emission computed tomography (SPECT) study showed that frontal hypoperfusion is common in WMD, whereas parietal-temporal hypoperfusion is common in AD (Hanyu et al., 2004). This is in accordance with the finding that in AD, dementia is the predominating symptom, and early UI is extremely rare (Del-Ser et al., 1996).

BRAIN TUMORS

Space-occupying lesions occur in all ages. Primary brain tumors mostly originate from glial cells, and metastases are the most common space-occupying lesions in adults in developed countries. In adults, tumors are more frequent in the frontal and temporal lobes (Larjavaara et al., 2011).

Incidence of LUTD

The incidence of LUT symptoms among frontal tumor has been reported as 14% (OAB with or without UI, seven of 50 frontal tumors versus none in other cortical tumors) (Maurice-Williams, 1974), and 28% (UI, seven of 25 frontal gliomas) (Direkze, 1971).

Ueki (1960) analyzed the urinary symptoms of 462 patients who had come to surgery for brain tumors;

among them were 34 cases of frontal lobectomy and 16 cases of bilateral anterior cingulectomy. Based on the intraoperative findings, he illustrated his conclusions with a diagram of the brain showing a strong positive influence on micturition of an area in the pons and an inhibitory input from the frontal lobe (Fig. 15.8). Andrew and Nathan (1964, 1965; Andrew et al., 1966), also described a series of patients who developed LUT symptoms (with brain tumor, anterior frontal-lobe damage following rupture of an aneurysm, penetrating brain wounds, and leucotomy). These patients were collected separately over a period of 24 years. Their typical case is worth quoting for the good description of this clinical picture:

> *The patients described here were not demented, indifferent or lacking in social awareness; they were much upset and embarrassed by these symptoms. . . . The acts of micturition and defecation occur in a normal manner; what is disturbed by this frontal lesion is the higher control of these acts. The lesion causes frequency and extreme urgency of micturition when the patient is awake, UI when asleep. The sensation of gradual awareness of increasing fullness of the bladder and the sensation that micturition is imminent are impaired. When the syndrome is less pronounced, the sensation underlying the desire to micturate is absent, whereas the sensation that micturition is imminent still occurs. Then the patient is waylaid by a sudden awareness that he is about to pass urine; when neither sensation is experienced, the patient is amazed to find that he has passed urine.*

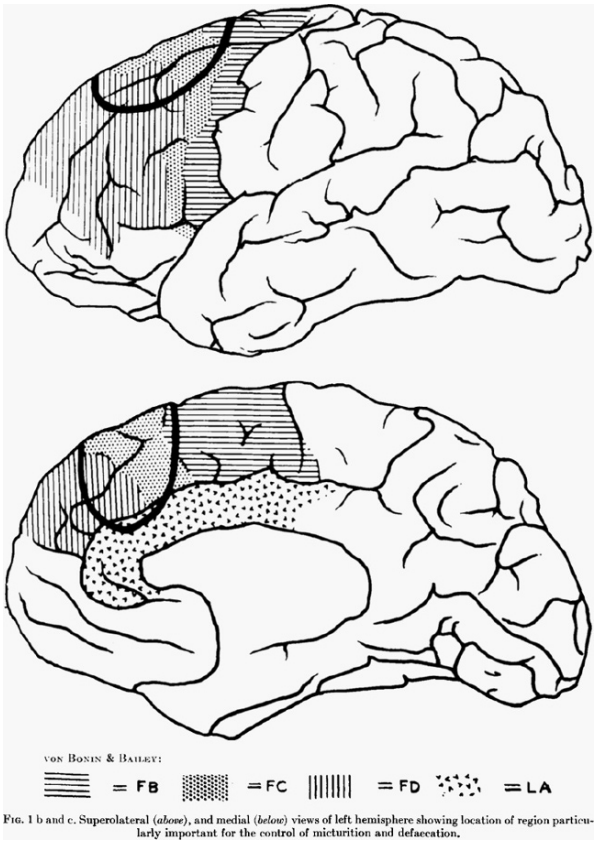

Fig. 1 b and c. Superolateral (*above*), and medial (*below*) views of left hemisphere showing location of region particularly important for the control of micturition and defaecation.

Fig. 15.8. The frontal micturition center. In 1966, John Andrew, a neurosurgeon at Oldchurch Hospital (now Queen's Hospital), Romford, UK, and Peter Nathan, a neurologist at the National Hospital, Queen Square, London, UK, described a series of patients with frontal-lobe lesions due to stroke, aneurysm, or brain tumor who presented with severe micturitional disturbances. The area was depicted outside (top) and inside (bottom) the frontal lobe, now referred to as the frontal micturition center. (Reproduced from Andrew and Nathan, 1964.)

In their paper the authors described 38 patients with disturbances of micturition (mostly UI) as a result of lesions in the anterior frontal lobe (Fig. 15.9). The lesion site was that lying immediately anterior to the tips of the ventricles and the genu of the corpus callosum.

Tumor characteristics and LUTD

In subsequent studies the lesion sites to produce OAB/urinary urge UI (or sudden unexpected UI) were mostly the same as that described by Ueki and Andrew, e.g., prefrontal cortex (Soler and Borzyskowski, 1998; Hirato, 2002; Pettersen et al., 2007; Abdel Hafez et al., 2010), medial surface of frontal cortex, including anterior/middle cingulate gyrus (Laplane et al., 1981; Sekido and Akaza, 1997; Duffau and Capelle, 2005), supplementary motor area (Pool, 1949), and insula (Duffau and Capelle, 2005; Duffau et al., 2006).

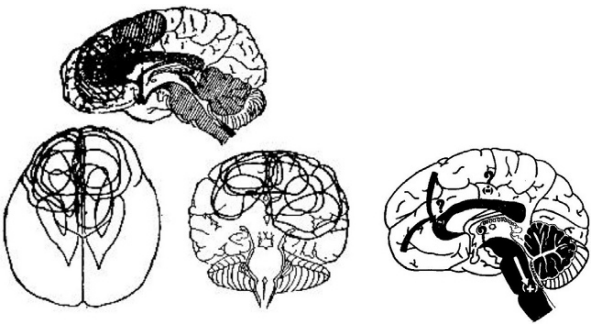

Fig. 15.9. Left: Lesions from a frontal-lobe tumor that caused urinary incontinence. Right. Schematic representation of cerebral control of micturition. (Reproduced from Ueki, 1960, with permission from Neurologia Medica Chirurgica.)

There are some reports on the association of LUTD and tumors in other brain areas. Hypothalamic tumors produce LUTD (Brouwer, 1950; Andrew and Nathan, 1965; Yamamoto et al., 2005). But reports are few, probably because the general effect in patients with hypothalamic tumor easily masks LUTD. In 1950, Brouwer reported on a patient initially presenting with UI. Autopsy proved that he had a glioma located in the hypothalamus and the third ventricle. In 1965, Andrew and Nathan described a patient presenting with loss of visual acuity, urinary frequency, urge UI, and nocturnal enuresis. Surgical exposure of the brain revealed a cystic lesion compressing the optic chiasm, anterior hypothalamus, and septal area. More recently, Yamamoto et al. (2005) reported three cases of pituitary adenoma that extended to the hypothalamus (Fig. 15.10). None of these patients had diabetes insipidus with polyuria but instead, they complained of nocturnal frequency, urinary urgency, and either UI (case 1) or voiding difficulty and urinary retention (cases 2 and 3). Case 3 also had visual disturbance, anorexia, psychiatric symptoms, and syndrome of inappropriate secretion of antidiuretic hormone. None of the three patients had diabetes insipidus (polyuria) due to posterior pituitary insufficiency.

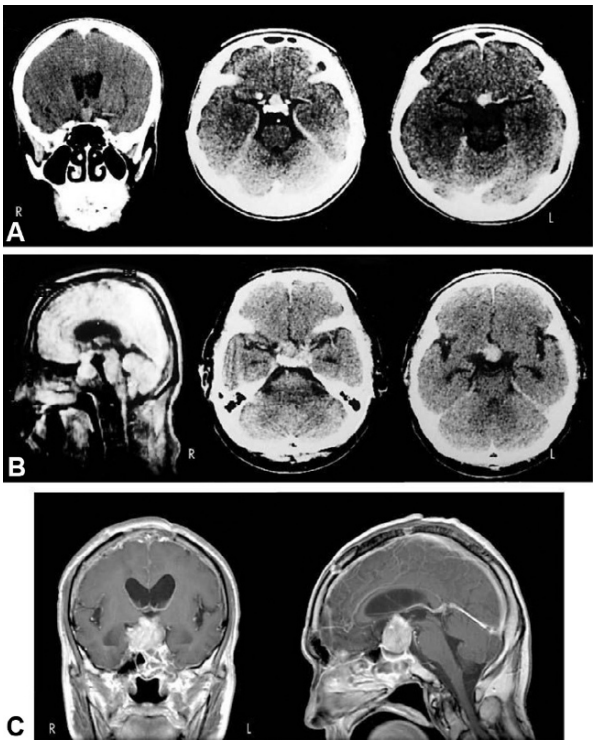

Fig. 15.10. Brain imaging of a pituitary adenoma that extended to the hypothalamus. (**A**) Brain computed tomography (CT) scans of case 1 (coronal and axial planes with contrast enhancement) showed a pituitary tumor extending upward to the hypothalamus and compressing the hypothalamus, optic chiasm, stria terminalis, septal area, and supraoptic area. (**B**) Magnetic resonance imaging (MRI) scan (sagittal plane, proton-weighted image) and CT scans (axial plane with contrast enhancement) of case 2 showed a similar-sized pituitary tumor. (**C**) MRI scans of case 3 (coronal and sagittal planes, gadolinium-DTPA images) showed a pituitary tumor extending upward to the third ventricle and compressing the hypothalamus bilaterally. (Reproduced from Yamamoto et al., 2005.)

In 1926, Holman noted that voiding difficulty could be a sign of posterior fossa tumors. In the series of patients with brain tumors reported by Ueki (1960), voiding difficulty occurred in 46 (30%) out of 152 patients with posterior fossa tumors and UI in three (2%). Children with pontine tumors were reported to suffer from urinary retention (Renier and Gabreels, 1980). Betts et al. (1992) reported voiding dysfunction and diplopia as the presenting symptoms in a young man with a probable dermoid involving the upper pons. Other case histories have been described of patients with retention and focal pontine lesions (Manente et al., 1996; Sakakibara et al., 1996b; Komiyama et al., 1998) (Fig. 15.11). The proximity of the medial longitudinal fasciculus in the dorsal pons to the presumed PMC means that a disorder of eye movements such as an internuclear ophthalmoplegia is highly likely in patients with pontine pathology causing a voiding disorder (Betts et al., 1992; Sakakibara et al., 1996b).

On rare occasions, brain tumor causes bladder-related epilepsy. Andrew and Nathan (1964) described three patients with frontal-lobe tumor who presented with epilepsy; e.g., urinary urgency and UI as a sole seizure or as a prodrome of convulsion. Recently, a similar seizure (Rosenzweig et al., 2011) and a reflex epilepsy

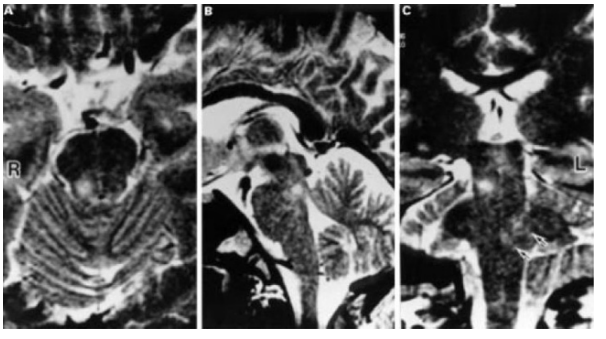

Fig. 15.11. (**A**) Axial view, (**B**) sagittal view and (**C**) coronal magnetic resonance imaging of a patient with rhombencephalitis causing urinary retention and horizontal diplopia. T2-weighted images show a hyperintense focus in the right dorsolateral tegmentum of the rostral pons and arrows indicate amorphous lesions (**C**). (Reproduced from Sakakibara et al., 1998.)

induced by micturition (Okumura et al., 2007; Higuchi et al., 2011) have been reported.

Urodynamic analysis

Not much data are available concerning the urodynamics in UI patients caused by brain tumors. A case of Andrew and Nathan (1965) with a cystic lesion in the frontal basis showed DO. Soler and Borzyskowski (1998) described two children with brainstem tumor. One had DO and normal voiding. The other had DO and incomplete emptying. Yamamoto et al.'s (2005) three cases of pituitary adenoma extending to the hypothalamus showed DO in all three and in two, there was an underactive detrusor during the voiding phase. More recently, Akhavan-Sigari et al. (2014) described 22 skull-base chordoma patients with LUT symptoms. They found DO in 55%, low-compliance bladder in 14%, and uninhibited sphincter relaxation in 27%.

There are further case reports on brain tumor causing urinary retention: tumors in the right motor area (Watts and Uhle, 1935; Ueki, 1960) in three cases. Andrew and Nathan observed that lesions in similar areas to those causing DO led to urinary retention (Andrew and Nathan, 1964, 1965; Andrew et al., 1966). Subsequently Kuroiwa et al. (1981) described a patient with a calcified mass at the rolandic fissure and urinary retention, and Yamamoto et al. (1995) described a woman with a right frontal-lobe abscess who had urinary retention and an acontractile detrusor on cystometry; both her general condition and her bladder function were improved by antibiotic administration. Lang et al. (1996) reported on two elderly female patients with frontal pathology and retention, one of whom recovered bladder function following a successful neurosurgical intervention. As seen in Yamamoto et al.'s (2005) cases, patients with brain tumor may show DO during bladder filling and underactive detrusor during voiding phase (DHIC).

Subdural hematoma and LUTD

Similar to brain tumors, chronic subdural hematoma (CSH) is known to cause UI (Jolobe, 2010). Goto et al. (1986) studied 10 patients with bilateral CSH and stated that the triad of neurologic manifestations, e.g., intellectual deterioration, new-onset UI, and gait disturbance, can be applied not only to NPH (discussed later) but also to bilateral CSH. More recently, Abdel Hafez et al. (2010) reported a UI and DO after subdural hematoma in the left frontal area.

TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) is prevalent all over the world; falls and TBI are also a common occurrence in the elderly (Mosenthal et al., 2004). After various intervals and degrees of consciousness disturbance, motor, sensory, cognitive, and bladder dysfunction may become apparent in any combination. The mechanism of TBI is thought to be heterogeneous, and includes direct trauma, secondary bleeding and infarction, deep shearing injury, and diffuse axonal injury (Andriessen et al., 2010; Jang, 2011). The severity, extent, and site of brain damage following brain injury are variable, but the frontal lobe is a common lesion site.

Reports of LUTD (urinary retention) in TBI date back to 1900s (Friedmann, 1903), but there have not been many studies focusing on bladder function in TBI, particularly LUTD in mild TBI remains unclear.

Moiyadi et al. (2007) described 20 patients with TBI (mean age 32 (9–63) years; 19 men, one woman; main lesion site, diffuse/multifocal four, frontal seven, temporal eight, parietal one). Urodynamics showed DO in seven, low-compliance detrusor in three, and only one patient had postvoid residuals. Bladder dysfunction was more common in patients with severe TBI. Seven of 11 subjects with abnormal urodynamic studies had frontal-lobe injuries. Singhania et al. (2010) described 11 patients with TBI. Three out of 11 patients (27.3%) had DO. All three patients had significant contusions in the right frontal region and two had subarachnoid hemorrhage. None of them had postvoid residuals. At 1-year follow-up, all three patients had a normal voiding pattern.

Little has been described about bladder behavior in patients in a coma or in a vegetative state. Wyndaele (1986) studied the ability to void spontaneously in 135 comatose patients of various etiologies. Seventy-six percent emptied their bladder as soon as the indwelling catheter was removed, although elderly men had more difficulty in becoming independent of an indwelling catheter. Krimchansky et al. (1999) performed urodynamics in 17 patients in a vegetative state 1–6 months after brain injury. Cystometry results indicated that 100% of the patients had a neurogenic DO bladder but none showed DSD.

NORMAL-PRESSURE HYDROCEPHALUS

NPH is characterized by a clinical triad of gait disturbance, memory deficit, and UI, combined with dilated cerebral ventricles and normal cerebrospinal fluid (CSF) pressure (Ishii et al., 2011). Studies analyzing the intracranial hydrodynamics related to the pulse pressure (Greitz, 2004) have indicated that CSF pressure in NPH is not truly "normal," although there is an expected low threshold range. The syndrome was first described by Hakim and Adams in 1965. After five decades of investigation, the effectiveness of the diversion of CSF flow by shunt operation in treating this syndrome is well documented (Ishii

et al., 2011). Recent population-based MRI studies also suggest that the incidence of NPH or asymptomatic ventriculomegaly with features of idiopathic NPH (iNPH) on MRI is around 1% (0.51–2.9%) in the general population of persons over 65 years of age (Iseki et al., 2009), which is about one-tenth the prevalence of WMD, whose clinical picture may be quite similar.

We have studied bladder function in 42 iNPH patients (Sakakibara et al., 2008b) who were diagnosed as having iNPH by clinical symptoms/signs (gait, cognitive, and urinary disorders) with typical imaging features (ventricular enlargement) and normal CSF pressure by a spinal tap test (normal range of opening pressure, 90–180 mm H_2O). The subjects included 36 men and six women and mean age was 72 years (62–83 years). As a result, LUT symptoms were seen in 93% of patients; these symptoms included storage symptoms in 93% of patients (nocturnal urinary frequency, 64%; urinary urgency (OAB), 64%; urgency UI, 57%; diurnal urinary frequency, 36%) and voiding symptoms in 71% (retardation in initiating urination, 50%). As shown above, the majority of our patients (93%) had storage symptoms, and some had OAB dry. These findings indicate that OAB may precede UI in iNPH. Therefore, for both urologists and non-urologic clinicians, it is important to think about not only vascular incontinence but also NPH when we see elderly patients with OAB.

Urodynamic findings in NPH

We performed urodynamics in 42 iNPH patients (Sakakibara et al., 2008b). In the voiding phase, the mean Q_{max} was 11.7 mL/s and the mean PVR volume was 42.1 mL. Among patients whose PVR was increased, PVR >100 mL was noted in six patients. In the storage phase, bladder volume at the first sensation was low (<100 mL) in 33% of patients, normal (100–300 mL) in 67%, high (>300 mL) in none, and the mean bladder volume at the first sensation was 134 mL. In contrast, bladder capacity was decreased (<200 mL) in 57%, normal (200–600 mL) in 43%, and increased (>600 mL) in none, and the mean bladder capacity was 200 mL. DO was seen in 95% of patients. Therefore, the significant urodynamic abnormality that underlies bladder dysfunction in iNPH appears to be DO, which was noted in 95.2% of our 42 patients. Previous reports of NPH have indicated results similar to our own, although the number of cases included in these reports was small (range, 4–12 cases) (Jonas and Brown, 1975; Ahlberg et al., 1988). The reported frequency of DO has ranged from 63% to 100%. Although DO is not uncommon in general older populations, the high prevalence of DO in NPH cases strongly suggests altered brain autonomic control in this disorder.

Cerebral control of the bladder and how it is affected by NPH

Although NPH is a diffuse brain disease with dilated ventricles, hypoperfusion in the frontal lobe has been documented in NPH patients using positron emission tomography (Owler et al., 2004). Therefore, it is possible that the frontal lobe is the anatomic substrate for the development of UI in NPH. We recently studied the correlation between UI and frontal-lobe function in 100 iNPH patients by SPECT and statistical brain mapping (Sakakibara et al., 2012d). There was a significant decrease in tracer activity in the right-side-dominant bilateral frontal cortex and the left inferior temporal gyrus in the severe urinary dysfunction group ($P < 0.05$) (Fig. 15.12).

Shunt surgery of NPH on bladder function

Importantly, bladder dysfunction and frontal-lobe hypoperfusion in NPH can be reversed after shunt surgery. The recovery rate of OAB and UI in iNPH ranges around 20–80%. Among them, cerebral perfusion in the prefrontal cortex and mid-cingulate gyrus tended to return to normal, particularly in patients with good OAB/UI recovery (data not shown). Nowadays, endoscopic third ventriculostomy is being increasingly acknowledged as an alternative treatment for ventriculoperitoneal/lumbar peritoneal shunt, or even as a first-line treatment, in selected patients.

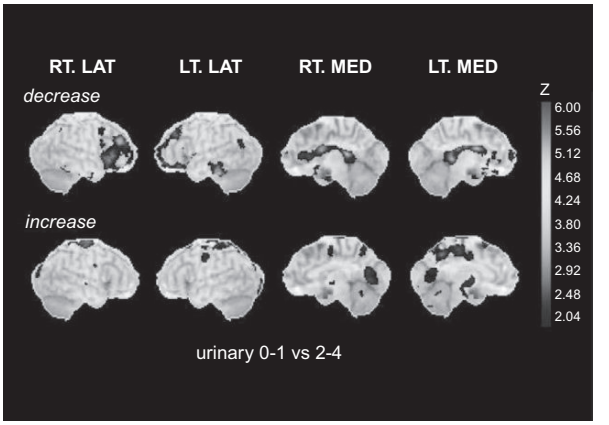

Fig. 15.12. Three-dimensional stereotactic surface projection maps of differences of cerebral blood flow as measured by [123I]-labeled IMP in patients with normal-pressure hydrocephalus with urinary grades of 0–1 and 2–4 ($n = 97$). Upper panel: decrease of tracer accumulation in the group with severe urinary dysfunction as compared to mild urinary dysfunction; lower panel: increase of tracer accumulation in the group with severe urinary dysfunction. Colored areas indicate the areas of statistically significant difference ($P < 0.05$). (Reproduced from Sakakibara et al., 2012d.)

DEEP BRAIN AREAS, BRAIN DISEASES, AND LUTD

Substantia nigra pars compacta

Degeneration of substantia nigra pars compacta leads to an altered fronto-nigro-striatal, dopamine D1-GABAergic direct pathway (Sakakibara et al., 2012c), which is thought to be an anatomic substrate of DO in Parkinson's disease (Sakakibara et al., 2012c; Winge and Nielsen, 2012). No focal diseases affecting substantia nigra and causing LUTD have been reported.

Striatum

Striatum is the major site of lesion in Huntington's disease, where GABAergic cell loss occurs. Degeneration of striatum may also lead to altered fronto-nigro-striatal pathway in experimental animals (Yamamoto et al., 2009). However, in contrast to common bladder dysfunction in Parkinson's disease, bladder dysfunction in Huntington's disease, a degenerative disease affecting both striatum and the cerebral cortex, is not recognized, but has been reported by Wheeler et al. (1985). Four of six patients in their study showed DO. No focal diseases affecting striatum and causing LUTD have been reported.

Hypothalamus

Experimental studies have shown that there are direct fiber connections from the frontal cortex to the periaqueductal gray (PAG) and the PMC, as well as indirect fiber connections via the hypothalamus. In freely moving animals, stimulation of the PAG strikingly reproduced behaviors that are elicited by hypothalamic stimulation, including micturition (Yamamoto et al., 2005). Functional brain imaging has shown activation of the hypothalamus during bladder filling (Fowler and Griffiths, 2010). In experimental settings, chemical stimulation of the medial hypothalamus in freely moving rats elicited defense-like reactions such as locomotion, rearing, and micturition (Silveira and Graeff, 1988), which are akin to those elicited by PAG stimulation (the emotional motor system) (Vargas et al., 2000). This is presumably because the hypothalamus has fiber connections with the limbic brain: the anterior frontal cortex, cingulate cortex, and amygdala. Under anesthesia, electric stimulation of the hypothalamus in cats and dogs elicited either facilitation (particularly in the anterolateral part and the preoptic area) or inhibition (medial part and the Forel's H1 area) of the micturition reflex (Yamane, 1989). The hypothalamus also projects to the sacral Onuf's nucleus that innervates the urethral sphincter muscles (pudendal nerves) (Yamane, 1989). Clinical findings suggest that the hypothalamus has a crucial role in regulating micturition in humans; the reports linking focal lesions of hypothalamus and LUTD have been mentioned under stroke and brain tumors.

Cerebellum

Spinocerebellar ataxia type 6 (SCA6) is a rare neurodegenerative disorder that selectively affects the cerebellum and the olivary nucleus. The responsible gene is the alpha-1A subunit of voltage-gated CaV2.1 (P/Q-type) Ca^{2+} channels (*CACNA1A*), where prolonged cytosine-adenine-guanine (CAG, coding glutamine) repeat is found. While it is believed that SCA6 has a pure cerebellar phenotype, recent studies have shown the presence of LUT symptoms in this disease (Tateno et al., 2012). A case of cerebellitis with LUTD has been reported (Sugiyama et al., 2009). A 43-year-old woman, at age 35, had an acute onset of encephalitis that led to fever, generalized convulsions, and coma. Six months after disease onset, she regained consciousness and developed generalized myoclonus, cerebellar ataxia, and OAB with UI. Eight years after disease onset, she was revealed to have cerebellar atrophy on MRI, cerebellar hypoperfusion on SPECT, and DO on urodynamic study.

Other reports linking focal lesions of cerebellum and LUTD have been mentioned under stroke and brain tumors. A functional SPECT study of multiple system atrophy, in which DO is common, showed reduced tracer activity in the cerebellar vermis during urinary storage and micturition in the patient cohort as compared with a control cohort (Sakakibara et al., 2004). In addition, an MRI study of lesion sites in multiple sclerosis revealed a correlation between LUTD and the cerebellum (Charil et al., 2007). In experimental animals, stimulation of the cerebellum and fastigial nucleus either inhibited or facilitated the reflex (Bradley and Teague, 1969; Martner, 1975; Huang et al., 1979), whereas lesioning mostly facilitated the reflex (Bradley and Teague, 1969; Nishizawa et al., 1989). There are fiber connections between the bladder and the cerebellar vermis both morphologically (Dietrichs and Haines, 2002; Zhu et al., 2006) and electrophysiologically (Bradley and Teague, 1969). Cerebellum furthermore has a dense fiber connection with the prefrontal cortex.

The above clinical and experimental studies suggest that the cerebellum has an inhibitory influence on the micturition reflex. Loss of the cerebellum's inhibition may have led to DO in patients with cerebellar lesion.

Brainstem

Midbrain tegmentum

The midbrain PAG is prone to neuronal degeneration due to vitamin B_1 deficiency (Wernicke's encephalopathy). Clinical characteristics of this disorder include

disturbance of consciousness, nystagmus, gaze palsy, and OAB (Sakakibara et al., 1997), suggesting that the PAG is involved in supraspinal control of micturition. Inflammatory lesions localized at the PAG also caused urinary retention (Yaguchi et al., 2004). The reports linking focal lesions of brainstem and LUTD have been mentioned under stroke and brain tumors.

The PAG plays an important role in emotional responses necessary for basic survival. Stimulation in the PAG of the freely moving rat and cat elicits defense behaviors such as fight, threat display, flight, and immobility. It also triggers reproductive behaviors and analgesia. These behaviors during PAG stimulation can accompany various autonomic responses such as pupil dilatation, piloerection, cardiovascular and respiratory changes, and micturition. Areas adjacent to the PAG include neural pathways for the ascending vigilance system and vertical gaze control (Bandler and Keay, 1996; Blok and Holstege, 1996). As mentioned in Chapter 7, the PAG is the major site of the spino-bulbo-spinal micturition reflex. Electric stimulation of the PAG inhibited the micturition reflex and there were micturition-related neuronal firings in the PAG in cats, suggesting that the PAG is involved in neural control of micturition (Liu et al., 2004).

Pontine tegmentum

The PMC in the pontine tegmentum is the site of the coordination of the spino-bulbo-spinal micturition reflex (Barrington, 1921; Fowler et al., 2008; see Chapter 7). The PMC is located in or adjacent to the locus coeruleus, and the projecting fibers from the PMC to the sacral preganglionic cells are thought to be glutamatergic. Ventral to the PMC is located the pontine storage center (PSC) (Sakakibara et al., 2002), although no direct connection between PMC and PSC is observed. PSC projects fibers to the sacral Onuf's nucleus via a sacral central gray area. This area is involved in lesions due to many different types of lesions, but few reports with small focal lesions can be found in the literature – see under stroke and brain tumors (tumor, Betts et al., 1992; stroke, Sakakibara et al., 1996a; multiple sclerosis, Araki et al., 2003; Charil et al., 2003).

Pontomedullary basis: the medullary raphe area

Parkinson's disease (Doder et al., 2003) and multiple system atrophy (Benarroch et al., 2004) are diseases that result in a depletion of brain serotonin (5-hydroxytryptamine: 5-HT and DO. In particular in multiple system atrophy, the raphe area is commonly involved as a longitudinal line of the cross sign in the pons. In clinical settings, focal lesions at the pontomedullary basis can produce tetraplegia and urinary retention, by affecting bilateral pyramidal tracts (with descending fibers to the bladder) and presumably the raphe nucleus. Recent evidence has suggested that decreased brain 5-HT function might underlie depression (Kalia, 2005), and OAB is common in this disorder (Moghaddas et al., 2005; Sakakibara et al., 2007; Ito et al., 2012). The pontomedullary raphe nucleus has an important amount of 5-HT. The raphe/serotonergic (5-HT) system is known to play a critical role in mediating emotion, regulation of skeletal-muscle motoneurons, spinal transmission of nociceptive signals, sleep, and a variety of visceral reflexes, including respiration, gastric motility, and cardiovascular function (Jacobs and Azmitia, 1992). Recent experimental studies have shown that the raphe/serotonergic system inhibits the micturition reflex (de Groat, 2002), where micturition-related neuronal firing exists (Ito et al., 2006). Focal stroke lesions affecting this area have been described (Tokushige et al., 2012).

MANAGEMENT OF LUTD IN BRAIN DISEASES

The care of patients with LUTD in brain diseases is in accordance with the general LUTD treatment regimen, which should depend on the pathophysiology and be individualized. As discussed above, UI in brain diseases can be divided into two types: neurogenic UI ("OAB wet," in urologic parlance) and functional UI (immobility and loss of initiative/cognition). These two types of UI may occur together. However, the management of the two types of UI differs significantly. Management of neurogenic UI includes anticholinergic drugs to treat the bladder directly, whereas management of functional UI includes behavioral therapy (timed/prompted voiding with physical assistance; bladder/pelvic floor training) (Fig. 15.13) and possibly drugs to treat gait (antiparkinsonian drugs) as well as cognition (antidementives) that further facilitate continence.

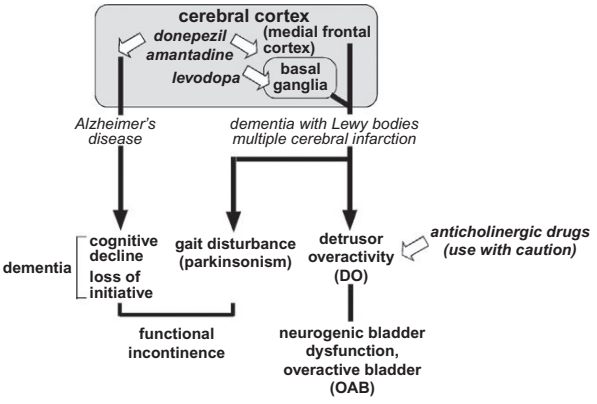

Fig. 15.13. Relationship between functional incontinence and neurogenic incontinence.

In 2005, Thomas et al. meta-analyzed interventions to reduce the occurrence of poststroke UI. Seven trials with a total of 399 participants were included in that review. Four trials tested an intervention against usual care, including acupuncture, timed voiding, and two types of specialist professional intervention. One cross-over trial tested an intervention (estrogen) against placebo. One trial tested a combined intervention (sensorimotor biofeedback plus timed voiding) against a single-component intervention (timed voiding alone). One trial tested a specific intervention (oxybutynin) against another intervention (timed voiding). The interpretation was that there were insufficient data at that time in most studies. However, a single small trial suggested that structured assessment and management of care in early rehabilitation may reduce the number of people with UI at hospital discharge, and have other benefits. Also, continence nurse practitioners in a community setting may reduce the number of urinary symptoms, and increase satisfaction with care. This report suggests that, between functional UI (due to immobility and loss of initiative/cognition) and OAB with UI in patients with brain diseases, treatment of the former has a greater impact. A similar review of behavioral therapies for poststroke UI was done by Dumoulin et al. (2005). Tibaek et al. (2005) reported on the effectiveness of pelvic muscle training in 24 women with poststroke UI (irrespective of type of UI) in a randomized, controlled and blinded study.

In contrast to the intervention of functional UI (due to immobility and loss of initiative/cognition), drug trials for OAB with UI in patients with brain diseases are scarce. Propiverine, an anticholinergic, has been used to treat idiopathic as well as neurogenic DO, including brain diseases (McKeage, 2013). More recently, we (Sakakibara et al., 2013) used an anticholinergic drug imidafenacin in 62 OAB patients following brain disease, including 29 with WMD. We found an improvement of OAB after 0.2 mg/day imidafenacin, without cognitive decline. Subsequently, we (Sakakibara et al., 2014) also used tolterodine in 13 OAB patients following brain diseases, including five with WMD, and found an improvement of OAB after 4 mg/day tolterodine.

Anticholinergic drugs are widely used to treat OAB, including neurologic patients. However, it should be mentioned that most such patients are elderly, and thus their blood–brain barrier (BBB) may be disrupted (Chancellor et al., 2012). The use of medications with anticholinergic side-effects in the elderly is of concern (Donnellan et al., 1997). By crossing the BBB, they can act at the M1-muscarinic receptors in the cerebral cortex and hippocampus, or M4-receptors in the basal ganglia. Factors predisposing patients to cognitive side-effects include central muscarinic receptor affinity, e.g., high M1-receptor selectivity, and permeability across the BBB: size, lipid solubility, fewer hydrogen bonds, neutral or low degree of ionization, and a small number of rotatable bonds (Sakakibara et al., 2008a; Wagg et al., 2010; Pagoria et al., 2011). Darifenacin is an M3-selective antagonist and thus has fewer marked cognitive side-effects, whereas trospium, a quaternary amine, has high polarity and therefore poor permeability across the BBB. It has been shown that the addition of propiverine (a peripheral anticholinergic) to donepezil (a central acetylcholinesterase inhibitor) ameliorated OAB without worsening cognitive function in elderly OAB patients with dementia (Sakakibara et al., 2009). Mirabeglon, a novel selective adrenergic beta-3 receptor agonist, seems to be promising for lessening DO with fewer central side-effects (Tyagi et al., 2011).

For ameliorating poststroke UI, complementary therapies have also been studied. Electroacupuncture showed an improvement together with a bladder capacity increase in poststroke patients (Song et al., 2013). Electroacupuncture has also been reported in the treatment of incomplete bladder emptying after stroke (Yu et al., 2012).

Botulinum toxin has been successful in treating poststroke UI. Kuo (2006) applied 200 U suburothelial injection of botulinum A toxin in 24 patients with DO due to stroke in 12 and suprasacral spinal cord diseases in 12. He found 91.6% achievement of continence in spinal cord diseases but only 50% achievement in stroke.

Transcranial magnetic stimulation at the motor area or the prefrontal cortex was able to lessen DO in multiple sclerosis (Centonze et al., 2007) and Parkinson's disease (Brusa et al., 2009). In stroke, no similar studies are available.

CONCLUSION

Stroke and brain tumor are well-known brain diseases. The incidence of LUTD in these patients ranges from 14% to 53%, mostly OAB, and is higher when the frontal cortex is involved. This presumably reflects damage at the prefrontal cortex, cingulate cortex, and other areas that regulate (mainly inhibit) the micturition reflex. WMD is a chronic, bilateral form of cerebrovascular disease, leading to a high prevalence of OAB of up to 90%. Since WMD is common, particularly in the elderly, WMD may be one of the anatomic substrates for elderly OAB. TBI and NPH affect the brain rather diffusely, and cause OAB at a prevalence rate of 60–95%. Recent neuroimaging studies have shown a relationship between LUTD and the frontal cortex in these diseases. Data on other brain diseases, particularly affecting deep brain structures, are limited. Small infarctions, tumors, or inflammatory diseases affecting the basal ganglia,

hypothalamus, and cerebellum lead to mainly OAB. In contrast, similar diseases affecting the brainstem lead to either OAB or urinary retention. The latter reflects damage at the PAG and the PMC that directly relay and modulate the micturition reflex. UI in brain diseases can be divided into two types: neurogenic UI and functional UI (immobility and loss of initiative/cognition). These two types of UI may occur together, but management differs significantly. Management of neurogenic UI/OAB includes anticholinergic drugs that do not penetrate the BBB easily. Management of functional UI includes behavioral therapy (timed/prompted voiding with physical assistance; bladder/pelvic floor training) and drugs to treat gait as well as cognition that facilitate continence. These treatments will maximize the quality of life of patients with brain diseases.

ACKNOWLEDGMENT

I sincerely thank Clare J. Fowler in the Uro-Neurology Department, the National Hospital for Neurology and Neurosurgery, Queen Square, London; Takamichi Hattori in the Neurology Department, Chiba University, Japan; and David B. Vodusek in the Neurology Department, Lubljana University, Slovenia, who acted as scientific as well as cordial mentors to help produce this manuscript.

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 16

Sexual function after strokes

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Strokes represent the second leading cause of death and the third leading cause of disability-adjusted life years (DALYs), accounting for over 44 million DALYs lost in adults worldwide (Mukherjee, 2011; Hankey, 2013). Thanks in part to better and more available diagnosis, treatment, and rehabilitation, the vast majority of stroke patients tend to survive strokes, particularly in the industrialized world. It is estimated that close to 65 million people have survived a stroke and may need assistance in activities of daily living. The burden of both ischemic and hemorrhagic strokes has significantly increased between 1990 and 2010, including absolute number of strokes (37% ischemic, 47% hemorrhagic), mortality (21% ischemic, 20% hemorrhagic), and DALYs lost (18% ischemic, 14% hemorrhagic) (Krishnamurthi et al., 2013). Both the incidence and the prevalence of strokes are expected to continue to increase markedly within the next two decades as the global population and life expectancy continue to grow (Truelsen and Bonita, 2009).

Motor disability and cognitive changes such as aphasia and visuospatial disorders are most often considered among the major contributors to stroke burden. However, lower urinary tract dysfunctions and disorders of sexual functions are also frequent sequelae of stroke. Sexual dysfunctions after strokes deserve to be emphasized and discussed in detail because they may contribute significantly to lower quality of life and also because their study may improve our understanding of brain physiology and neuropsychology. This chapter discusses the psychologic, psychosocial, and physical changes surrounding sexual dysfunction after stroke and also presents geographic and cultural peculiarities particular to sexual dysfunction. While most strokes cause hyposexuality, this chapter will also address hypersexuality as a sequela to stroke, as well as the role of medications in sexual dysfunctions.

As mentioned in Chapter 1, the new DSM-5, released in 2013 (American Psychiatric Association, 2013), creates a paradigm shift compared to DSM-IV (American Psychiatric Association, 1994), and recommends that we keep in mind that sexuality may be experienced differently according to gender and therefore should be classified and managed accordingly (Sungur and Gunduz, 2014). This chapter will take this point into account and present the few available data concerning differences between men and women.

PHYSICAL, PSYCHOLOGIC, PSYCHOSOCIAL, AND ANATOMIC FACTORS AS DETERMINANTS OF POSTSTROKE SEXUAL FUNCTIONING

Strokes induce physical and psychosocial barriers to sexual activity and both aspects of the problem need to be addressed. Physically, mobility restrictions such as hemiplegia or hemiparesis may affect comfort and positioning and therefore play a significant role in sex after stroke. Most studies show a direct association of decreased sexual activity and level of motor disability. A British study suggests that the level of independence in activities of daily living can be used as a predictor of sexual activity after stroke (Rosenbaum et al., 2014). However, a study by Cheung (2002) demonstrated that even patients with mild or no physical disability reported significantly decreased sexual activity and difficulty resuming sexual activity after stroke, underscoring the multifactorial nature of poststroke sexual dysfunction.

Depression and anxiety, which are common after stroke, are strongly correlated with sexual dysfunction (Rosenbaum et al., 2014). An often-quoted study by Korpelainen et al. (1999) assessed sexual functioning of stroke patients ($n = 192$) and their spouses ($n = 94$).

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Etiologies included brain infarction and intracerebral hemorrhage; in addition, 12 subjects had a subarachnoid hemorrhage. The main intent of the study was to assess the associations of clinical and psychosocial factors with poststroke changes in sexual functions. The authors reported a marked decline in most measures of sexual function, including libido, coital frequency, erectile dysfunction (ED) in men, and disorders of lubrication in women, as well as a general decline in sexual satisfaction. A large majority of the interviewed patients (79%) and spouses (84%) considered that they had a normal prestroke sexual life. Forty-five percent of patients and 48% of spouses complained of a marked decrease in sexual life following a stroke. Almost one-third of patients and spouses said they no longer had sexual intercourse. A decrease in libido was reported by 57% of participating subjects. According to Korpelainen et al. (1999), psychologic, social, and relationship factors were mainly responsible for this decrease. The most important explanatory variables were a general attitude toward sexuality, which was felt to be "unimportant" by a great majority of subjects with decreased libido. In the Korpelainen et al. (1999) study, 24% of patients ceased sexual activity entirely due to fear of causing a new stroke. Furthermore, 14% of male patients also feared impotence. Depression and drugs such as antihypertension medications were also found to be contributing factors. No relationship was found between sexual function after stroke and gender, marital status of the patients, or etiology of stroke. The authors also concluded that the location of the lesion bore no relation to sexual function changes. Such conclusions, however, are not built on solid ground, since very little information other than the presence of right or left hemiparesis is available on these patients. It is obviously questionable to compare a patient with an intracerebral infarct with one who has suffered a subarachnoid hemorrhage.

Some other studies have attempted to identify a correlation between psychosocial factors, sexual activity, and location of the stroke lesion. Giaquinto et al. (2003) studied sexual changes in 68 patients 1 year after stroke. Sexual decline was common, mainly related to age and physical disability. Further analysis led the authors to conclude that psychologic rather than medical causes are responsible for a decline or discontinuity of sexual activity in stroke survivors. Giaquinto et al. (2003) also stated that their statistical analysis showed no relation between decreased sexual activity and the hemisphere in which the lesion was located, thus failing to support the hypothesis of a critical anatomic location responsible for sexual activity. A selection bias may have been involved, since the authors' exclusion of patients with pronounced aphasia probably excluded those patients with the most severe left-hemisphere lesions. Lesion location apparently played a role in a small group of patients with hypersexuality (see below).

On the other hand, some data suggest that the side and location of the hemispheric lesion make a difference, but here again, there are some apparent contradictions. In an older study, Kalliomaki et al. (1961) found that a decrease in libido was greater following left-hemisphere lesions (37.8%) compared to right-hemisphere lesions (16.7%). Several other studies have also found loss of libido and depression more often associated with left-hemisphere lesions (Renshaw, 1975; Goddess et al., 1979; Kauhanen, 1999). However, opposite results were found in a study focused on changes in sexual functions after strokes in males (Coslett and Heilman, 1986). This study found that the prevalence of major sexual dysfunction (mainly reduced libido and sexual potency) was significantly greater after right- than after left-hemisphere stroke. It is reasonable to conclude that lesions of either hemisphere can affect sexual activities, but for different reasons: aphasia and depression after left-hemisphere lesions, a deficit in arousal and perhaps visuospatial disorders after right-hemisphere lesions. Furthermore, the temporal lobes seem to play a special role in sexual behavior, as shown by patients with the Klüver–Bucy syndrome (see Chapter 6).

Psychosocial factors can also influence poststroke sexual functioning. These factors include a perceived loss of identity, shift in gender roles, and inadequate communication with physicians. In a study by Schmitz and Finkelstein (2010), 29 patients were given semistructured interviews and provided information about sexual issues and their perspectives. The study shows that participants often felt discomfort in talking about sex with their partner. Nearly all participants suggested that the stroke resulted in a shift in their respective relationships, often disrupting defined gender roles and interactions. In some, the new role as "caregiver" conflicted with their sexual needs. In one interview, a husband explained, "it's hard to get rid of that role [caregiver] and be a husband again. I still help her get up, help her move. When she takes a shower, I help her transfer from the tub seat, and help her dry. These are things I don't mind doing. Is that as the husband or the caregiver? I would like to be a husband again" (Schmitz and Finkelstein, 2010). The loss of identity and dependency have significant impacts on the self and, as a result, on sexual functioning.

Participants in the Schmitz and Finkelstein (2010) study also noted that they were uncomfortable talking about sex not just with their partner but also in discussions with their physicians. One stroke survivor commented, "well I think they're ashamed. . .you don't ask about your penis or anything like that because that's

bad." Furthermore, this study also indicated that only one physician discussed sexuality as part of the acute rehabilitation experience, and many patients felt that physicians are uncomfortable discussing sensitive sexual issues. For instance, one of the patients interviewed stated, "[Physicians] haven't been educated enough about being open. They might be a little inhibited themselves" (Schmitz and Finkelstein, 2010).

Does age play a role in the burden of poststroke sexual dysfunctions? A recent paper by Bugnicourt et al. (2014) studied specifically the occurrence of impaired sexual activity in young (less than 60 years old) ischemic stroke patients. They found that one-third of these relatively young persons are affected. In addition, they found that, in some cases, impaired sexual activity occurs even after ischemic events with limited sequelae such as transient ischemic attacks. The main factors associated with sexual impairment were depression and medications. One would expect that stroke-related sexual impairment might affect younger subjects more severely because they and their spouse expect a higher level of sexual activity. For some subjects still of reproductive age, there may also be repercussions for family planning. The literature, including the Bugnicourt et al. (2014) study, does not address these aspects.

THE IMPACT OF POSTSTROKE MEDICATIONS ON SEXUAL DYSFUNCTION

Aside from physical and psychosocial obstacles causing sexual dysfunction, medications which are commonly prescribed after stroke can also have significant effects on sexual functioning. Depression is an important factor influencing sexual dysfunction, and affects 30–50% of poststroke patients in the first year alone (Dafer et al., 2008). While antidepressant effects on sexual dysfunction are detailed in Chapter 27, it is worth reiterating that many of the medications prescribed to attenuate depression tend to substantially impact sexual functioning, including tricyclic antidepressants, monoamine oxidase inhibitors, and selective serotonin reuptake inhibitors (SSRIs). In fact, SSRIs have been shown to induce sexual dysfunction with delayed orgasm, diminished sexual desire, and ED in a greater proportion (30–60%) of treated patients than those in other classes (Gregorian et al., 2002). However, not all antidepressants have been shown to cause hyposexuality. Korpelainen et al. (1998) described a case series where two stroke patients and one patient with Parkinson's disease were treated with the monoamine oxidase inhibitor moclobemide, which resulted in hypersexuality. It is important for physicians and patients to recognize that both depression and antidepressant medications can lead to sexual dysfunction.

In addition to antidepressants, it is certainly worth mentioning that drugs commonly prescribed after a stroke, such as antihypertensive and lipid-lowering medications, also have sexual side-effects. Some of these medications are sexually enhancing, while others cause sexual dysfunction. In a recent review, Nicolai et al. (2014) reviewed cardiovascular drugs and sexual functions. Beta-blockers have been shown to cause serious side-effects of ED and loss of libido in about 21.6% of patients (Nicolai et al., 2014). It is thought that beta-blockers inhibit the sympathetic nervous system, which controls erection, emission, and ejaculation, as well as luteinizing hormone and testosterone release. This is particularly true of first- and second-generation beta-blockers. However, nebivolol, a newer third-generation beta-blocker, appears to have a very low risk of sexual side-effects and in one study and was seen to significantly improve erectile function due to possible nitric oxide modulation.

Angiotensin-converting enzyme (ACE) inhibitors, particularly captopril, have been shown to improve sexual function. However, in the Treatment of Mild Hypertension Study (THOMS), enalapril was associated with a significant decrease in sexual activity when compared to placebo. It is believed that ACE inhibitors prolong the half-life of nitric oxide, and limit degradation of bradykinin, which can lead to improved erectile function. Interestingly, the ACE inhibitor lisinopril has been shown to only temporarily decrease sexual activity (Nicolai et al., 2014). Furthermore, angiotensin II receptor antagonists have a positive effect on sexual function. A study comparing valsartan with atenolol reported an increase in sexual intercourse in patients treated with valsartan (Nicolai et al., 2014). Valsartan also has been associated with improved libido and an increase in sexual fantasies as compared to atenolol (Nicolai et al., 2014). Overall, angiotensin II receptor antagonists show significant beneficial effects on sexual function and can be initiated in patients with sexual side-effects.

Early studies with calcium channel blockers indicated a negative association with ejaculation difficulties as well as gynecomastia. However, the THOMS study demonstrated that amlodipine did not cause sexual dysfunction. This suggests that calcium channel blockers, based on their ability to increase dilation of blood vessels by reducing calcium in smooth muscles, do not have a detrimental effect on sexual function. Statins and lipid-lowering medications have also been reported to improve erectile function in patients who had no cardiovascular risks other than ED. However, in patients with cardiovascular risk factors such as smoking or diabetes, it was suggested that ED was more likely to occur after statin initiation (Nicolai et al., 2014). It is thought that statins may provide sexual benefit due to

antioxidant effects. Overall, the Nicolai review proposes that beta-blockers, cardiac glycosides, and diuretics have a negative effect on sexual function, while alpha-blockers, ACE inhibitors, and calcium channel blockers have no effect, and angiotensin receptor blockers and statins may have a positive effect on sexual function.

THE PREVALENCE AND IMPACT OF POSTSTROKE SEXUAL DYSFUNCTION AROUND THE WORLD

Sexual dysfunction following strokes is fairly frequent and, not surprisingly, is prevalent throughout the world, as shown by studies in Europe (Calabrò et al., 2011), in the USA (Coslett and Heilman, 1986), in Africa (Akinpelu et al., 2013), China (Cheung, 2002), and in the Middle East (Bener et al., 2008; Tamam et al., 2008). In southwestern Nigeria, Akinpelu et al. (2013) aimed to determine the influence of clinical and psychologic factors on sexual dysfunction in poststroke survivors ($n = 77$; 60 males, 17 females). Approximately 95% of participants reported dysfunction in at least one sexual activity (libido, coital frequency, vaginal lubrication, erection, ejaculation, orgasm, or satisfaction with sexual life) after stroke. The participants' sexual function was not affected by the side of hemiparesis; however changes in psychologic factors such as willingness to have sex, general attitudes about sex, and the ability to express sexual feelings were reported to have a negative influence on sexual functioning. These findings indicate that psychologic factors are important in determining sexual function in Nigerian stroke survivors. This study also suggests that a decline in sexual functioning is common amongst Nigerian poststroke patients.

A similar study was conducted in China, where Cheung (2002) attempted to determine the impact of stroke on sexual functioning in patients with minimal or no poststroke disability ($n = 106$; 63 males, 43 females). Approximately 55% of all patients in the study reported a decline in sexual libido after stroke, and coitus became less frequent or absent after stroke in about half of all patients compared to coital frequency before stroke. In addition, almost 53% of males reported either diminished or absent ejaculation after stroke and approximately 75% of females experienced decreased or absent poststroke vaginal lubrication. Regarding sexual satisfaction, only 25% of patients reported adequate sexual satisfaction after stroke. Cheung (2002) mentions that the psychosocial factors likely contributing to poststroke sexual dysfunction include an unwillingness for sexual activity as well as the inability to discuss sexuality with one's partner. This study highlights that psychosocial factors play an important role in libido, sexual activity, and sexual satisfaction. This is in agreement with current western literature regarding poststroke sexual dysfunction.

The prevalence of poststroke sexual dysfunction in different parts of the world is further documented by studies from the Middle East. Bener et al. (2008) conducted a study in Qatar with the goal of investigating the prevalence and risk factors of poststroke ED amongst male patients ($n = 605$). Approximately 48% of participants reported some degree of ED, with 36% reporting severe, 33% moderate, and 31% mild ED. Advancing age (60–75 years), diabetes, hypertension, and hypercholesterolemia were significantly higher in stroke patients with ED compared to stroke patients without ED. The higher prevalence of ED was clearly associated with decreased sexual performance. According to Bener et al. (2008), recent changes in socioeconomic status and lifestyle, such as increased smoking, unfavorable eating habits, and decreased daily physical activities, increased the incidence of stroke and subsequent prevalence of SD in Qatar, leading to more problems with sexual functioning in men.

Another study conducted by Tamam et al. (2008) assessed sexual function in 103 Turkish stroke patients (63 male, 40 female) with no or mild disability. Approximately 6% of participants reported a poststroke coital frequency greater than twice per week compared to approximately 26% of participants reporting the same coital frequency prestroke. In addition, female patients had a significant decline in vaginal lubrication (46% prestroke, 12% poststroke) and orgasm (35% prestroke, 12% poststroke), while male patients were affected in regard to erection (77% prestroke, 37% poststroke) and ejaculation (80% prestroke, 35% poststroke). These results illustrate the importance and prevalence of sexual dysfunction in Turkish stroke survivors.

Given that poststroke sexual dysfunction is prevalent around the world, it is interesting to note that the interpretation of sexual satisfaction after stroke can be influenced by cultural bias amongst different countries. For example, in the Nigerian study conducted by Akinpelu et al. (2013), only 30 participants (40%) reported a dissatisfaction with sexual life despite an overwhelming majority of enrolled patients reporting dysfunction in at least one sexual activity. According to Akinpelu et al. (2013), in the Nigerian cultural context, the ability to have children is perceived as a major determinant of satisfaction with sexual life and this cultural perception may have influenced the participants' responses, resulting in low sexual dissatisfaction scores. In China, Cheung (2002) reported that only six female participants (14%) felt sexuality was important compared to 36 male participants (57%)

who felt the same way. This gender discrepancy in sexual importance may lead to an unwillingness for sexual activity that subsequently contributes to sexual dissatisfaction in the Chinese population.

A third example of cultural influences on sexual satisfaction is mentioned within the Middle Eastern study conducted in Turkey (Tamam et al., 2008). In this study, Tamam et al. (2008) reported a less prominent poststroke decline in sexual satisfaction (despite an overall decrease in sexual functioning) due to a cultural bias of living in a predominantly Muslim population, in which masculinity is equated with virility and femininity is equated with submissiveness and virtue. In light of this concept, nine male patients (14%) and 11 female patients (27.5%) reported prestroke sexual dissatisfaction compared to 29 male (41%) and only 10 female (25%) participants reporting sexual dissatisfaction after stroke (Tamam et al., 2008). Regardless of cultural influences on sexual satisfaction, the overall results from different parts of the world are consistent with the current literature in poststroke sexual dysfunction, confirming that different cultures and ethnicities across the world may influence the reported prevalence of sexual dysfunction in stroke survivors.

HYPERSEXUALITY AFTER STROKE

Are poststroke sexual activities always decreased? An interesting finding of the Korpelainen et al. (1999) study is that about 10% of patients (but none of the spouses) reported increased libido after the stroke without relation to the side and location of the lesion. Those patients, however, were significantly younger than the others. Giaquinto et al. (2003) found increased sexual activity in two of their 68 patients, both of whom had a lesion of the right temporal lobe.

Braun et al. (2003) specifically addressed the question of hypersexuality after stroke. Their study concluded that there are "opposed left and right hemisphere contributions to sexual drive." Their study consisted of a review of previously published case reports of patients with frank hypo- or hypersexuality. Hyposexual patients (seven cases) tended to have left-hemisphere lesions, primarily of the temporal lobe, while hypersexual patients (11 cases) mostly had right-hemisphere lesions, again primarily of the temporal lobe. Libido, they state, seems to be organized in the brain in a doubly dissociated manner. The normal right hemisphere probably inhibits libido and the normal left hemisphere enhances it. Assuming that there is a link between libido and affect, these data are compatible with a number of studies showing a greater incidence of depression in patients with left-hemisphere lesions (Paradiso et al., 2013; Jiang et al., 2014).

CORRELATION BETWEEN STROKE AND SEXUAL INTERCOURSE

In addition to whether stroke can cause hypersexual activity, another interesting question is whether stroke can happen as a result of sexual intercourse. Currently, stroke during sexual intercourse is thought to be quite unusual; however, a few case studies have proposed some underlying pathology that may help establish a relationship between cerebral ischemia and coitus. One of the reported predisposing risk factors to stroke during sexual intercourse is the existence of a patent foramen ovale (PFO). According to current literature, a PFO is present in approximately 35% of the population between the ages of 1 and 29 years, 25% between the ages of 30 and 79 years, and in 20% between the ages of 80 and 99 years (Velicu et al., 2008). It is thought that having a PFO, especially in young patients, can lead to a paradoxic embolus and subsequently cause infarcts in a cardioembolic distribution. However, only a few reports have described stroke in the setting of a PFO during sexual intercourse.

Velicu et al. (2008) published a case report of a young woman on oral contraceptives with a complex atrial septal abnormality, large PFO, and right lower-extremity deep-vein thrombosis who had a striatocapsular ischemic infarct during sexual intercourse. According to Velicu et al. (2008), a paradoxic embolism through a PFO may likely result from the physiologic changes during coitus that are believed to be similar to the Valsalva maneuver. The intrathoracic, central venous, and right atrial pressures that occur during Valsalva, and possibly during sexual intercourse, may result in right-to-left shunting through a PFO if the pressure of the right atrium exceeds the pressure of the left atrium. Interestingly, the patient described by Velicu et al. (2008) had a stroke while at rest, suggesting that an increase in right-to-left shunting that occurs with the Valsalva maneuver may be less important than shunting through a PFO at rest.

A similar phenomenon of right-to-left shunting at rest causing subsequent paradoxic embolism is described by Becker et al. (2004). In their case series, Becker et al. (2004) reported anterior and posterior circulation strokes in four young female patients (ages 23–38 years), all with a PFO. Some of these patients also had additional risk factors of either cigarette smoking or using oral contraceptives. Becker et al. (2004) suggest that, while heart rate and blood pressure increase significantly during coitus, the intrathoracic pressure and direction of flow through interatrial defects during sexual intercourse and orgasm are unknown. This might indicate that, as mentioned above, an increase in intrathoracic pressure is not required to precipitate paradoxic embolization

when right-to-left shunting occurs at rest (Becker et al., 2004). Despite the above case reports proposing a mechanism for stroke in the setting of a PFO, it is important to note that the existence of a PFO, either alone or together with an atrial septal abnormality, is not enough to constitute an increased stroke risk (DiTullio et al., 2007).

Postcoital headache is another predisposing factor that may provide insight into the underlying relationship between sexual intercourse and stroke. Headaches have served as an indicator of acute stroke immediately after intercourse, but have typically been attributed to either intracerebral hemorrhage or subarachnoid hemorrhage (Yeh et al., 2010). Few cases exist in which postcoital headaches lead to acute ischemic strokes. Calabrò et al. (2013) describe a young female patient, aged 23 years, on oral contraceptives who suffered from a right ischemic striatal stroke after suddenly experiencing an "explosive" headache during orgasm. According to Calabrò et al. (2013), hyperventilation during the normal human sexual response may lead to reduced cerebral blood flow by up to 50% of baseline and cause subsequent headaches due to cerebral artery narrowing shortly after orgasm. Segmental cerebral artery vasospasm may be a presumed pathogenesis for acute strokes as a complication of these postcoital headaches (Calabrò et al., 2013).

These case reports highlight that sexual intercourse could be a possible, though unusual, trigger for stroke. Even though there is proposed underlying pathology that may explain a mechanism between coitus and cerebral ischemia, the relationship between stroke and sexual intercourse is still largely unknown.

CONCLUSION

A few points should be raised in conclusion. DSM-5 (American Psychiatric Association, 2013) urges us to be aware of possible differences between men and women in terms of sexual dysfunction. None of the post-stroke studies reviewed in this chapter addresses this question directly. Kalliomaki et al. (1961) and Kauhanen (1999) found that gender was not related to development of depression or loss of libido. The few data available from other studies suggest that, if differences exist, they are mainly related to psychosocial and cultural factors.

We have stated that sexual dysfunctions after a stroke are frequent. This is also because strokes often occur within a background of other sexual dysfunction risk factors, such as generalized atherosclerosis or diabetes. It needs to be stressed, however, that in some cases they do not occur or are temporary. To quote an autobiographic report by a physician who suffered a left-hemisphere stroke:

> *I had heard it said that following a stroke, sex is finished. I want to clear up that misapprehension now. It is true of course that certain physical difficulties, such as hand or leg paralysis might alter athletics, but physical difficulties do not alter orgasmic potential (Dahlberg and Jaffe, 1977).*

On the other hand, when they occur, sexual dysfunctions are clearly multifactorial. A better understanding of the psychosocial and physiologic mechanisms underlying sexual functioning can provide insight into improving sexual activity and therefore quality of life in patients affected by strokes and other brain lesions.

ACKNOWLEDGMENT

We wish to thank Margaret Forbes for her judicious advice on an earlier version of this chapter.

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 17

Sexuality in patients with Parkinson's disease, Alzheimer's disease, and other dementias

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INTRODUCTION: NEURODEGENERATIVE DISEASES OF THE NERVOUS SYSTEM

Neurodegenerative diseases of the nervous system comprise a group of disorders which range from being very rare to very common, in which there is a progressive decline in function of a neurologic system or systems from a previous level of normalcy to a lower level of function. Clinically these disorders usually begin insidiously, after a long period of normal nervous system function and pursue a gradually progressive course. Each disease presents with distinct clinical features derived from the fact that they affect specific parts or functional systems of the nervous system; most of the degenerative diseases are characterized by the selective involvement of anatomically and physiologically related systems of neurons and some have been also appropriately called system atrophies. In many degenerative diseases, the pathologic changes are somewhat less selective and eventually quite diffuse, but still restricted, largely to certain groups of neurons. Pathologically, neuronal loss is associated with gliosis and, frequently, with misfolding and aggregation of proteins leading to the relentless accumulation of abnormal extracellular and intracellular filamentous deposits in specific cell types, mainly neurons and glia, representing the core features/hallmarks of many neurodegenerative disorders (Jellinger, 2007, 2010).

The major basic processes inducing neurodegeneration are considered multifactorial ones, caused by genetic, environmental, and endogenous factors related to aging. In many cases these diseases appear in more than one member of a family. In both familial and non-familial-appearing forms, involvement of underlying genetic changes is being unraveled; thus it may be more proper to use the term heredodegenerative for this group of disorders. In most cases, even when the causative mutation is known, the precise subcellular mechanism for cellular loss is not. A common underlying phenomenon typical of degenerative diseases is that of aggregation within specific neurons of normal cellular proteins, such as amyloid, tau, synuclein, ubiquitin, and Huntingtin, which becomes a pathologic hallmark for these disorders. This may evolve from protein overproduction, aberrant enzymatic cleavage leading to increased aggregability of a normal protein, or failure of normal mechanisms of protein removal, resulting in its excess accumulation and consequently, these aggregates interfere with cellular function and lead to cell death.

A genetic or molecular classification of diseases may not be practical as there exists a diversity of pathologic changes and clinical syndromes that may accompany a single-gene abnormality as well as several cases for single pathologic or clinical phenotype caused by diverse genetic defects.

For practical purposes, the neurodegenerative disorders are divided based on the presenting clinical syndromes and their pathologic anatomy and the two most common are as follows: (1) syndrome of progressive parkinsonism; and (2) syndrome of progressive dementia.

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PARKINSONISM

Parkinsonism is a common, age-related syndrome, characterized by resting tremor, bradykinesia, rigidity, and postural reflex impairment. Parkinsonism is not very difficult to recognize, but it is important to distinguish among the most common identifiable parkinsonian syndromes. The most common of these various syndromes is Parkinson's disease (PD), which is also the second most common neurodegenerative disease in humans, after Alzheimer's disease. Parkinsonian patients with disorders other than PD are increasingly recognized, and some of them have a degenerative background and have been labeled "atypical parkinsonian disorders" or "Parkinson-plus" because of additional ("plus") features beyond the classic parkinsonian presentation, while others are secondary to various pathogenetic backgrounds and are labeled secondary parskinsonism; one example of the latter group is vascular parkinsonism (Koller, 1992; Tolosa et al., 2006; Wenning et al., 2011).

The National Parkinson Foundation (2010) estimates that there are approximately 4–6 million people with PD across the world. PD is an age-related chronic multisystem disorder, characterized by typical motor and nonmotor manifestations, that progress over time with growing physical disabilities. Pathologically it is characterized by a profound and selective loss of nigrostriatal dopaminergic neurons and widespread accumulation of alpha-synuclein in the nervous system, that begins away from the substantia nigra and propagates toward the caudal brainstem (Fahn, 2010). Studies implicate mitochondrial dysfunction, oxidative damage, abnormal protein accumulation, and protein phosphorylation as key molecular mechanisms compromising dopamine (DA) neuronal function and survival as the underlying cause of pathogenesis in both sporadic and familial PD. While the etiology of these processes leading to dopaminergic neuronal loss is elusive, a combination of genetic susceptibilities and environmental factors seems to play a critical role. The majority of PD cases are sporadic; however, several genes have been discovered, linked to rare familial forms of disease (encoding alpha-synuclein, parkin, DJ-1, PINK-1, LRRK2, and others) (Jellinger, 2007, 2010; Fahn, 2010).

PD appears in all ethnic groups and its incidence rises with age, from $17.4/10^5$ at 50–59 years of age to $93.1/10^5$ at 70–79 years, with a lifetime risk of developing PD of 1.5%. The median age of onset is 60 years, but in 10% of people it begins at 45 years or younger and it is more common in males than in females. The mean duration of the disease from diagnosis to death is 15 years, with a mortality ratio of 2 to 1 (Lees et al., 2009).

The clinical picture of PD comprises both progressive motor (parkinsonian) features and highly prevalent and diverse non-motor symptoms (NMS) that may precede the appearance of motor parkinsonism and as disease progresses may have a greater adverse impact on quality of life (QoL), institutional rates, and health economics than do motor symptoms (Martinez-Martin et al., 2007; Lim and Lang, 2010). Additionally the NMS contribute more to caregiver strain and depression than motor symptoms (Carter et al., 2008). NMS can be divided into the following domains: neuropsychiatric (e.g., depression, anxiety, apathy, hallucinations, cognitive impairment, and dementia); autonomic (e.g., constipation, orthostatic hypotension, urinary disturbances, sweating abnormalities); sleep-related (e.g., insomnia, sleep fragmentation, excessive daytime sleepiness, rapid eye movement sleep behavioral disorder, and restless-leg syndrome); and sensory dysfunction (e.g., pain, changes in smell and olfaction) (Martinez-Martin et al., 2007; Lim and Lang, 2010). Sexual dysfunction (SD) is an additional non-motor problem closely related to a combination of other NMS as well as motor dysfunction.

The most commonly described primary NMS are autonomic dysfunction, sleep disorders, and mood disorders (depression), followed by cognitive abnormalities, pain, and sensory disorders. Additionally it should be mentioned that there are NMS in PD that are secondary to pharmacologic therapy treatment, such as impulse control disorders (ICDs), discussed later in this chapter (Hwynn et al., 2011).

The management approaches for PD can be subdivided into three categories: (1) protective or preventive treatment; (2) symptomatic treatment; and (3) restorative or regenerative treatment. The search for compounds that can slow or halt the progression of PD is an active area of clinical research but as of today PD is still an incurable progressive disease, and no treatment modality has shown convincing evidence-based disease course modification ability.

Restorative approaches represent one step beyond neuroprotection and include cell replacement therapy, wherein cells lost in PD are replaced. Early clinical trials were with human fetal ventral midbrain tissue ectopically transplanted into the striatum of PD patients. There have been mixed results in clinical trials attempting this strategy and, while autopsy and imaging studies verified that the transplanted tissue can survive and functionally integrate, there was a special concern regarding problematic runaway dyskinesia reported in many successfully grafted patients. Several debated issues are yet unsettled, particularly concerning the source of transplanted cells (fetal tissue vs human embryonic stem cells, induced pluripotent stem cells or fetal porcine dopaminergic cells), but also concerning other technical and surgical issues, localization of the graft (putamen versus substantia nigra), level of immune suppression, the risk

for tumor formation and more; as of today cell transplantation cannot be recommended as a routine therapeutic option. The ability to promote endogenous repair through targeted growth factor delivery has been likewise attractive. Several strategies have been studied and are in various stages of research, including intracerebroventricular or intraputaminal infusion of glial-derived trophic factor, transfection of adenoviral and lentiviral vectors for gene delivery (glial cell line-derived neurotrophic factor derivative neurturin or a mixture of tyrosine hydroxylase, aromatic L-amino acid decarboxylase, and guanosine triphosphate cyclohydrolase 1). Gene transfer of glutamate decarboxylase has also been used to inhibit the subthalamic nucleus (STN) and convert STN neurons projecting to the globus pallidus interna (GPi) into an inhibitory pattern (Lees et al., 2009).

Symptomatic treatment of the motor parkinsonian features includes selective type B monoamine oxidase (MAO-B) inhibitors, amantadine, anticholinergic agents, and dopaminergic medications – levodopa and dopamine agonists.

The selective MAO-B inhibitors, selegiline and rasagiline, seem to be associated with delayed disease progression when started early in the course of PD, and, along with amantadine, are considered well-tolerated drugs that exhibit mild antiparkinsonian effects and can be used as initial treatment for newly diagnosed patients. They are less efficacious than the dopaminergic medications, namely levodopa and dopamine agonists (ropinirole, pramipexole, and rotigotine), that are the mainstay of treatment of PD and other parkinsonian disorders. With the latter, most motor symptoms improve, including bradykinesia, rigidity, and gait and, less consistently, tremor. Fatigue lessens, as do a few NMS. Speech, swallowing, and postural instability can improve initially, but axial symptoms are generally less responsive.

Dopaminergic medications substantially improve motor scores and functional capacity and are associated with augmented QoL. Oral levodopa (always given in combination with a peripheral dopa decarboxylase inhibitor, benserazide or carbidopa and possibly with the catechol-*O*-methyl transferase inhibitor, entacapone), is the most effective therapy for PD. However, chronic levodopa therapy is complicated by the development of motor complications, which can be disabling and difficult to treat, and limit the usefulness of the drug. These appear in most patients after 5 years of therapy and include motor fluctuations and involuntary movements, termed levodopa-induced dyskinesia. The motor complications can be delayed or reversed by DA agonists, which are long-acting dopaminergic drugs that theoretically provide more continuous stimulation of striatal DA receptors.

The development of surgical therapies, such as pallidotomy and deep-brain stimulation (DBS) of the STN and the GPi, can provide effective treatment for the motor parkinsonian syndrome as well as levodopa-induced motor complications. Additional strategies offered for advanced PD patients are infusion therapies consisting of continuous infusion of levodopa/carbidopa intestinal gel (Duodopa) by a portable pump directly to the duodenum via percutaneous endoscopic gastrojejunostomy and "rescue" use of a subcutaneous apomorphine penject or subcutaneous infusion of apomorphine (a potent DA agonist) (Rascol et al., 2002; Lees et al., 2009; Connolly and Lang, 2014).

Various treatment approaches are available for the diverse NMS that patients encounter all through their disease course. These include antidepressants, anxiolytics, sedatives, and laxatives. Only treatment of SD will be addressed in this chapter.

Around 15–20% of patients with a tentative diagnosis of PD have a distinct diagnosis at postmortem neuropathologic analysis. The most common misdiagnoses are progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal ganglionic degeneration (CBD), and Lewy body disease (LBD).

These atypical parkinsonian disorders are less common than PD and they bear a graver prognosis, as patients exhibit additional extraparkinsonian affliction and are usually less responsive to dopaminergic and other therapy.

The classic PSP phenotype is characterized by postural instability and early falls, early cognitive dysfunction, abnormalities of vertical gaze, and early bulbar dysfunction. The classic CBD phenotype consists of asymmetric parkinsonism, cortical signs (e.g., apraxia, cortical sensory loss, alien limb), and possibly other signs such as dystonia and myoclonus; it is referred to as corticobasal syndrome. MSA is typically characterized by parkinsonism, autonomic dysfunction, and a combination of cerebellar and pyramidal signs. MSA is classified according to the predominant phenotype at onset into MSA parkinsonism or MSA cerebellar type, and up to 80% of patients develop most of the characteristic features during the course of the disease. LBD is addressed in the dementive disorders section (Wenning et al., 2011).

DEMENTIA

Dementia describes a global deterioration in cognitive abilities. It is often associated with behavioral and psychologic symptoms and interferes with functional daily activities, in a previously unimpaired person, beyond what might be expected from normal aging. The global prevalence of dementia is about 24 million, and has been

predicted to quadruple by the year 2050 (Thies et al., 2013). The incidence rate for dementia increases exponentially with age, with the most pronounced increase occurring through the seventh and eighth decades of life. Dementia may be static and result from strategically located focal brain damage, or progressive, resulting from evolving brain pathology. The most common causes of progressive dementias are the degenerative diseases, Alzheimer's disease (AD), frontotemporal dementia (FTD), LBD, and vascular brain disease, i.e., vascular dementia. The cognitive and behavioral syndromes in these conditions are caused by neuronal dysfunction and loss of synapses which culminate in neural network disconnection and loss of function.

Most forms of dementia develop gradually and have a preclinical stage, during which there is a decline in one or more cognitive domains, typically including memory, greater than would be expected for age and education. The term mild cognitive impairment (MCI) describes these prodromal stages in which the person is no longer cognitively healthy but does not fulfill clinical criteria for the various forms of dementia. MCI is a risk factor for future cognitive decline and dementia. The annual rates of conversion of MCI to dementia is between 10% and 15%, compared with 2–3% seen in cognitively normal elderly persons (Petersen et al., 2001a, b). MCI is frequently associated with behavioral symptoms: depression, apathy, irritability, anxiety, and agitation are reported most frequently. Inappropriate sexual behavior has been reported in patients diagnosed with MCI (Lyketsos et al., 2002; Hwang et al., 2004; Alagiakrishnan et al., 2005).

Alzheimer's disease

AD is the most common cause of degenerative dementia. Based on its age of onset, AD is classified into early-onset AD (onset <65 years), accounting for 1–5% of all cases, and late-onset AD (onset ≥ 65 years), accounting for $>95\%$ of affected individuals. The key pathologic changes observed in AD brain tissue are amyloid-β peptide deposited extracellularly in diffuse and neuritic plaques, and hyperphosphorylated tau protein, a microtubule assembly protein accumulating intracellularly as neurofibrillary tangles. Additional changes include amyloid angiopathy, granulovacuolar degeneration, reactive microgliosis, and widespread loss of neurons and synapses. Cell loss in the nucleus basalis of Meynert in the basal forebrain, which is responsible for most cortical cholinergic projections, results in depletion of cortical acetylcholine, the most notable neurochemical alteration in AD. Deficiencies in DA, norepinephrine, and serotonin have also been detected. The cause of AD has not yet been discovered. Both genetic and environmental risk factors are held responsible for the clinical manifestation and rate of clinical deterioration. About 2% of all AD cases are associated with autosomal-dominant mutations causing early-onset familial AD. These include mutations of the APP gene on chromosome 21, of presenilin 1 gene (PSEN1) on chromosome 14, and of presenilin 2 gene (PSEN2) on chromosome 1. The allelic variant of apolipoprotein E (APOE), ϵ4, on chromosome 19 has been associated with elevated risk for late-onset AD. Clinically AD is diagnosed when there is an insidious onset and a gradual deterioration of cognition and behavior, usually characterized initially by memory impairment and word-finding difficulties. Gradually additional deficits such as impairment of visual recognition and of executive functions increase. Behavioral changes, impaired reasoning, judgment, and problem solving may emerge as the initial presentation of the disease or may surface along the course of the gradual deterioration. Most patients with AD exhibit some form of behavioral disturbances in the course of their disease (Lyketsos et al., 2002) and up to 25% exhibit inappropriate sexual behavior (ISB) (Tsai et al., 1999; Black et al., 2005; Derouesné, 2009).

Dementia with Lewy bodies

LBD is the second most common cause of neurodegenerative dementia in the elderly and accounts for 15–20% of cases. LBD is clinically characterized by progressive cognitive decline, predominantly of executive functioning, fluctuating cognition, or level of consciousness, visual hallucinations, rapid eye movement sleep behavioral disorder and spontaneous motor signs of parkinsonism. Sensitivity to neuroleptic compounds and low DA transporter uptake on single photon emission computed tomography or positron emission tomography images are additional characteristic features. Pathologically, LBD is characterized by Lewy bodies, comprised primarily of abnormal aggregations of the protein alpha-synuclein, affecting the brainstem substantia nigra, locus coeruleus and raphe nuclei and in addition limbic, paralimbic, and neocortical regions. Amyloid plaques, the pathologic hallmark of AD, are present in most individuals with LBD, whereas neocortical neurofibrillary tangles are almost absent. The neuropathologic processes in LBD affect dopamine, norepinephrine, serotonin, and acetylcholine neurotransmitters. The clinical symptoms of LBD overlap with those of both AD and PD (McKeith et al., 2005). Up to 98% of patients with LBD experience neuropsychiatric symptoms, including delusions, hallucinations, apathy, anxiety, irritability, and agitation. ISB has been described rarely (Prakash et al., 2009).

Vascular dementia

Vascular cognitive impairment encompasses all instances where cognitive impairment is attributed to brain injury due to cerebrovascular disease. Vascular dementia is diagnosed when the cognitive and behavioral impairments are severe enough to interfere with everyday social and occupational function. Risk factors for vascular cognitive impairment include atherosclerosis, arteriolosclerosis, amyloid angiopathy, and other blood vessel wall or blood pathologies causing ischemic or hemorrhagic brain injury. About 25–32% of persons meet criteria for dementia 3 months poststroke (Pohjasvaara et al., 1998; Desmond et al., 2000). Pathologically, all degenerative dementias coexist with vascular brain pathologies. The most common cause of vascular dementia is multiple subcortical lacunar infarcts. A single strategically placed symptomatic infarct (in the anterior or dorsomedial, thalamus, genu of the internal capsule) can also lead to a dementia syndrome by disrupting frontal-subcortical networks. Clinically, the cognitive and behavioral impairments reflect the location and extent of the vascular brain injury and the neural networks that become disconnected due to the vascular event. The ensuing neuropsychologic profile due to subcortical ischemic vascular disease is characterized by impairment of attention and executive function, depression, emotional lability, and apathy. Aberrant sexual behavior has repeatedly been reported in association with vascular dementia (Tsai et al., 1999; Alagiakrishnan et al., 2005).

Frontotemporal lobar degeneration (FTLD)

FTLD is a clinically, genetically, and pathologically heterogeneous syndrome, characterized by progressive decline in behavior or language associated with degeneration of the frontal and anterior temporal lobes. FTD denotes the clinical syndromes whereas FTLD describes the neuropathologic manifestations. FTLD is a leading cause of dementia in patients presenting before the age of 65 years. FTLD overlaps clinically and pathologically with neurodegenerative diseases associated with prominent movement abnormalities, including PSP, CBD, and amyotrophic lateral sclerosis. Clinically, three predominant variants of FTLD have been described: (1) the behavioral-variant (bvFTD), characterized clinically by emotional and behavioral deterioration and pathologically associated with frontal cortical degeneration; (2) the semantic dementia variant, clinically characterized by progressive loss of knowledge about words and objects and pathologically associated with anterior temporal neuronal loss; and (3) the non-fluent aphasia variants, characterized by effortful language output, loss of grammar and motor speech and associated with left perisylvian cortical atrophy. There are three major histologic types associated with FTLD: (1) FTLD-TAU, characterized by inclusions of misfolded tau protein (tau-positive); (2) FTLD-transactive response DNA binding protein 43 (TDP-43) characterized by inclusion of TDP-43 in neurons and glia cells; and (3) FTLD fused in sarcoma protein (FUS), which is characterized by FUS misfolded protein-positive inclusions. Although most cases of FTD are sporadic, several gene mutations causing various FTD manifestations have been described, including mutations in tau (MAPT), progranulin (PGRN), CHMP2B, VCP, TDP-43 (TARBP), and C9ORF72 genes. Clinically, bvFTD is frequently associated with disrupted executive functions, inappropriate interpersonal behavior, disinhibition, apathy, impulsivity, loss of empathy, sympathy, and insight, and is the dementia syndrome that is at the highest risk of being associated with aberrant and inappropriate sexual behavior (Neary et al., 1998; Harris et al., 2013).

SEXUALITY AND QUALITY OF LIFE IN NEURODEGENERATIVE DISORDERS

The World Health Organization (2006) refers to sexuality as a central aspect of life and declares that it is a fundamental right of the individual to enjoy and control sexual and reproductive behavior in accordance with social and personal ethics.

Sexual functioning is a complex process that requires functioning of the body's autonomic, sensory, and motor systems and depends on the neurologic, vascular, and endocrine systems, allowing sufficient blood supply to and from genital organs, a balanced hormonal system, and a healthy emotional state (Basson et al., 2010). Four main factors are involved directly and indirectly in the deterioration of sexual health of patients with chronic disease (Bronner, 2001). SD may be caused directly by: (1) the disease and comorbid illness; (2) medications and other treatments; and indirectly by: (3) general consequences of a chronic illness (fatigue, weakness, impaired mobility, concentration problems); and (4) psychosocial problems (depression, anxiety, change in self-esteem and body image, aging, role changes, relationship difficulties) (Rees et al., 2007; Basson et al., 2010; Verschuren et al., 2010; Martin et al., 2014).

Patients or partners may fear resuming sex and become anxious whenever they try to participate in intimate activities. It is not surprising that about one-quarter of sexually active men and women stopped having partnered sex after their PD diagnosis (Bronner et al., 2004). Recognizing the importance of sexual health leads to an understanding that sexual assessment should become an integral part of the neurologic assessment, involving

patients and their partners (Bronner, 2009; Bronner and Hassin-Baer, 2012), and treatment of sexual issues should be handled comprehensively by experts presenting multifaceted disciplines (Bronner and Vodusek, 2011).

The occurrence of SD in patients with neurologic disabilities may be associated with a considerable amount of unhappiness and poor QoL (Chandler and Brown, 1998). In a study of 91 PD patients, it was found that the patient's general satisfaction from life was significantly correlated with the patient's quality of sexual life (QoSL), measured by QoSL questionnaire (Moore et al., 2002).

The impact of PD on QoL was reported to be greater among younger than older patients (Schrag et al., 2003), and this may be attributed to higher frequency of loss of employment, disruption of family life, greater perceived stigmatization, and prevalence of depression. Young-onset PD patients represent a more vulnerable group, at higher risk for worsening of their QoSL and QoL (Koller et al., 1990; Wermuth and Stenager, 1995; Schrag et al., 2003; Wielinski et al., 2010).

PARKINSON'S DISEASE AND SEXUALITY

Dopamine and sexual behavior

The most prominent neurotransmitter deficit in the brains of patients with PD is that of DA, followed by other deficits regarding norepinephrine, serotonin, and acetylcholine (Lang and Lozano, 1998). Experimental and human evidence suggests that dopaminergic mechanisms have a role both in determination of desire and in induction of penile erection. The issue whether DA is important in sexual reward has been debated for many years; compounds that modulate DA transmission have been shown to exert a major effect on motor function and general arousal; thus it has been difficult to differentiate between the latter and a specific influence on sexual arousal and incentive.

Paredes and Agmo (2004), in their extensive review on the physiologic role of DA in control of sexual behavior, found no convincing experimental data indicating that DA has any distinct effect on sexual motivation; they did present experimental evidence that DA is of no importance for sexual reward. They argued that DA release by the nucleus accumbens is associated with diverse events, aversive as well as appetitive, and that it promotes arousal and activation of non-specific motor patterns. They concluded that the nucleus accumbens is a structure with at most a marginal importance for sexual behavior.

Aside from the mesolimbic pathways, additional dopaminergic pathways do have specific roles in sexual function. In the tuberoinfundibular system, DA reduces the release of prolactin (that has an antilibidinal effect) and may also influence gonadotropin-releasing hormone and gonadotropin secretion. In the incertohypothalamic system dopaminergic neurons from the zona incerta project to nuclei, including: (1) the medial preoptic area, which was shown in animals to be a critical structure for male sexual behavior; and (2) the paraventricular nucleus, where DA activates oxytocinergic neurons that project to the hippocampus, medulla oblongata, and spinal cord, and play an important role in the consummatory phase, sexual motivation, and sexual reward (Paredes and Agmo, 2004).

Dopaminergic cells in the dorsal and posterior hypothalamus, in the diencephalospinal system, extend into the periventricular gray of the caudal thalamus and project to several levels of the spinal cord, where they are involved in the regulation of erection, activity of the penile striated muscles, and ejaculation. Moreover the motor neurons of the ischiocavernosus muscle have a high density of DA D2 receptors (Paredes and Agmo, 2004).

Evidence suggesting involvement of DA in desire and sexual motivation is driven by several cases of hypersexuality (HS) arising from treatment with dopaminergic agents. As mentioned in more detail further in the chapter, HS is one of a spectrum of ICDs associated with dopaminergic therapy for PD, found to occur in up to 17% of patients with PD, that also include pathologic gambling and eating, compulsive shopping, as well as the DA dysregulation syndrome (Vilas et al., 2012).

Sexual dysfunction in men and women with Parkinson's disease

Gender and age differences

Sexual problems are commonly reported in PD (68% of men, 36% of women) (Brown et al., 1990). Gender differences of SD patterns have been demonstrated. In men the predominant SD were found to be erectile dysfunction (ED), difficulties in reaching orgasm, and premature ejaculation (PE), whereas the predominant symptoms for women with PD were low sexual desire and difficulties with arousal and with orgasm (Wermuth and Stenager, 1992; Basson, 1996; Bronner et al., 2004; Kummer et al., 2009) (Table 17.1). Female patients were less dissatisfied with their sex life than males (Brown et al., 1990; Bronner et al., 2004). In a recent study of 89 PD patients, although men reported significantly higher sexual desire, women were more satisfied with their sex life (Bronner et al., 2014); the explanation offered was that the male SD interfered with the traditional active role, creating a devastating effect on the man's self-esteem and his overall sexual experience; this idea has been suggested by others as well (Brown et al., 1990; McCabe and Taleporos, 2003).

Table 17.1

Sexual problems in men and women with Parkinson's disease (PD)

Type of sexual problem		All patients (%)	Men with PD (%)	Women with PD (%)
Deterioration of sexual functioning		70[1] 55[2]	76.7[3] 38[4] 33[2,5]	80[2] 78.1[3] 75[4] 59.1[5]
Sexual dissatisfaction		37[6]	65.1[3] 59[7] 36[8]	37.5[3] 36[7] 20[8]
Desire disorders	Decreased sexual desire		84[9] 59.2[10] 44[1] 27[2] 23.3[3]	83[9] 75[10] 70[2] 62[1] 46.9[3]
	New-onset heightened sexual interest	8.8[11]		
	Compulsive sexual behavior/hypersexuality	1.7–3.5[12–14]	5.2[12]	0.5[12]
Arousal disorders	Erectile dysfunction		79[9] 68.4[3] 54[1]	
	Impaired arousal			87.5[3] 67[1]
	Vaginal dryness			38[1]
Orgasm disorders	Premature ejaculation		40.6[3]	
	Difficulties in reaching orgasm (or delayed ejaculation in men)		87[9] 50[1] 39.5[3] 23.8[4]	75[1–2]
Sexual pain disorders				21.9[3]

[1]Koller et al., 1990; [2]Wermuth and Stenager, 1992; [3]Bronner et al., 2004; [4]Basson, 1996; [5]Hand et al., 2010; [6]Wielinski et al., 2010; [7]Brown et al., 1990; [8]Jacobs et al., 2000; [9]Sakakibara et al., 2001; [10]Kummer et al., 2009; [11]Giladi et al., 2007; [12]Weintraub et al., 2010a; [13]de Chazeron et al., 2011; [14]Voon et al., 2006.

Younger PD patients have been found to be significantly more dissatisfied with their sex life, especially when the patient was a man, unemployed, and complained of ED or PE (Brown et al., 1990; Jacobs et al., 2000). Sexual dissatisfaction was significantly affected by motor symptoms in men, by anxiety in women, and by depression in both (Kotková and Weiss, 2013).

Decreased interest in sex was reported by 65.6% of PD patients and it was associated with motor sign asymmetry, which was more common with left-side predominant parkinsonism (Kummer et al., 2009). Women with PD reported reduced sexual activity more commonly than men (80% vs 33.4%) and 70% reported reduced libido compared with 27% of men (Wermuth and Stenager, 1992). Regression analysis showed that age, female gender, lower education, higher Beck Depression Inventory scores, and depression (but not antidepressant therapy) were associated with decreased sexual desire (Kummer et al., 2009). The risk of reduced sexual activity and libido increased with PD duration and with advancing Hoehn and Yahr stage (Wermuth and Stenager, 1992).

Sexual dysfunction in women with PD

While the female sexual response involves neurotransmitter-mediated vascular and non-vascular smooth-muscle relaxation, resulting in increased pelvic blood flow, vaginal lubrication, and clitoral and labial engorgement, it is readily affected by psychologic and relationship factors (Berman et al., 2000). Due to this highly complicated mechanism, sexual problems are common among women in the general population, and it is estimated that 40–45% of adult women suffer from some form of SD (Lewis et al., 2010). SD in women with PD are presented in Table 17.1.

A general deterioration in sexual life was reported among 78.1% of women with PD, and the most frequently mentioned problems were related to arousal (87.5%), orgasm (75.0%), and desire (50%) (Bronner et al., 2004). Female patients describe changes in the nature of orgasm, not reaching a distinct peak, but rather a number of high points, followed by an abrupt decline (Basson, 1996). Women with PD suffer from vaginal dryness (Bronner et al., 2004) and reduced arousal and sensuality (Brown et al., 1990). When compared with age-matched healthy women, women with PD had a significant increase in vaginal tightness, involuntary urination during intercourse, anxiety, depression, and sexual dissatisfaction (Koller et al., 1990; Welsh et al., 1997). Urinary incontinence, one of the PD NMS, negatively influences libido and sexual activity in women, but not men (Wermuth and Stenager, 1992). This finding is not specific for women with PD, as sexual function was negatively affected by the presence of lower urinary tract symptoms (urinary incontinence, detrusor overactivity) in 236 non-parkinsonian women, causing a great degree of SD (Cohen et al., 2008). The sexual domains most affected were desire, lubrication, orgasm, and satisfaction.

Worsening of menstrual symptoms was reported by young PD females, especially in those with more advanced disease (Rubin, 2007). Since the onset of PD these women complained of increased premenstrual symptoms, pain, and excessive bleeding. Women in support groups were concerned by their body and sexual image, and frequently raised the topic of feeling distressed and unattractive (Posen et al., 2000; Schartau et al., 2003). These issues were rarely addressed by healthcare professionals who work with PD patients.

Sexual dysfunction in men with Parkinson's disease

ED is the most studied and published SD in PD (Brown et al., 1990; Koller et al., 1990; Singer et al., 1992; Raffaele et al., 2002; Bronner et al., 2004; Papatsoris et al., 2006; Gao et al., 2007; Safarinejad et al., 2010). Usually ED affects men several years after the diagnosis of PD, and the risk increases with advancing Hoehn–Yahr stage. ED frequency was higher in PD patients compared with healthy age-matched controls (60.4% vs 37.5% respectively) (Singer et al., 1992). In recent years there has been clinical evidence for the appearance of ED as one of the non-motor signs and symptoms of PD several years before motor symptoms are seen. An association between erectile function and risk of developing PD was studied (Gao et al., 2007). Analyses included 32 616 men free of PD at baseline in 1986. In 2000 the subjects completed a retrospective questionnaire on ED in previous years. Men who reported ED before 1986 were 3.8 times more likely to develop PD during the follow-up than were those with very good erectile function. PE is a prevalent SD in men at all ages, with significant sexual and psychosocial comorbidities (Porst et al., 2007). Forty percent of male PD patients reported PE (Bronner et al., 2004). Based on our clinical experience, PD patients are surprised by an abrupt new onset of inability to control their ejaculation, even before vaginal penetration. The high estimates of ED, orgasmic and ejaculatory disorders (Table 17.1) may explain the reports on lower sexual satisfaction in men with PD (Hand et al., 2010; Bronner et al., 2014).

Feeling apathetic and lack of sexual interest, despite still being potent, are common complaints reported by male patients or their spouses. While these feelings may reflect coexistent and undiagnosed depression, they can exist independently; testosterone deficiency was found to be a possible explanation for this phenomenon in some patients (Okun et al., 2002; Ready et al., 2004). Nearly 50% of men with PD studied by Ready et al. (2004) were testosterone-deficient, and the level of testosterone correlated with the degree of apathy measured. Generally, androgen deficiency is thought to be responsible for various age-associated conditions such as mobility limitations, cognitive impairment, decreased libido, lack of energy, and depression. Testosterone replacement may lead to relief of some symptoms (Seidman and Weiser, 2013), but a short-term double-blind, placebo-controlled trial that included 30 PD patients with testosterone deficiency failed to improve motor and non-motor symptoms of PD (Okun et al., 2006).

Sexual dysfunction in parkinsonian patients and their partners

SD and relationship problems are reported by PD patients and their partners, across both genders and all age groups (Hand et al., 2010). Couples complain of reduced frequency of sexual activity, decreased desire, difficulty in sexual communication, difficulty in reaching orgasm, and general sexual dissatisfaction (Brown et al., 1990; Bronner et al., 2004; Wielinski et al., 2010). The most affected were couples in which the PD patient was a man. While 65% of male patients and 52% of their female partners reported moderate to severe sexual problems, only 34% of female PD patients and none of their partners perceived these difficulties (Brown et al., 1990). In another study, sexual function of 17 female partners was severely compromised in all dimensions: arousal, behaviour, orgasm, fantasy, and drive (Yu et al., 2004). Some underlying factors could explain the reduced sexual function in

female partners of PD patients: the need to fill the role of a caregiver, the burden that becomes heavier as the disease progresses both physically and mentally, the reduced attractiveness of the PD partner due to abnormal movements, sloppy dressing, masked facies, excessive sweating, or salivation. Bed separation in reaction to tremor and sleep disturbances probably contribute to the lower rate of sexual activity. The considerable effect of PD on the sexual and couple relationship challenges healthcare professionals to focus on the needs of both partners and plan specific interventions that may improve the QoSL and consequently QoL of these couples (Hand et al., 2010).

Effect of Parkinson's disease medications and other interventions on sexuality

A few studies have reported "positive" or favorable increases in sexual desire and sexual well-being associated with dopaminergic therapy. This has not been adequately studied. In 1972 Yahr and Duvoisin reported on resumption of sexual activity in 8% of PD patients following treatment initiation with L-dopa. The suggested mechanism was the positive effect of the drug on motor function. Since then there have been numerous reports of spontaneous erections on DA agonist treatment, including pergolide, ropinirole, and apomorphine. In 2002 Kanovský and colleagues reported spontaneous penile erections in PD patients treated with pergolide and studied this issue further in a small prospective open-label study of PD patients who were treated for motor dysfunction with add-on pergolide; they found global improvement of sexual function (Pohanka et al., 2004, 2005).

The erectogenic effects of apomorphine hydrochloride, a synthetic morphine derivative with potent short-acting DA receptor agonist activity, have been used in the treatment of ED in PD as well as the non-PD population (O'Sullivan and Hughes, 1998).

Dopaminergic therapy may affect sexual behavior through direct stimulation of the D2 receptor in the medial preoptic area, inhibiting prolactin secretion (thus eliminating its antilibidinal effect) or by increasing the plasma level of oxytocin, which produces erectogenic effects in the lumbosacral spinal cord (Paredes and Agmo, 2004; Mohee et al., 2012).

Rare cases of sexual changes were reported in association with medications used in PD, including spontaneous ejaculation and female orgasm (O'Sullivan and Hughes, 1998; Fine and Lang, 1999; Chuang and Lang, 2009; Kaut et al., 2012). A case of frequent spontaneous ejaculations secondary to rasagiline (a selective irreversible MAO-B inhibitor) taken in combination with levodopa therapy was described in a 65-year-old man. These ejaculations occurred without an erection and without being engaged in any self-stimulating or pleasurable situation. In between, the patient had normal sexual function and no other autonomic abnormality. The phenomenon disappeared when rasagiline was discontinued (Chuang and Lang, 2009). Undesired and highly embarrassing spontaneous orgasms were experienced by a 52-year-old woman with multifocal dystonia, following initiation of pramipexole therapy as well as with ropinirole, and disappeared when they were discontinued (Kaut et al., 2012).

While depression, caused through serotonergic, noradrenergic, and dopaminergic mechanisms, occurs in approximately 45% of all patients with PD (Lemke, 2008), it is commonly underdiagnosed and undertreated. Levodopa and other dopaminergic therapy does not seem to have consistent antidepressant effects. There are only a few randomized, controlled, double-blind studies of antidepressant treatment in PD. However, tricyclic antidepressants (TCA) and newer selective antidepressants, including selective serotonin reuptake inhibitors (SSRI) and norepinephrine reuptake inhibitors appear to be effective in treating depression in PD and are very commonly used. Selective reuptake inhibitors seem to be generally better tolerated than TCA because of their favorable side-effect profile, but adverse sexual consequences with significant SD are significant problems that limit compliance and use in PD, as frequently as, if not more so, in the non-PD population (Lemke, 2008, Rocha et al., 2013).

TCAs cause SD, especially anorgasmia, in 20–30% to 90% of patients treated with imipramine and clomipramine, respectively (Segraves, 2007). SSRIs cause anorgasmia or delayed orgasm in 30–40% of treated patients, with paroxetine being the most commonly attributed, followed by sertraline, fluvoxamine, citalopram, s-citalopram, and fluoxetine. The mixed serotonin and norepinephrine reuptake inhibitor venlafaxine has a similar rate of SD as the SSRIs but duloxetine has a lower incidence, as do mirtazapine (an α_2-antagonist +serotonin 5HT-2 and 5HT-3 blocker) and bupropion (norepinephrine and DA reuptake inhibitor).

Medications used to treat anxiety, agitation, insomnia, and psychosis are commonly associated with SD. Benzodiazepines may independently cause anorgasmia.

Patients with PD may develop psychotic phenomena and nighttime behaviors that necessitate treatment with atypical antipsychotics, the most accepted of which are quetiapine and clozapine (Connolly and Lang, 2014). Treatment with antipsychotic agents is frequently associated with SD, namely delayed ejaculation. Data are available on psychiatric populations, such as patients with schizophrenia, that are treated with high

doses of these medications, and this problem was more significant for clozapine than for quetiapine; data are lacking concerning SD caused by these medications in patients with PD who are usually treated with much lower doses (Serretti and Chiesa, 2011).

DBS is a well-established therapy for patients with advanced PD, with clear benefits on many of the motor symptoms and improvement of QoL. The effects of DBS on the NMS have not been studied extensively (Ashkan et al., 2013). Emergence of tools to measure the non-motor burden in PD will allow a more objective assessment of impact of DBS on NMS in the coming future. Still, the items addressing SD included in these tools are not elaborate enough and will probably provide unsatisfactory data. The effects of DBS on sexual well-being were studied in a single study. Twenty-one men and 10 women with PD were followed up for a year after bilateral STN DBS. Sexual functioning was assessed using a reduced form of the Gollombok Rust Inventory of Sexual Satisfaction (GRISS) scale. While female patients improved motorwise, they reported no change in sexual well-being; however, male patients reported slightly, but significantly, more satisfaction with their sex life and this effect was more pronounced for patients younger than 60 (Castelli et al., 2004).

Treatment of sexual dysfunction in Parkinson's disease

Various therapeutic interventions are available for sexual difficulties in the PD and non-PD population, including pharmacotherapy (phosphodiesterase type 5 (PDE5) inhibitors; SSRIs), cognitive behavioral therapy, sex therapy, mindfulness-based cognitive therapy, psychologic therapies, and specific sex education. However, due to the complexity of PD, it is important to evaluate the underlying factors that play a crucial role in creating sexual difficulties. This evaluation should be addressed first, before formulating a sexual diagnosis and deciding on an adequate treatment. It is recommended that the assessment involves both partners, seen together and individually. A detailed description of assessment and modalities of treatment and rehabilitation for sexual difficulties and dysfunction in neurologic disease can be found in Chapter 24.

Underlying factors

The following underlying factors of sexual problems in PD should be taken into account:

1. motor dysfunction (e.g., rigidity, tremor, immobility in bed, or difficulty in fine finger movement may impair intimate touching needed for sexual pleasuring and arousal)
2. non-motor dysfunction (e.g., depression and anxiety may result in decreased desire and arousal; sleep disturbances may lead to bed separation, thus decreasing opportunities for intimate contact; fear of urinary incontinence may inhibit arousal and orgasm)
3. drug-induced SD (antidepressants may negatively affect desire, arousal, and erectile function and result in delayed orgasm and ejaculation)
4. spouse sexual problems (SD in PD patient may result in partner's SD, and vice versa; untreated SD in partners may disturb a normal couple sex life)
5. relationship problems (the burden of PD may increase marital tension, followed by decreased interest in sex; speech problems in PD limit couple's intimate communication).

Various pharmacologic, psychologic, and mindfulness treatments for SD are widely discussed by Bronner and Basson (see Chapter 24). We describe here interventions aimed exclusively at sexual difficulties of PD patients and their partners (Bronner, 2009). Depression should be addressed first, given that when patients are severely depressed, sex is the furthest thing from their mind. Depression is one of the common NMS, found in about 30% of advanced patients (Chaudhuri et al., 2006), with a strong association between depression and SD (Koller et al., 1990; Jacobs et al., 2000). Delayed ejaculation is common when men take antidepressants. Consequently, the duration of intercourse may be too long, and female partners may experience sexual pain followed by reduced desire. To prevent the negative effects of delayed ejaculation, a multifaceted intervention should be designed (Bronner, 2009): (1) limiting penile–vaginal penetration time, independently of reaching ejaculation; (2) using effective pleasuring techniques instead of penile–vaginal penetration, e.g., oral or manual stimulation; and (3) trying a "medication weekend vacation," if reaching orgasm or ejaculation is impossible. An interval of 24–48 hours without antidepressants may enable orgasm and ejaculation.

In order to overcome fatigue, pain, motor limitations, and concentration difficulties, patients are advised to adjust medication doses and plan sexual activity in time periods when "they are at their best." They should choose comfortable sexual positions (e.g., side by-side, "spoons" or partner-on-top positions) that demand minimal effort and movement. Patients may overcome difficulties in fine finger movement by using lubricants when they caress and arouse their partners. Use of water-soluble lubricants or almond oil may enable comfortable penile–vaginal penetration for both genders.

When speech is problematic, patients are advised to prepare written notes with pre-planned sentences, covering a variety of topics and enabling them to continue flirting, complimenting, sharing intimate feelings and communicating their feelings of gratitude towards their partner.

Treatment of ED

Oral pharmacotherapy with apomorphine or sildenafil citrate has demonstrated promising results in most patients with PD and ED (O'Sullivan and Hughes, 1998; Giammusso et al., 2002; Raffaele et al., 2002). Raffaele et al. (2002) evaluated the efficacy of sildenafil in depressed patients with PD. At the end of the study, improved erections were reported by 85% of patients, and improvement in depressive symptoms was observed in 75%. In 2010 a report of the Quality Standards Subcommittee of the American Academy of Neurology evaluated treatment options for the non-motor symptoms of PD, including SD (Zesiewicz et al., 2010). Controlled clinical trials were available only for ED. One class II study evaluated the efficacy of sildenafil citrate in treating ED in 12 patients with PD (Hussain et al., 2001). Sildenafil citrate enabled men to achieve and maintain an erection with an improved sex life compared to placebo, with minimal changes in blood pressure. Although orthostatic hypotension is uncommon in early PD, researchers have suggested supine and standing blood pressure measurements before prescribing sildenafil citrate to patients with PD (Hussain et al., 2001). Such patients should be followed up with blood pressure measurements and made aware of the need to seek medical advice if they develop symptoms suggesting orthostatic hypotension. In such cases, apomorphine should be regarded as an alternative to sildenafil in treating patients with PD and ED (O'Sullivan and Hughes, 1998). After the subcommittee's recommendations, a large double-blind placebo-controlled study confirmed the efficacy of sildenafil citrate in PD patients. The study included 236 PD patients with ED, who were randomized to receive 100 mg sildenafil 1 hour before sexual activity, or similar regimen of placebo (Safarinejad et al., 2010). Patients were instructed to use at least 24 doses. Sildenafil was significantly effective in 56.9% of patients in the sildenafil group vs 8.7% in the placebo group.

When PD patients with ED report failure with PDE5 inhibitor treatment, one may consider the possibility of ineffective use of the medication. Due to possible autonomic gastric slowness in patients (Pfeiffer, 2003), men with PD should be instructed to wait longer (approximately 2 hours) than the standard recommended time (1 hour) for PDE5 inhibitors, before attempting intercourse (Bronner, 2009).

Hypersexual behavior in Parkinson's disease

HS, later defined as compulsive sexual behavior (CSB), is one of a broad range of ICDs often reported in PD (Weintraub et al., 2006; Giladi et al., 2007; Voon and Fox, 2007; Avanzi et al., 2006; Voon et al., 2009; Weintraub et al., 2010a). HS was the earliest-recognized PD-related ICD before recognition of the whole syndrome, and was presented as a consequence of antiparkinsonian therapy (Uitti et al., 1989). ICDs refer to compulsive, repetitive, reward-based behaviors, which result from a failure to resist an urge or temptation to perform an act considered to be harmful to the patient or to others (Merims and Giladi, 2008; Lyons and Pahwa, 2011). ICDs have been identified among 13.6% of 3090 PD patients (Weintraub et al., 2010a). They include pathologic gambling, compulsive shopping, binge eating, and CSB, and may evolve into a significant clinical concern with devastating consequences for patients and their families (Giladi et al., 2007; Voon et al., 2009).

CSB has been reported in 1.7–3.5% of PD patients, more frequently among men (Table 17.1) (Weintraub et al., 2010a; de Chazeron et al., 2011). Studies highlight the link between CSB (as well as other ICDs) and dopaminergic medications, namely levodopa and DA agonists (pramipexole, ropinirole, and others), used in routine treatment of PD (Uitti et al., 1989; Weintraub et al., 2006, 2010a, b; Driver-Dunckley et al., 2007; Voon et al., 2011). The odds of having a single ICD were 2–3.3 times higher in patients treated with DA agonists compared with untreated patients (Weintraub et al., 2010a). CSB was reduced when DA replacement treatment was discontinued or replaced by other medications (Klos et al., 2005; Voon et al., 2006; Cannas et al., 2007). Risk factors associated with CSB include early onset of PD, male gender, depression, presence of another ICD, family or personal history of drug or alcohol abuse, and personal history of ICDs prior to PD onset (Harvey, 1988; Evans and Lees, 2004; Klos et al., 2005).

DBS of the STN has been associated with both positive and negative outcomes in terms of ICDs and related disorders, highlighting the lack of consistent knowledge in this area (Broen et al., 2011). A few cases demonstrated an association between HS and DBS of the STN (Romito et al., 2002). Romito et al. (2002) followed 30 PD patients treated successfully by bilateral STN, and found remarkable disorders of mood or sexual behavior after the implant in five younger-onset PD patients (age <60 years). The five PD patients included a 57-year-old woman with increased sexual drive, which appeared a month after the implant, lasted for about 18 months, and then gradually disappeared, and two men (42 and 52 years old) who developed manic episode and HS a

few days after the implant that lasted for some months and then gradually disappeared spontaneously. Another case demonstrated a persistent HS with DBS of the GPi, requiring its removal (Roane et al., 2002).

Vitale et al. (2011) compared the neuropsychologic profile of 49 PD patients with ICDs with controls (14 PD patients matched for age and education without ICDs). They found that all ICD patients were impaired on tasks exploring spatial-planning and set-shifting tasks compared with the controls. The severity of the impaired cognitive function decreased in the following order: multiple ICDs or CSB > compulsive eating > pathologic gambling. Another study found that PD patients with ICDs have distinct psychiatric and neuropsychologic profiles, encompassing multiple psychiatric and cognitive impairments, including affective and anxiety symptoms, increased obsessionality, novelty seeking, and impulsivity (Voon et al., 2011).

In clinical settings, PD patients may show behaviors that seem like hypersexual behavior (such as increased sexual drive, discussing sex often, frequent attempts to have sex with partner, frequent masturbation, or frequent use of pornographic materials). Actually these patients may experience a retrieved libido following initiation or augmentation of medical treatment (Pohanka et al., 2004). In other cases, PD patients were confronted with a frustrating sexual problem, leading them to repeated attempts to engage in sex, solve the problem, and reach sexual satisfaction. Their behavior might be confusing and erroneously diagnosed as HS. A recently published diagnostic algorithm may assist neurologists and other healthcare professionals in differentiating between true hypersexual behavior and SD disguised as HS (Bronner and Hassin-Baer, 2012). The algorithm (Fig. 17.1) describes features and associated factors of HS in comparison to SD, and offers practical interventions in both cases. The main features of true hypersexual behavior are: (1) a sexual behavior that did not exist previously; (2) the behavior involves aberrant, excessive, and/or time- and money-consuming sexual activities, including: pornography use, cybersex, sexual activity with multiple partners, use of sex workers, paraphilias or sexual harassment (verbal or physical). The associated factors which should be explored are: (1) use of antiparkinsonian medications: DA agonists, levodopa; (2) DA dysregulation or self-administered increased doses of DA replacement therapy; (3) recent changes in medications; (4) early PD onset (age <50 years); (5) history of drug and alcohol abuse; (6) concomitant psychiatric problems (depression, psychosis, anxiety); and (7) concomitant additional ICDs. The suggested interventions for CSB include: (1) medical changes (reduction or discontinuation of DA agonist, adjusting L-dopa dose, considering advanced therapeutic options to spare DA replacement treatment, such as DBS or levodopa intestinal gel via gastrostomy); (2) patient and spouse education to prevent sexual health problems (e.g., AIDS and other sexually transmitted diseases, unplanned pregnancy, sexual abuse) and sexual harassment accusations. Involvement of a multidisciplinary team (PD nurse, psychologist, psychiatrist, couple and sex therapy, PD group support) may enable a significant and effective change.

In addition to the algorithm presented in Figure 17.1, assessment of CSB or HS can be done using two questionnaires, discussed in the next section: the QUIP-RS (Weintraub et al., 2012) and the PD-SAST (Pereira et al., 2013). Patients with HS tend to deny their problem and quite often it is the spouse who informs health professionals about problematic behavior. Therefore, it is recommended that administration of these questionnaires as well as an assessment by the neurologist will involve the spouse and/or caregiver.

CSB is underrecorded and medical files of PD patients tend to contain little documentation of sexual functioning (Klos et al., 2005; Voon et al., 2006; Cannas et al., 2007; Bostwick et al., 2009). Although CSB is not a common problem in PD, it may have significant consequences on patients' relationships with their partners and families. Considering that partners and families encompass the support system of patients, hypersexual behavior as well as other ICDs can contribute considerable family discord. Therefore, it is critical to uncover and treat HS as early as possible (Merims and Giladi, 2008; Bronner and Hassin-Baer, 2012).

Sexual dysfunction in Parkinson's disease: how is it measured?

While SD is very common among patients with PD and contributes substantially to reduced QoL, high-quality data regarding the diagnosis and rating of these problems and consequently high-level evidence for the efficacy and safety of their treatment are sparse (Raffaele et al., 2002; Zesiewicz et al., 2010). Most studies published on SD in PD have not used sex questionnaires adapted for the PD population. The complexity of PD, affected by both motor and non-motor manifestations, as well as the medication burden and effects, demands special consideration when SD is studied. In fact, the number of controlled studies on SD among PD patients is embarrassingly low. As of today there is no comprehensive tool adjusted for evaluation of SD in PD patients.

Two of the most widely used questionnaires for SD are the International Index of Erectile Function (IIEF) and the Female Sexual Function Index (FSFI). These are multidimensional self-report instruments for the

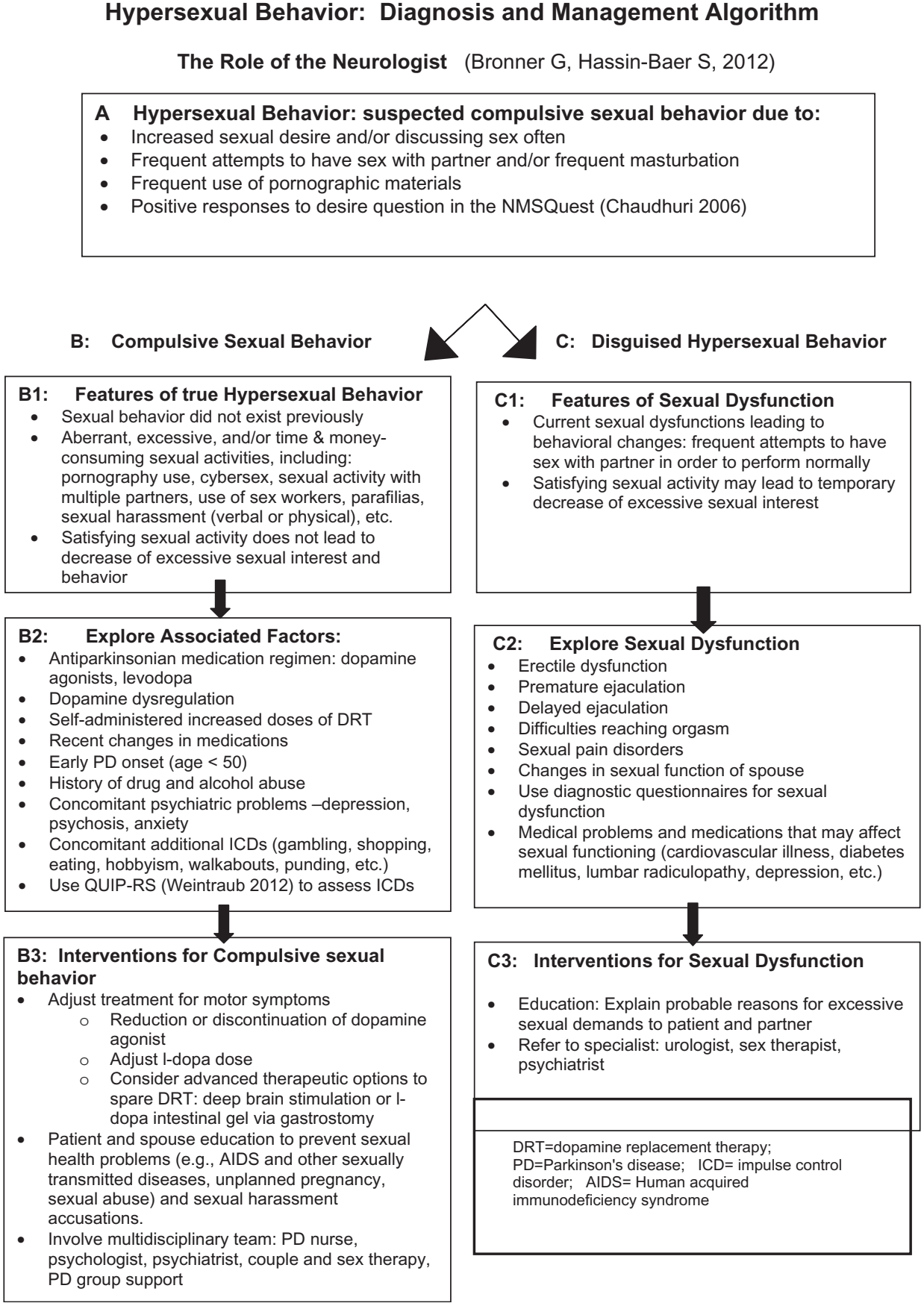

Fig. 17.1. Hypersexual behavior: diagnosis and management algorithm. DRT, dopamine replacement therapy; PD, Parkinson's disease; ICD, impulse control disorder. (Reproduced from Bronner and Hassin-Baer, 2012, with permission from IOS Press.)

evaluation of male and female sexual function (Rosen et al., 2000, 2002). These questionnaires have been used in clinical trials in men and women with different medical disorders (diabetes, spinal cord injury, heart disease, depression, and cancer). Only a single study used the FSFI for women with PD (Kotková and Weiss, 2013) and a few authors used the IIEF (Hussain et al., 2001; Raffaele et al., 2002; Pohanka et al., 2004; Safarinejad et al., 2010; Kotková and Weiss, 2013). The Israeli Sexual Behavior Inventory (ISBI), a 35-item questionnaire primarily designed to assess the impact of chronic illness and disability on sexual functioning and experience, has also been used (Bronner et al., 2004). However, these questionnaires have never been validated in PD populations.

The only questionnaire validated for PD population is the Arizona Sexual EXperiences scale (ASEX). This questionnaire was assessed and validated with a random sample of 40 Thai PD patients (Jitkritsadakul et al., 2013). ASEX is a five-item, self-administered questionnaire with a six-point Likert scale designed to assess the core components of SD: drive, arousal, penile erection, vaginal lubrication, ability to achieve orgasm, and satisfaction (McGahuey et al., 2000). The ASEX is easy to administer, does not take long to complete, and may help physicians in the early detection of SD even in outpatient settings (Bronner, 2008; Celikel et al., 2008). The QoSL, a five-item self-administered questionnaire with a five-point Likert scale designed to assess quality of relationships and quality of sexual life (desire, rejection of sex, sexual satisfaction), has been used with PD patients and partners (Moore et al., 2002; Bronner et al., 2014).

SD is addressed in scales assessing NMS of PD. The Non-Motor Symptom Questionnaire (NMS-Quest) is a screening tool designed for detecting NMS (without any grading) (Chaudhuri et al., 2006) and it encloses two questions concerning sexual function, which address an alteration in sexual interest and the presence of problems having sex. Another scale is the Nonmotor Symptoms Scale (NMSS), a validated tool for rating the frequency and severity of non-motor symptoms in nine dimensions (Chaudhuri et al., 2007); it includes questions on the frequency and severity of the altered interest and problems having sex. The Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) has also been validated in PD and includes an assessment of NMS of PD (Non-Motor Aspects of Experiences of Daily Living: NM-EDL) but has not included questions on SD (other than as part of the DA dysregulation syndrome) (Goetz et al., 2007).

In the Scales for Outcomes in Parkinson's disease (SCOPA) project an assessment scale for each PD domain was developed. Prerequisites for the assessment scales were good reliability, validity, and (potential) responsiveness. The SCOPA-AUT consists of 25 items, including two items on SD concerning ED and ejaculation in men and vaginal dryness and orgasm in women, but SD is not addressed otherwise (Visser et al., 2004).

Interestingly, SD is not addressed at all in the PD QoL questionnaire, the PDQ-39 (Peto et al., 1995), the most commonly used instrument to assess QoL of patients with PD; and the PDQUALIF encloses a single general question on the effect of PD on intimate affection (Welsh et al., 2003).

Two questionnaires can be used to assess CSB or HS: the Questionnaire for Impulsive-compulsive disorders in Parkinson's disease-Rating Scale (QUIP-RS) (Weintraub et al., 2012) and the PD Sexual Addiction Screening Test (PD-SAST) (Pereira et al., 2013). The QUIP-RS is a brief, self-administered rating scale which evaluates the presence and severity of various ICD symptoms (gambling, shopping, eating, and HS) and related behaviors (punding, hobbyism, and DA dysregulation syndrome) reported to occur in PD (Weintraub et al., 2012). The PD-SAST, a shortened form of the Sexual Addiction Screening Test (SAST), covers multidimensional aspects of HS. It has been tested in 159 PD patients and shown to be acceptable to patients (Pereira et al., 2013).

Obviously, the area of evaluation of SD in PD for research purposes needs further development. This can be propagated in three different routes: one is introduction of sexual assessment items into existing PD rating instruments and the second is validation of existing SD instruments in PD patients and their partners. The third route is the development of a comprehensive tool specific for the evaluation of SD in patients with PD addressing several aspects mentioned in this chapter.

DEMENTIA AND SEXUALITY

Regardless of age, the need for intimacy, physical touch, and an affectionate relationship does not subside. Intimacy combined with sexuality may contribute to a sense of well-being and to self-esteem. Data from the US National Social life, Health and Aging Project (NSHAP) indicated that 53% of people aged 65–74 and 26% of those aged 75–85 were sexually active (Lindau et al., 2007). While cognitive impairment in dementia cannot be ignored, the myth that patients with dementia are asexual or that sex is not relevant to them is commonly used to discourage them from sexual activities (Shakespeare, 2000). The onset of AD does not erase sexuality, but rather changes the way in which love is given and received (Dourado et al., 2010). There are many studies on sexual activity and intimacy associated with dementia. Most of them focus on ISB, which will be discussed later in this chapter. Those that have been published usually report the perceptions of spouses,

caregivers, and health professionals (Davies et al., 1992; Ballard et al., 1997; Svetlik et al., 2005).

Sexual and marital problems in dementia

The dementing illness has a major impact on various dimensions of marriage and sexuality (Davies et al., 1992, 2012; Ballard et al., 1997; Wright, 1998; Mittelman, 2003; Series and Dégano, 2005; Dourado et al., 2010). An unsatisfactory marital relationship predicted a patient's institutionalization in a nursing home (Davies et al., 1998; Svetlik et al., 2005). Nearly 80% of 38 husband and wife caregivers perceived changes in their emotional relationship (Duffy, 1995). Decline in happiness was reported by spouse caregivers (Eloniemi-Sulkava et al., 2002), and the decreased sense of happiness was associated with declined opportunities for physical contact and sexual intimacy (Svetlik et al., 2005). Spouses of 36 Brazilian patients with mild to severe AD reported decreased sexual activity and satisfaction, which were significantly correlated with the severity of AD (Dourado et al., 2010). The caregivers characterized the relationship in non-sexual terms as the illness progressed (Duffy, 1995; Wright, 1998). In a semistructured telephone interview of 42 spouse caregivers of community-living demented patients in Finland, 60% reported on negative sexual behavioral changes in the patient (Eloniemi-Sulkava et al., 2002).

Changes in patterns of sexual initiation and activity were described in demented patients, and frequently they were unable to stay engaged in sexual activity due to becoming distracted or losing arousal (Davies et al., 2012). AD patients of both genders preferred non-intercourse intimate activities (e.g., kissing, hugging, cuddling, massaging); over 70% of them initiated the activities (not intercourse), but most patients (82.5%) responded positively to spousal initiation. Wright (1998) found that expression of affection was not significantly different in AD couples ($n = 30$) compared to healthy couples ($n = 17$), and the frequency of intercourse was similar to that of the general aging population.

Information about SD in demented patients and their partners is scarce. ED was reported by 50% of men with AD (Zeiss et al., 1996). Both patients and their partners perceived ED and lack of female desire as reasons for their sexual dissatisfaction.

Interestingly, couples affected by AD continue to maintain physical intimacy. A prospective survey in a UK psychiatric service and memory clinic, among 40 partners married to patients with mild to moderate dementia, found that 22.5% continued to have a sexual relationship, and all were satisfied with the situation (Ballard et al., 1997). Among those carers who were not sexually active, 38.7% were dissatisfied with the absence of a sexual relationship. As reported by spouses, 24% of the male AD partners were constantly expressing a need to make love, and in one-third expressions of tenderness towards the caregiver had increased (Eloniemi-Sulkava et al., 2002). The authors found that almost half of the couples still at home ($n = 19$) continued to have intercourse at 3 years from the onset of the dementia, declining to 28% at 7 years.

Partners of both genders felt distressed about sexual overtures from spouses, who no longer knew their name, and were not capable of paying attention to their feelings. While male spouses reported uneasiness and feelings of guilt, when intercourse happened without the woman's understanding, female partners of AD patients were anxious about the loss of intimacy (Davies et al., 1992; Svetlik et al., 2005). The loss of intimacy may interfere with the woman's sexual response, as one of the woman's initial motivations for sexual desire is intimacy-based (Basson, 2002). In addition, female caregivers reported higher levels of stress and depressive symptoms than male caregivers (Davies et al., 2012). A significant negative association between the burden of caregivers of AD patients and their satisfaction (both sexual and marital) was found by Simonelli et al. (2008). These findings may explain the gender differences in spouses of AD patients. While female spouses report decreased desire for sexual activity, male carers were more likely to be involved in a continuing sexual relationship (Dourado et al., 2010).

In conclusion, one might expect higher frequencies of SD among partners of demented patients, especially female partners, and intervention plans should address their need to improve their QoL and QoSL.

Inappropriate sexual behavior

Types and prevalence

Most patients with AD exhibit some form of behavioral disturbances in the course of their disease (Lyketsos et al., 2002). Deranged behaviors, such as agitation, disinhibition, impulsivity, and psychosis, in particular when associated with inappropriate sexual behavior, are among the most distressing and embarrassing aspects for caregivers and families, and health professionals find it complicated to evaluate and treat (Mendez and Shapira, 2013). The prevalence of ISBs associated with dementia varies widely (1.8–25%) depending on the setting, being generally more common in hospital inpatients and less common in community-dwelling people (Szasz, 1983; Burns et al., 1990; Devanand et al., 1992; Miller et al., 1995; Mayers, 1998; Alagiakrishnan et al., 2005; Black et al., 2005; de Medeiros et al., 2008; Derouesné, 2009).

Burns et al. (1990) found symptoms of ISB (exposure, obscene sex language, masturbation, propositioning others) in 6.9% of 178 AD patients (living at home, in residential care, or in hospital), with about equal frequency in men and women. There was a significant positive association with severity of dementia. ISB was found in 2.8% of patients in Japanese nursing homes (Onishi et al., 2006), 7.9% in residential care (de Medeiros et al., 2008), 15% in geropsychiatric unit (Tsai et al., 1999), 17% of outpatients, and 8% of inpatients (Drachman et al., 1992), and 25% in the extended-care unit (Szasz, 1983). In a study of 40 demented residents, Zeiss et al. (1996) systematically observed each of them on nine separate 5-minute occasions, coding for each minute of observation whether a sexual behavior was present, and if so, whether it was appropriate, inappropriate, or ambiguous. Of the 1800 1-minute coded segments, ISBs occurred in 27 (1.6%) and ambiguous behaviors in 67 (3.7%). Rabins et al. (1982) interviewed the caregivers of 55 demented patients and only one family (2%) reported ISB. Kumar et al. (1988) compared 28 AD patients with non-demented controls and found no significant difference in aggressive or ISB (7% in both groups).

Forty-eight demented patients were monitored for sexual behavior by 25 nurses in eight nursing homes over a period of 14 weeks. Three types of sexual expression were found: (1) love and caring; (2) romance; and (3) eroticism (Ehrenfeld et al., 1999). Staff reactions varied, being accepting of "love and care," objecting to "eroticism," and feeling a mixture of acceptance and amusement towards residents' "romantic behavior".

Masturbation is a common sexual activity among people of all ages throughout life, reported by half of men aged 60–69 and by 26.7% of married men over 70 (Herbenick et al., 2010). It has been traditionally prohibited and judged as immoral and sinful by several religions. Although it is no longer perceived as a negative behavior, confronting masturbation in dementia may create embarrassment and discomfort. Masturbation is often reported as one of the inappropriate public behaviors in dementia (Ballard et al., 1997; Davies et al., 1998), but there is little evidence on this behavior as a healthy activity in the elderly.

Gender differences

ISBs occur more commonly in men (Alagiakrishnan et al., 2005). In an observational study in eight nursing homes the demented men were almost always the initiators, directing their attention to female residents (Ehrenfeld et al., 1999). Women were the initiators in only 10% of the cases, and when this happened the women seemed to direct their behavior towards a man they misidentified as their spouse. In a minority of cases (16%) female staff members were sexually approached by male residents. These behaviors have usually occurred during care or bathing, and consisted of touching breasts or other body parts, and were interpreted as sexual harassment by the health professional. In some cases, a male resident invited a female staff member to his bed or tried to solicit sexual favors for pay. No case of an elderly female resident initiating this kind of relationship with staff was reported.

Inappropriate sexual behaviors in various dementia syndromes

Behavioral problems, including ISBs, are common in all patients with dementia at some point in the course of their illness. Signs and symptoms vary considerably from one person to another, over time, and by the type of dementia. Most behavioral disturbances are associated with disruption of executive function (McPherson et al., 2002; Alagiakrishnan et al., 2005).

The prevalence of ISB associated with dementia varies widely (1.8–25%) depending on the setting. Of the dementias, bvFTD appears particularly likely to be associated with ISB, which has been described among 8–18% of patients (Miller et al., 1995; Mendez et al., 2005; Mendez and Shapira, 2013).

Dementia usually develops subtly. An acute emergence of any behavioral derangement, ISB included, can indicate delirium or the unmasking of latent brain pathology (Miller et al., 1986). Therefore, when the behavioral changes develop abruptly, a prompt comprehensive medical evaluation should be made to rule out an underlying medical condition.

The neurobiologic basis of inappropriate sexual behavior in the various dementia syndromes is still vaguely understood. The sexual behaviors may reflect the prevailing behaviors associated with the dementia or may occur in relative isolation.

ISBs have generally been described in association with pathologies of the frontal lobes, the temporolimbic system, the corticostriatal circuits, and the hypothalamus (Black et al., 2005).

Apathy, characterized by lack of initiative and interest, limited affective response, indifference (Mega et al., 1996), and decreased sexual interest and desire (Joller et al., 2013), is the most common behavioral manifestation in the various dementia syndromes. In terms of ISB, these patients are at risk of becoming victims of sexual harassment and exploitation as due to their cognitive impairment they may have a limited ability to consent and due to apathy, their willingness to participate in a mutual voluntary sexual activity may be impossible to assess.

The opposite type of deranged behaviors, such as agitation, disinhibition, impulsivity, and psychosis, in

particular when associated with inappropriate sexual behavior, are among the most distressing aspects of dementia to evaluate and treat (Mendez and Shapira, 2013).

In health, sexual arousal results in activation of the right prefrontal, orbitofrontal, and anterior cingulate cortices (Karama et al., 2002; Ferretti et al., 2005; Baird et al., 2007).

Dysfunctions of these areas such as occurs in the frontal variant of AD and in the bvFTD often result in executive dysfunction and frontal-type behaviors, including impulsivity, disinhibition, agitation, and HS. This suggests that in the case of prefrontal-orbito frontal-anterior cingulated dysfunction, the altered sexual behaviors may be a part of a generalized behavioral disinhibition (Mendez and Shapira, 2013). Obsessive compulsive and stereotyped behaviors are common in bvFTD (Hodges and Miller, 2001; McKhann et al., 2001; Hou et al., 2004) and in autosomal-dominant forms of AD (Rippon et al., 2003) and may decrease following treatment with SSRIs (Anneser et al., 2007). This may suggest that in some instances the ISBs in the dementia syndromes may result from a generalized obsessive compulsive disorder with compulsive sexual preoccupation affecting the corticostriatal circuits (Black et al., 2005).

Recently, Mendez and Shapira (2013) suggested that in the case of bvFTD the hypersexual behavior of some patients may reflect, in addition to a "generalized disinhibition with sexual content," pure HS which may be described as increased sexual desire and arousal. The authors describe that the patients had "widened sexual interests and experienced sexual arousal from previously unexciting stimuli. One patient was aroused by slight stimuli such as touching her palms." In health, the right temporal lobe is involved in perception of sexual behaviors and in the inhibition of sexual thoughts and impulses (Ozkara et al., 2006). Erection and orgasm are associated with deactivation of temporolimbic areas (Holstege et al., 2003). In the right temporal variant of bvFTD, excessive sexual behavior and ISB may be the result of the impaired inhibition of the temporolimbic areas involved in sexual arousal and sexual expression (Müller, 2011; Mendez and Shapira, 2013). Similar hypersexual behaviors have been described following temporal amygdalar damage associated with stroke, surgery (Baird et al., 2004), and in the Klüver–Bucy syndrome (Lilly et al., 1983; Baird et al., 2004).

Perceptions and definitions of inappropriate sexual behaviors

Descriptions of excessive and maladaptive sexual behaviors in the general population were published by pioneer sexologists in the 19th century (Kafka, 2010). Nevertheless, firm research in this area is insufficient, the terms are confusing (ISB, HS, hypersexual behavior, disinhibited sexual behavior, and extreme sexual behavior), no clear criteria exist, and there are only few validated instruments for diagnosis and assessment. Overall this situation leaves substantial gaps for individual interpretations.

Perceptions of what constitutes appropriate sexual behavior vary between individuals and may be influenced by factors such as religious beliefs or prevailing societal views of elderly and demented persons (Joller et al., 2013), and by different environments (patient's home, public areas, residential home, or hospital) (Series and Dégano, 2005). Staff, patients, and families may disagree as to what constitutes appropriate behavior (Gibson et al., 1999). For example, two residents holding hands may be inappropriate for some, and for others, masturbating in bed may be considered a form of ISB.

ISB in patients with neurologic impairment has received limited coverage within the literature. This situation creates problems in the definition and quantification of ISB, in particular the absence of standardized measurement tools to record ISB within an inpatient setting (Johnson et al., 2006). Within the context of dementia, ISBs have been defined as behaviors that are "inappropriate, disruptive and distressing, and that impair the care of the patient in a given environment" (Black et al., 2005).

ISBs can be divided into normal behaviors that are misplaced in social context (kissing, hugging) and disinhibited, rude, and intrusive behaviors that would be considered inappropriate in most contexts (lewdness, fondling, exhibitionism) (de Medeiros et al., 2008). Szasz (1983) has divided ISBs into three types of behavior: (1) sex talk: using foul language that is not typical of the patient's premorbid personality; (2) sexual acts: touching, grabbing, exposing, or masturbating in public or private places; and (3) implied sexual acts: openly reading pornographic material or requesting unnecessary genital care. Higgins et al. (2004) reviewed the literature and found various expressions of ISB among demented people: (1) touching the breasts, buttocks, and genitals of staff and other residents; (2) kissing and hugging that exceeded mere affection; (3) exposing genital areas; (4) making sexual suggestive remarks; (5) attempting intercourse and oral sex; and (6) public masturbation.

Description of the ISBs in dementia is not sufficient, since some behaviors in cognitively impaired older adults may be erroneously interpreted as sexual, although the behavior has a non-sexual meaning to the individual. For example, public undressing or genital touching may be viewed as ISB, while the patient's

motivation may be from discomfort, hyperthermia, pain, or attempts to be freed from a restrained environment (Johnson et al., 2006).

Bartelet et al. (2014) studied the role of disinhibition as an important underlying cause of extreme sexual behavior. They investigated whether extreme sexual behavior in 179 demented Dutch patients may be regarded as a part of disinhibited behavior or could be considered as an independent neuropsychiatric symptom (e.g., HS). Examples of extreme sexual behaviors, used in their study, were sexual comments, public masturbation, public exposing of breasts or genitals, and approaching attendants or fellow residents for sexual contact. They concluded that the extreme sexual behavior should carry the label "sexually disinhibited behavior," and be perceived as one of the expressions of disinhibition in dementia. This approach may be implemented in educational training and briefings for healthcare providers and relatives, and as a result it may reduce the distress that accompanies the behavior.

In conclusion, demented people may exhibit three types of disturbing sexual changes: (1) ISB or sexually disinhibited behavior (e.g., lewd language); (2) normal sexual behavior occurring at an inappropriate time or inappropriate location due to misunderstanding and misperception of the setting (e.g., public masturbation); and (3) sexual behavior with the wrong person, due to misidentification of a spouse (approaching sexually another resident or a family member).

Treatment of sexual problems and inappropriate sexual behaviors in dementia

Currently only few studies specifically address the treatment of sexual problems and ISBs in dementia and no randomized controlled trials have been reported to date. This section will describe early interventions for couples who live with dementia, as well as non-pharmacologic and pharmacologic treatments of ISB. Early interventions are aimed at coping with role changes, educating patients and partners, focusing on intimacy and physical touch, and addressing specific female issues (caregivers and healthcare providers) (Table 17.2).

Early interventions

Role changes

As with early diagnosis, couples may be stressed by questions regarding the burden of the dementia, as well as future role changes, loss of companionship, and difficulties with communication (Wright, 1998; Marvardi et al., 2005; Simonelli et al., 2008; Hillman, 2012). The role transformation from a spouse and a lover to parenting the partner (feeding, changing diapers) and the changes in relationship equality can hamper the sex life of these couples (Eloniemi-Sulkava et al., 2002; Dourado et al., 2010). Total or partial separation of the two roles (caregiver and spouse) for the sake of defending the intimate and marital relationship may solve this problem (Duffy, 1995).

The role of health providers is to encourage a couple's discussions at the early stage of the disease. Redefinition of roles and preservation of intimate relations should be communicated as long as both partners are able to share ideas and feelings.

Information and sex education

Knowledge about sexual changes affected by dementia is essential and may contribute to lessening of stress and anxiety of both patients and partners. Caregivers should

Table 17.2

Role of health providers in the non-pharmacologic management of sexual issues in dementia

Sexual issues	Role of health providers
Role changes	Encourage couple's discussions regarding future role changes and preservation of intimacy, when both can communicate
Information and sex education	Acquire knowledge and communication skills regarding sexuality and dementia. Create open sexual communication with patients, partners, and caregivers. Address sexual problems or refer to specialists
Enhancement of intimacy and physical touch	Help couples adopt an open approach. Encourage them to experiment alternatives for pleasurable touch. Enable other opportunities for touch, when partner is not available (pets, dolls, massage)
Addressing female sexual issues (caregivers and healthcare providers)	Consider the possibility that caregivers, family members, and female staff members might be a target for the inappropriate sexual behavior and sexual harassment. Plan gender-specific interventions

be encouraged to raise sexual issues and ask for advice. Cultural values, personal beliefs, patient's gender and race, and absence or inadequate professional training provide obstacles for clinicians to address this issue confidently (Tsimtsiou et al., 2006; Parish and Clayton, 2007; Ports et al., 2014). It was not surprising that health professionals and administrators in 114 nursing homes asked for training that focuses specifically on dealing with residents' sexual expression (Holmes et al., 1997). Models for sexual communication with patients, such as the PLISSIT (Annon, 1976) and the Open Sexual Communication model (Bronner, 2009), may assist physicians and other health providers to discuss sexual health issues as an integral part of overall healthcare and offer adequate advice or treatment. You can read more about sexual communication with patients in Chapter 24.

The role of health providers is to acquire knowledge and communication skills regarding sexuality and dementia, and enable open sexual communication with patients, partners, and caregivers, and to address sexual problems whenever they arise, or refer patients and partners to specialists (urologist, gynecologist, psychiatrist, psychologist, sex therapist).

Enhancement of intimacy and physical touch

Social and cultural values place substantial emphasis on sexual intercourse, reducing sexuality to mere acts of penetration and orgasm (Svetlik et al., 2005). In a population with high rates of SD and inability to have intercourse, other kinds of sexual pleasures (kissing, cuddling, massaging, outercourse, or non-penetrative sex and mutual masturbation) are important options (Bronner, 2009). There are few of us who would argue that a child does not need physical touching or hugging. As dementia progresses, affected persons may find themselves in a situation where they are unable to reach out and touch, and are unable to simply ask for a hug. Research has shown that tactile stimulation may reduce stress and behavioral symptoms such as restlessness among AD patients (Woods et al., 2009). The relaxing role of physical touch, and the transformation to non-intercourse-oriented sexual activities may increase feeling of closeness and happiness of couples troubled with such a complicated health challenge. When a dyadic physical touch is unfeasible, it is recommended to increase opportunities for other tactile stimulations (e.g., using live pets or soft dolls, introducing face or head massage).

The role of health providers is to encourage couples to experiment with alternatives for pleasurable and relaxing touch, taking into account the patient's cognitive and functional deficits and the partner's physical and mental state, and to enhance other opportunities for touch in nursing home facilities.

Addressing specific female sexual issues

Since female partners and caregivers of demented patients report higher frequencies of intimacy loss and decreased desire associated with stress and depressive symptoms (Simonelli et al., 2008; Dourado et al., 2010; Davies et al., 2012), gender-specific interventions should be proposed to them. The reports from nursing homes on female staff members sexually approached by residents (mainly men) (Ehrenfeld et al., 1999) call for specific staff training and interventions.

The role of health providers is to pay specific attention to the needs of female caregivers and family members; to consider the possibility that female staff members may be a target for sexual harassment; and to plan appropriate gender-specific interventions.

Pharmacologic management of inappropriate sexual behaviors in dementia

Currently only few studies specifically address treatment of ISBs in dementia and no randomized controlled trials have been reported to date. Management should primarily be directed towards controlling environmental factors that have the potential to precipitate or aggravate the inappropriate behaviors. Distraction strategies and opportunities to relieve sexual urges need to be adapted to the individual patient (Lothstein et al., 1997; Tucker, 2010; Joller et al., 2013). Discontinuation of medications that potentially worsen disinhibition, such as benzodiazepines and DA agonists, may reduce the inappropriate behaviors. Case reports and small studies report various success rates following pharmacologic interventions with antidepressants, in particular SSRIs, hormones (antiandrogens and estrogens), antipsychotics, acetylcholine esterase inhibitors, and anticonvulsants, alone or in combination.

Non-pharmacologic management of inappropriate sexual behaviors in dementia

There are no randomized controlled studies describing efficient management of ISB, as most studies are based on case descriptions (Lichtenberg and Strzepek, 1990; Series and Dégano, 2005; de Medeiros et al., 2008; Ozkan et al., 2008; Tucker, 2010; Joller et al., 2013). Ill-defined terminology and the absence of relevant assessment tools and management algorithms add to the specific challenge of ISB within care facilities. An Australian study by Bird et al. (2007) demonstrated the positive value of non-pharmacologic interventions for ISBs in an intervention group (44 patients) compared

with a control group (22 patients). The control group received usual care and the intervention group was offered an individualized plan, tailored by a team of nurse and clinical psychologist. While most interventions in the intervention group were psychosocial (77%), in the control group the majority were pharmacologic. The control group had twice as many psychotropic medication changes and twice as many drug side-effects, and almost 25% of them spent time in specialist inpatient units, compared with only one patient in the intervention group. Decrease in difficult behaviors was seen in 44% of the intervention group. There are many practical and ethical concerns around the assessment and treatment of ISB in dementia, especially in the caring home setting (Tucker, 2010). These include balancing a resident's need for sexual expression with the expectation that sexuality is not relevant to elder and demented people. Further problems can arise and pose ethical and moral challenges. We have collected a few examples from our clinical experience:

1. A visiting spouse wishes to be intimate or have sex with a demented partner and asks for some privacy: how should home care staff react?
2. Two demented residents kiss and hug and both seem relaxed: is there any abuse or is this just a mutual caring behavior?
3. Two female patients are used to masturbating in their own bed early in the morning and react with violence to any disturbance: should the carer interfere or let them stay in bed longer?
4. A demented resident is found every morning in another resident's bed: is there a need to report this to the resident's children or find a discreet and respectful solution?
5. What should health providers do when a resident's children wish to bring a sex worker to serve their demented father in order to relieve his aggressive behavior?
6. When a male partner or patient has ED, should he receive treatment (e.g., PDE5 inhibitors) to enable intercourse to take place, or be refused as he is demented?
7. When two demented residents engage in sexual contact, is it obligatory to forbid any intimate contact between cognitively impaired people? Alternatively, is it preferable to evaluate whether it is a positive mutual activity and the absence of resistance is a sign of consent and satisfaction?

Lichtenberg and Strzepek (1990) describe guidelines on the assessment of institutionalized dementia patients' competencies to participate in intimate relationships. The assessment includes questions regarding the patient's awareness of the relationship, ability to avoid exploitation, and being aware of potential risks. These principles may assist staff members to decide how and when a patient should be defended. When competent, the patient might need support by staff members (e.g., planning privacy). When incompetent, there still remain ethical issues. How can we decide whether non-competent patients can participate in any physical, intimate, or sexual activity? Should we deprive these patients of any physical contact? Further discussions and research should be carried out, carefully taking into account detailed cases as well as staff attitudes. If needed, staff members should be adequately trained and supported in this sensitive area of sexual health.

ISB cases demand careful and comprehensive assessment of the behavior, setting, location, time, frequency and people involved. Predisposing factors, as well as physical, psychiatric, and social needs, concerning patients and their partners, should also be evaluated. A full understanding of both the behaviors and the contexts in which they occur is essential to create an unbiased and reasonable plan of intervention, agreed with staff and other interested parties such as the resident's family (Series and Dégano, 2005). Careful assessment should take into consideration risky aspects imposed by the behavior. On the one hand, there is risk of harm, distress, or discomfort to those involved, and on the other, people with dementia themselves might be vulnerable to exploitation and abuse without being able to defend themselves. Written observational records made by care staff, followed by open discussions in staff meetings, are recommended.

Multidisciplinary professional interventions, including physicians, nurses, social workers, and psychologists, may contribute to better assessment and may result in creativity and innovative ideas. Recommended reactions towards the various expressions of ISB (e.g., use of lewd language, public undressing, genital touching, misidentification, and attempts to have sex) are described in the following sections and in Table 17.3.

Management of lewd language problems

One of the distressing disinhibitions is the use of lewd language. As the dementia progresses, the person may be unable to monitor the use of language, usually in response to stressful or frustrating situations. Rather than reacting with anger or rebuking the person, it may be more effective to take the following steps:

1. Try to decrease the stress or avoid frustrating situations whenever possible.
2. When the use of such language becomes frequent and unacceptable it may be most effective to assertively state: "That is unacceptable!"

Table 17.3

Management of inappropriate sexual behavior, according to type of behavior

Type of sexual behavior	Recommended reaction
For all types of behavior	1. Assess the behavior carefully 2. Write a detailed record of the behavior 3. Get support and discuss it with your colleagues 4. Discuss with/explain to spouse, caregivers, family members 5. Plan an individual tailored intervention 6. Don't shame the person or increase the stress 7. Don't argue 8. Increase opportunities for physical touch (not sex) 9. Address spouse or caregiver's needs
Lewd language	1. Decrease the stress and avoid frustrating situations 2. Say assertively: "That is unacceptable!" 3. Leave the room for a few seconds, to break the cycle of the behavior
Public undressing or genital touching	1. Understand the trigger for the behavior (e.g., pain, discomfort, attempts to feel free, confusion, hyperthermia) 2. Use environmental approach (e.g., loose clothes) 3. Use distraction techniques (e.g., game, handcraft) 4. Solve privacy issues, if relevant
Misidentification	1. Use distraction techniques (take the patient for a walk, explain calmly that you're another person) 2. Discuss the behavior with spouse, caregivers, family members
Attempts to have sex	1. Use distraction techniques (e.g., walk outside, game, handcraft) 2. Separate the patient from the other resident or staff member when the other person appears to be the trigger for inappropriate sexual behavior 3. Find alternatives to relieve sexual urges

3. Leave the room, even for a few seconds. It breaks the cycle of the behavior, acts as a punishment, and may be sufficient to reduce the use of such language. Leaving the room is very effective for other inappropriate behaviors as well. Caregivers may find that leaving the room for a short time often extinguishes troublesome behaviors, without the caregiver ever having to get angry, become verbally or physically abusive, and end up feeling guilty and upset.

Management of public undressing or genital touching

Behaviors such as public undressing or genital touching are usually not sexually motivated. The behavior may be a result of pain, discomfort, hyperthermia, distraction while changing clothes, or attempts to be freed from a restrained environment (Johnson et al., 2006). Intervention of caregivers or health providers should attempt to understand the etiology and solve the problem. Environmental approaches, such as clothing modification and distraction techniques, have also been suggested (Hashmi et al., 2000). Distraction with other activities can be helpful, e.g., playing a game or taking part in handcrafts to occupy the hands and prevent inappropriate touching or public masturbation.

Management of misidentification

Misidentification of people is one of ISB etiologies, usually occurring later in the disease, and demands a sensitive approach. For example, an adult daughter may be upset and disturbed when her father tries to touch her breasts, probably mistaking her for her mother. This type of behavior is easily diverted if understood and dealt with in a calm and non-judgmental manner, by assisting the daughter in understanding that her father would probably be horrified if he could understand what he has done. One of the recommended reactions may be a distraction, e.g., by saying: "Hi, Dad, I'm your daughter. Let's take a walk." Offering something to eat, a walk, or other activity may prevent or stop the inappropriate advances. It is helpful to discuss these optional reactions with other healthcare providers.

Management of attempts to have sex

In the nursing home setting, it might be necessary to separate a patient from another resident or staff member

when the other person appears to be the trigger for ISB (e.g., by reminding the patient of his spouse). Moving a patient to another room, another floor, or another department might be necessary to stop the sexual harassment of the other person. A successful use of separation and distraction was described by Tune and Rosenberg (2008). A 3-foot-tall stuffed doll (a replica of the Pink Panther) was given to a 68-year-old man with dementia, who was sexually aggressive toward staff and female residents in his nursing home. First, he had been isolated from female residents and multiple antipsychotics unsuccessfully trialed, which "slowed him down" but had little effect on the problematic behaviors. His ISB stopped only after introduction of the doll, as it provided an alternate means of sexual release.

CONCLUSIONS

ISBs are common in patients with dementia and are distressing for the patients and for their caregivers. These altered sexual behaviors may either reflect the prevailing behavior (apathy associated with hyposexuality, disinhibition associated with sexual content or sexual compulsions) or occur in relative isolation (hyposexuality or increased sexual desire and arousal). Sometimes, the same individual may experience and manifest different type of ISBs.

Acute emergence of ISB should be carefully evaluated to rule out an underlying emerging medical condition. Persistent disruptive and distressing ISBs should be approached first non-pharmacologically and, if not successful, pharmacologic therapies should be tailored to the individual patient, taking into consideration the underlying neuropathology of the specific behavior. Management of ISBs should include careful documentation, which may also serve as a basis for future high-quality research, which is scarce in the field of sexuality and dementia. Non-pharmacologic interventions need to be adjusted to the individual patient, and they include removal of precipitating factors, distraction strategies, and opportunities to relieve sexual urges. Multidisciplinary team assessment and management may be effective in reducing dementia-related behaviors.

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 18

Relationship satisfaction and sexuality in Huntington's disease

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HUNTINGTON'S DISEASE

Huntington's disease (HD) is an autosomal-dominant, inherited, neuropsychiatric disease that manifests with progressive motor, cognitive, and behavioral symptoms due to an underlying loss of striatal neurons. Symptom onset typically occurs around age 40 in most cases. The first symptoms include inconspicuous movement disorders, proceeding to hyperkinesias of the limbs, uncontrolled movements of facial muscles, dysphagia, dysarthrophonia, tremor, and decreased control of the whole muscles. There are also psychiatric manifestations, including irritability, depression and, in terminal stages, dementia. The course of HD is steadily progressive, in most cases leading to death 10–30 years after diagnosis (Lange, 2002).

HD is associated with the mutation of CAG-type repetitive DNA sequences in the huntingtin gene (HTT) which is located on the short arm of chromosome 4 (Agostinho et al., 2013). This single autosomal gene leads to a multiplication of the base triplet CAG coding for a mutated toxic form of a protein (Huntington protein htt) while eliminating some of the functions of wild-type htt. A molecular test that determines the length of a CAG repeat can provide a definite diagnosis of HD. The diagnosis of HD is given if the patient has 38 or more CAG multiplications. Greater numbers of triplets are associated with an earlier onset of symptoms, and in rare cases HD can have an onset during childhood.

Progression of the disease can be measured with the United Huntington Disease Rating Scale (UHDRS), a clinical and research tool that has been developed to provide a uniform assessment of the clinical features and medical condition during the course of HD. The UHDRS has undergone extensive reliability and validity testing and has been used as a major outcome measure in controlled clinical trials. A patient's clinical condition can be summarized on motor symptoms of the UHDRS, which has a maximum score of 124.

Neurologically, the earliest change associated with HD is the degeneration of several regions in the basal ganglia, including the caudate and putamen in the striatum. The rate of atrophy is positively correlated with the length of the trinucleotide repeat. This striatal deterioriation has been directly linked to the motor symptoms in HD. In contrast, the neurobiologic substrates associated with the cognitive and behavioral symptoms in HD are controversial and remain unclear. Some have speculated that these symptoms may be related to diffuse cortical atrophy with neuron loss and dystrophic neurites leading to disruption of striatofrontal or limbic circuitries (Jellinger, 1998).

Additionally, sexual abnormalities have been reported early in the disease course of HD. In his original description of HD, George Huntington wrote about "two married men with HD who are constantly making love to some ladies, not seeming to be aware that there is any impropriety in it and they never let out an opportunity to flirt with a girl" (Huntington, 1872; Craufurd et al., 2001). Changed sexual interest and behavior and sexual disinhibition are common problems in HD and can create serious consequences for patients and their families due to the sociopsychiatric consequences (Dewhurst et al., 1970).

The current chapter will survey the literature regarding sexual behavior in HD. As sexuality and sexual dysfunction are based on more than biologic changes, we will first describe some general aspects of partnership in HD and the influence of genetic testing and diagnosis on partnership, reproductive behavior, and psychologic factors. Next, we discuss the current knowledge regarding sexual dysfunctions. We have integrated psychologic and psychotherapeutic interventions throughout the chapter; however the literature has been relatively sparse on intervention for sexual dysfunction in HD.

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PARTNERSHIP IN HUNTINGTON'S DISEASE

Burden of illness for the partner

HD is generally known as a family disease and inflicts a considerable burden on the patient and also on the other family members, especially on the patient's partner. Although, Codori and Brandt (1994) reported that the majority of HD mutation carriers revealed that the result of the predictive genetic testing had no impact on their relationships, it is evident that testing can have a psychologic impact on both potential carriers and their partners. With the deterioration of the disease, the patients often become demented or irresponsible, which can lead to impulsive sexual behavior and hinder the effectiveness of birth control methods. In an early paper, Evers-Kiebooms et al. (1989) pointed to the consequences of HD from the point of view of the partner of the patient. The authors reported that the mental impairment and the changes in personality seem to be the most difficult aspects to deal with. Also the knowledge about genetic inheritability of the disease and the threat that the patient's own children may later be affected are incisive themes. It has been shown that most partners were informed about the availability of predictive genetic testing for HD and were concerned about the related consequences, including postdisclosure distress, shame, anxiety, and depression as well as impact on reproductive decisions. The partners agreed on the need to attend psychologic counseling, and three-quarters of participants decided in favor of the availability of prenatal testing for HD.

Another study investigated partners of individuals identified with the HD mutation: itdemonstrated that partners reacted to the HD diagnosis with a series of emotions, including disbelief and denial, progressing to resentment and hostility (Hans and Koeppen, 1980).

Tibben et al. (1997) found that partners acknowledged the burden of the future disease. The authors observed that partners of HD gene carriers experienced almost the same levels of distress as the carriers themselves. Moreover, there was greater stress in partners with children than without offspring, demonstrating the emotional burden of the threat of their children having HD. However, satisfactory support from partners before test disclosure was associated with fewer feelings of hopelessness and avoidant thoughts at 6-month follow-up study in carriers, which emphasizes the important role of partners.

Stability of partnership

Decruyenaere et al. (2003) focused on the partner relationship 5 years after the test result. Although patients rated the quality of the relationship higher than their partners did and perceived more positive changes, no changes in marital status were observed over time.

Richards and Williams (2004) conducted a longitudinal study and compared the level of marital adjustment in couples undergoing testing and those not undergoing testing. According to the results of Decruyenaere et al. (2004), no significant differences were found in the levels of marital adjustment.

A recent study (Keenan et al., 2013) analyzed how partners experience hearing the results of genetic testing for their partners. They found that the partners' experiences of the patients' disclosure or non-disclosure regarding the results was associated with the couples' coping or marital problems.

In our study comparing sexuality and partnership in HD and multiple sclerosis we found that about 40% of HD patients had broken up their relationship since their diagnosis (Reininghaus et al., 2012). Nevertheless, HD carriers indicated to a high extent that the current partnership fulfilled their desire. They even reported fewer problems than a control sample without these conditions. Considering the severity and the progression of the disease and the problems presented for the patients and their families, the level of courage many patients have to cope with their prognosis is astonishing. Nevertheless, HD patients experienced more break-ups of relationship than multiple sclerosis patients, despite significantly higher relationship satisfaction in the HD patients (Reininghaus et al., 2012). One interesting aspect in this context could be the impaired self-awareness of cognitive, emotional, and functional deficits, which seems to be prevalent among HD patients (Chatterjee et al., 2005; Hoth et al., 2007) but, to our knowledge, has not been evaluated concerning partnership or sexual behavior. To date, surprisingly little attention has been paid to lack of awareness of social functioning or psychiatric symptoms, even though behavioral problems can be more distressing and disrupting for family members than motor symptoms (Hoth et al., 2007). Several authors have posited that denial of illness symptoms may serve as a coping mechanism to assist in dealing with the diagnosis of HD (Deckel and Morrison, 1996). In the existing literature, patients with HD consistently underestimated the degree of their own behavior and showed higher self-ratings of their own competency but not of their relatives, indicating limited insight (Ho et al., 2006; Hoth et al., 2007).

REPRODUCTIVE DECISION MAKING IN HD

As HD is an autosomal-dominant genetic disease, a child of one affected parent has a 50% chance of developing

the disease. Direct genetic testing has been available since 1993, and this provides a predictive diagnosis for individuals with a familial risk for the condition.

Nevertheless, at the current time, the number of people taking predictive genetic HD testing is still low.

Reasons for genetic testing

Reasons for taking the gene test in individuals who are at risk for HD include reducing uncertainty and family planning (Tibben et al., 1993; Decruyenaere et al., 2007). Evers-Kiebooms et al. (2002) named three possible motivations for using HD gene testing as an aid in reproductive decision making: (1) the desire to have children along with the desire not to transmit the HD gene to the next generation; (2) a desire not to have children who may be exposed to an affected parent in their childhood or adolescence; or (3) the need to know in terms of planning the exact number of children and timing of pregnancies.

Among those individuals found to have the genetic variance for HD, denial or minimization of the ultimate impact of the increased risk result was observed (Tibben et al., 1993). After receiving a positive test result, about 30% of respondents decided to have no children (Tibben et al., 1993; Decruyenaere et al., 2007). Contributing factors in this decision were female gender, personal experiences with HD in the own family, and ethical issues about prenatal diagnosis and preimplantation genetic diagnosis (Decruyenaere et al., 2007). More than a half of the couples who still wished to have children reported that they would choose to have prenatal testing (Tibben et al., 1993). An Australian study nevertheless found that few people at risk for HD and confirmed HD gene carriers chose to undergo prenatal testing and to explore alternative reproductive options when these services were available to them (Richards and Rea, 2005). The reasons for this low uptake remained unknown in this study. Other factors related to not using prenatal testing were an unwillingness to terminate a pregnancy following a positive test and optimism for future HD treatments (Decruyenaere et al., 2007).

Consequences of genetic testing

In a large study of reproductive decision making (Evers-Kiebooms et al., 2002), 180 carriers of HD genes were compared with 271 gene non-carriers in Europe. The authors tested whether a predictive test result for HD had an effect on subsequent reproduction decisions. In both groups, almost half of the investigated participants already had children prior to testing. A positive test result reduced the number of subsequent pregnancies in the carrier group and increased the use of prenatal testing. In gene-positive participants, who in the pretest period had reported that "family planning" was the motivation for the genetic testing, the percentage undergoing prenatal diagnosis was slightly higher than in carriers with alternate test motivation. Despite the request to be tested before reproductive decision making, several participants became pregnant before receiving their test result. Significant non-rational emotional factors may therefore be involved in reproductive decision making (Evers-Kiebooms et al., 2002).

Recently, the Prospective Huntington At Risk Observational Study (PHAROS) investigated reproductive decision making in persons at risk for HD. Quaid et al. (2010) aimed to analyze motives and changes in a couple´s decision to start a family after the knowledge of carrying the HD mutation. By using qualitative research methods, the authors identified three groups of persons and decision-making processes respectively: (1) decision to have children despite knowledge of HD risk; (2) having children before knowing the risk of HD; and (3) decision not to have children based on the risk for HD. In the first group of respondents, decisions for starting a family despite HD risk were accompanied by different categories of beliefs: (1) hoping for a cure ("We were pretty confident by that time that there would be more research and there would be getting closer to a cure or better treatment"); (2) feeling guilty ("And so we had our child and then we had another one. And I feel guilt over that probably every day"); (3) magical thinking ("My view is that I don´t have it and therefore I am going to live with the hope that I don´t, rather then find out for sure that I do"); and (4) just another something ("You could have this disease or could get hit by a truck some day").

The second group of respondents comprised people who had their children before knowing about their risk or having inaccurate information about the actual risk of HD. In this group two major themes were identified as: (1) too little, too late ("I had not heard of Huntington´s disease till I was married and had a baby"), and (2) getting it wrong ("Was there any risk of granddad having this disease? And at the time [the grandparents] said no. So they chose to have a child").

The third group identified in the PHAROS study included individuals who understood the risks of HD and therefore decided not to have children. The main theme in this group was (1) vigilant witness ("There´s not much I can do about it but deal with it as it comes but yet my decision not to have children certainly was directly related to the fact that Huntington's was in the family"). The second theme contained stopping HD ("I had been told by my parents that the only way to stop this disease is to stop having children"), and the third aspect being alone ("I´ve kind of prepared myself. No emotional relationships. No romantic

relationships. This is my bunker . . . I have no involvement, no children").

However, one study (Codori et al., 1997) found that carriers without children were more hopeless than non-carriers without children. In this respect, one can pose the question of how important having children is as a determinant of distress in individuals with HD.

PSYCHOLOGIC ALTERATIONS AFTER PRESYMPTOMATIC HD TESTING AND ASSOCIATIONS WITH FAMILY PLANNING

There are numerous studies investigating the psychologic impact of genetic testing for HD. Meiser and Dunn (2000) observed that most of the evidence on the psychologic impact of testing for HD suggests that non-carriers and carriers differ significantly in short-term, but not in long-term, general psychologic distress. In addition, higher psychologic distress 5-year posttesting was found to be associated with lower ego strength and unspecified motivation prior to testing (Decruyenaere et al., 2003).

Gargiulo et al. (2009) compared the psychologic well-being and social adjustment of carriers and non-carriers of the HD mutation after a long-term follow-up (up to 9 years), and found no differences in depressive symptoms between the two groups. In another study assessing the 6-month follow-up effects of testing, carriers experienced greater amounts of intrusive emotions, denial avoidance behavior, and pessimistic expectancies of the future and adjustment problems (Tibben et al., 1994). Furthermore, Decruyenaere et al. (1996) showed that, 1 year after receiving a gene-negative result, mean anxiety and depression levels were significantly decreased. In contrast, those who received a gene-positive result experienced no significant changes in depression and anxiety symptoms. Testing did appear to alter reproductive decision making for both gene-positive and gene-negative individuals alike. Overall, a positive test puts individuals at risk for psychologic changes, although not all individuals experience these changes.

CLINICAL IMPLICATIONS AND PSYCHOLOGIC COUNSELING DURING REPRODUCTIVE DECISION MAKING IN HD

We believe that psychologic care should be given to both HD gene carriers and individuals at risk for HD in reproductive decision making. Regardless of the results of genetic testing, an additive assessment of psychologic symptoms (especially depressive symptoms) and a history of previous familial burden of psychiatric events is essential in treatment planning. Possible interventions include psychoeducation treatments in order to provide information about the disease and to reduce cognitive biases affecting reproductive decision making. Thus, psychologic support and counseling involve the communication of realistic expectations about the progression of the disorder and potential consequences on the children, but also encourage the patients and their families to face this disease. Quaid et al. (2010) described that it is "a fine line to walk between offering hope to patients and families about the possibility of a treatment and cure, and making easy, and perhaps unfounded, predictions about when a treatment or cure might actually be found." Literature findings suggest that special attention should be paid to the potential impact of predictive testing on the couple's relationship. Referrals for couple therapy and professional counseling during the predictive testing process may be indicated. Counseling after receiving test results may stimulate better communication between partners, with consideration of the needs and fears of both partners (Decruyenaere et al., 2004).

SEXUALITY IN HUNTINGTON'S DISEASE

Sexual dysfunction is often reported in chronic diseases and is associated with a considerable amount of unhappiness and decreased quality of life (Ventegodt, 1996; McKee and Schover, 2001). Sexual responses are under the control of numerous central and peripheral neural systems. The central supraspinal systems are mainly localized in the limbic system, in the hypothalamus and its nuclei. Neural information traces through the brainstem, the medulla oblongata, the spinal cord, and the autonomic nervous system to the genital apparatus. Several neurotransmitters and neuropeptides, such as dopamine, glutamic acid, nitric oxide, oxytocin, and corticotropin Y melanocyte-stimulating hormone peptides, are known to facilitate sexual function, whereas serotonin, gamma-aminobutyric acid, and opioid peptides reduce it (Argiolas and Melis, 2003). Primary stress hormones, especially corticotropin-releasing hormone, also influence sexual activity. Mild stress can sometimes increase sexual urges; sustained stress diminishes sexual urges by producing corticotropin-releasing hormone in the brain, which dramatically reduces all prosocial and sexual activities (Panksepp, 2004).

The term "sexual dysfunction" describes a number of sexual problems that inhibit normal sexual relations and is defined as "disturbances in sexual desire and in the pathophysiological changes that characterize the sexual response cycle and cause marked distress and interpersonal difficulty" (American Psychiatric Association, 1994). From a more multifactorial point of view, everyone's sexuality is shaped by biologic, psychologic,

Table 18.1

Overview of studies on sexual dysfunction and paraphilia in Huntington's disease

Author	Number of patients	Sexual dysfunction	Prevalent paraphilia
Dewhurst et al. (1970)	102	29.4% Hypersexual: 18.6% (11.8% male, 6.9% female) Hyposexual: 10.8% (6.9% male, 3.9% female)	Morbid sexual jealousy Indecent exposure Homosexual assault Incestuous sodomy Voyeurism Assault on women Promiscuity
Oliver (1970)	100	Hypersexual: 6% Hyposexual: not stated	Uncontrolled sexual advances Sodomy Incest Masturbation in front of own children
Bolt (1970)	354	Hypersexual: 6% (3.9% male, 2.1% female) Hyposexual: not stated	Increased libido Indecent exposure Child perversity
Fedoroff et al. (1994)	39	Hypersexual (30% male, 25% female) Hyposexual (63% male, 75% female)	Transsexualism Exhibitionism Increase in sexual interest Obscene phone calls
Craufurd et al. (2001)	134	Hypersexual 6% sexual inhibition 5% sexually demanding behavior Hyposexual: 62%	Not stated
Reininghaus et al. (2012)	30	Hypersexual: 28% Hyposexual: 28%	Feeling of invulnerability

interpersonal, and cultural elements and includes different interacting individual factors.

The most important factors are listed as followed.

1. Sexual dysfunction as a consequence of depression. About 50–90% of depressive patients are found to have sexual dysfunctions; comorbidity between sexual dysfunction and depressive illness is high but the causal relationship is unclear (Kasper, 2002). Apart from antidepressant treatment, depression itself may cause a progressive decline in interest in sexual behavior, leading to low libido, difficulty in sexual arousal, orgasm problems, and frank sexual aversion. The psychosocial distress that often accompanies sexual dysfunction might increase the development of depressive illness, or, as some data suggest, depression may cause sexual dysfunction (Seidman, 2002).
2. Sexual dysfunction as a side-effect of medical treatment, especially antidepressant treatment with selective serotonin reuptake inhibitors, antihypertensives, and H_2 blockers, can cause sexual dysfunction with decreased libido and erectile dysfunction, but also result in a worsening of pre-existing sexual problems (Fava and Rankin, 2002).
3. Sexual dysfunction can furthermore be caused by metabolic, cardiovascular, urologic, andrologic, and psychiatric factors (Rosen et al., 2003).
4. In addition, cultural, ethnical, social, and religious factors can have an impact. That is to say, the whole problem in the area of sexual normality and abnormalities is very complex and is related to psychosocial interactions and must be treated individually.

Furthermore, studies in the field of sexuality, especially in chronic diseases, are difficult to compare because of differences in topics and methodology, and influences on sexuality may be dynamic and changeable (Levine, 2007; Verschuren et al., 2010). There are some studies about the sexual life and the frequency of sexual dysfunctions among the so-called "normal" population. In community samples a current prevalence of up to 10% for female orgasmic disorder, up to 5% for erectile disorder and premature ejaculation, and up to 3% for male orgasmic and hypoactive sexual desire disorder has been found (Simons and Carey, 2001). The prevalence of sexual dysfunction in the USA ranges from about 31% to 43% (Laumann et al., 1999).

Only a few studies have tried to explore sexuality and sexual dysfunction in HD. We conducted a search on

Medline using the following terms: "sexuality," "Huntington," "Huntington's disease," "chorea," "sexual," and "fertility." We only found six studies examining these keywords published between 1966 and July 2013 that included a minimum sample of 20 patients, conducted statistical analyses, and provided complete descriptions of the study population, summarized in Table 18.1 (Bolt, 1970; Dewhurst et al., 1970; Oliver, 1970; Fedoroff et al., 1994; Craufurd et al., 2001; Reininghaus et al., 2012). The major finding in the few studies that have tried to explore sexuality and sexual dysfunction in HD is a high frequency of sexual disorders in patients with HD (Schmidt et al., 2008). The most frequent sexual disorder reported was hypoactive sexual behavior, although increased sexual interest and paraphilia were also common. The prevalence of sexual dysfunction ranged up to 85% in men and 75% in women (Fedoroff et al., 1994).

INCREASED SEXUAL DESIRE AND BEHAVIOR

Hypersexual behavior is more prevalent in men, ranging from 3.9% to 30%, compared to 2.1–25% in women. Dewhurst et al. (1970) reported, in their study of the sociopsychiatric consequences of HD, that 30 of 102 patients displayed abnormal sexual behavior, including 19 (18.6%) with hypersexual behavior. Bolt (1970) found that only 20 (6%) of 334 patients had elevated libido or sexual deviation. Oliver (1970) also reported 6% of the patients displaying similar behaviors. A more recent study (Fedoroff et al., 1994) reported substantially higher rates of hypersexual behavior, including 30% of men and 25% of women with HD. However, Craufurd et al. (2001) found a prevalence of hypersexuality that was more comparable to the three studies from 1970. This study interviewed 134 patients attending an HD management clinic, using the Problem Behavior Assessment for HD (PBA-HD). Uninhibited sexual behavior was reported by 6% of the patients while demanding or persistent sexual behavior was described in 5%. Interestingly, only this study sought to determine changes in sexual interest with behavioral changes. Hypersexual behavior was associated with a behavioral profile characterized by irritability, mental inflexibility, and obsessive-compulsive or perseverative behaviors (Craufurd et al., 2001).

In our study comparing sexuality in HD and multiple sclerosis, the patients with HD were found to have higher partnership quality and increased self-confidence compared to those with multiple sclerosis. Further, those with HD were less concerned about their health, less sensitive about their appearance, and had higher levels of sexual arousal, a higher frequency of intercourse, and a higher influence on sexual initiative in contrast to patients with multiple sclerosis (Reininghaus et al., 2012). The results indicated that a certain feeling of invulnerability is present especially in the HD patients, who indicated fewer sexual dysfunctions by feeling very self-confident and attractive and who indicated fewer problems with their partners than the norming values. Another theory explaining the present results could be the loss of inhibitions discussed in the advanced stages of, and related to, dementia, being characteristics that do not apply to our patient groups. Possibly, incipient development is responsible for the disinhibited behavior.

The reasons for the possible mechanisms causing sexual abnormalities in HD are unclear. One proposed mechanism is through damage to cortical areas, which may worsen sexual functioning by influencing concentration and thinking (Fedoroff et al., 1994). Deficits in striatothalamically controlled areas of the frontal cortex have been reported in paraphilias (Tost et al., 2004). Striatal damage in patients with HD may play a role in inhibiting orgasm by interrupting motor patterns and similarly by changing dopaminergic and serotonergic pathways, which have been implicated in the regulation of sex hormones (Fedoroff et al., 1994; Markianos et al., 2005). The mutant huntingtin gene is ubiquitously expressed in many tissues of the body in HD but is at its highest levels in the brain and the testes and may cause striatal neuropathology and testicular degeneration (Leavitt et al., 2001; Van Raamsdonk et al., 2005).

HYPOSEXUALITY

In contrast to the aforementioned findings, some studies have reported that loss of libido and hyposexuality are much more common in HD than hypersexuality. Hypoactive sexual desire disorder is defined as a deficiency or absence of sexual fantasies and desire for sexual activity that causes marked distress or interpersonal difficulty. The dysfunction cannot be better accounted for by another psychiatric disorder (except another sexual dysfunction) and must not be due exclusively to the physiologic effects of a substance or a general medical condition. In the general population, hypoactive sexual desire occurs in approximately one in 10 adult women in the USA and its prevalence appears to be similar in Europe (Clayton, 2001). In the studies on sexuality in HD, decreased sexual interest ranged between 6.9% and 63% in men and between 3.9% and 75% in women (Table 18.1). In our study comparing HD and multiple sclerosis, about one-third of the HD patients reported on sometimes decreased sexual activity (Reininghaus et al., 2012).

In two studies there were no applicable data concerning hyposexuality (Bolt, 1970; Oliver, 1970). Fedoroff et al. (1994) reported that 63% of a sample of 27 HD men and 75% of 12 women showed a hypoactive sexual

disorder. In their sample 56% of men and 42% of women had orgasmic dysfunction. The most remarkable finding of Fedoroff et al. (1994) was the very high frequency of inhibited male orgasm. In the study significantly more men who had problems with inhibited orgasm as well as an increased sexual interest also had paraphilic disorders. Craufurd et al. (2001) found that loss of libido was reported in 61.8 % of patients and was significantly positively correlated with the "problem behavior assessment total score" and inversely correlated with "problem behavior total function capacity score," indicating that hyposexuality may progressively worsen with disease course.

Sexual problems in the partners of HD patients have also been reported. Fedoroff et al. (1994) interviewed 32 partners of HD patients and found one or more sexual disorders (using DSM-III-R criteria: American Psychiatric Association, 1987) in 66% of the sample. There was a significantly greater frequency of paraphilia in the HD cases than in their partners (19% of HD men versus 10% of male partners; 8% of the HD women versus 0% of female partners).

PARAPHILIAS

Paraphilia describes the experience of intense sexual arousal to atypical objects, situations, or individuals (American Psychiatric Association, 2000). In the literature incest and zoophilia, exhibitionism, child perversities, and increased/uncontrolled sexual behavior were the most frequently described abnormalities in individuals with HD (Bolt, 1970; Dewhurst et al., 1970; Oliver, 1970; Fedoroff et al., 1994; Reininghaus et al., 2012). Further and more detailed information is not available to date.

STUDIES AND LIMITATIONS

In the previously discussed studies, the authors used a variety of strategies in recruiting and studying patients with HD. Half of them provided retrospective explorations or described the lifetime prevalence of sexual problems in HD (Bolt, 1970; Dewhurst et al., 1970; Oliver, 1970). Only three conducted direct interviews in clinic waiting rooms (Fedoroff et al., 1994; Craufurd et al., 2001; Reininghaus et al., 2012). Evidence of sexual dysfunction was either based on personal information provided by individual patients, on statements by partners and family members, or on medical diagnosis by physicians. Therefore, the results are difficult to compare across studies.

As only three studies concerning sexual dysfunction in HD were published after 1993, diagnosis was only possible if the patients were already presenting with physical symptoms. Thus, the problem is that in most of the studies only severely ill patients were examined. Only one study interviewed both the patients and their partners and explored the agreement between them (Fedoroff et al., 1994). Couples were found to be more likely to agree on the absence of a particular disorder than on its presence, leading to the assumption that patients with HD are more likely to underreport than to overreport sexual problems. Moreover, psychosocial factors influencing sexual behavior, such as stability of partnership and marriage or break-up of relationships, were not further explored in the present surveys. Only Dewhurst et al. (1970) reported 38% of marriages divorced following diagnosis; likewise we found a similar break-up rate of 40% following diagnosis (Reininghaus et al., 2012).

An interesting finding from Fedoroff et al. (1994) is that men who have problems with inhibited orgasm and increased sexual interest more often show paraphilic disorders. Sexual problems and especially paraphilic disorders in patients and their partners are possibly partially caused, and aggravated by, the mismatch of a current sexual desire with the impossibility of it being able to be fulfilled. In a study with pedophilic perpetrators, structural impairments of brain regions critical for sexual development (not related to age) were found, including subtle defects of the right amygdala and closely related diencephalic structures (Schiltz et al., 2007). In addition, deficits in striatothalamically controlled areas of the frontal cortex have been reported in pedophilia (Tost et al., 2004). Changes in all these pathways have been described in HD, suggesting a possible etiology of the prevalent occurrence of paraphilia in these patients.

The age of the populations in these studies ranged from 20 to more than 80 years old; in some studies the exact range of the age of the patients interviewed on sexuality was not described. Only two studies were specifically focused on sexual dysfunction in HD (Fedoroff et al., 1994; Reininghaus et al., 2012); all the others explored neuropsychiatric or behavioral changes and found abnormal sexual behavior as a prominent symptom.

BEHAVIORAL CHANGES AND SEXUAL DYSFUNCTION

Only one study tried to associate behavioral changes with sexual behaviors (Craufurd et al., 2001). Hypersexual behavior was associated with a behavioral profile characterized by irritability, mental inflexibility; and obsessive-compulsive or perseverative behaviors. Suggestions for possible mechanisms causing sexual dysfunction were not discussed in the article by Craufurd et al. (2001), but others have speculated that damage to cortical areas

may worsen sexual functioning by influencing concentration and thinking (Fedoroff et al., 1994). Damage to cortical areas may worsen sexual functioning by influencing concentration and thinking (Fedoroff et al., 1994).

CEREBRAL DYSFUNCTION AND SEXUALITY

Damage to the striatum may play a role in inhibiting orgasm by interrupting motor patterns and changing dopaminergic and serotonergic pathways in patients with HD. These pathways have been implicated in the regulation of sex hormones (Fedoroff et al., 1994; Markianos et al., 2005). The striatum receives both dopaminergic and serotonergic input and many striatal local circuit neurons are cholinergic. In addition, different biochemical processes and atrophy of the diencephalon may be involved in sexual activity (Lange, 1981). Mice models of HD suggest that the characteristic striatal neuropathology and testicular degeneration in HD are caused primarily by the toxicity of mutant huntingtin (Van Raamsdonk et al., 2005). This large protein of uncertain function is ubiquitously expressed in many tissues of the body but is at highest levels in brain and testis (Leavitt et al., 2001). In animal models an inactivation of the HD gene resulted in male sterility due to reduced sperm production (Dragatsis et al., 2000). In addition atrophy of the reproductive organs, reduced testicular mass, and loss of fertility have been observed in mouse models of HD (Papalexi et al., 2005). As normal breeding behavior could be noticed, a defect in spermatogenesis is suggested to be responsible for the lack of fertility (Leavitt et al., 2001). Further, it is assumed that the spermatogenetic defect is not caused by a defective maturation or limited to a single stage of development of spermatocytes, as degenerating cells at various stages of development were identified in animal models (Leavitt et al., 2001; Papalexi et al., 2005).

HORMONES AND SEXUALITY

A reduction of circulating testosterone level in male patients with HD (Markianos et al., 2005) and decreased expression of gonatropin-releasing hormone (GnRH) in the hypothalamus and blood testosterone level (Papalexi et al., 2005) has been reported, as well as atrophy of gonads and sterility in transgenic mice model of HD (Sathasivam et al., 1999; Dragatsis et al., 2000; Leavitt et al., 2001; Papalexi et al., 2005; Van Raamsdonk et al., 2005).

Not only in male mouse models but also in male HD patients, testosterone levels were significantly lower compared to healthy men, suggesting the influence of GnRH, although this was not accompanied by a reduction in luteinizing hormone (LH) levels (Markianos et al., 2005). Thus, the reduction in testosterone might be caused by the reduced dopaminergic input to pituitary, possibly because of a loss of hypothalamic dopaminergic and GnRH neurons in the hypothalamus (Markianos et al., 2005; Papalexi et al., 2005).

Additionally, the physiologic basis of sexual behavior in female patients with HD indicates changes in concentration of GnRH (Bird et al., 1976). Infertility could be due to death of GnRH neurons or to a reduction in GnRH expression leading to a downstream impairment of the gonadotropic hormones (Papalexi et al., 2005). The hypothalamic–testicular pathway could interfere with the synthesis and secretion of testosterone in the Leydig cells independent of pituitary. This mechanism could explain the great reductions in testosterone in patients with severe symptomatology, in whom LH levels were found to be normal (Markianos et al., 2005). Interestingly, although reduced testosterone levels are known to be associated with a corresponding loss of muscle mass, testosterone treatment had no effect on body weight loss and did not restore motor function in transgenic HD mice (Papalexi et al., 2005).

Estrogens and derivatives have been shown to protect neurons from oxidative stress-induced death in animal models and could have a beneficial effect in HD, but did improve motor symptoms (Bonuccelli et al., 1992; Tunez et al., 2006).

TREATMENT OPTIONS

Treatment options with medication for HD patients with sexual disorder have not yet been studied in detail and are only reported sporadically; guidelines can only be obtained from non-HD patients and further research is needed.

CONCLUSION

HD is a chronic disabling disease that inflicts a considerable burden on the patients and their partners. Mental impairment and the changes in personality appear to be the most difficult aspects to manage in romantic relationships. Additionally, the knowledge regarding genetic inheritability of the disease and the threat that their own children may later be affected are incisive themes.

Despite the availability of predictive genetic testing for HD, the number of individuals utilizing these services is low. The decision to take the test in many people at risk for HD is associated with family planning in the near future. After receiving a positive test result, about 30% of respondents decide to have no children.

In the existing literature, HD patients consistently underestimated the degree of their own behavior and showed higher self-ratings of their own competency but not of their relatives. This finding is especially interesting in the context of sexuality and partnership because

a balanced interaction of social perception and self-awareness is often the basis of a functioning partnership; the impaired insight in patients with HD may indicate problems for relationships. Only a few studies have tried to explore sexuality and sexual dysfunction in HD. These studies conclude that up to 85% of men and up to 75% of women experience high levels of sexual problems, most of them having prevalent symptoms of a hypoactive sexual disorder, although increased sexual interest and paraphilia were found in a subset of patients.

There is no evidence of whether sexual dysfunction is mainly a specific symptom of HD and may be associated with the specific brain lesion itself or if it is chiefly related to the psychosocial factors associated with the steady worsening of the disease. Further studies should focus on asymptomatic individuals with positive genetic screening to explore sexual changes preceding neurologic and motor symptoms and should incorporate partners to identify sexual distinctive features. Investigations on the context of sexual dysfunction with depression, irritability, and dementia symptoms are needed to better understand reasons for sexual changes in HD.

Psychologic care should be given to both HD gene carriers and individuals at risk of HD in reproductive decision making. Thus, psychologic support and counseling involve on the one hand the communication of realistic expectations about the progression of the disorder and potential consequences on the children, and on the other hand encouragement for patients and their families to face this life-threatening illness.

ACKNOWLEDGMENT

We thank Mike Sugarman from the Research and Editing Consulting Program (RECP) within the International Neuropsychological Society's International Liaison Committee for proofreading and English-language editing this chapter.

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 19

Lower urinary tract dysfunction in patients with parkinsonism and other neurodegenerative disorders

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INTRODUCTION

Worldwide demographic aging is evidence of improvements in healthcare over the last century. Because many people now live longer and healthier lives, the world population has a greater proportion of older individuals. A negative outcome of aging, however, is an increase in the number of people with neurodegenerative disorders, particularly Alzheimer's disease (AD) and related dementias. It is estimated that 24.2 million people worldwide were living with dementia in 2001, with 4.6 million new cases annually, similar to the global incidence of non-fatal stroke (Ferri et al., 2005; Prince and Jackson, 2009; Prince et al., 2013). These numbers are predicted to double every 20 years, resulting in over 80 million cases by 2040, given that incidence does not change over time, an issue that has been debated (Matthews et al., 2013). In Europe, the total cost of brain disorders in 2010 was €798 billion, with dementia accounting for €105 billion and Parkinson's disease (PD) accounting for €14 billion (Olesen et al., 2012).

By 2030, it is estimated that the total burden of PD will increase by 25% relative to 2005. Regardless of its incidence, the future burden of neurodegenerative diseases will be significant, with important areas of concern being the ongoing need for medical care and hospital visits along with a reduced quality of life among the elderly. For PD, which is the most common neurodegenerative movement disorder, the incidence of dementia and thus dependence on others for help is very high, with up to a 70% risk of developing dementia within 8 years (Aarsland et al., 2005). Therefore, symptoms of advanced disease and comorbidity are expected to rise accordingly.

Caring for patients with neurodegenerative diseases demands that neurologists, specialist nurses, or primary care health providers focus on both the core symptoms of the disease as well as other symptoms that may affect quality of life.

In neurodegenerative disorders, bladder dysfunction may be an integrated part of the syndrome, it may be due to other conditions, or it may be a consequence of the treatment given. As in all disorders, comorbidity is important with respect to risk of complications. However, specific to neurodegenerative disorders, cognitive dysfunction and dementia often further increase the impact of lower urinary tract symptoms (LUTS) due to altered behavior and impaired attention. Further, patients rarely link the bladder dysfunction to the neurologic disorder, but see it as "normal aging."

The spectrum of neurodegenerative diseases includes multiple phenotypes. From the perspective of the affected patient, however, all share the burden of disease progression without hope for a cure. Therefore, regardless of the nature of the disorder, it is important to identify the symptoms and complications that can lead to further loss of mobility and poorer quality of life.

In this chapter, LUTS in patients with neurodegenerative disorders is addressed in the context of particular diseases. However, it should not be ignored that mixed pathology is very common, and psychosocial factors as well as cognitive deficits often interfere with the core disorder and the manner in which patients cope with urgency and impaired bladder emptying. Although most available knowledge of LUTS concerns patients with PD and atypical parkinsonism, LUTS also have a major impact on the ability of AD patients to stay independent.

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PARKINSONISM

Parkinsonian syndromes include PD and atypical parkinsonism. Atypical parkinsonism includes multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and dementia with Lewy bodies (DLB). Despite relatively well-established clinical diagnostic criteria (Litvan et al., 1996a, 2003; McKeith, 2006; Gilman et al., 2008), differential diagnosis remains a challenge due to the heterogeneity of clinical presentations for each parkinsonian syndrome and considerable overlap in clinical profiles. Differentiating among syndromes is particularly difficult in early disease stages. However, careful monitoring of the progression of symptomatology enables clinicians to establish a diagnosis during follow-up (Hughes et al., 2001, 2002). Ensuring an accurate diagnosis is important for managing motor symptoms, estimating prognosis, and providing information to patients and their caregivers. Differentiating among syndromes, however, is particularly important for LUTS, which evolve differently and with variable impact and prognoses.

Although PD is the most common primary parkinsonian syndrome, atypical syndromes are more common than generally thought, with 15–20% of patients presenting with conditions progressing to primary atypical parkinsonian syndrome or symptomatic parkinsonism.

Parkinson's disease

PD is a progressive degenerative neurologic movement disorder, and motor symptoms are characterized by resting tremor, bradykinesia, (cogwheel) rigidity, and postural instability.

PD is common. Although studies suggest some variability in prevalence among different ethnic groups, prevalence among Europeans is estimated to be 100–120 per 100 000 individuals (Tandberg et al., 1995; de Rijk et al., 1997; Wermuth et al., 2000). A recent metaanalysis have found a higher prevalence than previously suggested (>300 per 100 000 for persons older than 50 years), increasing with age and more common in persons of European origin compared to Asian (Pringsheim et al., 2014).

Motor symptoms result from degeneration of nigrostriatal dopaminergic neurons, and hallmark neuropathologic findings also include the presence of Lewy bodies in brain cells. These eosinophilic inclusions consist mainly of α-synuclein and can be found in neurons throughout the brain, including the substantia nigra, striatum, locus coeruleus, and neocortex. Lewy bodies and dopaminergic neuron degeneration are also observed in peripheral nerves innervating the gastrointestinal tract, even before the onset of motor symptoms (Braak et al., 2006).

Over the last decade, there has been increasing interest in and understanding of non-motor aspects of PD, which include dysphagia (30–82% of patients: Pfeiffer, 2003; Braak et al., 2006), constipation (>50%: Winge et al., 2003), orthostatic hypotension (20–58%: Senard et al., 1997), depression (>16%: Rojo et al., 2003), cognitive decline and dementia (>6 times higher than healthy individuals: Emre, 2003; Aarsland et al., 2005), sexual dysfunction (43–81%: Brown et al., 1990; Singer et al., 1991; Zesiewicz et al., 2000), and LUTS. The origin of these symptoms reflects the involvement of widespread and (in part) non-dopaminergic pathophysiologic mechanisms. However, both orthostatic hypotension and symptoms originating from the gastrointestinal tract are believed to result from peripheral dopaminergic denervation (Mathias, 2002).

Validated questionnaires and scales for evaluating non-motor symptoms in PD are available (Chaudhuri et al., 2007; Chaudhuri and Martinez-Martin, 2008). Although these scales do not evaluate bladder dysfunction or the nature of related symptoms in detail or with sufficient specificity, they can be easily applied to large cohorts and can help neurologists address important disease-related issues.

In the PRIAMO study (Barone et al., 2009), which thoroughly employed interviews and questionnaires to assess non-motor symptoms and their impact on quality of life among 1072 patients, almost all patients reported at least one non-motor symptom (98.6%). Although symptoms in the psychiatric domain were most frequent (67%), LUTS were also very common (57.3%), including urgency (35%) and nocturia (35%).

Several studies using specific questionnaires report a high prevalence of LUTS in PD patients that increases with disease severity. Older studies report that between 38% and 71% of patients have LUTS (Murnaghan, 1961; Hald and Bradley, 1982; Berger et al., 1987; Hattori et al., 1992; Gray et al., 1995), but these studies typically did not use validated questionnaires and were published before criteria for MSA (Quinn, 1989; Gilman et al., 1998) were established. In general, it has been difficult to establish the extent to which PD itself contributes to LUTS. Most PD patients are in an age group in which other conditions also influence continence and emptying, with some men experiencing outflow obstruction due to prostatic enlargement and some women experiencing stress incontinence. Also, idiopathic detrusor overactivity (defined as an involuntary contraction of the bladder smooth muscle (i.e., detrusor) during the storage phase) may occur in both men and women (Abrams et al., 2002), which could be due to previous cerebral ischemia in otherwise asymptomatic individuals (Sakakibara et al., 1999, 2012). More recent studies of PD patients treated in modern regimes report that the

prevalence of significant urinary symptoms is 27% (Araki and Kuno, 2000) to 39% (Campos-Sousa et al., 2003) when using validated questionnaires, but over 50% when using a non-validated questionnaire (Sakakibara et al., 2001b). However, the most widely used validated questionnaire, the International Prostate Symptoms Score (IPSS), does not contain questions on incontinence, in contrast to what has been used by Sakakibara et al. and others. In early-stage untreated PD patients, a high prevalence of bladder symptoms (64%) was reported based on a questionnaire (Uchiyama et al., 2011), but this study did not include an age-matched control group, thus making it difficult to identify PD-specific bladder symptoms during very early-stage untreated PD, as the mean duration of disease was 23 months.

Large-scale studies comparing PD patients and healthy individuals are not available. In a smaller study, 61 patients with PD and 74 control individuals were examined using the IPSS (Campos-Sousa et al., 2003). Whereas 39% of PD patients had urinary symptoms, only 10.8% of control individuals had such symptoms. Nocturia was reported by 64% of PD patients and 32% of control individuals, and urgency was reported by 32% of PD patients and 9% of control individuals. Patients with PD also had more storage symptoms than control individuals. A comparison of these results with those from large-scale studies of LUTS in the general population may not be appropriate, however, as demographics of the PD cohorts may not fit the general population, and healthy individuals may underreport their LUTS. In a population-based, cross-sectional survey in Canada, Germany, Italy, Sweden, and the UK, in which a total of 19 165 individuals were interviewed about LUTS, 64.3% reported at least one LUTS (Irwin et al., 2006), with nocturia being the most common symptom (men, 48.6%; women, 54.5%). Storage-related LUTS were also common (men, 51.3%; women, 59.2%), and LUTS generally increased with advanced age. Other studies report similar magnitude and impact of LUTS (Kay et al., 1999; Norby et al., 2005). However, these studies have used different questionnaires, making their direct comparison difficult, but larger studies in PD seem to be needed if specific LUTS are to be identified.

There seems to be no consensus on the nature, severity, and temporal occurrence of LUTS among PD patients. In studies using the Danish Prostate Symptoms Score (DAN-PSS) questionnaire, which includes questions on incontinence and the bothersomeness of symptoms, 72% had one or more symptom, 38% of patients with moderate PD scored more than 10 points (Winge et al., 2006), and 54% of patients with advanced PD scored more than 10 points (Winge and Nielsen, 2012), which is regarded by most urologists as "significant." However, this cut-off is arbitrary, and, compared to neurologically intact patients who present for urologic evaluation, PD patients generally have fewer symptoms, although some have symptoms that are quite severe (Winge et al., 2006). An important point is that there may be a difference between significant questionnaire scores and the severity of symptoms as judged by patients. For instance, urinary incontinence is experienced as more bothersome than hesitation. However, the DAN-PSS includes a "bother score" that in part addresses this point (Kay et al., 1999). Patients with PD referred for urologic evaluation score high on the IPSS (9–16 points), with bladder symptoms and the severity correlated with disease stage (Ragab and Mohammed, 2011).

Studies including a healthy control group report that PD patients have significantly more symptoms than healthy individuals (Lemack et al., 2000; Campos-Sousa et al., 2003; Hobson et al., 2003), although the absolute number of symptoms differs considerably among studies, and the usefulness of the questionnaires employed by these studies remains to be tested.

Previous studies using non-validated questionnaires report that LUTS are associated with neurologic disability (Araki and Kuno, 2000) and correlated with stage of PD (Sakakibara et al., 2001b), which was partly confirmed by a subsequent smaller study (Winge et al., 2004). Other studies, however, report no such correlation (Aranda et al., 1983; Gray et al., 1995; Campos-Sousa et al., 2003). Also, using two validated questionnaires (IPSS and DAN-PSS), one study demonstrated that the number of bladder symptoms assessed using the IPSS does not increase with disease severity but that the number of bothersome symptoms assessed by the DAN-PSS correlates significantly with the Hoehn and Yahr stage of disease among early and moderate PD patients and advanced patients receiving oral treatment (Winge et al., 2006; Winge and Nielsen, 2012). This indicates that other symptoms, both motor and non-motor, may influence the impact of bladder symptoms among PD patients, with slowness, tremor, gait, and balance deficits as well as attention difficulties being troublesome partners to the symptom of urgency.

In a recent study, the severity of bradykinesia was found to correlate significantly with overactive bladder symptoms (Tsujimura et al., 2014). Intriguingly, the authors demonstrated that the rate of finger taps, which is frequently used to assess bradykinesia in PD, predicted questionnaire score for overactive detrusor symptoms.

There is limited information regarding the time of appearance of PD-specific urinary symptoms. Several studies provide evidence that LUTS occur 5–7 years after the onset of motor symptoms (Bonnet et al., 1997;

Hobson et al., 2003; Winge et al., 2006; Sammour et al., 2009). However, one study reports a high prevalence of LUTS very early in the course of the disease (Uchiyama et al., 2011), although no healthy control group was included as confirmation of the specificity of the symptoms. Furthermore, autonomic, including urogenital, abnormalities may precede motor deficits in patients with PD. A cohort study of 100 oncologic patients aged 44–84 years without a clinical history of neurologic disease who had major abdominopelvic resection reported that 26% of patients showed α-synuclein aggregates in the vesicoprostatic plexus (Minguez-Castellanos et al., 2007). Six patients with α-synuclein aggregates and 10 patients without aggregates then underwent annual double-blind neurologic assessments. Thirty months after biopsy, lower cardiac meta-iodobenzylguanidine uptake and dopamine transporter values correlated, albeit not significantly, with higher Unified Parkinson's Disease Rating Scale-III scores in the group with α-synuclein-positive biopsies. Although this study lacked a long-term follow-up for all 100 patients due to the nature of their disease, and incident cases of PD were identified only after 30 months, its findings suggest that α-synuclein aggregates in peripheral autonomic neurons may be an early event in the development of PD. These findings have later in part been confirmed (Hilton et al., 2014).

The nature of bladder complaints in PD patients is dominated by storage symptoms. Overall, studies consistently report nocturia and urinary frequency as the most common LUTS in PD patients, with details provided in Table 19.1.

Pathophysiology

Under normal conditions, the net output from the basal ganglia (i.e., the internal part of the globus pallidus) inhibits the thalamus, and dopaminergic striatal activity induces selective disinhibition. In healthy individuals, this is believed to be achieved by a shift in activity from an indirect pathway (i.e., tonic stimulation of D2 receptors) to a direct pathway (i.e., stimulation of D1 receptors), as shown in Figure 19.1.

In PD, it is believed, this disinhibition cannot be performed due to degeneration of nigrostriatal dopaminergic neurons. The inhibitory indirect pathway becomes overactive, which induces inhibition of the thalamus, as shown in Figure 19.2. Motor symptoms, bradykinesia, and rigidity may result from this inhibition, as the supplementary motor cortex becomes unable to test planned actions against facts (Gombart et al., 2004; Wichmann and DeLong, 2004). Moreover, PD is associated with decreased input of sensory information to the cortex. PD patients show reduced ability to integrate and separate sensory input as the disease progresses (Duchesne et al., 2002). Also, studies of patients who received deep-brain stimulation (DBS) of the subthalamic nucleus (STN) suggest that LUTS are associated with cortical dysfunction in PD (Herzog et al., 2006, 2008). That is, frontal cortical areas become unable to stimulate the pontine micturition center at socially acceptable times, which disrupts the integration of sensory input from the bladder to the periaqueductal gray and the defective ventral tegmental area (VTA).

There is considerable experimental evidence that the basal ganglia, and in particular dopaminergic neurons originating in the substantia nigra, are deeply involved in physiologic bladder control.

Figure 19.3 outlines the current knowledge of the role of the basal ganglia and dopaminergic systems in normal bladder control, and Figure 19.4 illustrates possible mechanisms involved in the development of overactive bladder in PD.

The most widely proposed hypothesis is that, in healthy individuals, the basal ganglia have an inhibitory effect on micturition reflex, and detrusor overactivity develops after cell loss in the substantia nigra. In monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), overactive bladder is common, and selective dopamine D1 receptor agonists suppress detrusor overactivity. Subcutaneous injection of a dopamine D2 receptor agonist or dopamine D1/D2 receptor agonist (apomorphine) slightly but significantly reduces bladder volume threshold for the micturition reflex in both control and MPTP-treated groups (Yoshimura et al., 1993). Electric stimulation of the substantia nigra inhibits bladder contractions in normal cats (Yoshimura et al., 1992), and this effect is blocked by D1 antagonists in both cats and rats (Yoshimura et al., 1992; Sakakibara et al., 2002). Also, D1 agonists inhibit bladder overactivity in MPTP-treated primates via tonic inhibition of the micturition reflex (Yoshimura et al., 1993, 1998), and D2 receptors are involved in facilitating the micturition reflex (Seki et al., 2001).

In 6-OH-dopamine-treated rats, dopaminergic depletion of the VTA results in more severe bladder overactivity than substantia nigra lesions (Hashimoto et al., 1997). In cats, neurons facilitating micturition are concentrated in the caudal area of the VTA, and storage neurons are distributed in the medial-caudate part of both the VTA and substantia nigra (Sakakibara et al., 2002). These findings suggest that the VTA has a functionally heterogeneous role in micturition because both inhibitory and facilitatory responses were elicited in this area, whereas only inhibitory responses were found in the substantia nigra. Most dopaminergic neurons originating from the substantia nigra project to the neostriatum (i.e., nigrostriatal pathway). By contrast, most dopaminergic neurons originating from the VTA project to the hypothalamic nuclei (i.e., mesolimbic pathway)

Table 19.1

Lower urinary tract symptoms in patients with Parkinson's disease (PD)

Study	*n* in study Questionnaire	Nocturia (%)	Frequency (%)	Urgency (%)	Urge incontinence (%)	Incomplete emptying (%)	Intermittency (%)	Note
Campos-Sousa et al. (2003)	PD: 61 IPSS	63.9	36.1	32.8	NA	18	13.1	PD more symptoms than control persons
Sakakibara et al. (2001b)	PD: 115 Non-validated	Men: 63 Women: 53	Men: 16 Women: 28	Men: 54 Women: 42	Men: 25 Women: 28	NA	NA	
Barone et al. (2009)	PD: 1072 NMSS	34.6	26	35	NA	NA	NA	Not specific non-motor questionnaire
Bonnet et al. (1997)	PD: 35 Non-validated	NA	NA	43	23	8	NA	
Hattori et al. (1992)	PD: 110 Non-validated	Irritative symptoms: 28 Irritative and obstructive symptoms: 21				Obstructive symptoms: 11		
Ragab and Mohammed (2011)	PD: 49 IPSS	77	32.6	36.7	NA	8	6.1	Referred for urologic evaluation
Sammour et al. (2009)	PD: 110 IPSS	81	35	36	21	40	44	
Uchiyama et al. (2011)	PD: 50 Non-validated	38	46	36	12	12	NA	All untreated
Winge et al. (2006)	PD: 107 IPSS + DAN-PSS	IPSS: 49 DAN-PSS: 86	IPSS: 37 DAN-PSS: 71	IPSS: 60 DAN-PSS: 68	IPSS: NA DAN-PSS: 46	NA	NA	
Ransmayr et al. (2008)	PD: 15 Interview by advisor	NA	NA	53	27	NA	NA	

IPSS, International Prostate Symptoms Score; DAN-PSS, Danish Prostate Symptoms Score; NMSS, Non-Motor Symptoms Scale; NA, not available.

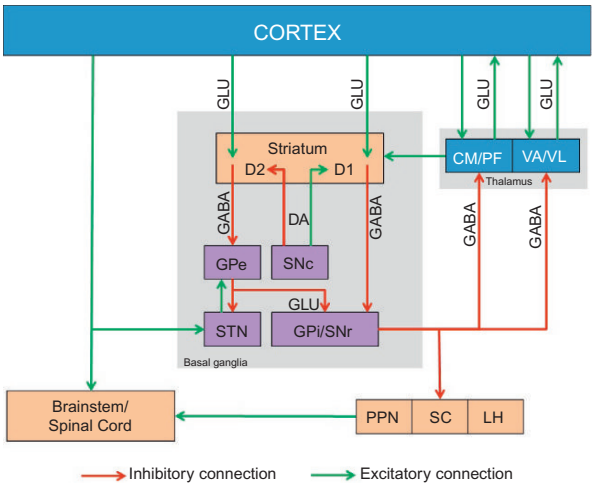

Fig. 19.1. Direct and indirect pathway model of the basal ganglia. The gray box indicates tightly interconnected basal ganglia nuclei that receive extrinsic inputs from cortical, thalamic, and brainstem regions. Extrastriatal SNc dopaminergic projections to the GPe, STN, and Gpi/SNr were omitted from the diagram. CM, centromedial nucleus of thalamus; D1 and D2, dopamine D1-type and D2-type receptors; GPe, globus pallidus exernal segment; Gpi, globus pallidus internal segment; LH, lateral habenula; PF, parafascicular nucleus of thalamus; PPN, pedunculopontine nucleus; SC, superior colliculus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; VA/VL, ventral anterior and ventrolateral nuclei of thalamus; GLU, glutamate; DA, dopamine; GABA, gamma-aminobutyric acid.

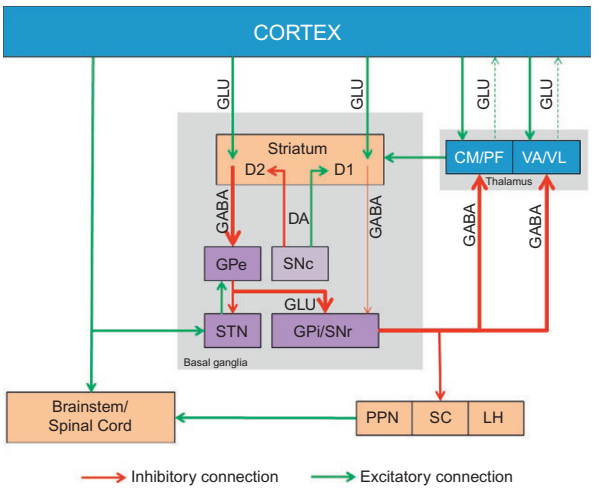

Fig. 19.2. Parkinsonism state of the basal ganglia model. Dopaminergic (DA) loss leads to inhibition of striatal medium spiny neurons, which increases their GABAergic input into the GPe. The GPe thus becomes hypoactive and reduces STN activity, leading to hyperactivity of the Gpi. DA depletion also causes hypoactivation of striatal medium spiny neurons in the direct pathway. The net result is excessive efferent input into the GPi, thalamus, and cortex. For abbreviations, see legend to Figure 19.1.

and the anteromedial frontal cortex (i.e., mesocortical pathway), which may be involved in neuropsychiatric behavioral disorders (Smith et al., 1998). Therefore, the substantia nigra and VTA may have distinct roles in regulating the micturition reflex and may exert their effects via different pathways to the rostral pontine tegmentum.

Patients with PD and bladder symptoms have less uptake of dopamine transporter (DAT- receptor) markers (beta-CIT or FP-CIT) in the striatum than patients with PD but no bladder symptoms, and the loss of neurons in the putamen correlates with the severity of LUTS, indicating an association between urinary dysfunction and degeneration of nigrostriatal dopaminergic cells (Sakakibara et al., 2001c; Winge et al., 2005).

Dopaminergic treatments

The relationship between motor symptoms and bladder dysfunction in PD is complex and non-linear. The neural mechanisms involved in bladder control are only partly dopaminergic. During the course of the disease, patients are typically treated with dopaminergic drugs as well as drugs that influence the metabolism of dopamine and other neurotransmitters, which may lead to overactive detrusor.

Several studies show detrusor overactivity in both treated and untreated PD patients (Pavlakis et al., 1983; Stocchi et al., 1997a; Winge et al., 2004). Experimental exposure to levo-dopa (L-dopa) results in significant changes in urodynamic parameters. In both stable and PD patients with wearing-off phenomenon and symptoms of overactive detrusor, a single dose of 100 mg L-dopa decreases the first sensation to void and bladder capacity but improves bladder emptying (Uchiyama et al., 2003; Brusa et al., 2006). In another study, urodynamic evaluation was performed for 87 patients with mild idiopathic PD and overactive bladder syndrome after acute administration of 200 mg L-dopa (Brusa et al., 2006). A subgroup of 70 patients underwent urodynamic evaluation after the co-administration of L-dopa with a central and peripheral D2 antagonist (L-sulpiride) or with a peripheral D2 antagonist (domperidone). Acute administration of L-dopa worsened detrusor overactivity, whereas the co-administration of L-sulpiride reversed this effect. No changes in deterioration of bladder function were observed when L-dopa was mediated through D2 central receptor stimulation. A similar pattern of change was found during acute L-dopa challenge, but chronic treatment improved both bladder filling and emptying, resulting in an overall improvement of LUTS reported by PD patients (Brusa et al., 2007). Also, the mixed D1/D2 dopamine receptor agonist apomorphine reduces bladder outflow resistance (Aranda and Cramer, 1993) and detrusor

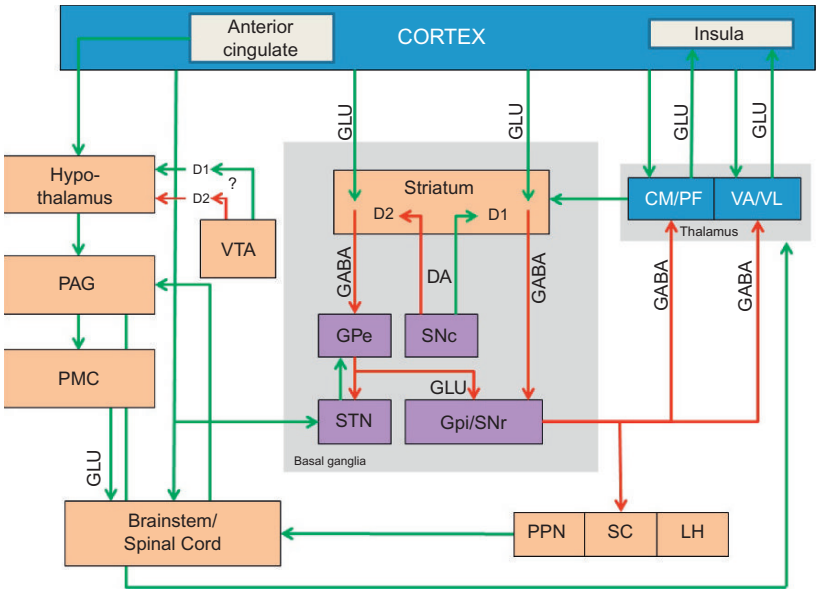

Fig. 19.3. Basal ganglia bladder control model. VTA, ventral tegmental area; PMC, pontine micturitional center; PAG, periaqueductal gray; see legend to Figure 19.1 for other abbreviations.

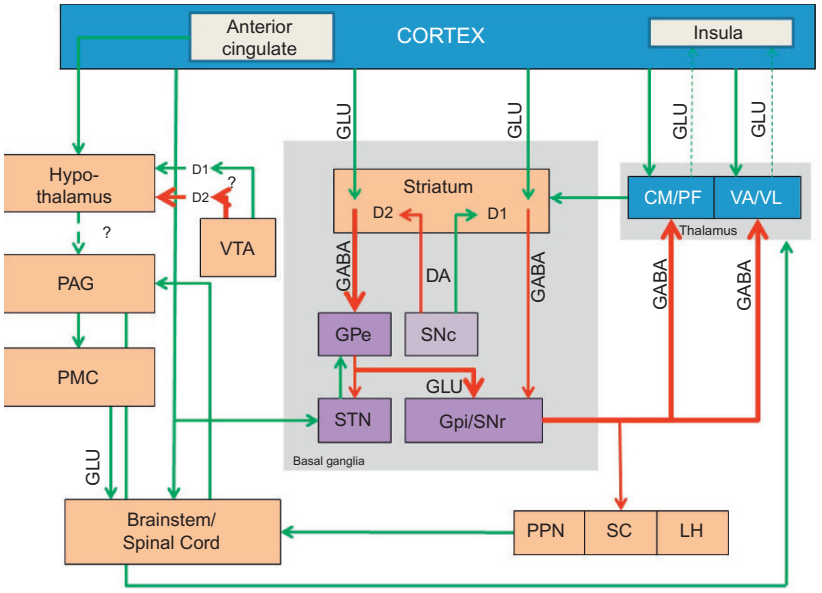

Fig. 19.4. Parkinsonism state of the basal ganglia bladder control model. As depicted in Figure 19.2, DA loss leads to hyperactivity of the Gpi and hence excessive efferent input to the thalamus and cortex. With DA depletion of the VTA, decreased activity of the PAG–thalamic–insula pathway results in neurogenic overactive detrusor. For abbreviations, see legends to Figures 19.1 and 19.3.

hyperreflexia (Stocchi et al., 1993), which is consistent with later findings in animal models (Uchiyama et al., 2009).

Most PD patients are treated with complex regimens of dopamine receptor agonists, L-dopa, and other drugs that could affect bladder storage and emptying. Although the effects of dopaminergic treatment on bladder control and urodynamic parameters are unpredictable in individual patients, most patients experience significant treatment effects (Winge et al., 2004). Specifically, patients who are severely bothered by LUTS as assessed by the DAN-PSS report significant improvement in total bladder capacity in the medicated state.

Deep-brain stimulation

DBS in the STN is an efficacious and cost-effective tool for managing motor symptoms in advanced PD patients troubled by fluctuations and dyskinesias (Deuschl et al.,

2006, 2013). Although recent studies suggest that DBS may not have significant effects on non-motor symptoms in general (Wolz et al., 2012), its effects on bladder control have been intensely studied, thus providing important information on neurogenic bladder control.

Overall, DBS of the STN reduces urgency and incontinence and improves bladder emptying. However, uncontrolled reports from patients may be biased by their subjective perception of complete relief from motor symptoms (Haahr et al., 2010). In animal models, stimulation of the STN not only improves bladder capacity but also improves bladder emptying (Dalmose et al., 2004). In a postoperative study of 16 PD patients in which urodynamic examinations were conducted 12 hours after withdrawal of antiparkinsonian medication, STN-DBS was turned on or off in a randomized order (Seif et al., 2004). DBS resulted in significant increases in the first urge to void and the bladder capacity and a decrease in residual urine.

In a complex experiment, changes in regional cerebral blood flow (rCBF) were measured by positron emission tomography (PET) in nine PD patients with bilateral STN-DBS turned on or off during both a dynamic bladder filling condition and an empty bladder condition (Herzog et al., 2008). Bladder filling increased rCBF in the periaqueductal gray, posterior thalamus, insular cortex, right frontal cortex, and bilateral cerebellum. Furthermore, during DBS, neural activity in the thalamus and insular cortex was found to be modulated by PAG activity. The authors conclude that DBS of the STN enhances afferent urinary bladder information processing and facilitates the discrimination of different bodily states by enhancing sensory perception and increasing activity of the insular cortex, as shown in Figure 19.5.

Another DBS study evaluated 16 PD patients who completed the DAN-PSS and IPSS before as well as 3 and 6 months after surgery and who underwent urodynamic examinations before implantation of the DBS stimulator and 6 months after DBS (all examinations occurred after discontinuation of medication for 12 hours) (Winge et al., 2007). Although there was no change in mean values overall for urodynamic parameters, some individual patients showed a dramatic effect. The authors speculate that a DBS-induced increase in the interval between first sensation of bladder filling and total bladder capacity is associated with an increased ability of patients to integrate and separate sensory input during bladder filling (Winge et al., 2007). These findings are consistent with the findings of Herzog et al. (2008) in a subsequent study, suggesting that bladder control may be improved during DBS in the STN.

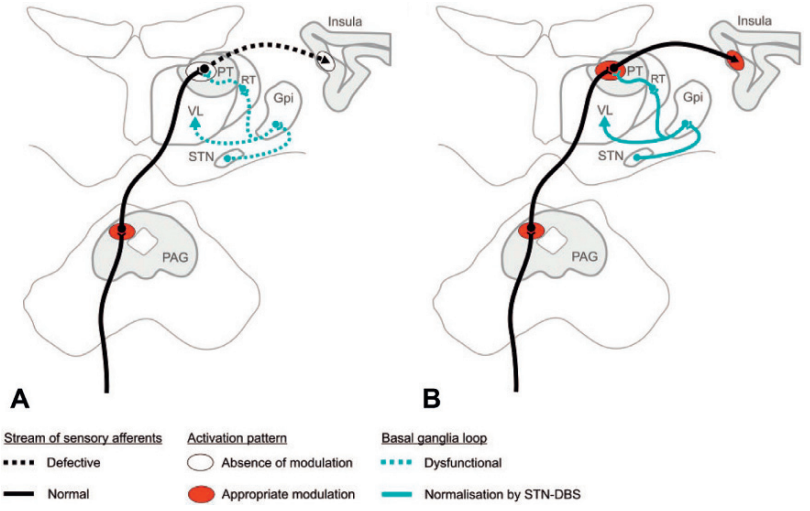

Fig. 19.5. Possible mechanisms underlying the influence of subthalamic nucleus deep-brain stimulation (STN-DBS) on cerebral areas involved in the processing of afferent urinary bladder information in the stimulation OFF (**A**) and stimulation ON (**B**) conditions. Urinary afferent bladder information is conveyed by the periaqueductal gray (PAG) and the posterior thalamus (PT) to the insula. Efferents from the internal globus pallidus (GPi) to the ventrolateral thalamus (VL) send collaterals to the reticular thalamus (RT), which modulates the flow of information between the thalamus and the cortex. In the stimulation OFF condition, the dysfunctional basal ganglia state leads to an insufficient activation of the RT, which results in aberrant or absent modulation of thalamic and insular areas. In the ON condition, stimulation of the subthalamic nucleus (STN) partially restores the basal ganglia circuit and eventually normalizes the modulation of the thalamocortical sensory projections by the RT. (Reproduced from Herzog et al., 2008, with permission.)

Another study, however, reports no difference in bladder symptoms between patients treated with DBS 2.5 years prior (range 0.25–7.0 years), patients under best oral treatment and medical care, and patients treated with continuous subcutaneous infusion of apomorphine (Winge and Nielsen, 2012). Across all groups, more than 50% of patients had severe bladder symptoms, the most frequent of which were symptoms of overactive bladder, suggesting that the effect of DBS on bladder control may be temporary.

A case report describes two male patients who underwent STN-DBS. Although their motor symptoms improved after DBS, the patients developed urinary retention after removal of a urethral catheter 2 days after DBS. Due to persistent urinary retention, both had a suprapubic catheter inserted for a period of 8 and 12 weeks, after which sensory function and detrusor motility recovered spontaneously. The authors hypothesized that this adverse effect may have been caused by the modulation of afferent bladder information by STN-DBS (Fritsche et al., 2009). This adverse reaction could be explained by the inhibition of the micturition reflex that is observed after STN stimulation in cats (Sakakibara et al., 2003).

Management

Patients with PD and LUTS may be particularly troubled by the combination of tremor, bradykinesia, postural instability, and urgency. Hence, a systematic and individualized approach involving the careful collection of relevant data and choice of an appropriate treatment accordingly may be of significant importance to individual patients. In a prospective study, patients with PD or DLB, orthostatic intolerance, and urinary incontinence showed poorer survival than patients with orthostatic symptoms alone or with neither orthostatic nor urinary symptoms (Stubendorff et al., 2012).

To collect relevant historic details from patients, a detailed interview concerning the patterns and temporal nature of bladder symptoms can be helpful. Often, patients do not understand the link between their movement disorder and autonomic symptoms. Although a validated questionnaire may be useful, addressing nocturia, urgency, frequency, feeling of incomplete emptying and (urge) incontinence often provides necessary information that can guide the choice of treatment. In addition to an interview, a bladder diary in which patients keep records of fluid intake and output for 3 days can be helpful. Bladder diaries are available in print from national sources and scientific societies, and several digital applications are also available that can even be used on smartphones. In this manner, the possibility of the presence of nocturnal polyuria can be addressed, as it is important to distinguish between nocturnal polyuria and nocturia due to overactive bladder, reduced capacity, or other reasons. Patients with orthostatic hypotension may have increased nocturnal urine production due to high glomerular filtration rate resulting from supine hypertension. The identification of patterns of detrusor contractions and urine production can lead to a better understanding of the nature of bladder symptoms and enable neurologists to make rational treatment choices.

Neurogenic bladder symptoms involving overactive detrusor are generally effectively treated with antimuscarinics (Madersbacher et al., 2013). However, no placebo-controlled double-blind or randomized studies have been performed specifically among patients with PD. Antimuscarinics are usually administered to patients with urgency and frequency because they reduce parasympathetic effects on the bladder. Overactive bladder can be treated primarily with antimuscarinics (e.g., darifenacine, fesoterodine, oxybutynine, solifenacine, tolterodine, or trospium chloride) or a β_3-adrenoceptor agonist (mirabegron). In general, the effect size of treatment relative to placebo is small, with a decrease in urination frequency of 1–2 times per day and a reduction in the number of incontinence episodes of 2–3 times per week (Palleschi et al., 2006). Part of this positive effect is due to increased "warning time," which can be evaluated by asking patients to keep micturition diaries.

A practical approach to managing patients with overactive bladder is outlined in Figures 19.6 and 19.7. Due to cognitive side-effects, oxybutynin is not first choice for PD patients despite its efficacy. All modern antimuscarinics are probably effective. It is important to evaluate postmicturition residual urine during treatment, which may be increased as a result of either disease progression or antomuscarinic treatment.

Efficacy and side-effects can be evaluated 3–4 weeks after treatment. With insufficient effects, a change in treatment or escalation in dose can be attempted. There is no evidence, however, of the efficacy or safety of combining antimuscarinics. In cases of a lack of effect after 3–6 months despite a change in treatment and/or increase in dose, treatment should be discontinued, and patients should be referred for urologic evaluation.

After antimuscarinic treatment consisting of 4 mg extended-release tolterodine, 24 of 32 PD patients showed improved Overactive Bladder questionnaire scores as well as significant reductions in urinary urgency rate and nocturia episodes (Palleschi et al., 2006).

The management of LUTS requires continuous evaluation, with Figure 19.7 outlining a possible management strategy. It is important to evaluate postmicturition residual urine during treatment, as this may increase as a

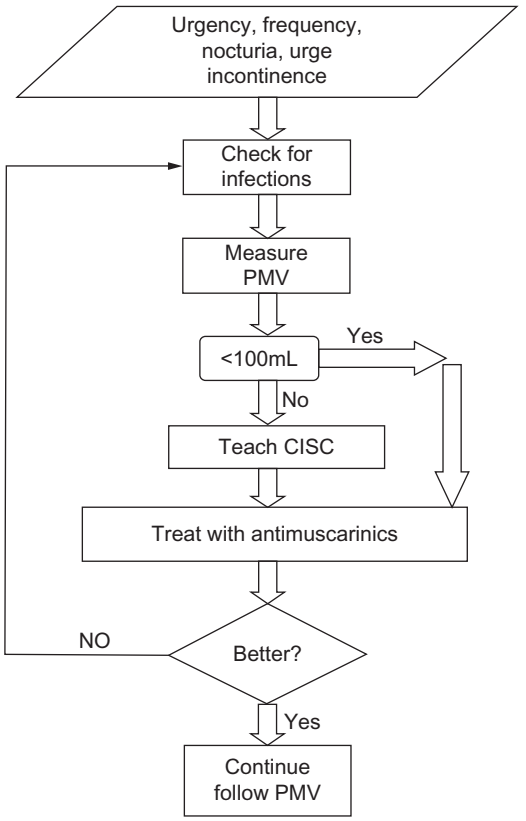

Fig. 19.6. Practical algorithm for the management of patients with symptoms of detrusor overactivity. The cornerstones in management are measurement of postmicturitional volume (PMV) and the use of anticholinergics. Clean intermittent self-catheterization (CISC) is needed if PMV is high (>100 mL) in several measurements. (Reproduced from Winge and Fowler, 2006, with permission.)

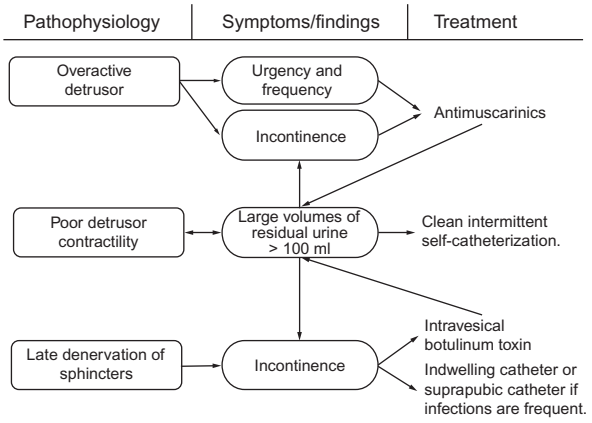

Fig. 19.7. Approach to the management of bladder dysfunction in Parkinson's disease. (Adapted from Winge and Fowler, 2006.)

result of either disease progression or antimuscarinic treatment.

Patients generally tolerate and benefit from pharmacologic treatments. A study among non-neurologic patients shows that extended-release tolterodine produces fewer side-effects than oxybutinin (Sussman and Garely, 2002). As new drugs are less lipophilic, they show reduced propensity to cross the blood–brain barrier (Todorova et al., 2001). Moreover, as they have greater specificity for M4 receptors, they may be used in patients with cognitive impairment, although there are no available studies that address the issue of possible worsening of cognitive impairment as a result of bladder-specific antimuscarinic treatment in patients with PD. One study demonstrates an increase in muscarinic acetylcholine receptors in the occipital lobes of PD patients with dementia or DLB using single-photon emission computed tomography, suggesting their vulnerability to visual hallucinations and visuospatial disturbances (Colloby et al., 2006). When considering the use of an antimuscarinic agent for the treatment of overactive bladder in elderly and/or potentially cognitively impaired patients, prescribers should routinely consider the agent's receptor selectivity and ability to enter the central nervous system. Physicians should also consider the agent's potential to induce or worsen cognitive impairment (Scheife and Takeda, 2005). Advantages of improved bladder control, including reduced risk of falls due to decreased urgency, frequency, and nocturia, should be balanced by the risk of side-effects such as drowsiness, confusion, and hallucinations.

If medical treatment fails, or if patients consistently have large volumes of postmicturition residual volume, referral for urologic evaluation is an option. Cystometry can be used to demonstrate detrusor overactivity, but treatment with anticholinergic medications can be started based on reported symptoms alone. It is important to measure postmicturition residual volume because symptoms alone are poor indicators of the extent of incomplete emptying, and a large residual is a major contributor to neurogenic bladder dysfunction. Cystometry may therefore provide a way to better understand patients' conditions and to improve treatment.

Over the last decade, botulinum toxin (BTX) has been shown to be highly efficacious in managing neurogenic overactive bladder (for review, see Mangera et al., 2014). In PD patients who are refractory to antimuscarinic therapy, BTX significantly decreases the number of urinary leaks, increases total bladder capacity, and improves quality of life (Kulaksizoglu and Parman, 2010). One of the complications of BTX treatment is the potential need for chronic clean intermittent self-catheterization. However, recent studies demonstrate that BTX is efficacious even at very low doses (100 U), and it is possible for

treated patients to maintain spontaneous bladder emptying (Giannantoni et al., 2009; Anderson et al., 2014). Patients with PD and urge incontinence who do not respond to oral medication should therefore be referred to a urologist who has experience with BTX treatment.

Several other therapies have been tested for their ability to treat bladder dysfunction among PD patients. In one study, a 2-week course of low-frequency (1 Hz) repetitive transcranial magnetic stimulation (rTMS) was given to eight patients with idiopathic PD and stable urinary symptoms (Brusa et al., 2009). Changes in urinary function then were assessed using urodynamic evaluation and the IPSS. After the cessation of treatment, there was an immediate significant improvement in IPSS score and irritative symptoms that persisted for 2 weeks. First sensation of bladder filling and bladder capacity also significantly increased after rTMS. The mechanism underlying this treatment effect is yet to be understood.

Stem cell therapy has faced many ethical and practical hurdles for its clinical investigation in PD. Most animal and clinical human studies of stem cell applications for PD have aimed to improve motor symptoms. A clinical trial testing the use of bilateral fetal nigral transplantation into the postcommissural putamen showed no significant overall treatment effect for the primary motor end point. Adverse urinary incontinence events were reported for two patients in the one-donor-per-side group, two patients in the four-donor-per-side group, and no patients in the placebo group. Similarly, urinary frequency was reported for one patient in the one-donor-per-side group, two patients in the four-donor-per-side group, and no patients in the placebo group (Olanow et al., 2003).

In a recent study, bone marrow-derived mesenchymal stem cells were found to temporarily ameliorate bladder dysfunction in an animal model of PD (i.e., 6-hydroxydopamine-lesioned rats) (Soler et al., 2012).

Dementia with Lewy bodies

DLB is a progressive neurodegenerative disorder that shares many pathologic and clinical features with PD. Core symptoms include fluctuating cognitive deficits with pronounced variations in attention and alertness, recurrent visual hallucinations that are typically well formed and detailed, and spontaneous features of parkinsonism (McKeith et al., 2005). Moderate to severe autonomic failure involving orthostatic hypotension, bladder dysfunction, and thermoregulation is common in patients with DLB (Thaisetthawatkul et al., 2004), and urinary incontinence is a supporting feature according to diagnostic criteria (McKeith et al., 2005).

Neuropathologic profiles of DLB and PD share several features, including the loss of dopaminergic neurons in the substantia nigra and the formation of Lewy bodies in brainstem structures, the basal ganglia, and the cortex. Most experts now believe that DLB represents one disorder in a spectrum of neurodegenerative disorders that share dysregulation and aggregation of α-synuclein. The clinical manifestations of Lewy body disease include DLB, PD, and pure autonomic failure.

So far, there has been little focus on the systematic use of validated questionnaires for LUTS in patients with DLB. In a study using a non-validated questionnaire, which included 15 DLB patients, 15 PD patients, and 16 AD patients, urge episodes and urge incontinence were observed in 93% and 53% of DLB patients, 53% and 27% of PD patients, and 19% and 12% of AD patients, respectively (Ransmayr et al., 2008). These findings are consistent with the results of urodynamic investigations, with detrusor overactivity observed in 92% of DLB patients, 46% of PD patients, and 40% of AD patients.

Patients with DLB had comparable daytime frequency and total bladder capacity relative to patients with PD or AD, suggesting that overactivity resulting in incontinence may be due to a specific loss of inhibition that could be linked to impaired attention in DLB.

In a study designed to evaluate the efficacy of memantine treatment in patients with DLB or PD with dementia (Aarsland et al., 2009), patients and their caregivers were asked about patients' ability to use the toilet at appropriate times and without "accidents." The presence of urinary incontinence was defined as a negative answer to either of these two questions (Stubendorff et al., 2012). Using this simple definition, 30% of DLB patients were considered incontinent, which was the same prevalence as that observed in PD patients. A clinical observation made by this author is that the need for pads is much more common in DLB patients than in PD patients, even those who are demented.

Multiple system atrophy

The term "multiple system atrophy" (MSA) describes a sporadic, progressive neurodegenerative disorder with adult onset and of unknown etiology, which is clinically characterized by autonomic failure, parkinsonism, cerebellar ataxia, and pyramidal symptoms and signs in any combination, leading to death after an average of 7–8 years (Schrag et al., 2008). Autonomic failure is often significant, parkinsonism responds poorly to dopaminergic treatment, and cerebellar ataxia may markedly impair gait and balance. Differential diagnoses may be difficult, but careful monitoring of the progression of symptomatology, particularly the temporal onset of

autonomic symptoms, enables clinicians to establish a diagnosis during follow-up (Wenning et al., 1999; Sakakibara et al., 2000; Hughes et al., 2001, 2002). Late onset and milder presentation of autonomic features improve chances of survival in MSA patients (Calandra-Buonaura et al., 2013), but controlled intervention studies are not available.

A number of patients first diagnosed with PD have MSA. The time of onset of urinary symptoms in relation to other neurologic symptoms in MSA is in most cases different from that which occurs in PD, and the prevalence of urinary symptoms is significantly higher, ranging from 45% to more than 95% (Kirby et al., 1986; Sakakibara et al., 1993a, 2000; Beck et al., 1994). A large proportion of patients with MSA have LUTS for several years before the diagnosis of a neurodegenerative disorder, sometimes leading to urologic surgery, which in most cases does not benefit patients (Mashidori et al., 2007; Roth et al., 2009). The nature of complaints also differs: urgency (63–67%), frequency (33–45%), incontinence (60–100%), and large volumes (>100 mL) of postmicturition residual urine are common (47–83%) (Sakakibara et al., 1993a, 2000, 2001a). Incomplete bladder emptying may be a factor that contributes to incontinence, with the complex combination of (urge) incontinence and inability to initiate and complete bladder emptying rather specific to parkinsonian patients with MSA (Ito et al., 2006).

Urodynamic investigations show that patients with MSA commonly have detrusor overactivity as the underlying cause of overactive bladder symptoms. Detrusor overactivity is thought to result from core MSA pathology, which includes neuronal loss in the nigrostriatal dopaminergic system, cerebellum, pontomedullary raphe, and frontal cortex (Benarroch, 2002; Benarroch et al., 2004).

Incomplete bladder emptying worsens with progression of the illness. A study of patients with MSA reports a steady increase in mean postvoid residual between the first and fifth years of the disease (Ito et al., 2006). Incomplete bladder emptying is now recognized as being so characteristic of bladder disorders in MSA that the finding of increased postvoid residual volume is regarded as suggestive of this condition (Hahn and Ebersbach, 2005), although it is not a significant factor in diagnostic criteria.

Continence is further compromised by the development of an open bladder neck and weakness of the striated urethral sphincter. The bladder neck receives sympathetic innervation from the hypogastric nerve, and MSA pathology commonly affects interomedial lateral cell columns in the thoracic cord that convey descending sympathetic innervation, resulting in deficits underlying the postural hypotension and open bladder neck found in this condition (Kirby et al., 1986). In one study, an open bladder neck at the start of bladder filling without accompanying bladder overactivity was found in 53% of patients with MSA but in none of the patients with PD (Sakakibara et al., 2001a). In women, an open bladder neck may be asymptomatic but may contribute to incontinence when it occurs in combination with other MSA-related deficits in bladder function.

Denervation of the striated sphincter, which is an abnormality that is fairly specific to MSA in the early years of the disease (Sakakibara et al., 2001a), results from a loss of anterior horn cells in the Onuf's nucleus of the sacral spinal cord (Burn and Jaros, 2001). Some controversy exists regarding the usefulness of electromyogram (EMG) recordings from the external anal sphincter in diagnostic build-up. Whereas some retrospective or cross-sectional studies suggest high specificity and sensitivity of EMG recordings (Rodi et al., 1996; Palace et al., 1997; Stocchi et al., 1997b; Tison et al., 2000; Gilad et al., 2001; Sakakibara et al., 2001a; Paviour et al., 2005; Winge et al., 2010), a prospective study on unselected patients with parkinsonism showed very limited usefulness of EMG recordings (Linder et al., 2012), confirming earlier negative studies (Schwarz et al., 1997; Giladi et al., 2000; Libelius and Johansson, 2000). Overall, in patients with a history of a cerebellar or akinetic rigid syndrome of less than 5 years' duration and serious urinary symptoms, normal results make the diagnosis of MSA unlikely (Paviour et al., 2005). In a recent study using a group-based analysis, sphincter EMG was found to be useful for MSA diagnosis (Yamamoto et al., 2012).

Some investigations have found abnormal anal sphincter EMG recordings in patients with PSP, but these studies did not distinguish between PSP and MSA (Valldeoriola et al., 1995; Scaravilli et al., 2000; Winge et al., 2010).

In general, the management of LUTS in MSA is demanding, but the principles shown in Figure 19.8 are often useful. Importantly, the combination of poor detrusor contractility and detrusor sphincter dyssynergia (i.e., loss of coordination between detrusor contraction and sphincter relaxation) often results in large volumes of postmicturition residual urine. Not uncommonly, patients with MSA have been seen by urologists before presenting with neurologic symptoms, allowing neurologists to address other autonomic features such as orthostatic intolerance. However, as the disease progresses, bladder emptying may worsen and may possibly be aggravated by the use of otherwise much-needed antimuscarinic medication. This increase in postvoid volume is best treated with clean intermittent self-catheterization or an indwelling catheter if hand function is poor or infections are common. Patients are often

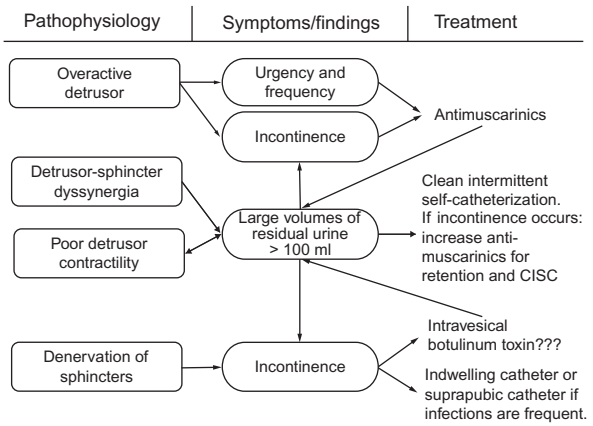

Fig. 19.8. Approach to the management of bladder dysfunction in multiple systems atrophy. CISC, clean intermittent self-catheterization. (Adapted from Winge and Fowler, 2006.)

satisfied with either solution once it is initiated, as the freedom from concerns of incontinence is seen as a relief in that it permits more social activities.

Infection may be common in patients with poor bladder emptying and is a significant problem for patients with MSA. As in all neurologic diseases, patients may develop severe worsening of pre-existing symptoms and may even develop life-threatening respiratory stridor during urinary tract infections for unknown reasons. Therefore, patients should be treated aggressively with antibiotics (e.g., mecillinam 400 mg × 3 for 5 days) and urine sent for cultivation if acute worsening of neurologic symptoms is reported or if there are more obvious signs of infection.

Other primary parkinsonian syndromes

PD, DLB, and MSA all share the neuropathologic feature of α-synuclein-positive inclusion bodies in the brain. In PD and DLB, α-synuclein forms Lewy bodies in neurons, whereas in MSA, accumulations are found in oligodendrocytes. However, other syndromes in which clinical parkinsonism is a dominant symptom are not associated with accumulation of α-synuclein. PSP and CBD are important differential diagnoses for PD and may be difficult to distinguish. Both are associated with accumulation of the microtubule-associated protein tau.

PSP is a rapid progressive neurodegenerative disorder characterized by axial parkinsonism, unresponsiveness to dopaminergic medication, progressive supranuclear gaze palsy, early falls, and frontotemporal dementia in various degrees. PSP can be divided into several clinical subtypes, and this separation provides some guidance on prognosis and natural history. The classic form of PSP is referred to as Richardson syndrome (also known as Steele–Richardson–Olszewski syndrome), and other variants include PSP parkinsonism, PSP pure akinesia with gait freezing, and PSP corticobasal syndrome (Williams and Lees, 2009).

In PSP, bladder symptoms are generally not a major complaint, possibly because cognitive and behavioral abnormalities, impaired gait and balance, and dysphagia affect quality of life to a greater extent for patients and their caregivers. However, some studies suggest that LUTS are important symptoms that deserve the attention of caring physicians, as symptoms of overactive bladder often increase the risk of falls. Smaller studies of pathologically confirmed PSP cases suggest that early falls and dementia (Papapetropoulos et al., 2005) as well as early dysphagia and urinary incontinence (Litvan et al., 1996b) are poor prognostic indicators. There are no prospective systematic studies of LUTS in PSP using validated questionnaires. Several retrospective studies report a high prevalence of incontinence of up to 78% (Sakakibara et al., 1993b). Very little is known about the mechanisms involved. Nocturia may be as frequent as in PD, and urge incontinence has been observed in four out of six patients, which are numbers that are consistent with similar small studies (van Dijk et al., 1991; Gutrecht, 1992). Neuronal loss in Onuf's nucleus may contribute to urinary incontinence (Valldeoriola et al., 1995; Scaravilli et al., 2000; Winge et al., 2010). Therefore, the origin of LUTS remains speculative and is often considered in the context of progressive gait and balance symptoms as well as frontal cognitive dysfunction and poor insight.

Falls and fractures are common in PSP, with early falls associated with poor survival of patients with parkinsonian syndromes. However, it has not been possible to establish a statistically significant link between urgency and fractures (Williams et al., 2006).

CBD is a rare, rapid progressive neurodegenerative disorder that is clinically characterized by asymmetric parkinsonism, apraxia, sensory or visual hemineglect, and myoclonus without response to dopaminergic therapy. Very little is known about LUTS in patients with CBD. In one small study, CBD patients were more frequently affected by LUTS than healthy individuals (80% vs 27%) (Sakakibara et al., 2004). Urinary symptoms appeared 1–3 years after the onset of the disease and were more common in patients with forced-grasp reflex. Nocturnal frequency was the most common and earliest symptom, followed by urinary incontinence. When assessed using urodynamic analysis, all symptomatic patients showed various abnormalities, including decreased bladder capacity and detrusor overactivity. In another study comparing 13 patients with CBD to patients with PSP, PD, MSA, or DLB, 62% of CBD patients were incontinent (Wenning et al., 1999). Bladder

dysfunction does not seem to affect survival of CBD patients (Wenning et al., 1998).

An important issue in patient management is acknowledging the combination of LUTS with core symptoms that are more or less specific to the neurodegenerative disorder. Movement symptoms are most often bradykinesia or tremor, making urgency troublesome and difficult to endure in daily life. In atypical parkinsonian syndromes, the combination of bradykinesia, gait and balance problems, and cognitive symptoms, including poor insight may contribute substantially to incontinence as well as an underestimated risk of falls and fractures (Williams et al., 2006; Yarnall et al., 2012), although a direct link has never been established outside of healthy elderly individuals (Booth et al., 2013) and clinical experiences with parkinsonian patients.

In disorders that mainly affect cognitive abilities, bladder dysfunction may interfere with activities of daily living and function, but it is perhaps more important to recognize that LUTS may be the origin of other diseases that should not be ignored. Furthermore, the seriousness of infections should also be considered.

ALZHEIMER'S DISEASE AND FRONTOTEMPORAL DEMENTIAS

The most frequent neurodegenerative disorder is AD, the prevalence of which roughly doubles every 5 years among individuals over the age of 65. Onset of AD before this age is relatively uncommon and often suggests a genetic cause. Depending on age, AD is the most common cause of dementia. AD results in the progressive loss of memory and other cognitive functioning and independence. In western countries, it is the most common cause for moving into a nursing home (Prince and Jackson, 2009).

LUTS are generally not well described for AD, but their impact on patients has been studied in some detail. Impaired attention and orientation may relate to reduced environmental and self-awareness, leading to an increased impact of overactive detrusor.

In a recent study examining incontinence among 310 patients with established AD, urinary incontinence was present in 18% of patients, and incontinent patients scored significantly lower on cognitive tests and were less likely to receive treatment with cholinesterase inhibitors than continent patients (Alcorn et al., 2014). A logistic regression analysis performed on data from a subgroup of 284 patients revealed that incontinence was significantly associated not only with advanced age but also with disinhibition, deficits in attention and orientation, and reduced verbal fluency, suggesting that factors other than the degeneration of continence-specific brain areas play a role in LUTS.

One study reports a high prevalence of incontinence among elderly persons living in long-term care facilities in Canada (Maxwell et al., 2013), with 21–27% of nursing-home residents experiencing some degree of incontinence.

In a study of a small cohort of patients with AD, DLB, or PD, 12% and 19% of AD patients experienced urinary incontinence and urgency, respectively (Ransmayr et al., 2008). The prevalence of both symptoms among AD patients was significantly less than that among DLB or PD patients. However, DLB patients had more detrusor overactivity than PD or AD patients.

There are no reports on bladder dysfunction among AD patients using validated questionnaires, and large-scale, questionnaire-based studies indicate that the magnitude of troublesome LUTS is roughly equivalent in AD patients and healthy elderly individuals (Kay et al., 1999). However, several studies suggest that incontinence is a particularly major problem in dementia. In a Canadian study of more than 1000 elderly citizens, incontinence was a strong predictor for admission to nursing homes (odds ratio 1.58), as was dependence on help from others for activities of daily living (odds ratio 1.52) and moderate to very severe cognitive impairment (odds ratio 2.66) (Maxwell et al., 2013). However, other studies have not found that LUTS influence the risk of loss of independence (Gaugler et al., 2009).

The management of overactive bladder symptoms in AD patients can be difficult for several reasons. First, impaired attention and orientation interfere with the self-management of an overactive bladder via preventive voiding, double voiding, and prompt response to urgency. Second, antimuscarinics may worsen cognition (Uusvaara et al., 2009) and interact with acetylcholinesterase inhibitors given to improve cognition and activities of daily living. In a study assessing activities of daily living among 376 individuals using the Minimum Data Set Cognition Scale, persons taking acetylcholinesterase inhibitors alone showed an average decline of 1.08 points per quarter, whereas those taking both antimuscarinic drugs (either tolterodine or oxybutinine) and acetylcholinesterase inhibitors showed an average decline of 1.62 points per quarter (Sink et al., 2008). This represents a $>50\%$ quarterly decline in function, resulting in a statistically significant difference among treatment groups. One small open-label study suggests that propiverine and donepezil may improve continence without overt progression of cognitive decline (Sakakibara et al., 2009), although this needs to be confirmed using validated tools and a placebo-treated group.

As bladder dysfunction and incontinence are important predictors of poor outcome and nursing-home admission, the systematic assessment of symptoms using directed interviews or validated questionnaires and the careful initiation of treatment with modern

hydrophilic antimuscarinics is often worth a try, as the impact of LUTS on patients and caregivers is significant.

A major challenge in assessing patients with cognitive dysfunction is to distinguish AD from vascular dementia or mixed pathology, including amyloid deposits and Lewy bodies.

White-matter hyperintensities (WMH) causing leukoaraiosis, or white-matter wasting, are often present in magnetic resonance imaging scans of older people and are linked to vascular risk factors. The association between WMH and urinary incontinence among the elderly was first recognized by a Japanese group, who observed that detrusor overactivity was found in 82% of elderly individuals with WMH but only 9% of those without WMH (Sakakibara et al., 1999). Furthermore, in those with mild leukoaraiosis, urinary incontinence was more common than cognitive impairment or gait slowness, suggesting that urinary dysfunction is a common and early sign in elderly people with leukoaraiosis or white-matter disease. These observations were later confirmed by studies suggesting that white-matter damage involves focal tracts connecting centers involved in bladder control (Kuo and Lipsitz, 2004; Poggesi et al., 2008). Using computer-based imaging techniques to identify connecting white-matter tracts and to quantify the amount of white-matter disease, the severity and degree of distress due to incontinence were shown to be associated with a high burden of WMH in the right inferior frontal region and specific white-matter tracts that connect frontal regions to other brain regions involved in maintaining continence (Kuchel et al., 2009).

The burden of incontinence seems to correlate with the severity of dementia (Wakefield et al., 2010). Early clinical studies (Kotsoris et al., 1987) and pathology-based investigations (Del Ser et al., 1996) report more frequent and earlier urinary incontinence in patients with dementia of vascular origin than in patients with AD. Urinary incontinence has been proposed to be a marker of vascular dementia, but a postmortem study of AD and PD patients both with and without vascular pathology for 5.6 years showed no difference in onset of incontinence between AD patients with or without vascular pathology, nor was there a difference in severity of dementia (Del Ser et al., 1996). In a recent study of nine patients with AD, 25 patients with white-matter vascular disease, and 15 patients with dementia of mixed origin, unvalidated questionnaires and urodynamic analysis showed that daytime urinary frequency (>8 times), nighttime urinary frequency, and urinary incontinence (>1 time per week) were most common among patients with white-matter lesions alone (68%, 84%, and 40%, respectively) than among patients with AD (33%, 44%, and 33%, respectively) or presumed mixed pathology (40%, 60%, and 27%, respectively) (Takahashi et al., 2012). These findings suggest that the nature and burden of total pathology in the brain are important, but the location of pathology and context of symptoms with respect to the overall situation of patients are more important in influencing continence.

RARE NEURODEGENERATIVE DISORDERS

A small number of neurodegenerative diseases progress rapidly with a fatal outcome. Patients with motor neuron diseases, of which amyotrophic lateral sclerosis (ALS) is the most common, rarely present with severe LUTS. So far, there have been no published data from studies using validated questionnaires among patients with motor neuron diseases.

ALS affects both central and peripheral motor neurons, including anterior-horn motor neurons that innervate the external sphincter. Several studies have addressed the physiology and pathology of neurons of Onuf's nucleus in sacral segments 2–4 in patients with motor neuron diseases. Although there appears to be a sparing of motor neurons in Onuf's nucleus, these neurons show morphologic changes, suggesting their involvement in the disease (Kihira et al., 1997). However, it has not been possible to diagnose neuronal dysfunction antemortem (Carvalho et al., 1995). Though no studies have been performed in motor neurons in Onuf's nucleus, a study on gene transcription in ALS-resistant eye muscle motor neurons suggests different susceptibility to degeneration in ALS between this population of motor neurons compared to neurons in the spinal cord. The transcriptional profiles of oculomotor and spinal motor neurons were distinct, with differences in nearly 2000 genes. Microarray and electrophysiology analyses suggested that reduced susceptibility to excitotoxicity, mediated in part through increased GABAergic transmission, may be an important determinant of the relative resistance of some motor neurons to degeneration in ALS (Brockington et al., 2013).

Hereditary spastic paraplegias (HSPs) are a group of rare neurodegenerative disorders characterized by progressive spasticity and hyperreflexia of the lower limbs (Silva et al., 1997). HSPs are associated with a high degree of clinical and genetic heterogeneity. Their main pathologic hallmark is the retrograde degeneration of corticospinal tracts and posterior columns. Clinical presentation may include a large variety of central nervous system symptoms, including ataxia, cognitive impairment, and distal amyotrophy. Several studies have investigated LUTS in patients with HSPs, showing the common occurrence of overactive detrusor, urgency, incontinence, and incomplete emptying (Durr et al., 1996; Jensen et al., 1998; Braschinsky et al., 2010).

In a recent study, among 38 patients with HSPs who were interviewed by a specialized continence advisor

using a structured interview rather than a validated questionnaire, 77% reported bladder symptoms (Braschinsky et al., 2010). Specifically, 69% reported episodes of urinary incontinence, 59% reported hesitancy, 55% reported increased frequency, and 37% reported incomplete emptying. Volume of postmicturition residual urine (>100 mL) correlated with neurologic symptoms, with more residual urine associated with higher spasticity scores and shorter walking distances. Consistent with these reported symptoms, urodynamic investigations showed that a high proportion of HSP patients with large residual volumes had detrusor sphincter dyssynergia, suggesting the spinal origin of symptoms.

In another study, incontinence was reported by six of 11 patients, urinary urgency or urge incontinence was reported by all patients who experienced urinary urgency or urge incontinence, and rectal urgency was reported by 10 of 11 patients (Jensen et al., 1998). Urodynamic analysis showed a mixed pattern of bladder dysfunction, with significantly prolonged bulbocavernosus reflex latency in seven patients and an increased cutaneous perception threshold in five patients, suggesting mixed pathophysiology. The most recent retrospective study, which included 29 patients with HSPs, found that urinary urgency and incontinence, suggestive of central pathophysiology, were the most common LUTS, although the authors did not use a validated questionnaire (Fourtassi et al., 2012). These findings were confirmed by urodynamic analysis, which showed signs of central neurogenic bladder in 24 patients (82.7%), detrusor overactivity in 15 patients (52%), and detrusor sphincter dyssynergia in 19 patients (65.5%). A postvoid residual of more than 10% of voided volume was found in 41% of patients. The authors also performed ultrasound examination of the upper urinary tract and found no signs of complication after an average of 22 years of follow-up. These findings are similar to those for multiple sclerosis but different from those for spinal cord injury.

Similar to HSP, spinocerebellar ataxias (SCAs) are a pheno- and genotypical heterogeneous group of autosomal-dominant inherited conditions in which cerebellar ataxia results in progressive balance difficulties related to neurodegeneration of Purkinje cells in the cerebellum or related neurons such as spinocerebellar, pontocerebellar, and olivocerebellar connections. Onset is typically subtle, with mild gait difficulties that can be preceded by difficulties in performing more skilled motor activities such as skiing, biking, or working on a ladder. Other cerebellar symptoms and signs usually follow shortly thereafter, including dysarthria, uncoordination of upper limbs, and eye movement problems such as nystagmus and inaccurate saccades, which can cause visual symptoms, as well as autonomic outcomes. The best studied SCA is SCA3, also known as Machado–Joseph disease, which is an autosomal-dominant neurodegenerative disorder caused by unstable expansion of CAG repeats in the *MJD1* gene that encodes ataxin-3. Clinically, the disease is characterized by variable combinations of cerebellar ataxia, pyramidal and extrapyramidal signs, dystonia, ophthalmoplegia, eyelid retraction, sensory impairment, and amyotrophy. LUTS are common in SCA3. In a study including 15 individuals with SCA3, 21 patients with early PD, and 23 healthy individuals, unvalidated questionnaires showed that autonomic symptoms, cold intolerance (53%), and nocturia (53%) were the most common symptoms in SCA3 patients and more prevalent than in the two other groups (Yeh et al., 2005). Incontinence was reported in 13% of SCA3 patients. In a larger, more recent study that retrospectively evaluated 122 patients with SCA3, 14% of patients reported LUTS, and only 9% of patients were incontinent (Musegante et al., 2011).

In a neuropathologic study, SCA3 patients were found to have a loss of motor neurons specifically in Onuf's nucleus as well as other anterior horn cells (Shimizu et al., 2010).

In a small study of nine patients with SCA2, bladder symptoms were reported by all patients, and neurophysiologic investigations showed both sympathetic and parasympathetic involvement, with a highly variable degree and pattern of dysautonomia (De et al., 2008).

In patients with neurodegenerative disorders involving the spinal cord or cerebellum, LUTS are highly prevalent, and neurologists should be aware of symptoms affecting the quality of life as well as morbidity, as abnormal bladder emptying may increase the risk of urinary tract infections.

LUTS are also common among patients with Huntington's disease. Urinary incontinence was reported by 32% of manifest patients, 14% of pre-manifest carriers, and 14% of control individuals (Aziz et al., 2010). Manifest patients also reported urgency more frequently than pre-manifest and control individuals (44%, 19%, and 27%, respectively). Severe urinary symptoms are common in patients with neurologic and neuropsychiatric symptoms, but it is unclear whether LUTS are due to specific dysfunction in the brain or to behavioral deficits, including impaired attention. Patients with Huntington's disease seem to have no abnormalities in Onuf's nucleus (Kolenc et al., 2014).

CONCLUDING REMARKS

Progressive neurodegenerative disorders are devastating diseases with often fatal outcomes. LUTS add to morbidity and increase the risk of becoming dependent on the help of others (e.g., nursing-home referral). Voluntary voiding is the last of the "basic functions" that children

achieve and one of the first functions to be lost as the end of life approaches. During the complex pathophysiologic mechanisms of neurodegenerative disorders, either specific pathologies (such as those in PD) or more complex mechanisms that interact with behavioral functions and basic daily management (such as those in AD) play an important role in LUTS and the quality of life of patients.

The systematic and careful tracking of symptoms, evaluation using non-invasive techniques, and conservative management including pharmacological treatments can often markedly improve the lives of patients and their caregivers.

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 20

Sexual dysfunction in patients with multiple sclerosis

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INTRODUCTION

Multiple sclerosis (MS) is a chronic, autoimmune, inflammatory, demyelinating, neurodegenerative disease of the central nervous system (CNS) and one of the most common causes of neurologic disability in young adults. Worldwide, an estimated 2–2.5 million people are affected, including 400 000 in the USA and 500 000 in Europe (WHO, 2008; Public Health Department, 2013; Flachenecker et al., 2014). The prevalence shows a high variability across different regions and ethnic populations. The countries reporting the highest estimated prevalence of MS include Hungary (176 per 100 000), Slovenia (150), Germany (149), USA (135), Canada (132.5), Czech Republic (130), Norway (125), Denmark (122), and Poland (120).

The etiology of MS remains unknown and many genetic, infectious, dietary, metabolic, environmental, and lifestyle causes have been considered (Oksenberg et al., 2004; Ascherio and Munger, 2007a, b; Gregory et al., 2007; Hafler et al., 2007; Ebers, 2008; Waubant and Cross, 2014). The major histopathologic changes consist of the loss of myelin and axonal damage due to inflammatory and neurodegenerative mechanisms (Stangel, 2012). Any location within the CNS may be involved and the course of the disease is often unpredictable.

MS symptoms can start anywhere between 10 and 80 years of age, but they usually begin between 20 and 40 years, with a mean age of 32 years. The 20–40-year age range is that with the highest sexual and reproductory expectations. Women are affected twice as often as men (the ratio being from 1.1 to 3.0 across different regions) (Sadovnick and Baird, 1982; Liguori et al., 2000; Kingwell et al., 2013). Common clinical manifestations include spasticity in 40–85%, fatigue in 69–97%, ataxia and tremor in up to 80%, bladder dysfunction in 80–96%, bowel dysfunction (constipation and/or incontinence) in 29–54%, pain (acute or chronic, neuropathic, somatic or psychogenic) in 29–86%, optic neuritis in up to 70%, and cognitive impairment in 40–70% of patients during the course of the disease (Chia et al., 1995; Krupp et al., 1995; Hennessey et al., 1999; Foster, 2002; Bakshi, 2003; Rizzo et al., 2004; Solaro et al., 2004; Mills et al., 2007; Chiaravalloti and DeLuca, 2008; Toosy et al., 2014). Patients have a clearly diminished health-related quality of life which is related not only to neurologic symptom severity and the level of disability but also to many psychologic, cultural, and socioeconomic factors (Pluta-Fuerst et al., 2011; Tapavcevic et al., 2014). Sexual dysfunction (SD) is one of the symptoms which may have a significant influence on patients' well-being, relationships with partners and family, and their overall quality of life.

Sexuality and intimacy have a wide range of values and benefits. Meston and Buss (2007) looked at the question 'Why do people have sex?'. They found 237 different motives for having intercourse, ranging from mundane (e.g., physical pleasure) to spiritual, and from altruistic to vengeful. Relevant in relation to chronic disease were, for instance, physical reason subfactors (including stress reduction, pleasure, and physical desirability); emotional subfactors (including love and commitment and expression); and insecurity subfactors (including self-esteem boost, duty/pressure, and mate guarding). Gradually practitioners with knowledge of sexology became aware that sexual expression has health benefits, which can be especially relevant for patients with MS who are hospitalized for longer periods of time.

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PREVALENCE OF SEXUAL DYSFUNCTION IN PATIENTS WITH MS

Barak et al. (1996) found at least one SD in 50.5%, Zorzon et al. (1999) in 62.9%, and Lew-Starowicz and Rola (2013a) in 82.5% of women with MS. Differences across these reports could be due to different screening tools and slightly different characteristics of the study groups. In any case, SDs are clearly much more common than in the general female population. Women with MS also exhibit diminished frequency of sexual activity when compared to the general female population (Lew-Starowicz and Rola, 2013a; Lundberg, 1981). According to a review paper by Bronner et al. (2010) dealing with the prevalence of SD in women with MS, significant differences were found among authors in the estimation of decrease in sexual desire (31.4–63.6%) and impaired arousal (33.0–51.5%) and much less difference when it came to evaluating orgasmic difficulties (37.0–38.3%). However, in a recent study by Merghati-Khoei et al. (2013), orgasmic difficulties were found in more than 60% of Iranian women with MS.

Lombardi et al. (2011) assessed 55 women with MS using the Female Sexual Function Index, a well-designed and validated questionnaire for the evaluation of female SD. They found desire to be the most affected domain of sexual functioning (57.4%). More recently, the prevalence of SD was also evaluated in 137 women with MS by Lew-Starowicz and Rola (2013a) using another validated screening tool, the Female Sexual Function Questionnaire (SFQ28). The findings are presented in Table 20.1.

A review paper on the prevalence of SD in men with MS was published by Schmidt et al. (2005). SDs are reported in 64–91% of patients, most commonly ED (19–62%). Other frequent complaints include decreased sexual desire, decreased sensation during sexual stimulation, and ejaculatory and orgasm dysfunction. SDs in 67 men with MS were also recently evaluated by Lew-Starowicz and Rola (2014a) with the 15-item version of the International Index of Erectile Function (IIEF). ED was the most common SD, found in 52.9%, followed by decreased sexual desire in 26.8%, orgasmic difficulties in 23.1%, and absent or delayed ejaculation in 17.9% of patients. Patients with MS had decreased sexual frequency compared to the general population and only 41.6% were satisfied with their sexual life. In other research premature ejaculation was found in 48% of men with MS (Redelman, 2009).

HOW DOES MULTIPLE SCLEROSIS AFFECT SEXUALITY?

Sexual response is determined by a variety of physiologic, psychologic, relational and even socioeconomic factors. Similarly, MS can affect sexuality in many ways. A division into primary, secondary, and tertiary SDs has been proposed by Foley (Foley and Sanders, 1997; Foley and Gimbel, 2005). One pathology (e.g., lesion within the CNS) does not necessarily imply a certain SD since there may be many other symptoms affecting it indirectly. Most authors reported that the duration of the disease (time since diagnosis of MS) was not a predictor of sexual functioning and only a few found a negative correlation (Lilius et al., 1976; Valleroy and Kraft, 1984; Hulter and Lundberg, 1995; Mattson et al., 1995; Zivadinov et al., 1999; Fraser et al., 2008; Khan et al., 2011; Celik et al., 2013; Gumus et al., 2014; Lew-Starowicz and Rola, 2014a). This could be explained by a highly variable course

Table 20.1

Sexual dysfunction in women with multiple sclerosis measured on the Female Sexual Function Questionnaire (SFQ28)

	SFQ28 domain						
Measure	Desire	Arousal (sensation)	Arousal (lubrication)	Arousal (cognitive)	Orgasm	Pain	Enjoyment
HP FSD	79	43	45	42	37	5	34
n%	57.7%	47.3%	48.4%	45.2%	39.8%	5.7%	35.8%
Borderline SF	40	25	32	34	38	12	40
n%	29.2%	27.5%	34.4%	36.6%	40.9%	13.6%	42.1%
HP NSF	18	23	16	17	18	71	21
n%	13.1%	25.3%	17.2%	18.3%	19.4%	80.7%	22.1%

Reproduced from Lew-Starowicz and Rola (2013a).

HP FSD, high probability of female sexual dysfunction; borderline SF, borderline sexual function; HP NSF, high probability of normal sexual function.

of the disease with different dynamics of neurologic impairment. Moreover, different findings are presented according to the correlations between the general MS severity and SD (Zorzon et al., 1999, 2001; Fraser et al., 2008; Khan et al., 2011). This suggests that certain CNS lesions and associated symptoms may have a prominent influence on sexual functioning but also supports the idea of multifactorial etiology of SD in MS patients, including psychosocial aspects of a chronic disease. Therefore, in practice patients should be treated with a holistic approach. However, for better understanding of the determinants of SD in MS patients, it is convenient to describe the influence of certain factors separately, keeping in mind that the "real" influence depends upon their interplay.

Primary SDs are caused by demyelination and axonal damage within the special areas of the brain and spinal cord or peripheral neurons that are directly engaged in sexual response. Neuronal pathology related to MS does not always result in sexual hypofunction. An interesting case of hypersexual behavior as a manifestation of MS relapse was described by Yang et al. (2004). A 51-year-old woman with MS presented with increase in libido, genital arousal, and sexual activity associated with general body hypersensitivity and behavioral impulsiveness that occurred during disease exacerbation. The authors related this manifestation to frontal-lobe lesions confirmed by magnetic resonance imaging (MRI) examination, and the causal relationship with the disease was further confirmed when all the symptoms resolved after two courses of intravenous methylprednisolone. This example shows that MS inflammation can sometimes cause periods of increased desire, or clitoral hypersensitivity with periods of easier orgasm.

Diminished sexual function is, however, much more prevalent in the course of MS and may be related to neuronal changes. According to the brain MRI study of Zorzon et al. (2003), SDs were correlated with pontine atrophy in MS patients. In another MRI study, Janardhan and Bakshi (2000) associated impaired quality of life in relation to sexual functioning with white-matter lesions in the inferior parietal lobe, pontine atrophy, and enlargement of the lateral ventricles. The authors suggested a causative role of disruption in the circuits of the caudal brainstem involved in controlling sexual behavior as well as in the areas of the primary sensory cortex which process sensory information essential for sexual response.

Lesions in the sacral segments of the spinal cord that affect the sacral reflex arc may cause vaginal and clitoral sensory deficits and lead to decreased physical arousal (lubrication, sensations) and anorgasmia in women (Gruenwald et al., 2007). Yang et al. (2000) found by testing somatosensory evoked potentials on dorsal clitoridal nerve stimulation in women with MS that nearly all had a prolonged latency time, which may to some extent explain their orgasmic disturbances. Similarly, in men, neurophysiologic assessment suggests that spinal lesions situated proximal to the sacral cord may lead to erectile dysfunction (ED) and most patients with MS who suffer from ED have pudendal evoked potential abnormalities (Kirkeby et al., 1988; Betts et al., 1994). On the other hand, Ghezzi et al. (1995) found no direct relationship between neurophysiologic abnormalities (assessed by pudendal evoked potentials, motor evoked potentials of the bulbocavernosus muscle to magnetic stimulation and bulbocavernosus reflex) and the presence or severity of ED. This might be due to the dual central and peripheral control of erectile response in men. Moreover, in a study by DasGupta et al. (2004), latencies from pudendal evoked potentials correlated with more commonly performed tibial evoked potentials but neither predicted the extent of SD in MS women. According to Delodovici and Fowler (1995), the use of pudendal evoked potentials in the assessment of neurogenic bladder and SD should be reconsidered due to their limited diagnostic value.

To sum up, it is hard to find definite correlations between brain and spinal cord lesions and particular SDs that will explain the dysfunction in the majority of MS patients. This may also be due to the multifactorial nature of the sexual response. Most authors do not find any relationship between duration of disease and sexual functioning (Lilius et al., 1976; Valleroy and Kraft, 1984; Hulter and Lundberg, 1995; Mattson et al., 1995; Zivadinov et al., 1999; Fraser et al., 2008; Khan et al., 2011). In some studies, a negative correlation was found (Celik et al., 2013; Gumus et al., 2014). This is consistent with the high variability in the progression of neurologic impairment in the course of MS. Some data suggest that the relapsing, remitting type has a better prognosis as regards sexual functioning, while primary progressive and secondary progressive types are negative predictors (Szasz et al., 1984; Bakke et al., 1996; Zivadinov et al., 1999; Demirkiran et al., 2006; Mohammadi et al., 2013).

Secondary SDs include the impact of such common MS symptoms as fatigue, bladder and bowel dysfunction, spasticity, pain, muscle weakness, impaired mobility, or tremor on sexual functioning. Bladder and bowel incontinence contribute to physical discomfort, and especially may cause fear of unwanted urination or defecation during vaginal or oral sexual contact. Khan et al. (2011) found in their study of 19 men and 52 women with MS significant negative correlations between the Total Personal Experiences Questionnaire (PEQ) Sexual

Frequency scale and Neurological Disability Scale (NDS) as well as the Quality of Life item from the American Urological Association Bladder score, suggesting the significant impact of bladder dysfunction on sexual functioning. Symptoms of weakness of the pelvic floor, bladder and bowel dysfunction are correlated with changes in lubrication and orgasmic capacity (Sipski et al., 2001; Gruenwald et al., 2007).

According to a study by Fraser et al. (2008) involving 32 men and 219 women with MS, moderate correlation between SDs and lower-limb and bladder disability in men ($r = 0.46$ and 0.45, respectively, $P < 0.01$) was found and a relatively weak, but significant, relationship with all MS disabilities in women, fatigue being the most relevant ($r = 0.34$, $P < 0.01$). A relationship between SDs and fatigue, as well as bladder and sphincteric dysfunction, was also found by Zivadinov et al. (1999). The role of a common autonomic innervation is suggested in relation to coexisting bladder and SD (Zivadinov et al., 1999; Fraser et al., 2008). Women with urinary problems can additionally be disturbed by sex-related incontinence. This was found in 60% of incontinent women, with 42% experiencing sex-related incontinence during penetration and 44% during orgasm (Jha et al., 2012). This is especially disturbing during cunnilingus (oral stimulation of the female genitalia). In sexually liberal countries, cunnilingus is part of the sexual repertoire in more than 50% of women and for a substantial number, it is their most common way of reaching orgasm. Among gay men, oral sex is the most common sexual shared activity. Sex-related urinary incontinence will be very disturbing for this group as well.

Whereas urinary incontinence during sex is shameful and disturbing, fecal incontinence will be even more embarrassing, especially when it takes place during orgasm and particularly during oral sex. Part of the incontinence will be the result of increased pressure in the abdominal compartment by voluntary and involuntary muscle contractions in the later stage of arousal and during orgasm and in some people also by Valsalva maneuvers during sex (Reynolds et al., 2011). An additional reason for fecal incontinence could be the oxytocin increase during high arousal and orgasm. Oxytocin is known to stimulate colonic activity (Ohlsson et al., 2004).

Finally, the term tertiary SD refers to the influence of psychologic and sociocultural aspects of a chronic disease on sexual functioning. This includes negative changes in mood and self-image, changing gender roles and roles within the couple, difficulties in communicating with one's partner, feelings of guilt, dependency, being less attractive, and fear of being sexually rejected, abandoned, or isolated (Foley and Sanders, 1997). Nearly half of all patients with MS report mental comorbidity along with depression as the most common change – an estimated 46% in a study of 8.983 MS patients by Marrie et al. (2009). Depression is a well-known cause of many SDs, including disorders of desire, arousal, and orgasm. The correlation between depressive symptoms and SDs in men and women with MS has been documented by several authors (Zivadinov et al., 1999; Mohammadi et al., 2013; Gumus et al., 2014; Lew-Starowicz and Rola, 2014b) (Figs 20.1 and 20.2). Taking into account the very high rate of depression in patients with MS, it is apparently one of the major causes of SDs. Therefore, in MS patients depression should be routinely investigated and, when found, it should be properly treated. Cognitive impairment may also contribute to a deterioration in sexual functioning (Zivadinov et al., 1999).

Another important topic is the relationship between MS and sex hormones. There are several more or less distinct explanations for hormonal disturbances in MS. Both in the prevalence and in the clinical progression of MS there are sexual dimorphic differences. In the brains of MS patients gender-specific responses in steroid synthesis and signaling have been identified as possible contributors to these differences, with MS males having induced estrogen synthesis and signaling and MS females having induced progestogen synthesis and signaling (Luchetti et al., 2014). MS is also accompanied by demyelinating lesions of fiber bundles in and adjacent to the hypothalamus (Huitinga et al., 2001). That could have a direct impact on the hypothalamic–pituitary–gonadal (HPA) axis. Besides, there is an indirect effect of MS on the HPA axis, playing a role in the susceptibility to, and recovery from, MS. Controlled by hypothalamic neurons that produce corticotropin-releasing hormone (CRH), the HPA axis is activated more than average in MS, as seen in an increase in CRH cell numbers and CRH neuron activity (Erkut et al., 1995). This immune system modulation of activation of the HPA axis is also accompanied by increased cortisol in the cerebrospinal fluid (Erkut et al., 2002; Huitinga et al., 2003). However, the HPA axis is activated in most, but not all, MS patients with implications in disease progression and comorbid mood disorders. HPA axis activity was found to correlate with disease severity (Melief et al., 2013). High cortisol levels were associated with slower disease progression, especially in females with secondary progressive MS. Patients with low cortisol levels had greater numbers of active lesions and tended towards having less remyelinated plaques than patients with high cortisol levels. The other side of the coin is that increased cortisol levels induce a diminishment of sex hormone levels.

In an Italian study one-third of women with MS showed abnormal hormone alterations, but no significant statistical correlations were detected between

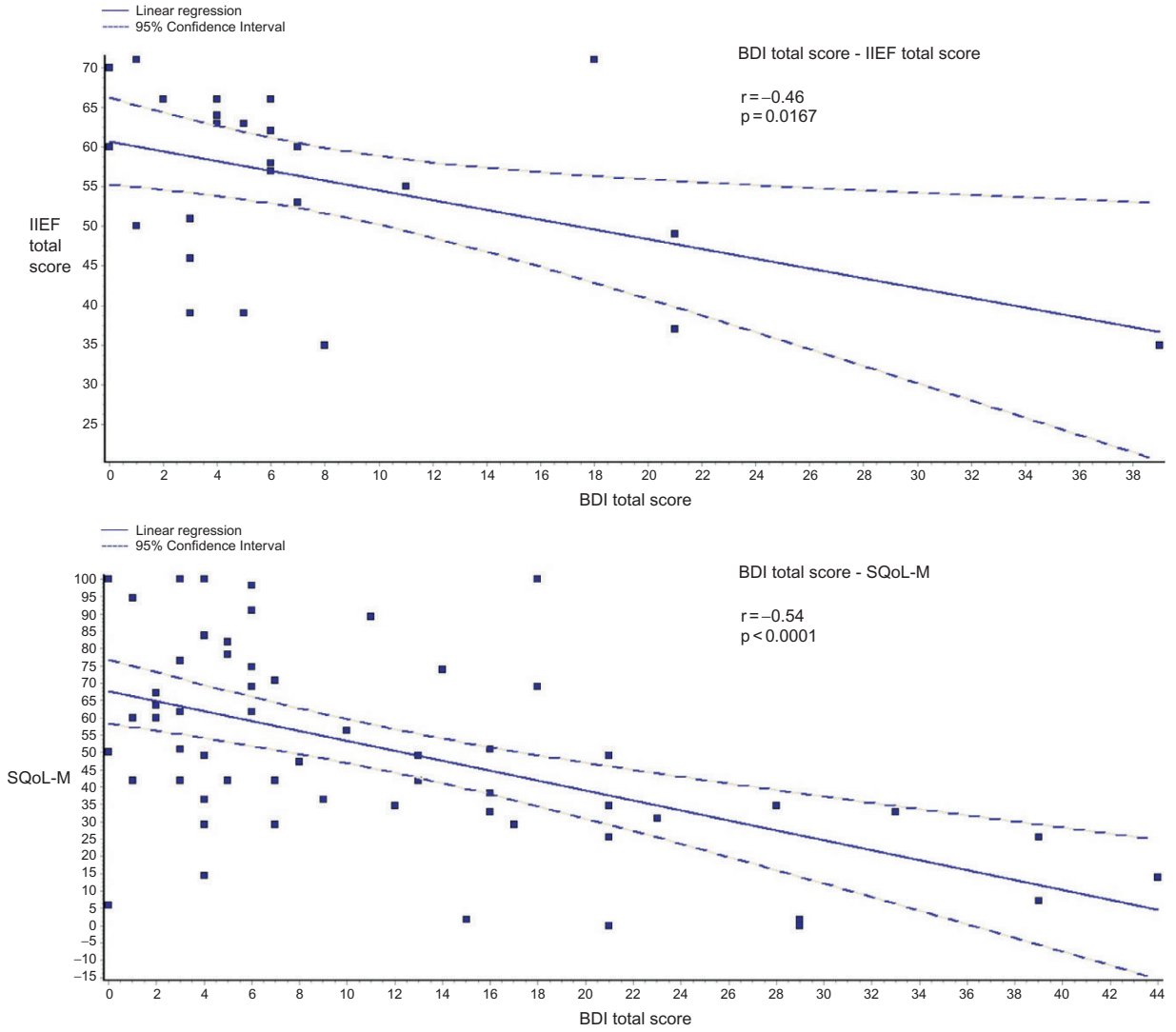

Fig. 20.1. Correlations of depressive symptoms with sexual function and sexual quality of life in men with multiple sclerosis (SQoL-M). BDI, Beck Depression Inventory; IIEF, International Index of Erectile Function. (Reproduced from Lew-Starowicz and Rola, 2014a.)

hormonal status and sexual function (Lombardi et al., 2011). This is a common finding in females. Serum testosterone levels were found to be significantly lower in MS women than in controls (Tomassini et al., 2005). Serum estradiol levels were found to be low in 25% of premenopausal women with MS (Wei and Lightman, 1997). In another study a low serum concentration of estradiol was found in 60% of women with relapsing, remitting MS, with the hormonal levels significantly increasing during remission (Trenova et al., 2013).

Some aspects are different for men with MS, since their reaction to changes in sex hormones is more direct than in women. A quarter of men with MS were found to have lowered testosterone (Wei and Lightman, 1997). The HPA axis was found to be damaged both at pituitary and gonadal level, causing hypogonadal hypogonadism with the HPG axis to be more disturbed in progressive than in relapsing, remitting MS (Safarinejad, 2008). Hypogonadotropic hypogonadism was also found in an American study where low testosterone levels were associated with worse clinical outcomes (Bove et al., 2014).

The consequences of hormonal disturbances can be approached from different perspectives. Practitioners with an interest in sexology will focus on the connection between sex hormones and sexual functioning. At least in males the effect of lowered testosterone levels will be diminished sexual desire, impaired mood, and less stamina. For professionals with an autoimmune disease perspective the possible neuroprotective effect of sex

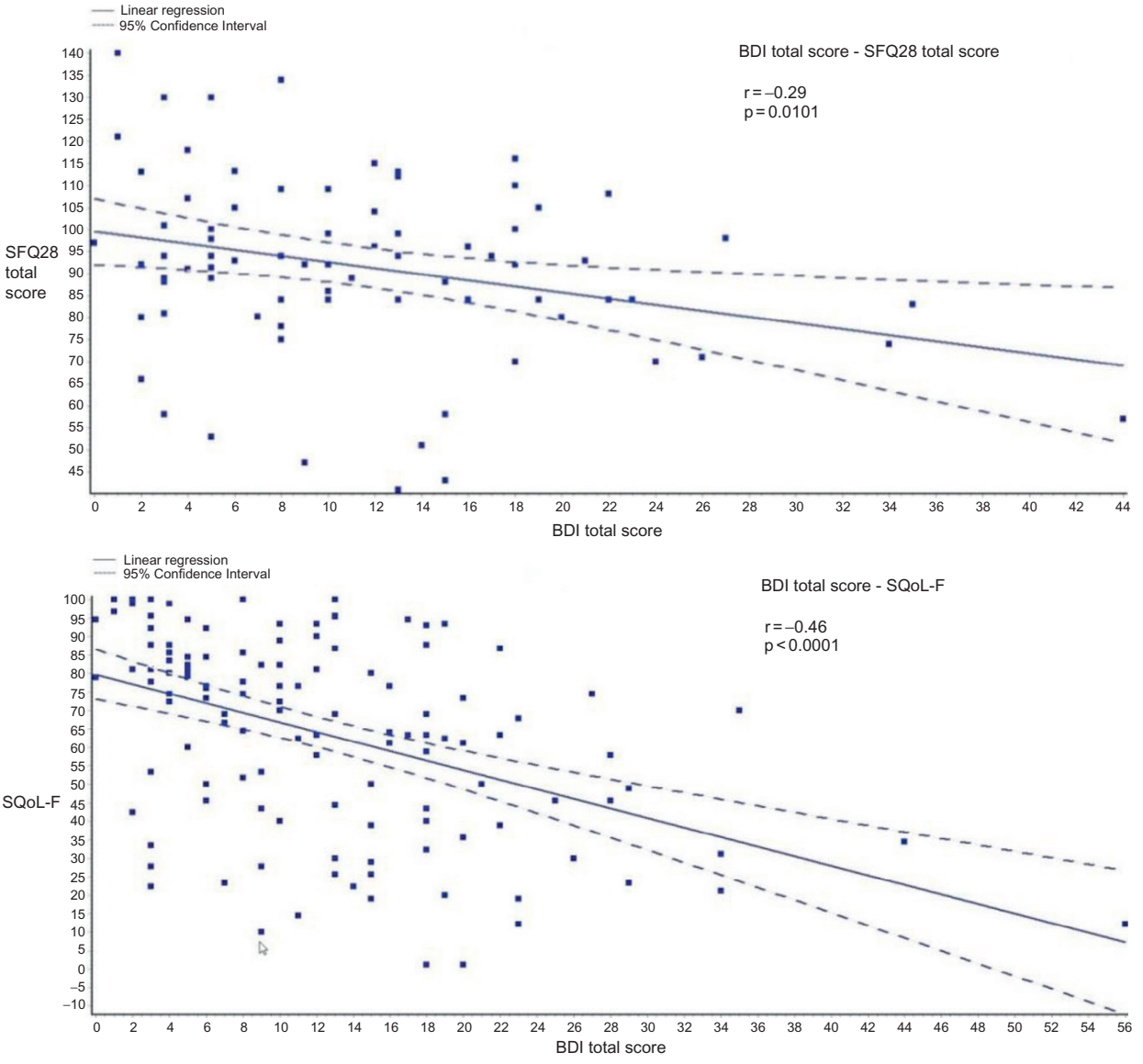

Fig. 20.2. Correlations of depressive symptoms with sexual function and sexual quality of life in women with multiple sclerosis (SQoL-F). SFQ28, Female Sexual Function Questionnaire; BDI, Beck Depression Inventory. (Reproduced from Lew-Starowicz and Rola, 2014b.)

hormones in CNS inflammation and neurodegeneration could be more interesting (Spence and Voskuhl, 2012).

SDs in patients with MS have a distinct impact on their health-related quality of life (HRQoL). According to Schairer et al. (2014), the detrimental impact of SDs on the mental aspects of HRQoL was even larger than the impact of physical disability. Lew-Starowicz and Rola (2013a, 2014a, b) found that deterioration in all domains of sexual functioning in women with MS and in almost all domains in men with MS were strongly correlated with patients' decreased sexual quality of life. The only exception was the desire domain in male patients. This would suggest that men are much more focused on performance during sexual intercourse and that they will suffer less when they do not feel the desire for sexual activity.

MULTIPLE SCLEROSIS AND RELATIONSHIPS

Sexual relationships are one of three important pillars of sexuality, the others being sexual function and sexual identity. Regarding sexual function, we distinguish sexual desire, sexual arousal, orgasm or ejaculation, sexual pain, the sexual function of the (pelvic floor) muscles, and sexual pleasure. Under sexual identity, we put for instance feeling male or female and experiencing the

self as attractive as a lover. Under sexual relationships we look at what is happening between the person and her/his partner. Function, identity, and relationship are interrelated, corresponding with more or less sexual activities.

In 1981, an Australian epidemiologic study with >2300 patients with MS looked into the relationship status. The proportion of people who reported being divorced or separated increased with level of severity of disease, from 6% to 18% in men and from 8% to 13% in women (Hammond et al., 1996). No figures were given for the general population. Compared with the low-disability group, the estimated risk ratio for divorce or separation was 1.1 for men with moderate disability and 4.1 for men with severe disability. For women the corresponding risk ratio estimates were 1.6 and 2.0.

Between 1986 and 1989 an English study looked into the lives of 305 MS patients (Hakim et al., 2000). The marital status of most patients had not changed since the start of the disease, with 9% either divorced or separated. This contrasts with an average divorce/separation rate of 13% in the general population.

Other aspects of their social connections were however impaired. Patients saw the effects of this impairment in jobs, social contacts, and leisure activities. Many caregivers reported symptoms of organic pathology (especially backache), anxiety, and symptoms of depression. In 57% of relatives their professional career had been adversely affected by the patient's illness.

Another Australian study looked into the impact on patients and caregivers of four different neurologic illnesses. They focused on differences in relationship satisfaction, sex life satisfaction, and social support satisfaction between patients and caregivers (O'Connor et al., 2008). The group contained 112 MS patients (of which 76% female) and 61 carers (of which 62% male). Whereas in former studies caregivers were found to have lower marital relationship satisfaction and lower sex life satisfaction than patients, this was not found in this study. Marital relationship satisfaction and sexual life satisfaction were not so much predicted by duration of illness and the severity of symptoms, but more by social support satisfaction. Caregivers, however, had significant lower levels of social support satisfaction than patients. Since support services tend to focus on the patients, the needs of carers are frequently secondary or forgotten.

In a US study on divorce or separation, 515 couples were followed between 2001 and 2006 after a primary brain tumor ($n = 214$), a solid tumor without nervous system involvement ($n = 193$), or MS ($n = 108$) (Glantz et al., 2009). For the whole group divorce or separation occurred at a rate similar to that reported in the literature (11.6%), although in the MS group this was 21.3%. What was surprising was the dramatic asymmetry in the occurrence of divorce and separation based on the sex of the affected partner. The woman was the affected spouse in 88% of separations that occurred among the total patient cohort. The same occurred in the MS cohort, where 94% of the separations concerned female patients and male carers. Men, apparently, do not seem to be that good at caring.

There are also differences from the sexual expression perspective. Whereas many men tend to have more explicit (coital and orgasmic) sexual needs than women, many women tend to be more submissive and adaptive to the sexual requests of their partner. When in such a couple the woman gets MS, will they continue with their sexual pattern? Here, apparently relational and personality factors are relevant. A rather common clinical scenario is as follows: the MS decreases the woman's orgasmic capacity; the "considerate" man doesn't want to be the only one achieving orgasm. So, the couple either tries (in vain) to let the woman have an orgasm, or they stop having sex completely. In the first scenario this not only brings emotional pain and disillusion, but also dyspareunia caused by too long or too heavy stimulation.

DIAGNOSING SD IN PATIENTS WITH MULTIPLE SCLEROSIS

SDs in MS are highly underdiagnosed. Only 2.2–5.7% of female patients and 6.0–10.5% of male patients have discussed their sexual issues with doctors or were diagnosed with SD (Zorzon et al., 1999; Lew-Starowicz and Rola, 2013a, 2014a). These are alarming findings if we take into account how detrimental the effects of SD on the HRQoL has been documented to be. There are several possible explanations for these facts. First of all, physicians may feel neither confident enough nor educated enough to discuss sexual issues with their patients who, from their patient perspective, are too ashamed to ask about such issues spontaneously. Secondly, therapeutic interventions are often focused on primary targets like treating MS relapses, specific neurologic symptoms, or neurologic rehabilitation. Other problems that seriously interfere with patients' well-being are often neglected. This is also true for mental health issues, especially depression, which is underdiagnosed and undertreated in MS patients (Marrie et al., 2009), although not to such an extent as SDs. Finally, starting a discussion on sexual issues may be uncomfortable if the possibilities for referring patients to a specialist who could provide appropriate treatment are limited.

However, talking with patients about their sexual issues may bring considerable benefits in itself. Patients

may be relieved by the possibility of talking openly about their sexual concerns and by knowing that SD is a common problem among MS sufferers and other chronically ill people. Paying attention to such an important aspect of life may additionally reinforce the therapeutic alliance and patients would be more likely to be referred or independently seek professional help, which could result in improving their sexual functioning. This was confirmed in a study by Zorzon et al. (2001), who found that the possibility of talking about sexual matters with a physician increased significantly during a 2-year follow-up from 7.4% to 28.4%, whereas the opportunity to profit from counseling about sexual issues increased from 12% to 25.3%. Moreover, diagnosing SD in men with MS is relevant since effective methods to treat these conditions are increasingly available. One way to improve screening of SD in patients with MS is the use of validated questionnaires like the IIEF, the SFQ, Female Sexual Function Index (FSFI), Multiple Sclerosis Intimacy and Sexuality Questionnaire-19 (MSISQ-19), or Arizona Sexual EXperiences (ASEX) scale, all of which have been found useful in MS patients (Sanders et al., 2000; Celik et al., 2013; Lew-Starowicz and Rola, 2013a, 2014a; Gumus et al., 2014).

MANAGING SEXUALITY IN MULTIPLE SCLEROSIS

Before dealing with sexual disturbances, another potential role of the professional involved in the treatment of MS needs to be addressed. Modern sexology has become aware of the health benefits of sexual expression. Regular (i.e., more frequent) sexual expression has been found to diminish, for instance, depression, cardiovascular death, prostate cancer, vaginal atrophy, and obstetric problems (Gianotten et al., 2006; Whipple et al., 2007). This chapter highlights some health benefits that could be relevant for MS patients.

Penile vibration, both with and without ejaculation (orgasm), decreases muscular spasticity in men with an injured spinal cord and even improves bladder function (Alaca et al., 2005; Biering-Sorensen et al., 2005). In men with spinal cord injury, 4 weeks of vibration, done every third day, resulted in a significant increase in bladder capacity at leak point. By thoroughly examining the detrusor pressure curves, the researchers had the impression that this effect was due to a decrease in detrusor hyperreflexia (Laessøe et al., 2003). For some MS patients it is common to have fewer muscular spasms for several hours after orgasm. Sex can distract from pain in both men and women. In women, however, vaginal and clitoral stimulation concretely increases the pain threshold by endorphin release (Whipple and Komisaruk, 1988). Massage, touching, being touched, breast stimulation, and orgasm all increase the oxytocin level. This neurohormone, with anxiolytic and sedating effects, also increases interpersonal trust (Scantamburlo et al., 2009).

Sexual expression promoting muscle relaxation, easier sleep, less pain, and lessening of depression will favor the patient's general condition. That could indicate a proactive role for professionals working with a perspective of holistic care. Simply addressing sexuality already tends to "give permission." Explicitly explaining that various aspects of sexuality and intimacy can be useful expresses also aspects of care, especially in admitted patients.

Next to "care" we dare to start thinking about some "curative" effects of sexual expression. One of these occurs because sex causes an increase in the levels of testosterone (Dabbs and Mohammed, 1992; van Anders et al., 2007). Testosterone is known to have anti-inflammatory and neuroregenerative effects (Spence and Voskuhl, 2012). In addition sex seems to diminish cognitive decline. There were eight studies that related cognitive functioning to sexual behavior in the aging population. The results indicated a trend for older people who continue to engage in sexual activity in later life to have overall better cognitive functioning (Hartmans et al., 2014).

Data on specific pharmacologic treatment of particular SDs in patients with MS are very limited. Two randomized, double-blind, placebo-controlled trials on the efficacy of sildenafil citrate in men with MS with ED have been published; both show promising but very different results. The superiority of active treatment over placebo was 89% vs 24% in the earlier (Fowler et al., 2005) and 33% vs 18% in the later trial (Safarinejad, 2009). Both studies, however, included young patients with relatively low levels of disability and were judged as at high risk of attrition bias (Thompson et al., 2010; Xiao et al., 2012). One open-label study showed a possible benefit of tadalafil (Lombardi et al., 2010). Another study by DasGupta et al. (2004) on 19 women with MS with SD has shown a beneficial impact of sildenafil, limited to the lubrication domain, and with no overall change in quality of life. ED in men with MS can be alternatively treated with intracavernosal injections, as described by Chao and Clowers (1994).

Both testosterone and estriol seem to have anti-inflammatory and neuroprotective effects. Estrogen replacement therapy in women and testosterone replacement therapy in both genders have been used with success in the treatment of SD (Goldstein and Alexander, 2005; Panzer and Guay, 2009; Corona et al., 2011). In men, testosterone is a vital element in sexual desire, mood, and stamina. So, men with MS suffering from the sexual consequences of a lowered

testosterone level should receive testosterone replacement therapy for their sexual and general well-being, which will probably also lead to positive effects in the MS process. Besides, there is a growing body of evidence that testosterone has neuroprotective effects (Spence and Voskuhl, 2012; Hussain et al., 2013). Its possible therapeutic use for MS has been considered in ongoing clinical trials (Gold and Voskuhl, 2009). In men with relapsing, remitting MS, testosterone treatment proved safe and well tolerated and had neuroprotective effects (Sicotte et al., 2007). We may guess that, in the near future, testosterone will be found to have therapeutic value in the treatment of neurodegenerative diseases and will therefore find a place in MS guidelines (Hussain et al., 2013).

As well as pharmacologic interventions, sexology or sexual medicine professionals have an extensive range of treatment modalities for various SDs, including vibrators, erection-enhancing tools, a cognitive behavioral approach, and a sensate focus approach.

Secondary SDs seem to be an important target for intervention. The management strategies for common MS symptoms were well described in an article by Thompson et al. (2010). Many of these methods can be used as well to improve sexual functioning. Patients with spasticity that results in mobility limitations, contractures, pain, and difficulties in maintaining some of the sexual positions may benefit from finding more comfortable positions, using facilitatory devices like pillows and muscle-relaxing strategies (massage and stretching exercises). Some patients are helped by warming up the muscles, whereas in others warmth causes diminished neural function (the Uhthoff's sign). Alternatively, prior to sexual intercourse, patients may take on-demand medication that reduces muscular tension, like baclofen, tizanidine, benzodiazepines, or tolperisone. Incontinence during sexual activity may be avoided or reduced by fluid intake limitation, coffee and alcohol restriction, emptying bowel and bladder before intercourse, pelvic floor training with or without pelvic floor electric stimulation (Vahtera et al., 1997), catheterization before sexual intercourse in women, or using a constriction ring around the base of the penis that closes the urethra.

In countries where cannabis is medically allowed, it is used in patients with MS to prevent pain and limb spasticity (Pryce and Baker, 2012). One potential additional benefit of cannabinoids is their neuroprotective effect, preventing disease progress in MS (Baker et al., 2000; Zogopoulos et al., 2013). The other positive side-effect is that, with low-dose cannabis, sexual sensations tend to improve, with more desire, more sexual relaxation, and more sexual pleasure. These sexual benefits are dose-dependent and more consistent in females than in males (Gorzalka et al., 2010).

Sexual activity in the morning, after rest, and in more comfortable positions is recommended to avoid the negative impact of fatigue. A strong vibrator can take over the function of too tired muscles. When the neural bundles from clitoris or penis to the spinal cord center for orgasm are damaged, a strong vibrator can add the necessary stimulation to reach the orgasm threshold.

Many pharmacologic interventions have been proposed to deal with neuropathic pain and dysesthesia, along with gabapentine, lamotrigine, carbamazepine, amitryptyline, or topical anaesthetics. More research is needed on their efficacy, especially in connection with hypersensitivity or other sources of pain interfering with sexual activity.

It is important to evaluate whether medication used in a particular patient may interfere with his/her sexual activity. Some of the immunomodulatory treatments may seriously interfere with sexual and reproductive health. For example, mitoxantrone can induce premature menopause (Cocco et al., 2008). These patients need additional counseling. Special interventions should be considered in case of planned pregnancy (i.e., oocyte cryopreservation). Anticholinergics, commonly used in case of incontinence, can also cause vaginal dryness and diminish vasocongestion-dependent genital arousal (Vermote and Peuskens, 1996). By contrast, oral and intravenous corticosteroids in the treatment of MS relapses may have a positive impact on patients' sexual functioning (Mattson et al., 1995).

Many patients need regular treatment with antidepressants. However, many of these drugs may cause a decrease in sexual desire or arousal, ED, and orgasmic dysfunction. Cognitive behavioral therapy can be used as an effective treatment alternative which is free from the negative sexual side-effects typical of antidepressants (Hind et al., 2014). If pharmacologic treatment of depressive symptoms is needed, drugs with fewer sexual side-effects like agomelatine, bupropione, mirtazapine, mianserin, moclobemide, tianeptine, or trazodone should be considered (Phillipp et al., 2000; Montejo et al., 2001; Clayton et al., 2002, 2006; Atmaca et al., 2003; Kennedy et al., 2008).

There are limited data from interventional studies showing the beneficial effects of education and counseling, as well as the importance of partner support in restoring sexual function and sexual satisfaction in patients with MS (Christopherson et al., 2006; Blackmore et al., 2011). Sexual rehabilitation in patients with MS needs a holistic approach that includes as essentials education, pharmacologic treatment, and coping strategies for symptoms that interfere with sexual functioning, specific treatment of SD (if available), treatment of mood disorders, and sometimes couple therapy. We recommend that patients and partners are both (and together) included in the educational process.

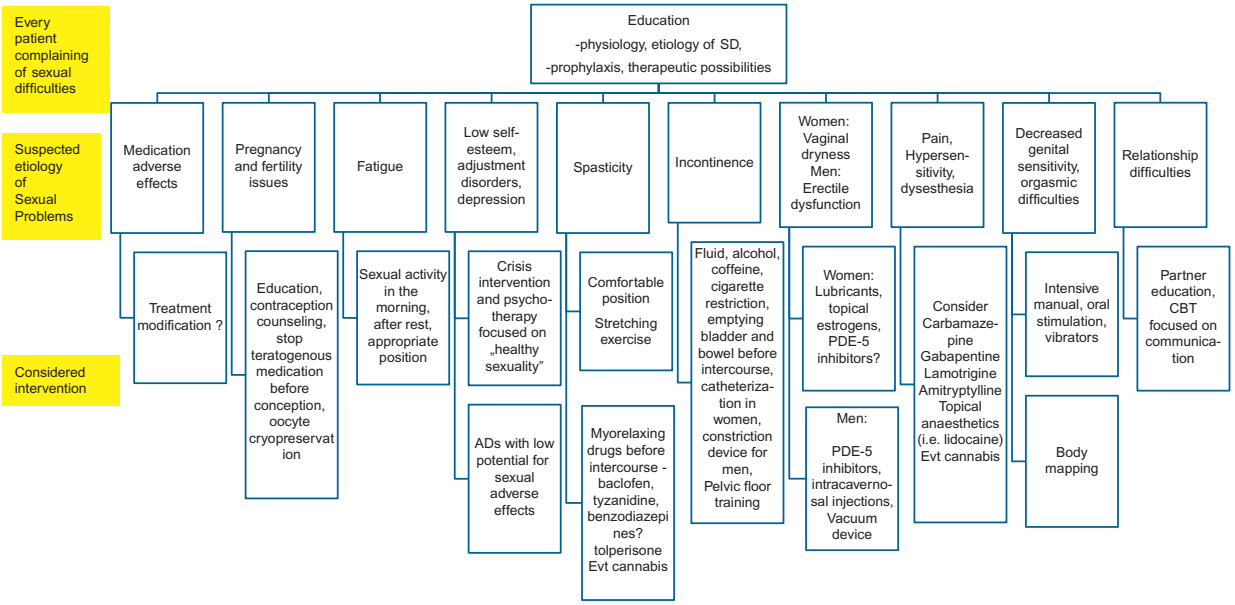

Fig. 20.3. Intervention algorithm for clinical use in patients with multiple sclerosis who are complaining of sexual problems. SD, sexual dysfunction; ADs, antidepressants; PDE-5, phosphodiesterase-5; CBT, cognitive behavioral therapy. (Modified from Lew-Starowicz and Rola, 2013b.)

Foley et al. (2001) have documented, in a small sample of nine couples, that an intervention that consisted of 12 counseling sessions, education, and tailoring symptomatic treatment led to significant improvement in affective and problem-solving communication, marital and sexual satisfaction as compared to patients on the waiting list. More evidence is needed to establish the efficacy of particular interventions. Specific algorithms for sexual therapy and rehabilitation should be implemented and further evaluated in medical care centers for patients with MS. In clinical practice, neurologists and other healthcare providers working with patients with MS usually don't feel confident in coping with sexual health issues and most of the sexologists don't have relevant experience in treating patients with MS. Therefore, the first intervention should primarily focus on simple procedures that could be used without specialist training. An intervention algorithm for clinical use in patients who complain of sexual difficulties is presented in Figure 20.3. More complicated cases should be managed by sexual medicine specialists, preferably in a multidisciplinary setting.

CONCLUSIONS

SD seriously impacts the quality of life of patients with MS. Clinicians, especially those working in neurology and MS, must be aware of that important area and pay sufficient attention to diagnosing and treating SDs in this particular population. On the other hand, professionals from the fields of sexology and sexual medicine should develop sufficient additional expertise to treat sexual disturbances in the MS population. It is important to notice that SDs in MS are not only related to certain brain or spinal cord lesions within areas directly involved in sexual response but also to many secondary and tertiary determinants that specifically affect sexual functioning. SDs are often accompanied by mood disorders and a bidirectional relationship should be considered. Clinical interventions include a variety of methods, and many of them may be applied by non-specialists.

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 21

Lower urinary tract dysfunction in patients with multiple sclerosis

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INTRODUCTION

Multiple sclerosis (MS) is the commonest progressive neurologic disorder in young individuals, affecting over 100 000 people in the UK. According to its clinical course, four subtypes have been identified. Relapsing, remitting MS (RRMS) is the commonest, affecting 85% of patients, but nearly half of these patients convert to secondary progressive MS (SPMS) over a median time period of 11 years (Confavreux et al., 1980). About 10% of patients may have progressive symptoms from the onset (primary progressive MS: PPMS) and a minority have progressive relapsing MS (PRMS) (Compston et al., 2006).

MS is characterized by a chronic autoimmune T-cell-mediated inflammation of the central nervous system resulting in disruption of myelin sheaths. RRMS is characterized by new and active focal inflammatory demyelinating lesions in the white matter, whereas progressive MS is characterized by diffuse injury of normal-appearing white matter, cortical demyelination, and axonal loss (Kutzelnigg et al., 2005; Furby et al., 2008).

The disorder almost inevitably progresses, leading to increasing disability and a decline in mobility due, in part, to spinal cord involvement. Whereas the Expanded Disability Status Scale (EDSS) is a useful tool to measure progression of neurologic disability (Kurtzke, 1983), lower urinary tract (LUT) dysfunction is not satisfactorily captured by the EDSS, as it does not include a score for incomplete bladder emptying. Clinical evidence suggests that LUT dysfunction most often results from spinal cord disease and, indeed, there exists a correlation between LUT symptoms and the degree of pyramidal symptoms in the lower limbs (Betts et al., 1993; Fowler et al., 2009). Moreover, bladder symptoms become more difficult to manage with increasing disability. The mean time from disability level EDSS 4 to 6 (when intermittent or constant assistance is required to walk 100 meters), has been estimated to be 6–8.4 years (Confavreux et al., 1980, 2000, 2003), irrespective of any factors which at the onset may have been regarded as indicative of a good prognosis. LUT dysfunction progressively deteriorates as well, and it is for this reason that surgical options, which are often successful in managing bladder problems following traumatic spinal cord injury, may not always be appropriate (Fowler et al., 2009).

PATHOPHYSIOLOGY OF LUT DYSFUNCTION

Chapter 2 provides an indepth account of the neural control of LUT functions in health. Lesions of the central nervous system result in characteristic patterns of LUT dysfunction according to the site of localization. Whereas subcortical white-matter lesions result in detrusor overactivity (DO), lesions of the spinal cord result in the combined picture of detrusor overactivity and detrusor sphincter dyssynergia (DSD) (Fowler et al., 2008). However, considering the multitude of lesions characteristic of the condition, it is often not possible to establish the relative contribution of individual lesions to LUT dysfunction. In general, LUT dysfunction occurs most often following spinal cord involvement (de Seze et al., 2007; Fowler et al., 2009). A few studies have attempted to evaluate the association between site of lesion and LUT dysfunction. Araki et al. (2003) demonstrated that the finding of DSD in urodynamic studies was indicative of cervical spinal cord lesions. The same group demonstrated detrusor hyporeflexia to be indicative of a pontine lesion (Araki et al., 2003). Significant correlation has been shown between the presence of midbrain lesions and urinary dysfunction (Grasso et al., 1991).

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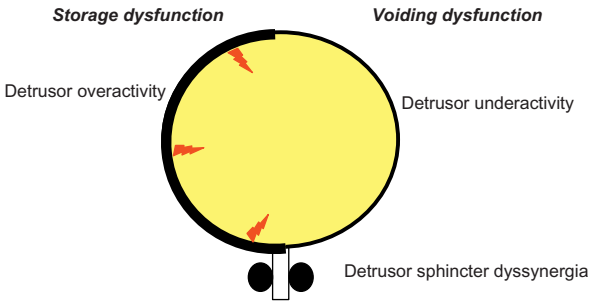

Fig. 21.1. Schematic diagram of the lower urinary tract showing the pathophysiology of storage and voiding dysfunction in multiple sclerosis.

Table 21.1

Lower urinary tract symptoms in patients with Multiple sclerosis may be multifactorial

Lesions affecting neurologic pathway resulting in lower urinary tract dysfunction, e.g., detrusor overactivity, detrusor sphincter dyssynergia
Cognitive problems: memory loss, amotivation, apraxia, language dysfunction
Urologic causes: bladder outlet obstruction, urinary tract infection, genuine stress incontinence
Functional incontinence: reduced mobility, general debilitation
Medications, e.g., opiates, tricyclic antidepressants

In patients with MS reporting LUT symptoms, cystometric studies have demonstrated the most frequent abnormality to be DO (mean occurrence 65%), followed by detrusor underactivity (mean occurrence 25%) and poor bladder compliance (2–10%). The prevalence of DSD in studies is varied, probably due to technical difficulties in detecting abnormal sphincter contraction, but with a median prevalence of 35%, becoming more common if patients are followed up over time (Porru et al., 1997). Both DSD and detrusor underactivity may result in incomplete bladder emptying (Fig. 21.1).

LOWER URINARY TRACT SYMPTOMS IN MULTIPLE SCLEROSIS

Estimates of the proportion of patients with MS reporting LUT symptoms vary according to the severity of the neurologic disability in the group under study; however, a figure of around 75% is frequently cited (Marrie et al., 2007). Several studies have shown that urinary incontinence is considered to be one of the worst aspects of the disease, with 70% of a self-selected group of patients with MS responding to a questionnaire as classifying the impact bladder symptoms had on their life as "high" or "moderate" (Hemmett et al., 2004). Urinary incontinence represents a considerable psychosocial burden to patients and their carers, while urinary tract infections (UTIs) and complications thereof may result in multiple hospital admissions.

Patients with MS experience storage or voiding symptoms, or a combination of both. Storage symptoms, also known as overactive bladder symptoms, consist of urinary frequency and urgency, with or without urge incontinence, and nocturia. Voiding symptoms include hesitancy, poor urinary stream, dribbling of urine, a sensation of incomplete bladder emptying and double voiding (pis-en-deux), whereby the patient often voids again after a short period. Symptoms, particularly urgency, incontinence, and nocturia, can limit activities of daily living and negatively impact on a patient's social activities, leading to social embarrassment, isolation, and depression (Ouslander, 2004). The nighttime symptom of nocturia is associated with poor-quality sleep, low vitality, poor emotional health, and an overall reduced quality of life (Kalsi et al., 2008). Evidence from surveys suggests that one of the least tolerable aspects of the condition is urinary incontinence and that treatment of this symptom can lead to greatly enhanced quality-of-life measures.

Considering the multitude of symptoms which patients with MS report, not surprisingly, LUT symptoms may be overlooked in the clinical management of MS. The North American Research Committee On Multiple Sclerosis questionnaire survey found that, of more than 5000 patients in North America with troublesome urinary symptoms, only 43% had been referred to urologic services and 51% had been treated with antimuscarinic medications (Mahajan et al., 2010). Recently, a tool for screening patients with MS for bladder symptoms has been developed and validated, called the Actionable Bladder Symptom Screening Tool (Burks et al., 2013). There may be numerous factors contributing to LUT symptoms in patients with MS (Table 21.1).

Often, incomplete bladder emptying and an overactive bladder coexist, the residual urine exacerbating overactive bladder symptoms. Whereas the symptoms of an overactive bladder are a reliable indicator of underlying LUT dysfunction (i.e., DO), patient reports of incomplete bladder emptying are often not. In a cohort of patients with MS studied by Betts et al. (1993), patients who thought they did not empty their bladder were found to most often be correct; however only half those who thought they did were correct. Hence, measurement of the postvoid residual volume (PVR) is a critical investigation in the management of LUT symptoms in patients with MS (Fig. 21.2) (Fowler et al., 2009).

INVESTIGATIONS

Urine testing

Urine dipstick analysis helps to detect evidence for UTI and should be performed in all patients during the initial evaluation, or subsequently when reporting new

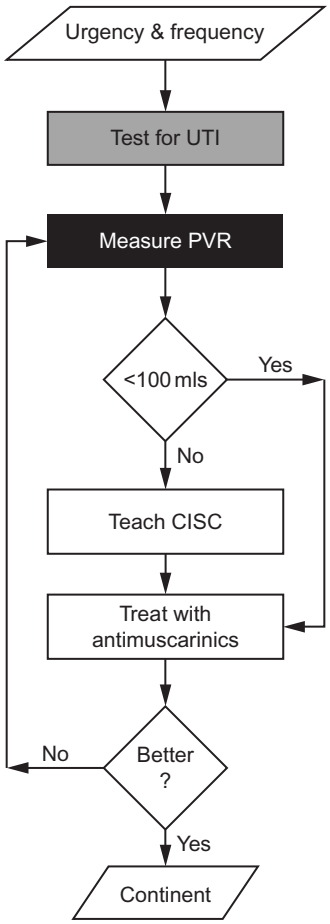

Fig. 21.2. Algorithm for the initial management of lower urinary tract symptoms in multiple sclerosis. UTI, urinary tract infection; PVR, postvoid residual volume; CISC, clean intermittent self-catheterization. (Reproduced from Fowler et al., 2009.)

symptoms. The test is useful in excluding infections as it has a high negative predictive value (>98%); however, it has a low positive predictive value of around 50% (Fowlis et al., 1994; Fowler et al., 2009). When an infection is clinically suspected, midstream or catheter urine specimens should be sent for microbiologic culture.

Measurement of the postvoid residual volume

The PVR should be measured by ultrasound, or alternately by single in–out catheterization. Incomplete bladder emptying is reflected by a high residual volume (>100 mL). The PVR should be part of the initial assessment and should be performed preferably before antimuscarinic treatment is started (Fig. 21.2). Furthermore, if there is reason to suspect a patient already established on treatment has developed incomplete bladder emptying, for example, a poor response to antimuscarinics or reporting recurrent UTIs, the PVR measurement should be repeated. It is recognized that a single measurement of a PVR is often not representative and, if possible, a series of measurements should be made over the course of 1 or 2 weeks (Fowler et al., 2009).

Urodynamic studies

"Urodynamic studies" (referring here to multichannel cystometry and pressure–flow studies of voiding), with or without additional synchronous fluoroscopic screening (videourodynamic studies), are useful to examine the functions of the LUT, evaluating the pressure–volume relationship during non-physiologic filling of the bladder and during voiding. The need to perform a complete urodynamic study in all patients with MS is somewhat controversial. Whereas the test is essential in the management of patients with spinal cord injury or spina bifida to ensure bladder pressures are "safe" and silent upper urinary tract (kidney and ureter) damage is not a risk, for some as yet not understood reason, complications of the upper urinary tract are much less common in patients with MS. Although urinary sepsis, stone formation, and upper tract dilatation may occur in patients with MS, this is usually in the context of advanced LUT dysfunction and so do not occur as a clinically silent, isolated problem. Upper urinary tract problems can include infections or upper tract dilatation (8%), vesicoureteral reflux (5%), and urinary lithiasis (2–11%) (Bemelmans et al., 1991; Betts et al., 1993; Sirls et al., 1994; Kasabian et al., 1995; Koldewijn et al., 1995; Porru et al., 1997; Gallien et al., 1998; de Seze et al., 2007). The risk for renal failure in patients with MS however is no higher than the risk in the general UK population (Lawrenson et al., 2001). Risk factors predisposing to upper tract damage in MS include long duration of the disease, advancing disability, presence of an indwelling catheter, and high-amplitude uninhibited detrusor contractions on cystometry (de Seze et al., 2007; Castel-Lacanal et al., 2015).

On the other hand, urodynamic studies provide an opportunity to evaluate urologic conditions that may occur concomitantly. For example, women with MS may complain of stress urinary incontinence in addition to urge incontinence and, if surgical treatment is being considered, full urodynamic evaluation, ideally by videourodynamic studies, is necessary. Moreover, if patients do not respond to first-line treatments, or invasive treatment for LUT symptoms is being considered, urodynamic assessment is generally recommended (Fowler et al., 2009). Similar recommendations have been put forward by the recent International Consultation of Incontinence (Abrams et al., 2013) and UK National Institute for Health and Care Excellence (NICE) recommendations for urinary incontinence in neurologic disease (NICE, 2012). This is somewhat

different to the French approach, in which these tests are more central in management planning (de Seze et al., 2007). In the absence of data comparing these two models of management, the decision to perform complete baseline urodynamic studies would depend upon local resources and recommendations.

MANAGEMENT

In recent years, concerted efforts have been made to produce consensus guidelines for the management of LUT symptoms by stakeholders responsible for the care of MS patients in several countries, such as the UK (Fowler et al., 2009), France (de Seze et al., 2007; Amarenco et al., 2013), Belgium (De Ridder et al., 2013), and Turkey (Cetinel et al., 2013), and highlight the need for multidisciplinary long-term follow-up in MS (Pannek et al., 2013). Such guidelines have been developed by a review of the existing literature and often have involved not only urologists, but also neurologists, rehabilitation physicians, continence advisors, and the stakeholder groups representing patients. These guidelines have helped to define the best therapeutic options, taking both the neurologic disability and patient's environment into consideration.

General measures

Patients with overactive bladder symptoms often tend to restrict their fluids. The fluid intake should be individualized and an assessment of fluid balance using a voiding diary is often helpful; 1.5–2.5 liters a day is generally recommended. Caffeine reduction below 100 mg/day has been shown to reduce symptoms of urgency and frequency, though not specifically in patients with MS (Bryant et al., 2002).

Physical treatments

There are a number of physically based interventions that can be of benefit to patients with overactive bladder symptoms. Pelvic floor exercises can enhance the inhibitory effect of pelvic floor contraction on the detrusor. Bladder retraining involves the patient voluntarily "holding on" for increasingly longer periods, often in an incremental program supervised by specialist continence advisors or physiotherapists. These interventions can only be expected to be effective in patients with intact neural pathways to pelvic floor muscles and an assessment of pelvic floor contractions should be made prior to initiating treatment. A prospective trial of pelvic floor rehabilitation in treating DO in 30 female patients with MS demonstrated significant improvements in urinary frequency and number of daily incontinent episodes, and found significant increases in mean cystometric capacity after 1 month (De Ridder et al., 1999). Intravaginal non-invasive electric stimulation can also be used to stimulate pelvic floor muscle contractions. These have an inhibitory effect on detrusor activity, in keeping with the effects of voluntary contraction of pelvic floor muscles. The combination of intravaginal electric stimulation and pelvic floor training and electromyography biofeedback was found to be effective and without harm (McClurg et al., 2006).

Managing incomplete bladder emptying

In patients with impaired voiding, a PVR $>$100 mL or more than one-third of bladder capacity is thought likely to contribute to LUT dysfunction. The most commonly offered solution is clean intermittent self-catheterization (CISC), which should be taught by a specialist nurse (Fowler et al., 2009). Most often, single-use disposable catheters are used and these are ready lubricated. Frequency of catheterization depends upon the PVR, but 2–5 catheterizations per day are usually recommended.

CISC is rarely necessary in the early stages of MS (Kirchhof and Fowler, 2000), but becomes increasingly likely to be needed as mobility deteriorates. There are several factors that can impede a patient's ability to perform CISC, including impaired manual dexterity and motivation. The ability of patients with MS to learn CISC may be influenced by the EDSS, but cognitive decline seems not to be a limitation (Vahter et al., 2009). There are several barriers that patients with MS may face when having to perform CISC, and these will have to be individually addressed (Table 21.2) (Seth et al., 2014). For patients with MS with severe limb spasticity and poor mobility, a willing carer may be taught to catheterize the patient.

There is limited evidence to suggest that the use of a battery-powered, hand-held, suprapubic vibrator can improve bladder emptying in patients who also have DO. The vibrating stimulus can initiate micturition in patients with DO (Prasad et al., 2003), though in clinical practice the benefits are often limited. Bladder compression comprises various techniques aimed at increasing intravesical pressure in order to facilitate bladder emptying and most commonly used are Valsalva (abdominal straining) and Credé (manual compression of the lower abdomen) maneuvers. These are potentially hazardous for the upper urinary tract due to functional obstruction at the level of the pelvic floor (Abrams et al., 2008); however, the possible long-term risks in patients with MS are unknown. Although a small study of patients with MS showed alpha-blocker medications reduced PVR volumes (O'Riordan et al., 1995), experience in clinical practice rarely shows a consistent benefit with this

Table 21.2

Barriers to performing clean intermittent self-catheterization (CISC) in patients with multiple sclerosis and proposed suggestions to improve adherence

Barriers	Suggestions
Internal factors (patient-related)	• Face-to-face instructions with a nurse with experience in teaching CISC
Physical disabilities	• Choosing the appropriate catheter
• Positioning	• Use of catheter appliances to help locate the urethra:
• Dexterity	• Thigh abductors
• Visual impairment	• Labia spreaders
• Cognition	• Mirrors
Psychologic factors	• Use of visual aids, leaflets, videos
• Misconceptions and anxiety	• Providing adequate time for teaching
• Embarrassment and poor confidence	• Ensuring regular follow-up when required
• Stigma	• Engaging with carer/partner when appropriate
• Fears	• Standardized training of continence nurses
External factors	• Adequate budgetary provision for catheters and appliances
• Access to public toilets	• Efficient catheter delivery system in the community
• Inadequate facilities in public toilets	• Optimizing communication between primary and secondary/tertiary care
• Availability of appropriate catheters and assisting appliances	• Engaging with district nurses for optimizing support in the community
• Quality of teaching and the training environment	• Access to locked disabled toilets (e.g., National Key Scheme)
• Community follow-up: access to help or advice	
• Availability of experienced nurse specialists	

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medication. However "diagnostic shadowing" should not be allowed to obscure the fact that men with symptoms of poor voiding may have outflow obstruction of prostatic origin.

Managing the overactive bladder

Antimuscarinics

Antimuscarinic medications are the first-line treatment for overactive bladder symptoms and their use is associated with better patient-reported cure/improvement and significant reduction of maximum detrusor pressures in patients with neurologic disease (Madhuvrata et al., 2012). In MS, the evidence base is limited (Nicholas et al., 2009), but there are a small number of studies which provide evidence for the efficacy of antimuscarinics in reducing incontinence, frequency, and urgency () (Gajewski and Awad, 1986; Ethans et al., 2004; van Rey and Heesakkers, 2011). Not all the antimuscarinics currently available have been systematically investigated and their use is often by inference of efficacy. Dual therapy (combinations of oxybutynin, tolterodine, and trospium) has been shown to be effective and well tolerated in a few patients (Amend et al., 2008).

In the presence of raised PVR volumes, detrusor contractions will continue despite the use of antimuscarinics. Consequently, antimuscarinics may exacerbate the situation by further impairing the efficiency of bladder emptying; it is for this reason that the algorithm shown in Figure 21.2 is recommended. Often, it is the combination of CISC and oral antimuscarinics that is most effective in managing LUT symptoms due to MS (Fowler et al., 2009). The PVR should be rechecked in patients who have not responded to antimuscarinics. Commonly used antimuscarinics are listed in Table 21.3 (Fowler et al., 2009).

In the cognitively impaired, antimuscarinics should be prescribed with a warning for carers to be vigilant about possible deterioration in cognitive function (Kay et al., 2006) or the onset of confusion. In the absence of positive evidence it seems sensible at this time to recommend the use of antimuscarinics that do not cross the blood–brain barrier, i.e., trospium chloride, or darifenacin, a selective blocker of the M3 receptor which is not known to be involved in cognition (Pannek et al., 2013).

Desmopressin

Synthetic antidiuretic hormone desmopressin has been shown to reduce nighttime voiding frequency in MS. Use of the medication is associated with restoration of sleep patterns and significant improvements in quality of life (Bosma et al., 2005). If taken during the day, desmopressin can also provide relief from urinary frequency for up to 6 hours without rebound nocturia

Table 21.3

Antimuscarinic medications available in the UK (presented alphabetically) (Fowler et al., 2009)

Generic name	Trade name	Dose (mg)	Frequency
Darifenacin	Emselex	7.5–15	od
Fesoterodine	Toviaz	4–8	od
Oxybutynin IR	Ditropan, Cystrin	2.5–20	bd–qds
Oxybutynin ER	Lyrinel XL	5–20	od
Oxybutynin transdermal	Kentera	36 mg (3.9 mg/24 hours)	One patch twice weekly
Propantheline	Pro-Banthine	15–120	tds (1 hour before food)
Propiverine	Detrunorm	15–60	od–qds
Solifenacin	Vesicare	5–10	od
Tolterodine IR	Detrusitol	2–4	bd
Tolterodine ER	Detrusitol XL	4	od
Trospium	Regurin	20–40	bd (before food)
Trospium ER	Regurin XL		

od, once daily; bd, twice daily; tds, three times daily; qds, four times daily; IR, immediate release; ER, extended release.

(Bosma et al., 2005). However, it is not recommended for use more than once in 24 hours, and should be used with caution in the elderly (aged >65 years) or with fluid overload and edema (Bosma et al., 2005). Hyponatremia is also a recognized side-effect, and sodium levels should be checked before the drug is administered to establish a baseline level, and at day 3 and 7 after daily administration (Hashim et al., 2009).

Botulinum toxin

The demonstrated efficacy of intradetrusor injections of botulinum toxin A in the treatment of neurogenic DO has transformed the management of urgency incontinence for patients with MS who have not responded adequately to antimuscarinics and CISC. The exact mechanism of action of botulinum toxin is uncertain; in addition to inhibiting the release of vesicular acetylcholine release from motor nerve terminals, it is likely to be inhibiting the release of transmitters involved in the afferent signaling pathway (Apostolidis et al., 2006).

Two placebo-controlled trials included a small number of patients with MS (Schurch et al., 2005; Ehren et al., 2007) and an open-label study showed it was highly efficacious in improving symptoms, urodynamic parameters, and quality of life (Kalsi et al., 2007). All patients with MS should have been taught or agreed to learn to do CISC before being treated with botulinum toxin (Fowler et al., 2009). However because this is usually only recommended for patients who have failed to respond to two or more oral antimuscarinics, many of them have already reached the stage when CISC has also become necessary. Almost all patients in the open-label study (42 out of 43) needed to perform CISC afterwards (Kalsi et al., 2007). However the need for CISC did not affect the patients' estimates of improvement in quality of life.

More recently, two multicenter, randomized, double-blind, placebo-controlled phase III clinical trials demonstrated efficacy in improving urinary incontinence episodes in patients with neurogenic DO, which included a sizable cohort of patients with MS. Both 200 U and 300 U of onabotulinumtoxinA were well tolerated with no clinically relevant differences in efficacy, and the median time to patient request for retreatment was the same (42.1 weeks). However the need to initiate CISC posttreatment was higher in those receiving 300 U (Cruz et al., 2011; Ginsberg et al., 2012). Based upon the results of these studies, botulinum toxin has been licenced for use in neurogenic DO in many countries since 2012. There is evidence to suggest that intradetrusor injections of botulinum toxin may benefit MS patients with an indwelling urethral catheter who report catheter bypassing (Lekka and Lee, 2006), and may also reduce the frequency of UTIs (Game et al., 2008).

Neuromodulation

Stimulation of peripheral nerves, most commonly the posterior tibial nerve or sacral nerve root S3, has been proven to be successful in managing overactive bladder symptoms. The mechanism of action is uncertain but is thought to be due to modulation of spinal cord-mediated pelvic reflexes through inhibitory interneurons.

Percutaneous tibial nerve stimulation, using a needle to deliver electric stimulation, has been shown to be effective in managing storage symptoms and improved urodynamic parameters in MS patients (Kabay et al., 2009; Gobbi et al., 2011). Significant improvements were noted in mean symptom and quality-of-life scores, with

89% of patients reporting treatment satisfaction of 70%. The efficacy of transcutaneous tibial nerve stimulation was proven in a recent study in patients with MS and symptoms of overactive bladder. The transcutaneous route of application utilizes an adhesive pad applied behind the medial malleolus, over the tibial nerve. In the study, 70 patients were enrolled, and significant improvements were noted at up to day 90 after the initiation of treatment, with regard to bladder diaries and symptom scores. The use of tibial nerve stimulation in the management of MS-related overactive bladder symptoms appears to be promising, with the appeal being minimal invasiveness and cost-effectiveness (de Seze et al., 2011).

Sacral neuromodulation (SNM) has been tried in small numbers of patients of MS, with limited success (Chartier-Kastler et al., 2000; Cappellano et al., 2001; Wallace et al., 2007). SNM may lose its efficacy as the disease progresses. Moreover, as patients with MS often require repeat MRIs over time, it is likely that SNM would be an option only in patients whose MS has a benign indolent course and yet having bladder symptoms that are problematic and not responsive to less invasive treatments (Kessler et al., 2010).

Surgery

Patients with predominant stress incontinence should first be offered the various treatment options, including surgery, if appropriate and available. If urge incontinence is intractable and not responding to botulinum toxin, then urinary diversion in the form of ileal conduit formation or bladder augmentation surgery may need to be considered. However, this is a major surgical procedure and not without its own complications, and patients should receive appropriate and realistic preoperative counseling (Marrie et al., 2007).

Other options

Cannabinoids

The scientific argument for cannabinoid use stems from the expression of cannabinoid receptors (CB1) in the bladder. In the animal rodent model of an inflamed bladder, the use of cannabinoid receptor agonists leads to a marked increase in micturition threshold (Jaggar et al., 1998). A small pilot study in 21 patients with advanced MS showed significant quality-of-life parameter improvements in urgency, frequency, nocturia, and number of urge incontinence episodes (Brady et al., 2004). In a large placebo-controlled study of 647 patients with MS, an oral cannabis extract of Δ9-tetrahydrocannabinol (THC) reduced urge incontinence episodes and pad weight significantly more than placebo (Freeman et al., 2006). A multicenter double-blind, placebo-controlled trial studying LUT symptoms in patients with advanced MS using sublingual Sativex (endocannabinoid modulator comprising THC and cannabidiol in a 1:1 ratio) demonstrated improvement in daytime frequency and nocturia. However there was no significant difference in the primary end point of the study, episodes of urinary incontinence, between the treatment drug and placebo at the end of treatment at 8 weeks (Kavia et al., 2010). A license was recently granted in the UK for the use of a cannabis-based medicine to treat spasticity in MS, but this does not cover LUT symptoms.

Stepwise approach to managing LUT symptoms in MS

The treatment options offered to a patient should reflect the severity of bladder dysfunction, which generally parallels the extent of neurologic disease (Fig. 21.3). However beyond a certain point, incontinence may become refractory to all treatment options and it is at this stage that a long-term indwelling catheter should be offered.

Long-term indwelling catheter

For patients with a significantly raised PVR volume and unwilling or unable to manage catheterization, or who have incontinence which is refractory to treatment, a long-term indwelling catheter becomes necessary. Urethral catheters can be uncomfortable and cause urethral and bladder neck trauma, and should therefore only be considered as a temporary measure before arrangements to insert a suprapubic catheter can be made. The patient should be referred to a urology service for

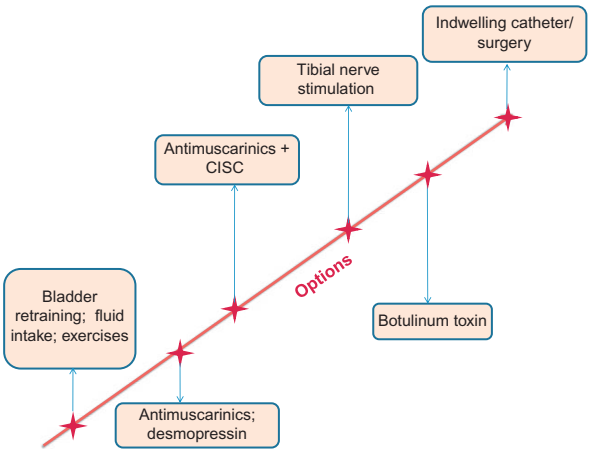

Fig. 21.3. Stepwise approach to managing lower urinary tract symptoms in multiple sclerosis, which often relates to the progression of disabilities (see text for details). CISC, clean intermittent self-catheterization.

suprapubic catheterization, which should be performed under both cystoscopic and ultrasound guidance to minimize the risk of inadvertent bowel injury (Kesselring et al., 2010). This is particularly hazardous in patients with small-capacity, thick-walled bladders and the procedure should not be left to an experienced urologist, ideally a neuro-urologist. Once inserted, the suprapubic catheter should not be changed for up to 8 weeks to allow adequate tract epithelialization, and can then be changed at intervals of up to 3 months. Long-term catheters can be fraught with complications, such as recurrent infections, encrustation, blockages, and bleeding, leading to hospital admissions (Fowler et al., 2009). This can be minimized by regular catheter changes, and attention to cleaning.

The catheter collecting bag system provides continuous drainage and can be attached to the patient's leg and worn discreetly. Catheters may be fitted with a "flip-flow" valve, which will preserve the bladder capacity by allowing for intermittent bladder drainage, obviating the need for wearing a daytime leg bag. This is suitable if patients have the mobility and dexterity to operate the valve mechanism over the toilet or pan, and if the patient's bladder has a reasonable storage capacity, which unfortunately is often not the case in patients with MS (Fowler et al., 2009).

Urinary tract infections

In general, clinical and epidemiologic evidence supports a link between the development of an infection and MS exacerbation. It has been reported that systemic infections can lead to disease exacerbation and radiologic activity in patients with MS (Buljevac et al., 2002; Correale et al., 2006). MS relapses associated with systemic infections may cause more sustained damage and deterioration of the neurologic status than those relapses which occur outside the context of infections (Buljevac et al., 2002).

UTIs commonly occur in patients with MS reporting LUT dysfunction (Nakipoglu et al., 2009). The factors that predispose to UTIs in MS have been poorly studied, but incomplete bladder emptying and use of a catheter, either intermittently or indwelling, are known to do so (Fowler et al., 2009). Having a UTI may precipitate an acute relapse (Leary et al., 2005), and recurrent UTIs significantly increase morbidity and mortality rates and have a detrimental impact on quality of life (Hennessey et al., 1999). Moreover, infections of the LUT may ascend to the upper urinary tract, resulting in pyelonephritis, or even spread systemically, resulting in urosepsis, which may adversely affect the MS patient's functional status.

Because of the association between UTIs and relapse, it is common clinical practice to test for a UTI before starting high-dose corticosteroid treatment and other immunosuppressive agents (Fowler et al., 2009). Corticosteroid treatment may lead to the unmasking of an infection and occasionally complications such as pyelonephritis or sepsis (Rakusa et al., 2013). Options for preventing recurrent UTIs could include antibiotic prophylaxis, cranberry preparations, methenamine prophylaxis, and topical estrogen. However, only a few strategies have been studied specifically in patients with MS. The downsides of long-term antibiotic prophylaxis are possible adverse reactions, costs, and increasing bacterial resistance to antibiotics. Therefore, alternative prophylactic agents, such as cranberry extracts and probiotics, have been extensively studied. Proanthrocyanadin in cranberry extract inhibits bacterial adherence to urothelial cells. Although cranberry preparations are widely used, their usefulness in preventing recurrent UTIs has not been clearly established and a recent Cochrane database review concluded that cranberry products cannot currently be recommended for the prevention of recurrent UTIs (Jepson et al., 2012). A recent randomized study of cranberry extract in patients with MS showed no difference in time to first symptomatic UTI across 1 year compared to placebo (Gallien et al., 2014).

CONCLUSION

LUT dysfunction is common in MS and can be extremely disabling and embarrassing for patients. Symptoms may be neglected, as attention often focuses on neurologic deficits affecting balance, mobility, and vision. During early stages of the disease, antimuscarinic medications are the first-line treatment, and CISC if there is concomitant incomplete bladder emptying. As the disease progresses, patients may experience worsening of symptoms and require a more formal assessment with urodynamic studies and potentially require other treatment options such as botulinum toxin. Treatment pathways are now available that guide management. Patients should be assessed and managed by appropriately experienced healthcare providers, who can offer one of the number of effective treatment options available. Patients with MS should be regularly reviewed as their LUT symptoms can change with neurologic progression.

ACKNOWLEDGMENTS

This work was undertaken at University College London Hospital/University College London Institute of Neurology and received a proportion of funding from the Department of Health's National Institute for Health Reseach Biomedical Research Centre's funding scheme.

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 22

Sexual dysfunction in patients with epilepsy

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People with epilepsy experience several gender-related physical and social problems, and the last decade has seen a focus on gender issues in epilepsy. Disturbances of reproductive and sexual health are common in men and women with epilepsy (Herzog et al., 1986a, b; Webber et al., 1986; Wallace et al., 1998). Being a woman with epilepsy is not the same as being a man with epilepsy (Tauboll and Luef, 2008).

Sexuality is an important and private aspect of life, and sexuality and epilepsy have been intimately linked since ancient times. In the modern medical era of epilepsy, Gastaut and Collomb (1954) reported that many patients with complex partial seizures have an apparent lack of interest in sexual activity (Luef, 2008).

Sexual desire is defined as the willingness to engage in sexual behavior when given appropriate sexual stimuli. Androgens are essential to support sexual desire (Huber, 1998).

Sexual arousal, on the other hand, is driven by both estrogens and androgens, and is defined as the capacity to respond to appropriate sexual stimuli (Huber, 1998).

Sexual dysfunction refers to a chronic inability to respond sexually in a way that is satisfying. It may be primary (i.e., someone who has never had satisfactory relations), secondary (i.e., someone who has had satisfactory relations, but now has chronic difficulty), situational (i.e., with certain partners or during certain activities), or global (i.e., across the board). Erectile disorder is commonly seen among males; females may complain of sexual arousal disorder or vaginismus. Sexual dysfunctions that may affect both sexes include hypoactive sexual desire disorder and, very rarely, dyspareunia (Huber, 1998).

Despite its fundamental role in human life, there has been surprisingly little research into the neurologic control of human sexual behavior. Multiple causes may lead to sexual dysfunction. The basis for hyposexuality has been attributed to both epilepsy and antiepileptic drug (AED) use, making it difficult to distinguish between the illness-specific and pharmacologic impacts on sexual functioning (Luef, 2008). Low levels of androgens are associated with sexual arousal insufficiency and sexual dysfunction. When examining sexual dysfunction in men and women with epilepsy, the Arizona Sexual Experience (ASEX) scale may be helpful in evaluating sexual function (McGahuey et al., 2000; Soykan, 2004; Luef, 2008). Laboratory tests for estrogen, free and total testosterone, and serum sex hormone-binding globulin (SHBG) may also be useful in evaluating sexual health.

Data from animal studies support the hypothesis that hyposexuality occurs as a result of epileptiform activity in the temporal lobe, but not in the motor cortex (Feeney et al., 1998; Luef, 2008). In patients with epilepsy, alterations in interictal sexual behavior have been frequently reported, particularly in temporal-lobe epilepsy (TLE). The most common interictal sexual dysfunction associated with TLE is hyposexuality (Kolarsky et al., 1967).

Sporadic case studies suggest that hypersexuality is a rare but dramatic outcome of unilateral temporal lobectomy (Blumer, 1970; Baird et al., 2002). Sexual seizure manifestations are also rare clinical phenomena during or after complex partial seizures and have received attention in the literature (Leutmezer et al., 1999; Dobesberger et al., 2004).

Enzyme-inducing AEDs, such as carbamazepine (CBZ), phenytoin, or phenobarbital, are metabolized in the hepatic P450 system (e.g., 3A4, 2C9, 2C19), induce hepatic enzymes, increase the hepatic synthesis of

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SHBG, and increase the metabolism of sex hormones (Stoffel-Wagner et al., 1998; Herzog et al., 2004) that might have an additional influence on sexuality in patients with epilepsy. Both men and women with epilepsy appear to have altered gonadal function. It is still unclear whether AEDs or epilepsy cause the abnormality involving prolactin, luteinizing hormone (LH), estradiol, SHBG, and dehydroepiandrosterone (DHEA) in women and also follicle-stimulating hormone (FSH), free testosterone, inhibin, DHEA, and 17α-OH progesterone in men with epilepsy (Bauer et al., 2004a, b; Luef, 2008).

HYPOSEXUALITY

Hyposexuality is defined as diminished sexual drive or libido, or typically as sexual activity less than once per month, and may or may not be accompanied by erectile or orgasmic dysfunction (Blumer, 1970; Luef, 2008).

Early studies describing a relationship between hyposexuality and TLE have received methodologic criticisms (Toone, 1995). Control groups and female patients were rarely included, and diagnostic criteria for epilepsy were often poorly defined. Many studies included heterogeneous or biased samples without consideration of comorbid conditions. Nevertheless, the majority of studies supported an association between TLE and hyposexuality (Shukla et al., 1979). Hyposexuality may be the result of altered neuroendocrine regulation caused by epilepsy itself (Herzog, 1993; Herzog et al., 2003) or AED exposure (Isojarvi et al., 2005). Gonadal toxicity of some AEDs (Tauboll et al., 1999), altered peripheral steroid and binding protein synthesis and metabolism (Isojarvi et al., 2005), and possibly altered neurotrophic effects of the limbic system, hypothalamus, and autonomic nuclei on the growth and maintenance of the ovaries, mediated via direct autonomic innervation of the gonads (Gerendai et al., 1995) may be factors. The relationship of pulse frequency to the nature and laterality of paroxysmal discharges makes it unlikely that endocrine abnormalities and hyposexuality can be attributed to AEDs alone and strengthens the notion that temporal-lobe epileptiform discharges may disrupt hypothalamic regulation of pituitary secretion (Herzog et al., 1990). Hormonal changes also can show close temporal relationship to the occurrence of interictal epileptiform discharges and may vary in relation to the laterality of the discharges (Herzog et al., 2005).

Although sexual dysfunction is common in epileptic patients, quantification of sexual dysfunction is limited by the paucity of validated, user-friendly scales. To evaluate sexual interest and function in people with epilepsy, standardized questionnaire are needed. Sexual interest and potency are equally weighted in the S-score questionnaire, i.e., two questions for each category with a maximum total score of 10 (McGahuey et al., 2000). Sexual functioning measured using the ASEX scale, a brief five-item scale designed to assess the core elements of sexual functioning – drive, arousal, penile erection/vaginal lubrication, ability to reach orgasm, and satisfaction with orgasm – is often used in studies for both men and women. Possible total scores range from 5 to 30, with the higher scores indicating more sexual dysfunction. Each item is rated with a six-point Likert system, with higher scores reflecting impaired sexual functioning. A total ASEX score $\geq$19, any one item with a score of $\geq$5, or any three items with a score of 4 have all been found to be correlated with sexual dysfunction (Baird et al., 2002).

HYPERSEXUALITY

Hypersexuality, or a dramatic increase in sexual drive, has been reported in some patients after unilateral temporal lobectomy (Cogen et al., 1979; Leutmezer et al., 1999). It is defined as "sexual arousal and response that is clearly abnormal in frequency and intensity for a given individual" (Cogen et al., 1979). Blumer (1970) identified common traits in three patients, including the manifestation of hypersexuality after a "postoperative silent period" of 3–6 weeks, persistent sexual arousal, homosexual behavior, accompanying dietary changes and loss of anger or "tameness." Luef (2008) suggested that hypersexuality after unilateral temporal lobectomy represented a partial Klüver–Bucy syndrome because of the underlying pathology in the contralateral temporal lobe. Overall, the sporadic case studies suggest that hypersexuality is a rare but dramatic outcome of unilateral temporal lobectomy.

ICTAL AND POSTICTAL SEXUAL BEHAVIOR

Sexual seizure manifestations are rare clinical phenomena during or after complex partial seizures. They can be subdivided into distinct symptoms: auras with sexual content, which have been related to seizure activity originating within the temporal lobes, somatosensory sensations in the genitals, reported in patients with parietallobe epilepsy, and sexual automatisms consisting of fondling and grabbing of the genitals as well as hypermotoric pelvic and truncal movements (Penovich, 2000). Genital automatisms (GAs), defined as repeated fondling, grabbing, or scratching of the genitals, are a rare symptom during or after epileptic seizures. They must be separated from other genital or sexual seizure manifestations. GAs occurred in seizures originating from the temporal lobe and frontal lobe, as well as in generalized seizures. In a study of 23 patients with epilepsy, men exhibited GAs significantly more often than

did women. GAs were associated with unilateral hand automatisms in 70% and with peri-ictal urinary urge in 22% (Dobesberger et al., 2004). The mechanisms for GAs are far from clear. The authors of this study support the hypothesis of transient bitemporal dysfunction leading to GAs.

PERI-ICTAL URINARY URGE

The lower urinary tract, the urinary bladder and urethra, serves two reciprocal functions: storage of urine without leakage and periodic evacuation of urine. Normal storage function includes: (1) sensation of bladder fullness; (2) postponement of micturition; (3) maintaining continence; and (4) low bladder pressure. Normal voiding function means to void voluntarily and smoothly without hyperpressure, straining, or postvoid residual urine. These two functions depend on central as well as peripheral autonomic and somatic neural pathways, but also on voluntary control, which requires the participation of higher centers in the brain. Because of the complex neural regulations, central and peripheral nervous control of the lower urinary tract is affected by a variety of neurologic disorders.

Patients with lesions above the pons commonly demonstrate detrusor overactivity, causing clinical symptoms of overactive bladder – urgency, urge incontinence, frequency – caused by lack of cortical inhibitory control, but they preserve coordination between detrusor and sphincter, which means there is no postvoid residual urine unless caused by comorbidity. With suprapontine lesions voiding itself is correct, but timing is wrong. However, some patients may purposely increase sphincter activity during an overactive detrusor contraction to avoid urge incontinence and this habit may lead to insufficient relaxation during voiding. Typical suprapontine lesions include cerebrovascular accident, dementia, brain tumors and cerebral palsy followed by epileptic seizures.

Analysis of clinical semiology in medically refractory focal epilepsy may add valuable information to localize the seizure onset zone during presurgical work-up (Trinka et al., 2003). Autonomic symptoms frequently occur during epileptic seizures. Some of them, such as ictal vomiting or peri-ictal urinary urge, have shown lateralizing significance in presurgical evaluation (Baumgartner et al., 2000). These symptoms result from a disturbance of the presumed central autonomic network which seems to have a hemispheric specific representation (Benarroch, 1993). Although urinary incontinence is a common feature of generalized tonic-clonic seizures, urinary incontinence and ictal urination are rare symptoms during focal seizures (Freeman and Schachter, 1995). In reviewing the videotapes of patients examined in an epilepsy monitoring unit, Baumgartner et al. (2000) observed some patients who expressed an intense urinary urge during their seizures. They termed this ictal urinary urge, and it must be distinguished from urinary incontinence occurring during generalized tonic-clonic seizures, from urinary urgency during typical absence seizures, and from ictal urination as a manifestation of simple partial seizures (Liporace and Sperling, 1997). A clarification of the mechanisms underlying ictal urinary urge may add to the understanding of central bladder control.

Baumgartner and coworkers (2000) systematically assessed the clinical characteristics of ictal urinary urge and investigated whether this symptom had any lateralizing or localizing significance, or both.

A lateralizing significance of ictal urinary urge can be explained by a hemispheric specific representation of central bladder control. Positron emission tomography (PET) studies on brain activation during micturition in normal subjects suggested a predominance of the right brain in central bladder control (Blok et al., 1997). In patients with stroke and brain tumors, incontinence correlated with right-hemisphere lesions (Maurice-Williams, 1974; Kuroiwa et al., 1987). In geriatric patients, urge incontinence with reduced bladder filling sensation was associated with hypoperfusion of the right frontal regions on interictal single-photon emission computed tomography (SPECT) (Griffiths, 1998). Concerning the specific brain areas responsible for the generation of ictal urinary urge, the involvement of the insular cortex is proposed. On ictal SPECT in two patients, a hyperperfusion of the superior temporal gyrus containing the insular cortex was observed (Baumgartner et al., 2000). This hypothesis is further supported by PET studies in normal subjects in whom urination was associated with a significantly increased blood flow in the right dorsal pontine tegementum and the right inferior frontal gyrus. In addition, during the filled bladder condition, the right frontal operculum, the right anterior insula, or both were significantly activated (Blok et al., 1998).

Thus, epileptic activity within the insular cortex could be the primary viscerosensory area responsible for a filled bladder sensation, resulting in ictal urinary urge. Another possibility is that ictal urinary urge was mediated by propagation of epileptic activity to frontal-lobe structures (e.g., the right inferior frontal gyrus), which have been shown to be important in suprapontine bladder control (Blok et al., 1997, 1998).

Studies have demonstrated peri-ictal vegetative symptoms in 86% of patients with TLE) (Janszky et al., 2007). Beside abdominal auras in 62%, goosebumps in 3%, hypersalivation in 12%, spitting in 1%, cold shivering

in 3%, water drinking in 7%, postictal nose wiping in 44%, and postictal coughing in 16%, urinary urge has been found in only 3% of patients with TLE. The presence of peri-ictal autonomic signs occurred more frequently in women, supporting the gender differences in epilepsy (Janszky et al., 2007).

SEXUAL DYSFUNCTION IN WOMEN WITH EPILEPSY

Sexual dysfunction in women with epilepsy is an important comorbidity. Many women with epilepsy have normal sexuality, but there is a significant fraction that has markedly decreased sexual desire and this fraction is not present in the general population. It appears that orgasmic dysfunction occurs more frequently in women with epilepsy than in the normal population. Sexual dysfunction generally manifests as loss of libido, impotence, and infertility in men (Herzog et al., 1986b), and it generally manifests as menstrual disorder, hirsutism, and infertility in women (Luef, 2009).

Bergen et al. (1992) evaluated 50 women with epilepsy in a tertiary epilepsy care center; 32 of 50 women had partial epilepsy, and 28 of 50 were taking only one AED. Women with epilepsy and a comparison group of women of similar age were asked how often they had the desire for sex, and how often they actually had intercourse. A much greater proportion of women with epilepsy than comparators had very infrequent sexual desire, with about 20% reporting that they almost "never" had sexual desire; very few women in the comparison group reported this low level of sexual desire. Several reports suggest that orgasmic dysfunction is overrepresented among women with epilepsy (Jensen et al., 1990; Duncan et al., 1997). Morrell et al. (1994) reported on genital blood flow (GBF) measured by vaginal plethysmography in women with TLE as they watched either erotic or sexually neutral videos. GBF was significantly decreased in women with epilepsy compared with controls during erotic visual stimulation. There was no difference in mood scales between the two patient and control groups; however, epilepsy subjects were less sexually experienced than the controls, and reported more anxiety upon imagining sexual situations than did controls. The authors proposed a central mechanism for this effect, that disruption of relevant regions of cortex by epileptic activity, specifically limbic and frontal areas, could be the cause of sexual dysfunction. The occurrence of decreased GBF in women with epilepsy could, at least in part, contribute to inadequate orgasm (Harden, 2008). AEDs that induce cytochrome P-450 isoenzyme 3A4 and therefore decrease free testosterone are also associated with sexual dysfunction. Right TLE also appears to be associated with sexual dysfunction compared to left TLE. Lack of seizure freedom could adversely impact psychosocial aspects of living with epilepsy, including sexuality (Harden, 2008).

Both epilepsy and AEDs have been causally implicated (Herzog et al., 1986a; Isojarvi et al., 1993). They can target a number of substrates to impact hormone levels. These include the limbic system, hypothalamus, pituitary, peripheral endocrine glands, liver, and adipose tissue (Herzog, 2002; Herzog et al., 2003). Reproductive endocrine disorders can lead not only to reproductive dysfunction but also to exacerbation of epilepsy (Herzog, 2002; Herzog et al., 2003). An understanding of these relationships and their underlying neurologic and neuroendocrine mechanisms is important to the comprehensive management of women with epilepsy.

Pathophysiology of sexual and reproductive endocrine disorders in women with epilepsy

The brain controls reproductive function primarily through hypothalamic regulation of pituitary secretion (Spratt et al., 1987). Regions of the hypothalamus that are involved in the regulation, production, and secretion of gonadotropin-releasing hormone (GnRH) receive extensive direct connections from the cerebral hemispheres, especially from temporolimbic structures that are commonly involved in epilepsy, and most notably from the amygdala (Herzog et al., 1986b; Herzog, 1989). Significant relationships have been uncovered through which epilepsy may influence the function of this complex neuroendocrine system.

Animal experimental studies have shown that the amygdala can be parceled into cytoarchitectonically distinct functional divisions that exert opposing modulatory influences on pituitary hormone secretion (Zolovick, 1972), reproductive function (Zolovick, 1972), and the resting membrane potentials of individual ventromedial hypothalamic neurons (Dreifuss et al., 1968). Following amygdaloid seizures, fos, a protein marker for neuronal activation, is increased in the sexually dimorphic regions of the hypothalamus that are involved in reproductive endocrine secretion and reproductive function, i.e., the medial preoptic, ventromedial, and ventral premammillary nuclei, but much less so in other hypothalamic nuclei (Silveira et al., 2000). Seizures also decrease GnRH fiber staining in the ventromedial hypothalamus (Friedman et al., 2002; Bauer et al., 2004a). Both of these responses to unilaterally provoked amygdaloid seizures occur in a laterally asymmetric fashion with significantly and substantially greater involvement ipsilaterally than contralaterally to the seizure focus (Silveira et al., 2000; Friedman et al., 2002). Preferential ipsilateral involvement is potentially important because there are lateralized biochemical and

physiologic differences between the left and right sides of the limbic system and also of the hypothalamus. Specifically, anovulatory cycles are more common with right than with left unilateral amygdalectomies (Sanchez and Dominguez, 1995).

GnRH content in the ventromedial hypothalamus of the female rat has been reported to be 50–100% greater in the right ventromedial hypothalamus than in the left ventromedial hypothalamus (Gerendai et al., 1995; Gerendai and Halasz, 1997). The left and right vagus nerves exert different modulatory influences on ovarian structure and function (Gerendai et al., 1995; Gerendai and Halasz, 1997). The experimental findings in the female rat are consistent with the notion that disruption of the normal temporolimbic modulation of hypothalamopituitary function may interfere with ovarian hormonal secretion and promote the development of reproductive endocrine disorders (Edwards et al., 1999). The findings suggest, moreover, that the reproductive neuroendocrine system, like many other brain systems, shows a lateralized asymmetry that might, by virtue of ipsilaterally predominating effects, contribute to the development of distinct reproductive endocrine disorders in association with unilateral left- and right-sided epileptic foci.

There are also important clinical findings which indicate that reproductive endocrine function differs between women with epilepsy and normal controls and that the laterality and focality of epilepsy may be important determinants of reproductive endocrine function (Herzog et al., 2003). Unilateral temporolimbic discharges are associated with laterally differing, consistent, predictable, stochastic directional changes in hormonal secretion at all levels of the reproductive neuroendocrine axis, i.e., hypothalamus, pituitary, and ovary. These directional changes are consistent with the finding that different sexual and reproductive disorders may develop in relation to left- and right-sided temporolimbic epilepsy. Specifically, left TLE is associated with significantly higher pulse frequencies of GnRH secretion (Herzog et al., 2003). Higher GnRH pulse frequency, in turn, is associated with higher LH/FSH ratios and higher serum testosterone levels.

The most common reproductive endocrine disorder in women with epilepsy as well as women in the general population is polycystic ovary syndrome (PCOS) (Herzog et al., 1986b; Bilo et al., 1988; Herzog and Schachter, 2001). PCOS occurs in 10–20% of women with epilepsy compared with 5–6% of women in the general population (Webber et al., 1986; Herzog and Schachter, 2001). This increased rate of occurrence may be of considerable medical significance because PCOS is associated with a higher prevalence of migraine, emotional disorders, diabetes, cardiovascular disease, and female cancers in the general population (Herzog and Schachter, 2001).

PCOS is probably not a single nosologic entity, but rather the common end point for a number of pathophysiologic mechanisms, some of which may be attributable to epilepsy itself (Herzog et al., 1986b, 2003; Bilo et al., 1988; Herzog and Schachter, 2001) or to the use of AEDs, most notably valproate (VPA) (Isojarvi et al., 1993; Morrell et al., 2002; Lofgren et al., 2007). PCOS represents the failure of the ovarian follicle to complete normal maturation during the menstrual cycle or a series of cycles, a failure that is perhaps related to the presence of inadequate levels of pituitary FSH, while levels of LH are normal or elevated (Herzog and Schachter, 2001; Herzog et al., 2003). These conditions can produce two results. There is a failure of ovulation and the partially developed follicle is retained in the ovary in the form of a tiny cyst (Herzog and Schachter, 2001; Herzog et al., 2003). This partially developed follicle is secretory but deficient in aromatase, the enzyme that converts testosterone to estrogen, and, therefore has testosterone as its principal secretory product. Testosterone may increase the positive feedback of estrogen on pituitary LH secretion (Eagleson et al., 2000), resulting in increased ovarian steroid secretion, which, under these circumstances, may be predominantly testosterone and can result in hyperandrogenism. The testosterone is aromatized in peripheral adipose tissue, generally producing high-normal levels of estrogens, and this is a major source of the estrogen feedback on the pituitary. The persistent occurrence of such cycles results in hyperandrogenic chronic anovulation, which is currently the simplest and perhaps the most utilitarian definition of PCOS (Lobo, 1995; Herzog and Schachter, 2001).

A potential role for the epileptic substrate has been suggested by the finding that among women with unilateral epileptic foci, PCOS is associated with left temporal and right non-temporolimbic foci whereas hypothalamic amenorrhea has been found to be more common with right TLE (Herzog, 1993; Kalinin and Zheleznova, 2007), and by the finding that untreated women with primary generalized epilepsy have higher pulse frequency GnRH secretion than normal controls (Bilo et al., 1991). Increased pulse frequency or amplitude of GnRHsecretion by the hypothalamus results in preferential LH versus FSH secretion by the pituitary (Knobil, 1980; Spratt et al., 1987), which would promote the development of PCOS.

AEDs (Table 22.1) have substantial and differential effects on reproductive hormone levels (Herzog et al., 2003; Luef, 2009). There are notable differences between enzyme-inducing and non-inducing drugs, with the former being associated with lower serum levels of

Table 22.1

Antiepileptic drugs in women with epilepsy

Influence of sexual steroid hormones					
Valproate	Androgens ↑	Risk of PCOS ↑			
Carbamazepine	SHBG ↑		DHEA ↓	E ↓	Fertility ↓
Phenytoin	SHBG ↑		DHEA ↓	E ↓	Fertility ↓
Oxcarbazepine (>900 mg/day)	SHBG ↑			E ↓	Fertility ↓
Primidone	SHBG ↑			E ↓	Fertility ↓
Phenobarbital	SHBG ↑			E ↓	Fertility ↓
Levetiracetam					
Lamotrigine					
Lacosamide					

SHBG, sex hormone-binding globulin; E, estradiol; DHEA, dehydroepiandrosterone.

some ovarian and adrenal steroids: estradiol, testosterone and DHEA sulfate (Herzog et al., 2003).

AEDs can change the rate of metabolism of endogenous sex steroid hormones in women with epilepsy. Serum levels of estrogens as well as androgens are reduced in women receiving enzyme-inducing AEDs. In women, estrogen is important to maintain normal physiologic sexual arousal. The first phase of physiologic arousal is excitement. In the excitement phase, blood is shifted to genital tissue, which gradually become engorged. In men, this is evident as an erection. The same phenomena occur in women within the vagina. When vasocongestion in genital tissues is maximal, the plateau phase begins and estrogen supports genital vasocongestion (Morrell et al., 1994). Inadequate blood flow is associated with painful intercourse, due to inadequate lubrication and muscle relaxation. Low levels of androgens are associated with sexual arousal insufficiency and sexual dysfunction (Herzog et al., 2004; Herzog, 2008; Isojarvi, 2008; Luef, 2009).

Special attention should be given to women presenting with weight gain or PCOS while taking VPA, as these women carry an increased risk for menstrual disturbances such as anovulation and, as a consequence, infertility. This is probably explained by the effects of insulin resistance associated with obesity and PCOS on the secretion of ovarian androgens, as well as on free active hormone (Isojarvi, 2008; Luef and Rauchenzauner, 2009).

Reproductive endocrine effects of VPA in women with epilepsy were not systematically studied until the early 1990s. The first report suggesting a high incidence of menstrual disorders, linked to obesity, hyperandrogenism, and polycystic ovaries, in women taking VPA for epilepsy was published in 1993 (Isojarvi et al., 1993). Thereafter, many studies on reproductive endocrine effects of AEDs in women with epilepsy have been published (Luef et al., 2001, 2002a, b; Isojarvi et al., 2005; Rauchenzauner et al., 2014).

The cross-sectional study from 1993 is the only study in this field that included a large hospital-based patient population. Altogether 238 women participated in the study (Isojarvi et al., 1993). The major finding in the study was that menstrual disorders were common among women taking VPA monotherapy for epilepsy (45%), and that they were frequently associated with PCO and/or hyperandrogenism, which were seen in 9/10 (90%) of the women on VPA monotherapy who had menstrual disorders. PCO and hyperandrogenism were especially common if VPA medication was started before the age of 20. Moreover, the serum mean androgen levels were increased in women on VPA (Isojarvi et al., 1993).

Later, similar findings were obtained from a three-center study conducted in three European countries (Finland, Norway, Netherlands): menstrual disorders were reported by 59% of women on VPA as compared to 12% of CBZ-treated women and 15% of control women. Hyperandrogenism and/or PCO were detected in 70% of VPA-treated women as compared to 20% in the CBZ-treated women and 19% among the control women. Moreover, a short-term (3-month) prospective study in newly diagnosed women starting treatment with VPA suggested that an increase in serum testosterone and androstendione levels could be seen in approximately half of the women within 3 months of starting VPA (Isojarvi et al., 2005).

Changes in serum androgen levels have been detected before and during pubertal development in young girls taking VPA for epilepsy (Vainionpaa et al., 1999; Rauchenzauner et al., 2014). The mean serum testosterone levels and free androgen index (FAI) were high in all pubertal phases in girls on VPA. Moreover, elevated serum testosterone levels were found in 38% of the prepubertal, 36% of the pubertal, and 57% of the postpubertal girls, whereas hyperandrogenism was seen in only 8% of the pubertal and in none of the pre- or postpubertal control girls (Vainionpaa et al., 1999).

A 5-year follow-up of these girls has been reported (Mikkonen et al., 2004). Sixty percent of the girls/women who were on VPA during the follow-up study had PCOS as compared to 25% of girls/women taking other AEDs, 5.5% of girls whose medication had been discontinued, and 8.3% of control subjects. Interestingly, out of the 15 girls who had hyperandrogenism while on VPA during pubertal development, 5/7 (71.4%) of the girls who still continued VPA at the time of follow-up had PCOS, as compared to 1/4 (25%) among girls/women who had been switched to other medication and 0/4 among girls whose medication had been discontinued.

Two studies by Murialdo et al. (1997, 1998) have also reported high prevalence of menstrual disorders and hyperandrogenic anovulation in VPA-treated women with epilepsy. However, a study by Bauer et al. (2000) did not show any differences between CBZ- and VPA-treated women with epilepsy with regard to reproductive endocrine parameters, but interpretation of the results of this study is difficult, because the age of the patients, the duration of medication, and seizure frequency in the different treatment groups were not given (Isojarvi, 2008).

Four other studies have also addressed the issue of reproductive endocrine function in women with epilepsy. Luef et al. (2002a) reported similar frequency of menstrual disorders and PCO in women taking either CBZ or VPA for epilepsy. Morrell et al. (2008) studied predictors of ovulatory failure in 94 women with epilepsy. Of women using VPA currently or within the preceding 3 years, 38.1% had experienced at least one anovulatory cycle, in contrast to 10.7% of women not using VPA within the preceding 3 years. Moreover, women with idiopathic generalized epilepsy receiving VPA were at highest risk for anovulatory cycles, polycystic-appearing ovaries, elevated body mass index, and hyperandrogenism. Another recent study by Morrell et al. (2005) reported higher serum testosterone levels in women taking VPA for epilepsy than in women taking lamotrigine (Isojarvi et al., 2005; Isojarvi, 2008). Finally, a study by Betts et al. (2003) found a 30% prevalence of PCOS in women ever treated with VPA only, as compared to 6% in women ever treated with either CBZ or lamotrigine only, or 14% among healthy control women.

It has been suggested that obesity and associated hyperinsulinemia could be implicated in the development of PCO and hyperandrogenism in women taking VPA. However, PCO and hyperandrogenism were also found in many lean VPA-treated women without hyperinsulinemia, and hyperandrogenism in prepubertal, pubertal, and postpubertal girls taking VPA for epilepsy was not associated with hyperinsulinemia (Vainionpaa et al., 1999; Isojarvi et al., 2005; Isojarvi, 2008). Hence, obesity and elevated serum insulin levels do not appear to be the main factors initiating the process leading to hyperandrogenism and the development of PCO in VPA-treated women. However, it seems that obesity and related hyperinsulinemia may exacerbate the VPA-related reproductive endocrine disorders in women with epilepsy. It seems likely that VPA has a direct effect on ovarian androgen production, or as an enzyme inhibitor; it may inhibit the metabolism of sex steroids and thereby lead to increased serum androgen levels (Luef et al., 2001; Isojarvi et al., 2005; Isojarvi, 2008).

The likelihood of developing components of PCOS with VPA treatment appears to depend on the age at which VPA is introduced. In a prospective study comparing the endocrine effects of VPA and lamotrigine, women with epilepsy beginning treatment with VPA at age <26 years were at highest risk for developing components of PCOS, whereas those women beginning treatment with VPA at age 26 years had no higher risk than women with epilepsy receiving lamotrigine. In addition, the women who started VPA at the younger age had a noticeable increase in serum testosterone levels. This observation is consistent with the possibility that a direct effect of VPA on ovarian androgen secretion may lead to the development of components of PCOS in women with epilepsy and that the younger ovary may be more vulnerable to this effect (Morrell et al., 2008).

SEXUAL DYSFUNCTION IN MEN WITH EPILEPSY

Sexual dysfunction in men with epilepsy generally manifests as loss of libido, impotence, and infertility (Herzog et al., 1986a; Luef et al., 2009). Diminished libido or potency occurs in approximately 20% of men with epilepsy, as determined by standardized questionnaire survey (Herzog et al., 2004).

Men with epilepsy have been found to have an increased risk of erectile dysfunction – up to 57% compared with 3–19% in the general population (Braun et al., 2000). Both epilepsy and AEDs have been causally implicated (Herzog, 1989; Herzog et al., 2005). Epilepsy and AEDs can target a number of substrates to impact hormone levels. These include the limbic system, hypothalamus, pituitary, peripheral endocrine glands, liver, and adipose tissue (Herzog, 2002). The function of the hypothalamic–pituitary axis (HPA), including production of LH, FSH, GnRH, and prolactin, and the concentrations and metabolism of its end products, such as estrogen, testosterone, and DHEA, were often found to be modified in epilepsy patients. The development of epileptiform discharges in medial temporal-lobe structures may disrupt the hypothalamic regulation of pituitary secretion and hence alter gonadal function and reproductive function (Herzog, 2002; Luef et al., 2009). Seizures therefore – especially in TLE – can alter the release of hypothalamic and pituitary hormones (Bauer et al., 2004a, b).

Enzyme-inducing AEDs, such as phenytoin, phenobarbital, and CBZ, can directly suppress gonadal testosterone synthesis, increase testosterone binding by the induction of SHBG synthesis, and increase serum estradiol levels in absolute or relative terms (Murialdo et al., 1995; Herzog et al., 2004). The increase of SHBG leads over time to reduced free (bioactive) testosterone, which may result in diminished libido and sexual function in men (Luef, 2004; Kramer et al., 2006). Moreover these alterations may contribute to reduced fertility as well. While already in the past health issues for women with epilepsy were increasingly subject of research, the discussion of gender-specific features of epilepsy and its treatment in men has come to the fore more recently.

Studies have shown that CBZ-induced liver enzyme induction and associated changes in endocrine and metabolic function become normal after CBZ is replaced by oxcarbazepine (Isojarvi et al., 1995; Luef et al., 2009). Oxcarbazepine, a keto-derivative of CBZ, shows different metabolic pathways in the liver and does not appear to induce the oxidative cytochrome enzyme system in a clinically relevant manner at commonly used daily doses (Larkin et al., 1991; Schmidt and Elger, 2004). There is some evidence that at high doses oxcarbazepine may induce liver enzymes (Patsalos et al., 1990; Andreasen et al., 2007). Corresponding to these data a study reported effects on the bioactivity of serum steroids of high daily oxcarbazepine doses, increasing SHBG and testosterone concentrations. Nevertheless the FAI ratios) were normal, suggesting normal bioactivity of testosterone in these patients (Rattya et al., 2001). The effects of AEDs (Table 22.2) on reproduction and sexual function mostly result from studies with determination of endocrine parameters in small sample sizes. We collected data on the effects of oxcarbazepine in a larger population of male patients with epilepsy in a naturalistic setting with special focus on sexual dysfunction. Such postmarketing surveillance studies are non-comparative, non-interventional prospective trials where the medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorization (Luef et al., 2009).

AEDs, as well as the epilepsy itself, may also adversely affect semen quality. Human studies have shown that phenytoin, CBZ, and VPA are associated with reduced sperm motility and particularly sperm morphology (Isojarvi et al., 2004), Both animal and human data suggest that chronic use of VPA may induce testicular atrophy (Isojarvi et al., 2004).

Abnormal semen analysis, including decreased sperm count, abnormal morphology, or impaired motility, has been reported in upwards of 90% of men with epilepsy (Isojarvi et al., 2005). Overall, men with idiopathic/cryptogenic epilepsy were only 36% as likely as male unaffected siblings ever to have fathered a pregnancy. In men, the reduced likelihood of fathering a pregnancy was associated with partial-onset seizures, early age at onset (<20 years), and a negative family history of epilepsy, and the effects of these epilepsy characteristics appeared to be mediated through reduced marriage rates. This reduction is associated with localization-related epilepsy, onset of seizures before 20 years of age, and absence of a family history of epilepsy (Schupf and Ottman, 1994). The effect is mitigated by reduced marital rates. Among men with epilepsy who had ever been married, reproductive disadvantage was confined to those with early-onset (<10 years) partial epilepsy. Overall, women with idiopathic cryptogenic epilepsy were only 37% as likely ever to have had a pregnancy as female unaffected siblings; this effect was not strongly influenced by seizure type, age at onset, or family history of epilepsy (Schupf and Ottman, 1994).

Hypogonadism refers to diminished gonadal function as determined by low serum testosterone level and/or decreased or abnormal sperm production (Herzog et al., 1986a). It can manifest as diminished

Table 22.2

Antiepileptic drugs in men with epilepsy

Influence of sexual steroid hormones					
Valproate	Androgens ↑	FSH ↓			Fertility ↓
Carbamazepine	SHBG ↑		DHEA ↓	BAT ↓	Fertility ↓
Phenytoin	SHBG ↑		DHEA ↓	BAT ↓	Fertility ↓
Oxcarbazepine (>900 mg/day)	SHBG ↑			BAT ↓	Fertility ↓
Primidone	SHBG ↑			BAT ↓	Fertility ↓
Phenobarbital	SHBG ↑			BAT ↓	Fertility ↓
Levetiracetam					
Lamotrigine					
Lacosamide					

FSH, follicle-stimulating hormone; SHBG, sex hormone-binding globulin; BAT, bioactive testosterone; DHEA, dehydroepiandrosterone.

sexual interest, potency, fertility, energy, mood, competitive drive, bone and muscle mass, and secondary sexual characteristics. Physical signs include a loss of male male genital alopecia, gynecomastia, and testicular atrophy. The clinical impression of hypogonadism can be verified by laboratory testing. Testosterone exists in three major forms: (1) tightly bound to SHBG (45–50%); (2) loosely bound to albumin (50–55%); and (3) unbound (1–2%) (Herzog et al., 1986a; Herzog, 2008).

The albumin-bound and free portions are available to tissues and, therefore, constitute the clinically important bioavailable portion. Measures of bioavailable testosterone (BAT) suggest that hypogonadism may occur in one-third of men with temporolimbic epilepsy (Herzog et al., 2005). BAT shows a substantially earlier and greater age-related decline in men with epilepsy than in controls (Herzog et al., 2005). In a sample of men with localization-related epilepsy, Herzog et al. (2004) found that BAT fell below normal control levels in 11% of men between 20 and 30 years, 27% between 30 and 40 years, and 89% between 40 and 50 years of age. Several (Toone et al., 1983; Fenwick et al., 1986; Herzog et al., 2005), but not all (Duncan et al., 1999), investigations have found significant relationships between reduced serum BAT measures and sexual dysfunction. Men with epilepsy may show evidence of sexual dysfunction in the setting of low-normal BAT levels at which men in the general population may not show clinical manifestations (Herzog et al., 1986a, 2004, 2005). This may constitute an argument against the importance of the BAT level. Alternatively, higher BAT levels may be required for normal sexual function in the setting of the altered brain substrate of temporolimbic epilepsy.

Pathophysiology of reproductive endocrine disorders in men with epilepsy

The etiology of hypogonadism as well as reproductive and sexual dysfunction in men with epilepsy has been attributed to a number of possible causes. These include: (1) psychosocial stress; (2) AEDs; and (3) epilepsy itself (Herzog, 2002).

Psychosocial stress associated with epilepsy may play an important role in hypogonadism (Taylor, 1969; Sapolsky, 1985). From a neuroendocrine perspective, stress response involves the activation of the HPA axis (Sapolsky, 1985; Herzog, 2008). Cortisol levels are higher in individuals with epilepsy than in controls, not unlike individuals with depression (Gallagher et al., 1984). Unlike depression, however, diurnal variation is often lost in epilepsy. Factors that increase the activity of the HPA axis interfere with reproductive endocrine secretion as well as reproductive function (Gallagher et al., 1984; Sapolsky, 1985; Herzog, 2002), and may contribute to seizure exacerbation (Herzog, 2002). Stress increases the release of proopiomelanocortin, the precursor protein that is cleaved to form adrenocorticotropic hormone and endorphin (Clarke et al., 1986), both of which inhibit gonadotropin secretion and reproductive function (Sapolsky, 1985). Adrenocorticotropic hormone increases cortisol secretion; endorphins increase DHEA production. Both of these steroids have gamma-aminobutyric acid (GABA)-negative allostearic modulatory properties that can lower seizure thresholds and increase anxiety (Jacobs et al., 1999; Herzog, 2002).

Changes in reproductive steroid concentrations may impact seizure tendencies as well as reproductive and sexual function. While estrogen is proconvulsant and progesterone is anticonvulsant in most adult animal models of localization-related epilepsy, the effect of testosterone on experimental seizures appears to be mixed. This may be related to its ready metabolism by aromatase to estradiol, which has neuroexcitatory effects (Wong and Moss, 1992), while it can also be metabolized by reductase to dihydrotestosterone and further to androstanediol, a potent GABAergic steroid with antiseizure properties (Frye et al., 2001; Herzog, 2002). While testosterone replacement has proven only moderately effective in restoring sexual function, possibly because of its ready metabolism to estrogen, especially in the setting of AEDs, one pilot study has reported superior results using combined treatment with testosterone and an aromatase inhibitor that blocked the transformation of testosterone to estradiol (Herzog et al., 1998). Combined therapy was associated with seizure reduction as well (Herzog et al., 1998). The neuromodulatory role of reproductive steroids suggests that a greater understanding of neuroendocrine regulation in men with epilepsy may be important not only for reproductive and sexual function but also for optimal management of seizure disorders.

CONCLUSION

Reproductive dysfunction is unusually common among women and men who have epilepsy. It generally manifests as menstrual disorder, hirsutism, and infertility in women, and loss of libido, impotence, and infertility in men. Reproductive dysfunction is often associated with, and is the consequence of, reproductive endocrine disorders. Both epilepsy and AEDs have been causally implicated. Epilepsy and AEDS can target a number of substrates to impact hormone levels. These include the limbic system, hypothalamus, pituitary, peripheral endocrine glands, liver, and adipose tissue. Reproductive endocrine disorders can lead not only to reproductive dysfunction but also to exacerbation of epilepsy. An understanding of these relationships and their underlying neurologic and neuroendocrine mechanisms is important to the comprehensive management of women and men with epilepsy.

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 23

Genital and sexual pain in women

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INTRODUCTION

Pain is a complex perceptive experience, involving biologic as well as psychologic and relational meanings. They become increasingly important with the chronicity of pain (Vincenti and Graziottin, 2004; Graziottin et al., 2013, 2014). Pain is almost never "psychogenic," except for pain from grieving. Pain has solid biologic bases, fueled by genital and systemic inflammation. Neuroinflammation becomes the prominent feature with the chronicity of pain (Walker et al., 2013; Skaper et al., 2014; Watkins et al., 2014; Xanthos and Sandkühler, 2014).

Neurologists are increasingly aware of the painful aspect of many neurologic disorders, including, but not limited to, multiple sclerosis (MS), Parkinson's disease (PD), stroke, peripheral neuropathies, either primary or secondary to diabetes, chemotherapy, radiotherapy, viruses, such as herpes zoster, immune diseases, and toxic agents, to mention just a few.

Lifelong and acquired genital and sexual pain is still neglected in a consistent percentage of women. The common, persistent reading is that psychologic factors play the most important/determining role: "Pain is all in your head," "It is psychogenic," or, at best, "It is psychosomatic" are the frequent physician comments reported by affected women. As a consequence of this diagnostic misreading/neglect, referral to a psychologist or psychotherapist is the frequent recommendation.

Meanwhile, the women who keep on having worsening symptoms undergo quite a number of repeated medical consultations, with a dramatic delay in correct diagnosis: 5–7 years for bladder pain syndrome/interstitial cystitis (BPS/IC), 4.7 years for vulvar vestibulitis/provoked vestibulodynia (Graziottin and Murina, 2011), and 9–11 years for endometriosis. Sexual pain disorders – dyspareunia and vaginismus – are even more sensitive issues, as pain involves emotionally charged behaviors: sexual intimacy and vaginal intercourse (Foster, 2001; Graziottin and Brotto, 2004; Graziottin, 2008, 2014).

As a consequence of the diagnostic delay, the biologic picture underlying the reported symptoms is dramatically changing: the persisting tissue inflammation induces pain to change from acute and "nociceptive," which indicates a "friendly signal," alerting one to ongoing tissue damage, to chronic and "neuropathic," a disease *per se*. The latter is characterized and maintained by a progressive inflammatory involvement of the central nervous system (CNS), massively involving the microglia (Walker et al., 2013; Skaper et al., 2014; Watkins et al., 2014; Xanthos and Sandkühler, 2014). With persistent neuroinflammation and pain, the microglia role shifts from neuroplastic to neurotoxic, with important behavioral and clinical changes. Whilst the primary disease is progressing and neuroinflammation becomes a prominent feature, affected women have to bear years of pain and distress, huge quantifiable and non-quantifiable costs, and a progressive deterioration of personal and relational health and happiness. The scenario is even more dramatic when pain complicates an already disabling disease.

Three main aspects will be considered in this chapter: first, neuroinflammation as a key feature of pain; second, genital and sexual pain as part of neurologic diseases; third, genital and sexual pain syndrome as primary problems, and their pelvic comorbidities.

PAIN TYPES AND CLASSIFICATIONS

Pain is defined by the International Association for the Study of Pain (IASP) as an unpleasant sensory and

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emotional experience associated with actual or potential tissue damage, or described in terms of such damage (Loeser and Treede, 2008). Pain is typically classified as either acute or chronic. Acute pain is of sudden onset and is usually the result of a clearly defined cause such as an injury. Acute pain resolves with the healing of its underlying cause. Chronic pain has gradually emerged as a distinct phenomenon, in comparison with acute pain. Chronic pain has been recognized as that pain which persists past the normal time of healing. With non-malignant pain, 3 months is the most convenient point of division between acute and chronic pain, but often, as in case of chronic pelvic pain (CPP), 6 months is preferred for clinical reasons. However, the definition related to the time of normal healing is not always sufficient to define pain. Some authors suggest that any pain that persists longer than the reasonably expected healing time for the involved tissues should be considered to be chronic pain. The recognition of chronic pain as a disease is one of the IASP aims.

In agreement with the latest modifications of IASP basic pain terminology (Loeser and Treede, 2008), pain is usually classified also on the basis of etiopathogenetic mechanisms. As mentioned above, "nociceptive pain" refers to pain that is generated by an injury that activates nociceptors in peripheral tissues. "Inflammatory pain" (pain associated with active inflammation) falls into the category of nociceptive pain, although it is recognized that the nociceptive system may be persistently altered in chronic inflammatory pain (Costigan et al., 2009; Walker et al., 2013; Skaper et al., 2014; Watkins et al., 2014; Xanthos and Sandkühler, 2014).

Nociceptive pain is an alarm mediated by high-threshold unmyelinated C or thinly myelinated Aδ primary sensory neurons and has a protective function. Nociceptive pain occurs in response to noxious stimuli and continues only in the maintained presence of noxious stimuli (Costigan et al., 2009).

In the case of inflammatory pain, the sensory nervous system undergoes a profound change in its responsiveness so that normally innocuous stimuli produce pain (allodynia) and responses to noxious stimuli are exaggerated and prolonged hyperalgesia follows (Loeser and Treede, 2008; Walker et al., 2013; Skaper et al., 2014; Watkins et al., 2014; Xanthos and Sandkühler, 2014).

Heightened sensitivity occurs within the inflamed area and in contiguous non-inflamed areas as a result of plasticity in peripheral nociceptors and central nociceptive pathways (Costigan et al., 2009). Typically, inflammatory pain disappears after resolution of the initial tissue injury. However, in chronic disorders such as rheumatoid arthritis (Michaud and Wolfe, 2007) and in all the pelvic pathologies, such as bladder pain syndrome, endometriosis, vulvar vestibulitis/provoked vestibulodynia and even irritable bowel syndromes (IBS), the pain persists for as long as inflammation is active (Graziottin et al., 2013, 2014).

Neuropathic pain occurs as a direct consequence of a lesion or disease affecting the somatosensory system. Peripheral neuropathic pain results from lesions to the peripheral nervous system caused by mechanical trauma, metabolic diseases, neurotoxic chemicals, including chemotherapic substances, infection, or tumor invasion, and involves multiple pathophysiologic changes both within the peripheral nervous system and in the CNS (Costigan et al., 2009). Central neuropathic pain most commonly results from spinal cord injury, stroke, or MS (Ducreux et al., 2006) with a progressive neuroinflammatotory component (Walker et al., 2013; Skaper et al., 2014; Watkins et al., 2014; Xanthos and Sandkühler, 2014). The lesions to the somatosensory nervous system in neuropathic pain alter its structure and function so that pain occurs spontaneously and responses to noxious and innocuous stimuli are pathologically amplified. When pain evolves into an expression of maladaptive plasticity within the nociceptive system, a series of changes takes place that constitute a neural disease state.

CELLULAR BASIS OF INFLAMMATION

Mast cells (MCs) are the key mediators of the inflammatory process. When activated, MCs rapidly release preformed mediators that include histamine, heparin, serotonin, chemotactic factors and various proteases such as peroxidase, tryptase, chymase, carboxidase, and beta-glucuronidase, and tumor necrosis factor-alpha (TNF-α) (Frenzel and Hermine, 2013). MCs generate and release abundant quantities of newly formed mediators such as prostaglandins, leukotrienes, numerous cytokines (e.g., interleukins (IL)-1, -3, -4, -5, -6, -10, -14 and -17), and trophic factors. MCs migrate to the inflammatory site, where they interact with other tissue-resident or infiltrating cells (Smrž et al., 2013). By releasing cytokines and/or fostering cross-talk with other immune cells, MCs mediate immunomodulatory functions (Gaudenzio et al., 2013). MCs, however, also play a primary role in the resolution of inflammation and maintenance of tissue homeostasis (Galli and Tsai, 2008).

NEUROLOGIC DISORDERS IN WOMEN AND COMORBID GENITAL AND SEXUAL PAIN

Pelvic and genital pain in multiple sclerosis

Pain is a frequent but underestimated symptom of MS. It is estimated to affect 29–86% of MS patients and

impairs rehabilitation and quality of life (Solaro et al., 2004). Pain in MS is generally caused by involvement and neuroinflammation of the nervous system. MCs and microglia have a critical role in the etiology of pain in MS (Naegele and Martin, 2014). Specifically, the shift of microglia from a neuroplastic to a neurotoxic role is one of the prominent features of neuroinflammation (Skaper et al., 2014). The possibility of modulating neuroinflammation is therefore a potential therapeutic option for MS-related pain (Naegele and Martin, 2014).

MS pain is usually of central neuropathic type (less frequently, of peripheral or nociceptive type). The most frequent pain subtypes include dysesthetic extremity pain, painful tonic spasms, Lhermitte's sign, trigeminal neuralgia, headaches and low-back pain (Brola et al., 2014).

The relationship between pain, especially during menstruation (associated with increased spasticity and pain), and sexual dysfunction (Redelman, 2009) is well characterized in women with MS. The fall of estrogens before periods triggers systemic MC degranulation with a peak of inflammatory cytokines (Graziottin et al., 2014). Systemic cytokines worsen local inflammation responsible for different menstrual symptoms. Inflammatory and autoimmune diseases typically have flares of pain during periods (Graziottin et al., 2014). MS is no exception.

Two lines of intervention, so far unexplored in MS, include:

1. preventing the premenstrual fall of estrogens and consequently avoiding periods, with a continuous estroprogestinic pill, such as that with natural estradiol (estradiol valerate) and dienogest (EV/DNG) (Graziottin, 2014). This EV/DNG pill improves perimenstrual headache and menstrual pelvic pain (Harmony I and II studies). Its effectiveness for catamenial pain in MS patients is therefore worth exploring in prospective controlled studies;
2. palmitoylethanolamide, a downregulator of MC hyperactivation, which has positive effects in neuroinflammation and depression associated with central and peripheral pain syndromes (Bettoni et al., 2013; Graziottin et al., 2013, 2014). Pelvic pain, when present in MS patients, turns out to be paroxysmal, with a tendency to spread throughout the entire sacral area. Different forced positions of the lower limbs may further contribute as triggers. In these cases, pain occurs frequently and is of brief duration, disturbing the night's sleep with multiple awakenings and significantly affecting the patient's quality of life.

Though lamotrigine, gabapentin and carbamazepine are established symptomatic treatments for pelvic pain in MS (Solaro et al., 1999; Wright, 2012), the therapeutic approach should etiologically target inflammation (Walker et al., 2013).

Rarely, pelvic pain can be the presenting symptom of a demyelinating disease. Loschner and Snyder (2008) reported the case of a 49-year-old woman who initially had pain and anesthesia in the perineum; her symptoms later evolved to include both lower- and upper-extremity weakness and were associated with enhancing spinal cord lesions on magnetic resonance imaging (MRI). Recognizing that the patient's disease was localized to the spinal cord led to an eventual serologic diagnosis of Devic's disease (Loschner and Snyder, 2008).

Women's sexual pain in MS

MS may damage all three key dimensions of women's sexuality: (1) sexual identity; (2) sexual function ; and (3) sexual relationship. Physical and emotional sexual pain may have a complex etiology, rooted in the three different components of human sexuality. Personal and contextual factors may further modulate the sexual impact of this disabling disease.

Sexual identity

Progressive disability impairs body image, whilst pain, paresthesias, fatigue, and physical impairment alter bodily feelings, respectively major visual and cenesthetic components of the personal sexual identity. Sexual limitations further contribute to the pervading feeling of "I'm no longer a woman," that is clinically reported to the listening physician by on average a third of women with MS – a feeling that becomes more pervasive with the progression and duration of the disease, severity of physical limitations, loss of autonomy, and perceived loss of beauty and physical attractiveness.

Sexual function

Sexual function is frequently affected in women with MS and some studies suggest that this occurs in women more than in men (Celik et al., 2013; see Chapter 20, this volume, for a review). Desire, arousal, and orgasm decrease with the progression of the disease (Borello-France et al., 2004; Salonia et al., 2004; Tzortzis et al., 2008). Orgasm seems to be more affected in women with a cerebellar component of MS (Gruenwald et al., 2007). Introital dyspareunia, i.e., coital pain perceived at the entrance of the vagina, is the complaint that is most frequently reported (Tzortzis et al., 2008) – in up to 63.9% in the series by Borello-France et al. (2004). Pathophysiologic contributors of introital dyspareunia include poor/inadequate arousal, one of the leading complaints in MS women, often overlapping with coital pain and hyperactive pelvic floor, particularly in nulliparous women.

Common denominators of female sexual disorder (FSD) include:

- self-reported degree of neurologic impairment, which was the only independent variable significantly correlated with orgasmic difficulties ($P < 0.05$);
- age, distress related to urge incontinence, sexual partner, and depression, all approached statistical significance ($P < 0.08$). Sexual partner status had the greatest influence in predicting the inability to become sexually aroused (women without a partner were 10 times more likely to have difficulties in getting aroused) (Borello-France et al., 2004; Celik et al., 2013).

Sexual relationship

The authors' clinical experience suggests that key factors affecting the relationship include: impact of a chronic and worsening disease; changes in partner's behavior; changes in lifestyle and role; increasing responsibility, problems, financial difficulties, burden of becoming a caregiver instead of a lover; loss of leisure, of freedom of movement; turmoil of emotions: fear, pity, shame, anger, depression, worry, sadness, aversion, guilt, anguish about the future, and despair.

Pelvic and genital pain in Parkinson's disease and other movement disorders

Pain is a non-motor symptom that affects the quality of life of one-third of patients with PD (Wasner and Deuschl, 2012). Pain in PD can be of different subtypes: musculoskeletal, dystonic, radicular neuropathic, and central (Fil et al., 2013). The concept of central pain in PD was proposed by Souques in 1921; he speculated that pain "in certain cases derives from a central origin" due to "abnormal connections between the corpus striatum and the thalamus." Neuroinflammation triggers pain in all pain syndromes (Walker et al., 2013; Skaper et al., 2014; Watkins et al., 2014; Xanthos and Sandkühler, 2014).

Patients refer central pain in different areas of the body, including mouth, rectum, vagina, abdomen, chest, and testes (Quigley, 1996; Clifford et al., 1998).

Pain in different extrapyramidal disorders has similar clinical features: constant or recurrent painful oral and genital sensory symptoms not related to the motor manifestations of the condition (Tison and Ghorayeb, 2005; Yoshii, 2012). Even though clinical manifestations often suggest a neuralgic genesis, usually no organic causes for the painful symptoms are detected, despite extensive gynecologic investigation. Pain can be localized primarily at the vaginal level, described as distressing inner vibration or motor sensation that can fluctuate with the motor fluctuations of PD and could be abolished or reduced by levodopa. Clozapine has also shown significant efficacy in treating it. Pain syndromes have a relentless and distressing quality that overshadows the other features of parkinsonism, so that patients develop an obsessive preoccupation with their symptoms. Several patients of the group also have symptoms of psychiatric disease, including depression, drug-induced psychosis, and obsessive-compulsive disorder. Sometimes, genital pain can be related to levodopa-responsive parkinsonism and levodopa-induced dyskinesias (Paulson, 1975). Neuroinflammation, comorbid with motor symptoms, depression, and progressive cognitive impairment, is emerging as a critical feature in PD patients as well (Walker et al., 2013; Skaper et al., 2014).

Rarely, pelvic pain represents the first onset of atypical parkinsonism with intractable bowel pain due to low rectal compliance (Sakakibara et al., 2010).

Pelvic pain in peripheral neuropathies

Mononeuropathies

Among peripheral nerve lesions, nerve entrapment syndromes could be the main cause of pelvic pain involving the pudendal, the genitofemoral, the ilioinguinal, the obturator, the inferior cluneal, and the posterior cutaneous nerve of thigh nerve syndrome.

- The pudendal nerve supplies sensation to the penis in males and the clitoris in females through branches of the dorsal nerve of penis and dorsal nerve of clitoris (Tagliafico et al., 2014a). Pudendal entrapment syndrome or pudendal neuralgia is characterized by pain involving cutaneous and deep layers from the anus to clitoris. Pain may be superficial or deeper in the anorectal region, is predominant while sitting, and does not awake the patient at night; no objective sensory impairment is shown and pain is relieved by diagnostic pudendal nerve block (Nantes criteria: Labat et al., 2008). Pudendal nerve entrapment typically occurs when the nerve is fused to nearby anatomic structures or trapped between the sacrotuberous and sacrospinalis ligaments. From an etiologic point of view, usually it is secondary to childbirth, childhood physical traumas during falls, pelvic surgery, bicycling or sacroiliac skeletal abnormalities (Elahi et al., 2013).
- The genitofemoral nerve originates from the first and second lumbar root, through the psoas major muscle. From here it comes above the inguinal ligament (level L3–4) and it divides into genital and femoral branches. The genital branch innervates the skin of the mons pubis, while the femoral branch supplies the skin of the upper, anterior thigh. The ilioinguinal

nerve is a branch of the first lumbar nerve (L1). It separates from the first lumbar nerve along with the larger iliohypogastric nerve. It pierces the internal oblique muscle. Its fibers are then distributed to the skin of the upper and medial part of the thigh, and to the skin over the root of the penis and upper part of the scrotum (in males) or to the skin covering the mons pubis and labium majus (in females).

- In entrapment syndromes of these two nerves, pain is located in the groin region from the perineum to the upper medial and lateral side of the pelvis.
- The obturator nerve is formed by the anterior divisions of the second, third, and fourth lumbar nerves. It descends through the fibers of the psoas major muscle and emerges from its medial border, then it enters the thigh through the obturator canal and splits into anterior and posterior divisions. This nerve has both motor and sensory functions; it innervates all the muscles in the medial compartment of the thigh (except the hamstring part of the adductor magnus, innervated by the tibial nerve). Moreover, through its cutaneous branch it supplies the skin of the middle part of the medial thigh. This nerve can be damaged during surgery involving the pelvis or abdomen. Pain is located in the inguinal region and anterointernal side of the thigh, going down to the internal side of the knee.
- The inferior cluneal nerve branches originate from the posterior femoral cutaneous nerve; inferior cluneal nerve pain is located from the perineum to the gluteal fold. In the posterior cutaneous nerve of the thigh, pain is located from the perineum to the posterior side of the thigh.

Diagnosis

Diagnostic nerve blocks are the most important procedures, including nerve blocks of the obturator, pudendal, posterior femoral cutaneous, sciatic, and sacral spinal nerve. However, the procedure requires experienced specialists. Although neurophysiologic tests are not mandatory, electromyography of external sphincter ani and levator ani are useful to rule out sacral root lesions. Routine neurophysiologic tests do not show small-fiber lesions. Pelvic MR, short-tau inversion recovery, and diffusion-weighted imaging sequences can aid the diagnosis of pudendal neuralgia showing swelling of the ischiorectal fossa, local venous plexus dilatation, levator ani thickening due to painful spasm, and obturator muscle fibrosis into the Alcock canal (Filler, 2009; Insola et al., 2010). MR shows indirect evidence of iliohypogastric nerve lesion; MR neurography is used for nerve blocks and injections using percutaneous drug delivery (Fritz et al., 2014). High-resolution ultrasound technique may help to show lesions of pelvic nerves (Tagliafico et al., 2014a, b).

Other pains located near the pelvic region are coccygeal, gluteal (gluteal nerve syndrome), pubic or hypogastric pain.

Treatment

Pharmacologic treatments include pregabalin and other GABAergic drugs, carbamazepine, amitriptyline, and opioids if the pain is severe, local nerve blocks and sacral stimulation/neuromodulation with the aid of neurophysiologic guidance (Carmel et al., 2010; Bellingham et al., 2012; Kim et al., 2012; Pouliquen et al., 2012; Vancaillie et al., 2012). Other optional treatments include behavioral modifications, physical therapy, and surgical nerve decompression. A new line of interventions includes palmitoylethanolamide (Cocito et al., 2014). In case of a hyperactive myalgic pelvic floor contributing or consequent to genital neuropathic pain, parallel rehabilitation of the pelvic floor, aimed at relaxing it, is to be recommended. It includes hands-on physiotherapy, stretching of the levator ani, and biofeedback.

Infectious peripheral polyneuropathy

Primary infection with varicella-zoster virus causes varicella (chickenpox), after which the virus becomes latent in ganglionic neurons along the entire neuraxis. With advancing age or immunosuppression, cell-mediated immunity to varicella-zoster virus declines, and the virus reactivates to cause zoster (shingles) with a dermatomal distribution, dermatomal pain, and rash. Chickenpox can affect any area of skin; the most common sites are the thoracic nerves and the ophthalmic division of the trigeminal nerve. Zoster is often followed by chronic pain (postherpetic neuralgia) (Gilden et al., 2013). In postherpetic neuralgia, pain persists or relapses within 30–120 days at the site of acute herpes zoster after rash healing. Postherpetic neuralgia is notable, affecting 10–15% of those with herpes zoster. Progressive central and peripheral inflammation is the key feature. The progressive, upregulated involvement of the MC and microglia promotes the change from acute to chronic pain up to neuropathic pain. Neuroinflammation may then maintain pain through mainly a neurogenic peripheral and central inflammation (Xanthos and Sandkühler, 2014). Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, and maprotiline), gabapentin, pregabalin, opioids, and topical lidocaine patches are effective and should be used in the symptomatic treatment of pain (Kim et al., 2014). Antiviral drugs such as human immunoglobulins are considered the etiologic treatment of the acute phase of clinical manifestations (Andrei and Snoeck, 2014).

Both in the acute phase and later in the course of a chronic form of pelvic neuropathy, the clinical picture is dominated by dull or burning pain that is very intense and generally severely interferes with sexual function.

Iatrogenic peripheral neuropathies

- Chemotherapy-induced polyneuropathy (CIPN) is a common, dose-limiting side-effect of many chemotherapeutic agents, including platinum agents, taxanes, vinca alkaloids, thalidomide, bortezomib, and ixabepilone. Hyperactivation of MC and microglia in response to the nervous toxic damage is a key feature. It progressively involves the MC within the Schwann folds with a kind of centripetal slow-acting inflammatory wave. CIPN commonly occurs in 30–40% of patients, but its incidence can vary from 0 to 70% (Pachman et al., 2011). The symptoms most commonly associated with CIPN are sensory neuropathies, including paresthesias and pain. Symptoms often start in the fingers and toes and spread proximally in a "glove and stocking" distribution. Autonomic neuropathy, with its classic symptoms, including sexual dysfunction, has been also described in cancer patients following chemotherapy (Hirvonen et al., 1989). Currently, there is a lack of data on the sexual and/or pelvic pain in CIPN. However, a recent study has shown a possible correlation between severity of autonomic neuropathy and perceived levels of experimental pain, although not with levels of spontaneous pain (Nahman-Averbuch et al., 2014).
- Radiation-induced peripheral neuropathy may be constant or become progressively worse. It may appear several months to several years after radiation treatment. Its occurrence is rare but increases with improved long-term cancer survival. There is great clinical heterogeneity in the neurologic presentation, since various anatomic sites are irradiated. Radiation-induced neuropathy is usually chronic, progressive, often irreversible, and refractory to medical management. The association between pelvic radiotherapy and lumbosacral radiculoplexopathy, particularly in Hodgkin's disease, is well known (Delanian et al., 2012). Among the different regional neuropathies, radiation-induced pudendal neuropathy is much less common than the more familiar brachial plexopathy secondary to radiation treatment for breast cancer. The clinical symptoms and signs depend on the part of the lumbosacral plexus involved and the temporal course. Serious sexual dysfunctions are reported after radiotherapy in cervical cancer patients. Attention should be paid to radiotherapy for cancer in other pelvic organs, e.g., bladder, rectum, and anus, that may severely affect sexual function in women (Incrocci and Jensen, 2013). Arousal disorders, vaginal retraction from scarring, introital and deep dyspareunia up to the impossibility to accept penetration of any kind may be the final dramatic result of diagnostic and therapeutic neglect of long-term consequences of any type of pelvic radiotherapy.
- Postsurgical: different types of surgical intervention may affect the pelvic peripheral sensory nerves and/or the pudendal nerve, causing genital pain. The most frequently complained of include: after episiotomy, hysterectomy (simple or radical), colporrhaphy (mainly posterior) in the scar area, the equivalent of the abdominal cutaneous nerve entrapment syndrome (ACNES), sometimes complicated with neurinomas in the site of the scar. The main pathophysiologic pathways include excessive scarring during the healing process, overlapping with the "entrapment syndromes"; neurinomas of the nerve endings; and a kind of "phantom" pain after nerve surgery, all showing variable degrees of associated peripheral and central inflammation (Graziottin, 2006b).

Metabolic peripheral neuropathy

The phenotypes of diabetic neuropathy include lumbosacral radiculoplexus neuropathy, which is characterized by pelvifemoral pain followed by weakness, beginning focally in the upper leg or thigh with spread to the contralateral limb, and variable weight loss (Dyck et al., 1999). Despite some studies suggesting that it may be due to immune-mediated inflammatory microvasculitis, at present there is no evidence to support any recommendation for the use of immunotherapy treatment in this condition (Chan et al., 2012).

Diabetic women are more likely to report lower sexual satisfaction and different problems with lubrication and orgasm (Copeland et al., 2012), but these symptoms are poorly understood (Pontiroli et al., 2012) and possibly associated with various parameters and not limited to pelvic neuropathy.

Guillain–Barré syndrome

Acute polyneuropathy of autoimmune genesis is characterized by the typical ascending paralysis, with weakness beginning in the feet and hands and migrating towards the trunk; some subtypes cause change in sensation or pain, as well as dysfunction of the autonomic nervous system (Van den Berg et al., 2014). Pain has been described in 3–89% of patients with Guillain–Barré syndrome (Moulin et al., 1997), with the most frequent

types characterized by paresthesias and dysesthesias, backache/root pain, meningism, muscle pain, joint and visceral pain (Pentland and Donald, 1994).

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Idiopathic neuropathy is defined by symmetric proximal and distal weakness with sensory signs and symptoms in both arms and legs in the presence of electrophysiologic features consistent with demyelinating neuropathy (Van den Bergh et al., 2010). Severe pain is present in only a minority of CIDP patients, affecting the feet and ankles, calves, and hands. Other possible locations are represented by knees, thighs, groin, abdomen, back, buttock, chest, arms, shoulder, neck, and head (Goebel et al., 2012).

Peripheral neuropathic outcomes of female genital cutting

Female genital cutting

Female genital cutting (FGC) or female genital mutilation (FGM) describes a cultural custom aimed at modifying the female genitalia through an invasive intervention (WHO, 1996; Obermeyer, 1999, 2005; el-Defrawi et al., 2001; Fourcroy, 2006; Graziottin, 2006b). The terms FGC and FGM are used interchangeably. The impact of FGM on women's sexuality encompasses a spectrum of outcomes. Women who suffered from early and/or late complications are more likely to report a negative impact on their sexuality; the more invasive the FMG, the higher the probability of serious consequences. A research study with 250 Egyptian women who underwent type 3 FGM showed that the women complained of dysmenorrhea (80.5%), vaginal dryness during intercourse (48.5%), lack of sexual desire (45%), less frequency of sexual desire per week (28%), less initiative during sex (11%), being less pleased by sex (49%), being less orgasmic (39%), less frequency of orgasm (25%), and having difficulty experiencing orgasm (60.5%) in comparison to uncircumcised women.

Pelvic and genital pain in genetic diseases

Fabry disease

Fabry disease is a lysosomal storage disorder that has an X-linked inheritance. Several mutations are known in the encoding gene of the enzyme α-galactosidase A that lead to a deficient activity or complete loss of enzyme function (Toyooka, 2011). A typical symptom of Fabry disease is pain during childhood (Burlina et al., 2011). Pain in Fabry disease often leads to a severe reduction in health-related quality of life (Hoffmann et al., 2007), representing at the same time a red flag that needs to be recognized by physicians. Pain is mostly localized in the hands and feet, with palms, soles, and fingertips most frequently affected. Moreover, Fabry patients also report a variety of other body areas where they experience pain, including abdomen, joints, and teeth (Uçeyler et al., 2014). Genital and pelvic pain is reported in individual cases.

Familial amyloidotic polyneuropathy

Familial amyloidotic polyneuropathy (FAP) is the most common cause of genetic systemic amyloidosis, with neurologic clinical manifestations similar to diabetes mellitus. It is classically due to transthyretin (TTR) gene mutation. The main clinical feature of TTR-FAP is a progressive sensorimotor and autonomic neuropathy, which predominantly involves small unmyelinated nerve fibers with the resulting dissociated sensory loss disproportionately affecting sensation of pain and temperature (Hund, 2012). Cardiac and renal involvement occurs frequently and may be life-threatening.

Regarding sexual pain and function in FAP female patients, among a group of 94 non-menopausal women with a sexual partner (51 with a diagnosis of FAP and 43 non-FAP as the control group), Oliveira-e-Silva et al. (2013) found that, of all the FAP patients, 39.2% reported problems with desire, 72.5% problems with arousal, 68% lubrication problems, 62% reported orgasm problems, 39.2% experienced pain, and 49% experienced sexual dissatisfaction.

Charcot–Marie–Tooth (CMT) disease

CMT disease is one of the most frequently inherited neurologic disorders. Whether axonal or demyelinating the damage in the peripheral nerve in different recognized subtypes, based on the inheritance pattern, CMT can be divided into dominant and recessive or X-linked types (Pareyson et al., 2014).

The clinical phenotype of CMT, presenting at various ages, is a wide range of motor and sensory neuropathies leading to a variety of clinical deficits mainly affecting lower limbs and slowly progressing towards amyotrophy and numbness (Wilmshurst and Ouvrier, 2011). Although the loss of sensory perception is characteristic of the disease and pain is not one of the cardinal symptoms directly related to the type of degeneration and to the disease, recent studies report the presence of sexual dysfunction in young women with mild CMT related to pain during intercourse (Gargiulo et al., 2013).

Chronic pelvic pain and neuroinflammation

CPP in women is the common outcome of many gynecologic, urologic, and gastrointestinal disorders, including

vaginal/vulvar syndromes, endometriosis, BPS/IC, and IBS (Graziottin et al., 2013, 2014). In men, it may be complained of or diagnosed as non-bacterial prostatitis/CPP syndrome (Engeler et al., 2013).

A high level of comorbidities among CPP disorders is well documented in the clinical setting. Shared neuronal pathways, together with MC infiltration, may sensitize adjacent pelvic organs, resulting in frequent overlap and/or co-occurrence in pelvic disorders (Ustinova et al., 2007, 2010; Fitzgerald et al., 2013). CPP occurs in around 48% of women with coexisting BPS/IC and endometriosis (Tirlapur et al., 2013). In pelvic diseases associated with CPP, such as endometriosis, vulvar vestibulitis/provoked vestibulodynia, BPS/IC, and IBS, chronic pain and underlying inflammation frequently co-occur with mood disorders such as anxiety and depression (Blackburn-Munro and Blackburn-Munro, 2001; Poleshuck et al., 2009; Silva et al., 2011; Smorgick et al., 2013; Graziottin et al., 2013, 2014).

There is increasing evidence of the role of neuroinflammatory processes in CPP occurring both in the peripheral nervous system and CNS. Proinflammatory cytokines, such as IL-6, IL-1β, and TNF-α, may directly modulate neuronal activity in the peripheral nervous system and CNS (Ozaktay et al., 2006; Graziottin et al., 2013, 2014). Among immune cells, MCs have been suggested to play a critical role in neuroinflammation onset and progression.

MCs are relevant in this regard as they are strategically located in close proximity to nociceptive neurons (Forsythe and Bienenstock, 2012) and therefore can directly participate in signaling in neuroimmune synapses (Forsythe and Bienenstock, 2012). MCs induce nociceptor activation through the release of chemical mediators during degranulation and can be activated by neuropeptides released from nociceptors upon injury. MCnerve is considered as a functional homeostatic regulatory unit of tissue, a key component of physiologic and pathophysiologic responses (Forsythe and Bienenstock, 2012). A progressive involvement of the microglia (which shows the same properties as MC within the brain) is another prominent feature of neuroinflammation and chronic pain, up to a severe neuropathic pain (Walker et al., 2013; Skaper et al., 2014; Watkins et al., 2014; Xanthos and Sandkühler, 2014).

Indeed, MCs might pilot the persistent low-grade inflammation which characterizes CPP, and sensitize peripheral somatosensory afferents to facilitate central sensitization and neuroinflammation by activating microglia in spinal and supraspinal areas. This hypothesis is widely supported by evidence displaying a dysregulation of MC activity in diseases associated with CPP, such as endometriosis.

Endometriosis

Elevated numbers and activation of MCs have been consistently reported in endometriotic tissue as compared to normal or ectoptic endometrial tissues (Sugamata et al., 2005; Anaf et al., 2006). Stem cell factor, the major growth, differentiation, and chemoattractant factor for MCs, is found in higher concentrations in the peritoneal fluid of patients affected by endometriosis. This augmentation in MCs is more evident in deep infiltrating lesions and in close proximity to nerve fibers. Pain intensity in patients with endometriosis, who have increased endometrial tissue MC, was higher compared with patients with endometriosis without MC increase and activation.

Provoked vestibulodynia/vulvodynia

Dysregulation of MC activity and nerve terminal density has been reported in vulvodynia (Bornstein et al., 2004, 2008; Leclair et al., 2011): tissues from women with localized vulvodynia (provoked vestibulodynia, former vulvar vestibulitis) have significantly increased vestibular numbers of MCs, paralleled by subepithelial heparanase activity along with greater epithelial innervation (Bornstein et al., 2004, 2008) compared to biopsies from controls. These studies were corroborated by independent findings of increased MC numbers and innervation in tender vs non-tender vestibular sites in patients with primary, provoked vulvodynia (Goetsch et al., 2010).

Bladder pain syndrome/interstitial cystitis

Accumulation and activation of MCs in bladder, especially in the detrusor, lamina propria, and submucosa, of patients with interstitial cystitis have been reported (Theoharides et al., 2001; Rudick et al., 2008). Clinical studies show increased urine levels of MC mediators (el-Mansoury et al., 1994; Boucher et al., 1995). Activation of urinary bladder-associated CNS circuits may initiate substance P release from bladder peripheral nerves to promote substance P-mediated MC activation, in turn inducing bladder inflammation by acting on the urothelium.

Gastrointestinal inflammatory diseases

Gastrointestinal inflammatory diseases, frequently associated with abdominal pain and distress, are also accompanied by MC infiltration. Patients with IBS have increased serum concentrations of IL-8, a cytokine capable of attracting MCs and granulocytes (Dinan et al., 2008). While reports on absolute MC numbers in the intestine vary considerably, they are qualitatively consistent in documenting an increase (Barbara et al., 2004;

Bian et al., 2009). Increased MC numbers associated with elevated numbers of serotoninergic cells are found in colonic biopsies from IBS patients, suggesting that release of serotonin directly or indirectly from intestinal MCs may be responsible for sensory neuron activation and abdominal pain (Cremon et al., 2011). MC tryptase and histamine can also activate enteric nerves, resulting in neuronal hyperexcitability (Traver et al., 2010). Degranulation of MCs in close proximity to nerves innervating the colonic mucosa correlates with abdominal pain in IBS patients. The density of colonic tissue MCs in IBS shows a linear relationship with pain intensity (Barbara et al., 2004). MC-induced sensitization of peripheral nociceptive afferents has been proposed as one of the principal mechanisms in the development of visceral pain and hypersensitivity.

Mast cells and microglia blend chronic peripheral and central inflammation

MC-induced peripheral organ inflammation can alter neuronal activity both within and outside the brain, thereby contributing to the shift from acute to chronic and neuropathic pain. It may also contribute to the onset of comorbid conditions such as depression and anxiety. Inflammatory mediators can sensitize the nervous system, both peripherally and centrally (Walker et al., 2013; Skaper et al., 2014; Watkins et al., 2014; Xanthos and Sandkühler, 2014).

Central microglial cells may enhance excitability within the spinal cord and alter central processing. MC microglia hyperactivity may trigger changes in the CNS and facilitate the maintenance of perception of pain in the absence of further or new acute peripheral injury. CNS changes may also account for psychologic effects which modify pain mechanisms *per se* as well as neuropathic features displayed by patients with CPP. Although direct evidence concerning microglia hyperactivation in spinal and supraspinal areas is still limited, the brain changes along with neuropathic symptoms and evidence of central sensitization reported in patients with CPP confirm their profound involvement.

For example, women with endometriosis-associated CPP show decreased gray-matter volume in brain regions involved in pain perception, including the left thalamus, left cingulate gyrus, right putamen, and right insula (As-Sanie et al., 2012), whereas those with CPP but without endometriosis had decreased gray-matter volume in the left thalamus. Such alterations are absent in patients with endometriosis but no CPP. Microglia, in synergy with brain MCs that are mainly thalamic in location, and that can be regulated by environmental and hormonal factors, stress, or neurogenic inflammation (Xanthos and Sandkühler, 2014), may trigger neuroinflammatory processes contributing to brain alterations. Brain MCs may, thus, behave like endometriotic MCs in inducing somatosensory neuron alterations and contribute, together with other non-neuronal cells, to brain thalamic alteration observed in patients with endometriosis associated with CPP.

Morphologic alterations have also been observed in patient with vulvar vestibulitis/provoked vestibulodynia, where supraspinal pain-modulatory circuitry have been suggested to contribute to the clinical symptoms of these patients (Schweinhardt et al., 2008). In experimental BPS the activation of spinal cord glia has been suggested to play an important role in the pain syndrome. Finally, alterations in structural brain networks have been reported in female patients affected by IBS.

Altogether, this evidence confirms that gynecologic disorders associated with CPP and comorbid diseases and symptoms – whether sexual, such as introital and deep dyspareunia, or non-sexual, such as fibromyalgia – are characterized by a neuroimmune dysregulation, with a strong involvement of MC distribution/function and nerve terminal fibers. Conceivably, MC dysregulation may also promote spinal and supraspinal alterations associated with CPP. Collectively, these observations propose that a pharmacologic strategy targeting MCs and microglia may represent an innovative strategy for the effective integrated management of these disorders.

CHRONIC PAIN AND MOOD DISORDERS

MCs may pilot the persistent low-grade inflammation which is present in both chronic pain and mood disorders such as anxiety and depression. This evidence opens the possibility of targeting immune cells, particularly MCs, to act on common mechanisms of mood disorders and chronic pain (Graziottin et al., 2013, 2014). Chronic pain and underlying inflammation frequently co-occur with mood disorders such as anxiety and depression (Blackburn-Munro and Blackburn-Munro, 2001). Co-occurrence of these debilitating disease states is common to many painful conditions. A higher prevalence of comorbid chronic pain and depression occurs in women affected by pelvic/gynecologic pathologies, in particular those with pelvic diseases such as endometriosis, vulvar vestibulitis/ provoked vestibulodynia, BPS/IC, and IBS, and conditions frequently associated with CPP (Poleshuck et al., 2009; Silva et al., 2011; Smorgick et al., 2013). Depression stemming from neuroinflammation associated with pain-provoking inflammatory pelvic diseases is a major (and neglected) contributor of low desire/sexual interest and arousal disorders in women affected by any such inflammatory disease and/or CPP.

GENITALS AND SEXUAL PAIN

Vaginal receptiveness is a prerequisite for intercourse, and requires anatomic and functional tissue integrity, both in resting and aroused states (see Chapter 4, this volume, on the anatomy and physiology of genital organs). Different biologic conditions are necessary to guarantee vaginal "receptivity/habitability": normal trophism; adequate hormonal impregnation; normal muscular tonicity of the pelvic floor; vascular, connective and neurologic integrity; and a normal local immune response (Graziottin and Murina, 2011). Vaginal receptiveness may be further modulated by psychosexual, mental, and interpersonal factors, all of which may result in poor arousal with vaginal dryness.

Coital pain – "dyspareunia" in medical terms – may be perceived at the entrance to the vagina (introital dyspareunia) or deep in the vagina (deep dyspareunia). Etiologies of coital pain are different depending on the site of pain, whether introital or deep, and the hormonal status of the woman (whether of childbearing age or postmenopausal).

During childbearing years, the leading etiology of introital dyspareunia is vulvodynia and its contributors, vulvar vestibulitis/provoked vestibulodynia, and/or clitoralgia: it should be the first etiology to be considered in the differential diagnosis of any introital coital pain (Table 23.1). The second (neglected) leading etiology of introital dyspareunia is episiotomy/episiorrhaphy and all the perineal tears that may traumatize the genital tissues during spontaneous or operative delivery: 52% of women complain of coital pain 8 weeks after delivery and 25% still have introital dyspareunia 1 year afterwards. The leading etiologies of deep dyspareunia in this age group include endometriosis, pelvic inflammatory disease, and CPP.

Table 23.1

Characteristics of pain in vulvodynia

Chronic/unremitting or intermittent/episodic pain
Spontaneous or provoked
Generalized or localized/limited to:
Vestibular area (vulvar vestibulitis/provoked vestibulodynia)
Clitoris (clitoralgia)
Periurethral mucosa
Limited part of the vulva
Isolated or comorbid with:
Medical conditions:
• Recurrent *Candida* vaginitis
• Painful bladder syndrome
• Irritable bowel syndrome
• Endometriosis
• Fibromyalgia
• Headache
• Anxiety and depression
Sexual problems:
• Dyspareunia (introital)
• Loss of desire
• Vaginal dryness
• Orgasmic (coital) difficulties
• Sexual aversion

Modified from Graziottin and Murina (2011).

After the menopause, vaginal dryness due to the loss of estrogen takes the leading role in etiology, with the contribution of vulvovaginal dystrophy and/or lichen sclerosus. Iatrogenic contributors of introital dyspareunia in this age group include posterior colporrhapy and outcomes of local radiotherapy for anal, cervical, or bladder cancer. Deep dyspareunia is associated with shortening/retraction/shrinkage of the vagina where there is severe atrophy, surgical shortening of the vaginal in cervical cancer and/or radiotherapy (Table 23.2 summarizes the leading etiologies of postmenopausal dyspareunia). The following paragraphs briefly describe the most frequent clinical pictures.

VULVODYNIA

Vulvar vestibulitis, recently renamed provoked vestibulodynia, is the principal cause of vulvodynia in women of childbearing age (Bachmann et al., 2006).

The diagnostic triad includes: (1) severe pain upon vestibular touch or attempted vaginal entry; (2) exquisite tenderness to cotton-swab palpation of the introital area (mostly at 5 and 7 o'clock, when looking at the introitus as a clock face); and (3) dyspareunia.

Vulvodynia is the leading etiology of introital dyspareunia, i.e., of coital pain perceived at the entrance of the vagina. It may affect 12–15% of women and its incidence is growing over the years. Currently it is estimated that 16% of women are affected by vulvodynia after puberty (Epsteiner et al., 2014).

Vulvodynia is generally multifactorial and results in a complex syndrome of vulvar pain with sexual dysfunction and psychologic disability (Graziottin and Murina, 2011). Its etiology remains elusive, but several lines of investigation support a neuropathic etiopathogenesis of the disease. The manifestation of vulvodynia may be caused by more than one factor and may vary in each patient at different periods of her life. The diagnosis requires careful listening to the woman's symptoms, an accurate reading of the pathophysiology of vulvodynia, a competent physical examination focused on detecting all the clinical signs, and attention to the frequent comorbidities (medical and sexual) with which vulvar pain can be associated. Medical comorbidities include bladder symptoms (postcoital cystitis, painful bladder syndrome), endometriosis, IBS, fibromyalgia,

Table 23.2

Etiologies of dyspareunia

Biologic

Superficial/introital and/or midvaginal dyspareunia

- Infectious: vulvitis, vulvar vestibulitis, vaginitis, cystitis
- Inflammatory: with mast cell upregulation
- Hormonal: vulvovaginal atrophy
- Anatomic: fibrous hymen, Müllerian anomalies
- Muscular: primary or secondary hyperactivity of levator ani muscle
- Autoimmune: vulvar lichen sclerosus
- Iatrogenic: genital or perineal surgery such as episiotomy or colporrhaphy; pelvic radiotherapy
- Neurologic, inclusive of neuropathic pain
- Connective and immune: Sjögren's syndrome
- Vascular
- Female genital mutilation, with introital/vaginal narrowing

Deep dyspareunia

- Endometriosis
- Pelvic inflammatory disease
- Chronic pelvic pain and referred pain
- Pelvic varicocele
- Outcome of pelvic radical surgery or endovaginal radiotherapy
- Abdominal cutaneous nerve entrapment syndrome (ACNES)

Psychosexual

- Comorbidity with desire and/or arousal disorders, or vaginismus
- Past sexual harassment and/or abuse
- Affective disorders: depression and anxiety
- Catastrophism as leading psychologic coping modality

Context- or couple-related

- Lack of emotional intimacy
- Inadequate foreplay
- Couple's conflicts: verbally, physically, or sexually abusive partner
- Poor anatomic compatibility (penis size and/or infantile female genitalia)
- Sexual dissatisfaction and consequent inadequate arousal

Modified from Graziottin (2003).

and headache. Sexual comorbidities include the leading symptom of coital pain (dyspareunia), with its cohort of secondary loss of desire, vaginal dryness, orgasmic difficulties, and sexual dissatisfaction (Graziottin and Murina, 2011).

The most recent terminology and classification of vulvar pain by the International Society for the Study of Vulvovaginal Disease (ISSVD) divides potential causes of vulvar pain into four categories: (1) infectious; (2) inflammatory; (3) neoplastic; and (4) neurologic. Conditions falling into the above categories must be ruled out prior to making a diagnosis of vulvodynia, defined as "vulvar discomfort, most often described as burning pain, occurring in the absence of relevant visible findings or a specific, clinically identifiable, neurologic disorder." It is not caused by infection (e.g., candidiasis, herpes), inflammation (e.g., lichen planus, immunobullous disorder), neoplasia (e.g., Paget's disease, squamous cell carcinoma), or a neurologic disorder (herpes neuralgia, spinal nerve compression). The classification of vulvodynia is based on: (1) the site of the pain; (2) whether it is generalized or localized; and (3) whether it is provoked, unprovoked, or mixed.

The ISSVD further classifies vulvodynia as follows:

- Generalized vulvodynia
- Provoked (sexual, non-sexual, or both)
- Unprovoked
- Mixed (provoked and unprovoked)
- Localized vulvodynia
- Provoked (sexual, non-sexual, or both)
  - ** Provoked vestibulodynia/vulvar vestibulitis syndrome
- Unprovoked
- Mixed (provoked and unprovoked)

These definitions limit vulvodynia to a subset of unexplained vulvar pain, thus missing all the conditions where vulvar pain has a clear etiology. It can be exacerbated by psychologic factors (anxiety, depression, chronic stress, former abuse) and sexual triggers such as intercourse. Indeed, the biologic contributors of pain may not be immediately visible at first vulvar examination, but may become evident when appropriate and skilled clinical examination is performed and/or when histological data express clear evidence of an inflammatory conditions, typical, for example, of vulvar vestibulitis (Graziottin and Murina, 2011).

VAGINISMUS AND DYSPAREUNIA

Vaginismus indicates the persistent or recurrent difficulties of the woman to allow vaginal entry of a penis, a finger, and/or any object, despite the woman's expressed wish to do so (Basson et al., 2004; Graziottin et al., 2004; Graziottin, 2006a; Graziottin and Rovei, 2007).

There is often (phobic) avoidance and anticipation, fear, and experience of pain, along with variable involuntary pelvic muscle contraction. The disorder may be lifelong or acquired, generalized or contextual, biologic and/or psychogenic and may (or may not) cause personal distress. In the vast majority of cases, however, coital pain is a powerful trigger of personal and relational distress. When severe, vaginismus is the leading female etiology of unconsummated marriages and relationships. When mild, it may allow difficult, painful penetration, becoming the most frequent etiology of lifelong dyspareunia, i.e., of coital pain present from the first sexual

intercourse. A lifelong hyperactive pelvic floor ("myogenic hyperactivity," sometimes associated with phobia of penetration, i.e., "true" vaginismus) anatomically reduces the entrance of the vagina and predisposes the introital vestibular mucosa to microabrasions mechanically provoked by any attempt at intercourse.

The contributing factor is inadequate genital arousal, due to the reflex inhibition pain has on vaginal lubrication and vulvar congestion and/or fear of pain. The mechanical mucosal damage immediately activates the MC response (Graziottin and Murina, 2011; Theoharides et al., 2001) when attempts at intercourse are recurrent, and/or coital damage is persistent, and/or concomitant factors such as *Candida* vaginitis further contribute to the vestibular inflammatory state, and localized vestibular pain, contributing to vulvodynia. Three key consequences are involved:

1. the MC is hyperactivated, with hyperproduction of inflammatory molecules and neurotrophins such as nerve growth factor, which induces
2. the proliferation of pain nerve fibers, responsible for introital hyperalgesia, and allodynia, and induces or worsens
3. hyperactivity of the pelvic floor.

In summary, vulvodynia can trigger dyspareunia, and painful intercourse (due to vaginismus or dyspareunia from any etiology) may worsen or precipitate vulvar pain, and maintain it. The only exception is vulvodynia in children or virgin adolescents, or in women of any age who do not have penetrative sex for a number of reasons.

DIAGNOSIS OF COITAL PAIN

Accurate differential diagnosis requires a very careful clinical history, and a competent physical examination to elicit any site of pain, with two main purposes (Graziottin and Murina, 2011):

1. to describe the "pain map," on the external and internal genitalia with a detailed reporting of pain, based on an analog scale from zero (no pain) to 10 (worst pain ever), which should be re-evaluated and reported at every follow-up visit to diagnose and document the response to treatment;
2. to diagnose the eliciting sites and hypothetic pathophysiology of the reported pain

The most common pain sites include:

- the vestibular area, with burning pain most frequently perceived at 5 and 7 o'clock, when looking at the entrance of the vagina as a clock face;
- the midvagina, at the insertion of the levator ani bilaterally on the ischiatic spine. Pressure on the myalgic muscle may elicit localized pain, either monolaterally or bilaterally (tender points), and/or an acute nonmetameric pain (trigger points), which may irradiate to the pelvis and/or to the external genitalia;
- the deep vagina, the Douglas pouch, and the uterosacral ligaments: in these cases, the leading etiologies to be considered in the differential diagnosis are deep endometriosis, followed by pelvic inflammatory disease and CPP.

When indicated, other examinations may be performed:

- pelvic MRI, when other anatomic and dysfunctional contributors of sexual pain may be in play (coccygeal, connectival, tendineal, muscular, posttraumatic, iatrogenic);
- electromyography, to evaluate the hypertonus, of the levator ani in cases of introital dyspareunia. Pelvic floor hypertonic dysfunction has been documented in 91.6% of patients with vulvar/vestibulitis/vulvodynia (Frasson et al., 2009); this diagnostic approach is, however, not generally accepted. (A "myogenic" hyperactivity of the pelvic floor may be diagnosed where there is severe primary vaginismus and may require the periodic topical injection of Botulinum toxin A, as an auxiliary pharmacologic treatment, until the problem is cured.)

TREATMENT OF GENITAL AND SEXUAL PAIN DISORDERS

Treatment for any medical disorder should be directed at the underlying mechanisms or pathophysiologic processes involved. This is difficult to achieve with vulvodynia in view of the heterogeneity of factors involved in the etiology of the disorder. Multimodal and multidisciplinary interventions should be part of a treatment strategy for patients with vulvodynia. The goals of vulvodynia treatment are the reduction of triggers and irritating stimuli, peripheral nociceptive blockade, central inhibition, treatment of associated pelvic floor dysfunction and of psychosexual ramification of the syndrome (Graziottin and Murina, 2011).

Vulvodynia is frequently associated with interstitial cystitis, a urologic condition of urinary urgency, frequency, and bladder spasms (Whitmore et al., 2007), IBS, and fibromyalgia, a condition encompassing pervasive muscle pain and sleep disorder. The frequent overlap of IBS, interstitial cystitis, vulvodynia, and other CPP disorders may be indicative of aberrant neuronal interactions or reflexes, such that the irritation of one organ leads to cosensitization of others. With continued irritation, neurotrophic factors produced by both smooth muscles and sensory neurons may influence neurite outgrowth and axonal sprouting, which could lead to motor and sensory changes in target organs.

Irritable bowel syndrome

IBS is a very common functional gastrointestinal disorder characterized by abdominal discomfort, bloating, and disturbed defecation. Many IBS patients have at least one comorbid somatic complaint and many meet diagnostic criteria for other functional disorders. MCs have been reported to play an important role in the inflammatory processes described in IBS. In this latter setting, inflammation can be triggered by food, immunoallergic factors, infections, antibiotics, disruption of colonic ecosystems, and/or systemic pathologies. Stress can further contribute through the corticotropin-releasing pathway by provoking MC degranulation.

IBS patients have increased serum concentrations of IL-8, a cytokine primarily responsible for attraction of MCs and granulocytes. Several studies have reported an increased prevalence of sexual dysfunction among IBS patients, including increased dyspareunia and more severe IBS symptoms following intercourse. The studies are consistent in their finding that the overlap among these disorders (vulvodynia–BPS/ICs–IBS) is greater than expected based on their separate prevalence rates. In addition, patients with more than one disorder have greater disease severity, higher rates of psychopathology, and more severely impaired health-related quality of life than those with only one disorder.

Bladder pain syndrome/interstitial cystitis

BPS/IC has also been reported to show an accumulation and activation of MCs. MCs number increases in bladder, mainly in the detrusor, lamina propria, and submucosa (Theoharides et al., 2001; Rudick et al., 2008). Clinical studies have confirmed increased urine levels of MC mediators, including histamine, tryptase, IL-6, and IL-8. Furthermore, serum and urine levels of YKL-40, a new biomarker expressed in bladder MCs, may serve as an index of bladder fibrogenesis as bladder cytoarchitecture is progressively disrupted by chronic inflammatory processes.

Functional urothelium and wall tissues are replaced by a connective afunctional tissue with progressive scarring until the final, irreversible stage of interstitial cystitis with its rigid bladder wall is reached. Activation of urinary bladder-associated circuits in the CNS may initiate substance P release from peripheral nerves in the bladder, thereby promoting substance P-mediated MC activation. MC activation may, in turn, induce bladder inflammation by acting on the urothelium. While histamine has been postulated to modulate pelvic pain, TNF-α seems to be involved in pathophysiologic changes in the urinary bladder, including inflammatory changes.

Lifelong coital pain is significantly higher in women with BPS/IC in comparison to controls, suggesting that the biomechanical inflammation of the urethra and trigonal area is one of the leading contributing factor to recurrent cystitis first and BPS/IC in the long term (Peters et al., 2007). Recurrent cystitis and introital dyspareunia associated with provoked vestivulodynia are comorbid in 60% of cases, suggesting that a common pathophysiology is in play (Salonia et al., 2013). Common denominators include intestinal factors such as IBS/constipation, hyperactive pelvic floor, recurrent *Candida* infections, recurrent *Escherichia coli* infections, recurrent antibiotics, and hypoestrogenism with arousal disorders and vaginal dryness. They should be diagnosed and properly addressed if an effective multidimensional therapy is to be considered (Graziottin, 2006a).

FEMALE SEXUAL PAIN AND DISORDERS: IATROGENIC FACTORS

Physicians and healthcare providers may contribute to sexual disorders, with a:

- predisposing role, when they do not recognize and diagnose conditions that may prelude to, precipitate in, or maintain an FSD (Graziottin, 2006b);
- precipitating role, through the inappropriate prescription of medications that may negatively affect women's and a couple's sexuality, or through the negative outcome of surgery, obstetrics, and/or of chemotherapy, hormone therapy, or radiotherapy (Graziottin, 2006b);
- maintaining role, through the most frequent mistake in the field of FSD: the diagnostic omission, which encompasses occasional or systematic diagnostic neglect, particularly in the area of biologic/medical etiology of FSD and/or comorbidity between medical conditions and FSD.

The term "iatrogenic" implies that the physician or surgeon causes the pain (Graziottin, 2006b). This can occur in many different ways:

- Vaginal/vulvar damage: vaginal pain can be iatrogenic, when the dyspareunia is complained of after episiotomy, after perineal or vaginal surgery (anterior or posterior colporrhaphy), or after radical surgery for cervical cancer or vulvar cancer.
- Pelvic radiotherapy: radiotherapy following cancer treatment may cause vaginal fibrosis, stenosis, and progressive damage of vaginal vessels, contributing to genital arousal disorders and both introital and deep dyspareunia.
- Bilateral oophorectomy is the most frequent iatrogenic surgery for benign reasons affecting women's

sexuality. It causes surgical menopause and the associated androgen insufficiency syndrome. There are several ways in which a lack of sexual hormones (estrogen and androgens) may contribute to the development of dyspareunia:

- Estrogen and/or androgen deficiency may cause vulval/vaginal atrophy/dystrophy, which can cause vaginal dryness.
- The lack of these hormones may reduce the perivaginal and periurethral vascular congestive response (Graziottin and Basson, 2004). An inadequate vascular response, secondary to poor genital arousal, may increase the vulnerability of the introital and bladder mucosa to coital microtraumas and acquired inflammatory response of the damaged tissue (Graziottin and Murina, 2011).
- Clitoral and cavernosal bulb congestion may also be affected since androgens are permitting factors for nitric oxide, a powerful vasodilating neurotransmitter in both men and women. Inadequate cavernosal arousal may contribute to vestibular and/or bladder pain (see Chapter 4).
- Hypoestrogenic conditions cause an increase in normal vaginal pH which facilitates vaginal and/or bladder infections from intestinal bacteria (e.g., *E. coli, Enterococcus faecalis*).
    - Chemotherapy has a complex effect: in prepubertal or fertile women, it may cause permanent ovarian damage, with, respectively, primary hypergonadotropic amenorrhea or premature menopause. This prolonged deprivation of sexual hormones, especially in women with hormone-dependent cancers, where hormone therapy is currently contraindicated, may negatively affect the whole sexual response: the younger the woman, the worse the effect (Graziottin, 2006b).
    - Hormone therapy: estrogen receptor-positive breast cancer has been treated with tamoxifen for almost three decades. Although reasonably well tolerated, this drug, which is used worldwide, may specifically affect sexual function. It has been demonstrated that during tamoxifen therapy the most frequent complaints were hot flushes (85%), disturbed sleep (55%), vaginal dryness and/or dyspareunia (47%), decreased sexual desire (44%), and musculoskeletal symptoms (43%). After discontinuation of tamoxifen, symptoms decreased significantly. More recent treatments with aromatase inhibitors such as anastrozole, which inhibit the conversion of androgens to estrogens, may also have a negative impact on sexual response (Graziottin, 2006b).

CONCLUSIONS

Genital pain and sexual pain disorders have a complex biologic etiology that requires thorough medical attention with a multidisciplinary approach. Their presence in the context of different neurologic diseases is increasingly recognized.

The inflammatory basis of genital and sexual pain is a key aspect of the clinical picture. It contributes to neuroinflammation and depression, with sexual correlates such as low desire/interest and inadequate arousal. The "iatrogenic" etiology of genital and sexual pain is a growing issue in the shadow of medical interventions, pharmacologic and surgical treatment, and radiotherapy.

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Section 5

Management and rehabilitation of neurologic patients with sexual and bladder dysfunction

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 24

Management and rehabilitation of neurologic patients with sexual dysfunction

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INTRODUCTION

Neurologic disease often alters sexual experiences due to lifestyle changes and disabilities as well as specific sexual dysfunctions imposed by the disease and its treatment. Nevertheless, our neurologic patients remain sexual persons with the fundamental right to love and be loved, to experience emotional relationships, to receive information to enable safe sexual experiences, and to exercise their own and others' rights and responsibilities in regard to privacy and sexual expression. The World Health Organization (2004) refers to sexuality as a central aspect of being human throughout life and declares that sexual health is a fundamental right, encompassing the right of the individual to enjoy and control sexual and reproductive behavior in accordance with social and personal ethics. However, societal attitudes frequently fail to acknowledge that people with chronic disease or with disabilities are sexual beings, such that patients' sexuality is still surrounded by silence. Research has shown that healthcare professionals rarely address it proactively (Dyer and Das Nair, 2013; Saunamäki and Engström, 2014). This can only change when, in addition to acknowledging a person's continued sexuality despite chronic illness, health professionals understand sexual rehabilitation and know of the various treatment modalities.

AN ABCD OF SEXUAL REHABILITATION

The following mnemonic can assist in managing the complexities of sexuality in the context of neurologic illness:

Assessment of patient's sexual difficulties and dysfunctions
Background necessary for sexual expression
Consequences of the neurologic condition on sexuality
Definitive treatment of sexual dysfunction.

Assessment of patient's sexual difficulties and dysfunctions

After a detailed assessment, preferably of both partners seen together and individually, a formulation of the patient's problems is made (see Chapters 2, 8, and 10 for details). Neurologic disease affects the sexual lives of both partners: female partners of men with Parkinson's disease (PD) have more sexual dissatisfaction than women diagnosed with PD (Brown et al., 1990). From the assessment, an understanding of the multiple items impacting sexual function guides subsequent management and rehabilitation. Factors affecting sexual motivation, the ability and willingness to attend to sexual stimuli to trigger subjective and physical arousal, along with factors modulating genital congestion, genital and non-genital sensation, and emotional and physical satisfaction are investigated (see Chapter 2).

Background necessary for sexual expression

Issues underlying the sexual concerns additional to the neurologic disease are frequently present, and need to be addressed first. Sometimes the neurologic deficit is not related to the dysfunction: multiple studies find diabetic neuropathy (and other diabetic complications) not to moderate sexual dysfunction in women. Instead,

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depressive symptoms and satisfaction with partner as a lover are strong predictors (Nowosielski and Skrzypulec-Plinta, 2011). Important background considerations include depression, interpersonal issues, and context of attempted sexual activity.

Depression

Optimal management of comorbid depression is a priority given its robust association with sexual dysfunction. A major finding from a recent probability survey in the UK using interview data from close to 12 000 men and women was the increased risk of low sexual function from depression, with adjusted odds ratios of 3.7 for men and 4.11 for women (Mitchell et al., 2013). It is important to stress that the sexual benefits of adequately treating the depression, so commonly comorbid with neurologic disease, far outweigh the potential negative sexual side-effects of the medications used to treat the depression. Nevertheless, selective serotonin reuptake inhibitors (SSRIs), may cause low desire, delayed orgasm and erectile dysfunction (ED) in some 60% of men and women (Gregorian et al., 2002), such that when the patient's sexual concerns appear to worsen or appear with the introduction of the antidepressant, non-pharmacologic management of the depression or medication change can be considered. It is clinically observed that medications activating dopaminergic and central noradrenergic receptors, and 5-HT_{1A} and 5-HT_{2C} receptors may augment sexual response, whereas those activating other 5-hydroxytryptamine (5-HT) receptors and prolactin and gamma-aminobutyric acid do the opposite. A meta-analysis found no significant difference between the effects upon sexuality of placebo and those of moclobemide (a reversible monoamine oxidase A inhibitor), agomelatine (an agonist of melatonin receptors MT1 and MT2, and antagonist at 5-HT_{2C}), amineptine (an atypical dopaminergic tricyclic with very limited availability due to potential liver damage and abuse: it is occasionally prescribed off-label for patients with PD), bupropion, or mirtazapine (Serretti and Chiesa, 2009). A recent study suggested that transdermal selegiline (a monoamine oxidase B inhibitor) may not impair sexual function (Citrome et al., 2013).

Adding another medication to temper antidepressant-associated sexual dysfunction can also be considered: a recent Cochrane review found that either sildenafil or tadalafil can be of benefit for antidepressant-induced ED, but of all other strategies studied, only bupropion at 150 mg twice daily was prosexual beyond placebo, this benefit applying to both men and women (Taylor et al., 2013).

Interpersonal difficulties

When the history identifies interpersonal difficulties – independently of coping issues linked to neurologic disease – referral for professional help may be needed. A recent British probability survey of some 12 000 men and women indicated low sexual function to be associated with unhappiness in the relationship, with adjusted odds ratios of 2.89 for men and 4.10 for women (Mitchell et al., 2013). In an 8-year longitudinal study of Australian women transitioning menopause, women's feelings for their partners, rather than hormonal factors, exerted a powerful effect on sexual desire: interpersonal problems along with daily hassles negatively affected well-being, thereby reducing sexual responsiveness and desire (Dennerstein et al., 2002).

Lack of appropriate context and environment

Unfavorable contexts for sexual activity can limit sexual response such that sexual stimuli appear ineffective, limiting pleasure and arousal. Patients may lack privacy due to living with a caregiver (rather than a potential sexual partner), living in an adult child's home, or residing in a long-term care facility and encountering negative attitudes towards sexuality (Zeiss and Kasl-Godley, 2001; Hajjar and Kamel, 2004). Frequently such facilities lack private areas where residents can disclose their emotions or have physical contact with their partner or with other residents.

Addressing such lack of suitable context for sexual activity is a priority (see the section on education of healthcare providers in long-term care facilities, below).

Consequences of the neurologic condition on sexuality

Addressing the sexual concerns of the neurologic patient involves far more than treating the sexual dysfunction *per se*. The sexual dysfunction may or may not be a source of distress: altered appearance, lack of facial expression, and fear of incontinence may discourage sexuality in women with PD more than any dysfunction from neurologic compromise (Welsh et al., 1997). Building on the original work of Szasz (1986) are some eight sexual consequences of a neurologic condition to potentially invite eight areas of sexual rehabilitation (Table 24.1).

Sexual self-image

A low sexual self-image is one of the many factors known to limit a person's ability to become aroused by sexual stimuli. Sexual self-image is frequently impaired when neurologic disease is present: there may be imposed unemployment, dependence on others, altered appearance, incontinence, and often physical inability to sexually stimulate a partner. Being able to talk about such losses with the clinician, and with the partner

Table 24.1

Eight areas of sexual rehabilitation

1. Sexual self-image
2. Sexual motivation
3. Sexual partnership
4. Fertility
5. Sexual function
6. Chronic pain
7. Incontinence
8. Reduced mobility

present, can prompt empathy, understanding, and often reassurance from the partner.

Sexual motivation

Men and women have multiple reasons to be sexually active over and beyond any sense of innate urge or drive (Meston and Buss, 2007). The fostering of emotional intimacy is of major importance in longer-term relationships. However, dealing with neurologic illness, possible changes in partner roles and lifestyle, and altered plans for the future can cause interpersonal difficulties, lessening sexual motivation. When sexual activity becomes physically unrewarding due to the neurologic disease, motivation may fade completely. Motivation may be further lessened by disease-associated fatigue, pain, and depression. Explaining how such factors interrupt the sex response cycle (see Chapter 2) can be therapeutic. Understanding the logic of their situation can lessen patients' distress. Sometimes the outcome is the acceptance of a relationship without sexual activity.

Sexual partnership

Finding a sexual partner can be challenging, especially when neurologic disabilities interfere with independence, mobility, or cognition. Afraid of rejection, many may not try (Basson, 1998). Online dating is increasingly used given the relative anonymity and the option to disclose only as much as the person wishes. Research shows that, despite the internet's capacity to facilitate disembodied anonymous interaction, the body and its impairment will still play an important role in how disabled people construct their self-identity and interact with others (Saltes, 2013). Information about how to use social network sites safely and effectively is very much needed (Shpigelman and Gill, 2014). Compared to the countless general online dating sites that exist, relatively few are designed especially for people with disabilities. Further difficulties include obtaining birth control, condoms, and information about safe sexual practices, fertility, and pregnancy, particularly when caregivers are hesitant to acknowledge and provide these needs. Protection from sexual abuse or exploitation may also be needed, especially when there is cognitive impairment.

Fertility

Neurologic illness such as spinal cord injury or multiple sclerosis can impair ejaculatory function as well as limit sperm quality in the case of spinal cord injury. Information on vibrostimulation or electroejaculation to obtain sperm can be given and referrals made (Phillips et al., 2014). When chemotherapy is needed for neurologic malignancy, preservation of fertility is now sometimes possible. Sperm banking for men is generally available but it is important for neurologists to also have some understanding of the current and emerging options to preserve fertility so that their female patients can be fully informed prior to definitive treatment of neurologic cancer (Jeruss and Woodruff, 2009).

Sexual function

Heightened sexual function

Whereas neurologic disease commonly leads to sexual deficit, unwanted hypersexuality can occur in men (and rarely in women) with PD given dopamine agonists. This syndrome of compulsive sexual behavior (which may involve sexual exhibitionism, multiple sexual liaisons, and excessive use of sex phone lines) may include non-sexual features such as pathologic gambling or shopping (see Chapter 17). Bronner and Hassin-Baer (2012) provide a comprehensive diagnostic and therapeutic algorithm to differentiate between true hypersexual behavior and sexual problems disguised as heightened sexual function (Fig. 24.1). Also severe trauma to the prefrontal lobes or to the amygdala can result in the Klüver–Bucy syndrome of disinhibited hypersexuality. Some researchers find that neurologic patients with cognitive impairment may demonstrate appropriate sexual behaviors that occur in the wrong place (Robinson, 2003; Wallace and Safer, 2009). These authors note that nursing-home residents can confuse public and private areas or misidentify strangers as their spouse or partner.

Sexual deficit

Neurologic disease far more frequently impairs erection, ejaculation, and orgasm and may be associated with pain with penetrative sex (dyspareunia), painful orgasm, or painful ejaculation (see section 4). Very common clinical concerns include multiple sclerosis and spinal cord injury-associated dysfunctions of erection, ejaculation, and orgasm, and PD-associated erectile and ejaculatory dysfunction, and complaints of low sexual desire and motivation in men and women with most chronic neurologic conditions.

Hypersexual Behavior: Diagnosis and Management Algorithm

The Role of the Neurologist (Bronner G, Hassin-Baer S, 2012)

A Hypersexual Behavior: suspected compulsive sexual behavior due to:

- Increased sexual desire and/or discussing sex often
- Frequent attempts to have sex with partner and/or frequent masturbation
- Frequent use of pornographic materials
- Positive responses to desire question in the NMSQuest (Chaudhuri 2006)

B: Compulsive Sexual Behavior

B1: Features of true Hypersexual Behavior

- Sexual behavior did not exist previously
- Aberrant, excessive, and/or time & money-consuming sexual activities, including: pornography use, cybersex, sexual activity with multiple partners, use of sex workers, paraphilias, sexual harassment (verbal or physical), etc.
- Satisfying sexual activity does not lead to decrease of excessive sexual interest and behavior

B2: Explore Associated Factors:

- Antiparkinsonian medication regimen: dopamine agonists, levodopa
- Dopamine dysregulation
- Self-administered increased doses of DRT
- Recent changes in medications
- Early PD onset (age < 50)
- History of drug and alcohol abuse
- Concomitant psychiatric problems –depression, psychosis, anxiety
- Concomitant additional ICDs (gambling, shopping, eating, hobbyism, walkabouts, punding, etc.)
- Use QUIP-RS (Weintraub 2012) to assess ICDs

B3: Interventions for Compulsive sexual behavior

- Adjust treatment for motor symptoms
  - Reduction or discontinuation of dopamine agonist
  - Adjust l-dopa dose
  - Consider advanced therapeutic options to spare DRT: deep brain stimulation or l-dopa intestinal gel via gastrostomy
- Patient and spouse education to prevent sexual health problems (e.g., AIDS and other sexually transmitted diseases, unplanned pregnancy, sexual abuse) and sexual harassment accusations.
- Involve multidisciplinary team: PD nurse, psychologist, psychiatrist, couple and sex therapy, PD group support

C: Disguised Hypersexual Behavior

C1: Features of Sexual Dysfunction

- Current sexual dysfunctions leading to behavioral changes: frequent attempts to have sex with partner in order to perform normally
- Satisfying sexual activity may lead to temporary decrease of excessive sexual interest

C2: Explore Sexual Dysfunction

- Erectile dysfunction
- Premature ejaculation
- Delayed ejaculation
- Difficulties reaching orgasm
- Sexual pain disorders
- Changes in sexual function of spouse
- Use diagnostic questionnaires for sexual dysfunction
- Medical problems and medications that may affect sexual functioning (cardiovascular illness, diabetes mellitus, lumbar radiculopathy, depression, etc.)

C3: Interventions for Sexual Dysfunction

- Education: Explain probable reasons for excessive sexual demands to patient and partner
- Refer to specialist: urologist, sex therapist, psychiatrist

DRT=dopamine replacement therapy; PD=Parkinson's disease; ICD= impulse control disorder; AIDS= Human acquired immunodeficiency syndrome

Fig. 24.1. Assessment and management algorithm. DRT, dopamine replacement therapy; PD, Parkinson's disease; ICD, impulse control disorder. (Adapted from Bronner and Hassin-Baer, 2012.)

Chronic pain

Chronic pain typically distracts from attending to sexual stimuli and the associated fatigue limits sexual motivation. As well, patients with certain neurologic diseases, including multiple sclerosis and peripheral neuropathies, may report pain specifically with sex, be it dyspareunia or pain with ejaculation. Noted clinically is an association between provoked vestibulodynia and multiple sclerosis, but the true prevalence of this comorbidity is unclear. Provoked vestibulodynia is the most common cause of pain with intercourse in premenopausal women, affecting some 12–18% of women in the community and an uncertain number of postmenopausal women (Danielsson et al., 2003).

Incontinence

As outlined in section 4, fear of urinary or bowel incontinence, especially with orgasm, can reduce or completely suppress sexual motivation, as may the presence of a catheter.

Reduced mobility

Neurologic disease may impair mobility so that it is difficult to caress the partner, hug and hold her or him, to sexually self-stimulate, to sexually stimulate a partner, as well as to move into positions for intercourse and to rhythmically move the pelvis. These are common concerns of patients with spinal cord injury, PD, brain injury, or other disease associated with tremor, immobility, or abnormal movements.

Definitive treatment of sexual dysfunction

Details of the sexual dysfunctions typically occurring in different neurologic conditions are found in section 4. Here we describe and evaluate the different treatment modalities.

MODALITIES OF TREATMENT AND REHABILITATION FOR SEXUAL DIFFICULTIES AND DYSFUNCTION IN NEUROLOGIC DISEASE

A number of different treatment modalities may be needed for any patient or couple so as to provide a truly biopsychosocial perspective (Althof, 2010). However, highlighted in a recent review is the frequent failure to meet this goal (Berry and Berry, 2013).

EDUCATION

Providing information about the impact of the disease and its treatment on sexual function and on the behavior of patients and their partners, learning about their different sexual needs as disease progresses, and practicing sexual communication are important aspects of education. Any or all of the eight areas of sexual rehabilitation may need discussion. The following resources can supplement the information given in the office: books, e.g., *The Ultimate Guide to Sex and Disability: For All of Us Who Live with Disabilities, Chronic Pain and Illness* (Kaufman et al., 2007) and websites, e.g., http://www.mass.gov/eohhs/docs/dph/com-health/prevention/hrhs-sexuality-and-disability-resource-guide.pdf (this pdf provides an extensive list of resources for patients, partners, care givers, and clinicians) and http://www.siecus.org/index.cfm?fuseaction=page.view page&pageid=580&grandparentID=477&parentID=572 (a bibliography for sexuality and disability). Another useful resource is the use of illustrations and anatomic models. Because patients as well as their partners may have considerable anxiety about the cause of their sexual dysfunction, these sources of information can lessen distress, and lessen self-blame and misunderstanding, to then foster intimacy and sexual interaction adapted to their situation.

Initiation of a discussion of the impact of neurologic disease on sexuality

A discussion about sexual activity is appropriate for all men and women of all ages. Misgivings that patients are too old for sex can be allayed by reports confirming that more than half of people aged 57–85 and about one-third of those aged 75–85 are still sexually active (Lindau et al., 2007). A 2004 World Health Organization declaration endorsed sexuality as the fundamental right for all persons (http:/www.who.int/hrp/publications/progress67.pdf). Even when information on sexual activity is provided to patients, it is more likely to be provided in a written form than verbally, to be provided to men but not to women, and rarely provided to partners (Ivarsson et al., 2009). Past research has confirmed that only a minority of patients actually discuss sexual issues with health professionals (Zorzon et al., 1999). Patients have difficulty expressing their sexual concerns to their partners as well as to their clinicians and their appreciation of explanations and assistance from their healthcare providers is well documented (Fisher et al., 2005). Sexual communication may be difficult for professionals as well as patients: questionnaires can be used to simplify these discussions (Bronner, 2009). The questionnaires convey a message to the patient that it is legitimate to talk about sex in medical settings, assist the clinician who finds such inquiry difficult, and efficiently provide the relevant information concerning the patient's sexual problems. Healthcare professionals on the first line of

patient care are an important resource for providing sexuality education and explanations. Effective management of this role requires sensitivity, tact, and the ability to put patients at ease (Dixon-Woods et al., 2002). When more indepth treatment is needed, referrals can be arranged.

Models to use in talking about sexuality

PLISSIT model

A traditional model for interventions with patient's sexual problems is the PLISSIT model (Fig. 24.2), involving four graded steps of offering permission (P), limited information (LI), specific suggestions (SS), or referring for more intensive therapy (IT) (Annon, 1976). The model is based on initially offering reassurance that it is appropriate and necessary to address sexual difficulties in a medical setting so that choices and changes can be made. The second level, limited information, includes asking questions to clarify the problem and then giving an explanation (e.g., medication side-effects). Examples of specific suggestions (level 3) include the use of lubricants for vaginal dryness, consideration of phosphodiesterase type 5 (PDE5) inhibitors, or specific positions for patients with limited mobility. Ideally both partners will have been seen to ensure appropriateness of suggestions: sexual dysfunction in one partner is a risk factor for dysfunction in the other partner (Cayan et al., 2004). The fourth level, intensive therapy, includes provision of, or referral for, sex therapy, couples' counseling, or more indepth psychologic or medical therapy. Neurologists are able to provide the first three levels of the PLISSIT model and probably many components of the fourth. Most patients will appreciate the first three levels of the model.

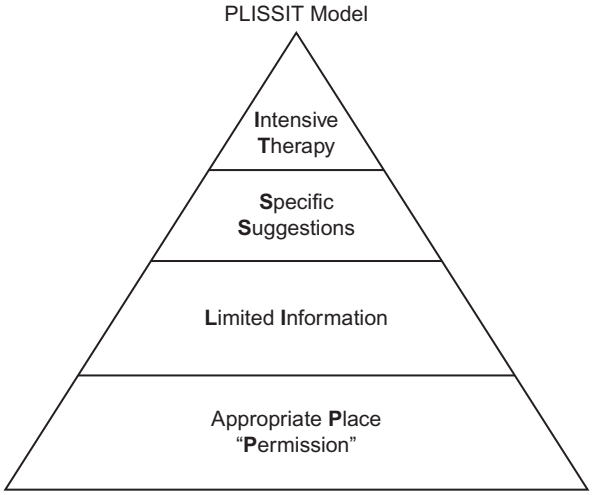

Fig. 24.2. The PLISSIT model involves four graded steps of offering permission (P) (and confirming the setting is the appropriate place (P) to address sexuality); limited information (LI); specific suggestions (SS), or referring for more intensive therapy (IT).

OSEC model

The Open Sexual Communication (OSEC) is another model designed to assist physicians to initiate a "sex talk" and offer advice or treatment (Bronner, 2009). The physician may initiate the "sex talk" by asking directly: "How did your illness affect your intimate life?" Alternatively, the physician may choose an indirect approach, which has been shown to identify problems far more effectively (Sadovsky et al., 2006), e.g., by asking: "Maybe you are unaware, but men and women with neurologic disease frequently find that it affects their sexual functioning. If you notice any changes, please tell me. Today we can treat sexual problems." When the patient identifies a sexual problem, the OSEC module suggests a short evaluation of the patient's expectations and the partner's support, past treatments and their outcomes. At this point, the clinician may offer treatment (e.g., prescribing PDE5-inhibitors) or refer to a physician experienced in sexual medicine, psychologist, couple therapist, or sex therapist. Again, as in PLISSIT, preferably the partner is involved in these recommendations. Referral may be for consultation only or for continuing care. Ideally the chosen specialist will understand the intricate blending of biologic and psychologic factors underlying sexual dysfunction. However, sometimes a team approach is needed, e.g., a joint referral for a couple for whom first-line PDE5-inhibitors are unsuccessful and whose previous sex life was very intercourse-focused: to a psychologist or sex therapist (to broaden the sexual repertoire, to address any psychologic factors in the ED, and adapt to the use of injection therapy if this is needed) and a urologist (to teach intracavernosal injection technique and dosage).

Education of healthcare providers in long-term care facilities

Education of staff such that residents in care are not viewed as asexual is essential (Hajjar and Kamel, 2004; Parker, 2006). While not all residents are concerned about sexual and affectionate relationships, a broad spectrum of sexual expressions has been noted among people both with and without dementia, to include "loving and caring," "intimate touching," and "eroticism" (Ehrenfeld et al., 1999). Staff members may report feelings of discomfort and unease when these intimate expressions are displayed in public areas. Friendly or intimate touch such as hugging, caressing, and kissing may be difficult to accept and erotic behavior usually generates disapproval (Ehrenfeld et al., 1999).

Frequently there is a lack of recognition of sexual diversity in care homes and most nursing-home directors lack training in working with lesbian, gay, and bisexual residents (Bell et al., 2010). Bell et al. (2010) call for the immediate development and dissemination of heterosexism and homophobia training of social service staff, policy changes within the nursing home, and policy advocacy priorities for social workers. Older gay, lesbian, bisexual, transgender, or intersex people may fear discrimination or abuse in disclosing their identity to service providers. Recognition of the comprehensive aspects of ongoing sexuality despite neurologic illness forms the basis of staff education.

Many, especially older, patients do not have available partners for intimate activity, even if they live with a spouse, and their only sexual outlet is self-stimulation. Indeed, one study found that about one-quarter of men and women, who were sexually active before the onset of PD, stopped having partnered sex after their PD diagnosis (Bronner et al., 2004). Self-stimulation can provide pleasure and also help a person maintain sexual responsiveness without others knowing. Health professionals can be supportive, provide assurance that it is normal and healthy, and provide the required privacy in long-term facilities and nursing homes. When patients live in their child's home, the privacy of both parties may be disturbed. Open communication between parents and children on intimate issues is often problematic. Therefore, patients as well as their adult children might also need some support from a healthcare professional who can raise such topics, and give appropriate information. This issue becomes more complicated when patients need assistance from their carers for partnered sex or self-stimulation. Along with subsequent privacy, initial help with undressing or positioning a couple in an efficient and comfortable way for sexual activity may be needed. Sometimes, specific preparations to enable the sexual activity, be it alone or partnered (e.g., intracavernosal medication for ED, condoms, lubricants, vibrators, towels) are required.

Differentiating between normal intimate and sexual behavior and hypersexual behavior of adults residing in long-term care facilities is one of the greatest challenges for healthcare providers. Normal sexual behavior displayed in public areas might erroneously be perceived as hypersexual (Wallace and Safer, 2009). The dichotomy between protecting autonomy and defending vulnerable adults from abuse gives rise to moral and ethical dilemmas (Elias and Ryan, 2011). Lack of policy guidelines and limited training contribute to the difficulties experienced by staff and lead to inconsistent and uncertain practice, with negative implications for the sexual health of residents. Very few of 198 Australian residential aged care facilities had any formal policy guidelines regarding sexuality-related issues, which were often dealt with in an informal and *ad hoc* way (Shuttleworth et al., 2010).

There is further need for interventions similar to the one designed for hypersexual behavior in PD (Bronner and Hassin-Baer, 2012). When PD patients demonstrate heightened interest in sex, it is essential to understand whether this behavior manifests a compulsive sexual behavior or whether the behavior is an expression of eagerness and urgency to solve a sexual difficulty (inability to reach orgasm, or ED). The algorithm shown in Figure 24.1 offers a modular assessment of these behaviors and suggests effective treatments and appropriate interventions. In addition, proposing specific rules, e.g., allowing conjugal and home visits, using "do not disturb" signs, or allowing doors to remain shut may help the staff and provide residents with the privacy needed (Hajjar and Kamel, 2004).

PSYCHOLOGIC THERAPIES

Psychologic methods are the basis of treatment of women's sexual dysfunction and an important component of the management of the same in men. Brief descriptions of the common psychologic approaches follow: of note is a definite overlap among the three most commonly used (Fig. 24.3).

Cognitive behavioral therapy

Cognitive behavioral therapy (CBT) is a psychologic therapy that emphasizes the important roles of thought

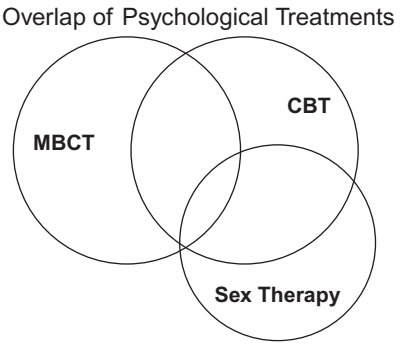

Fig. 24.3. Mindfulness-based cognitive therapy (MBCT) and behavioral therapy (CBT) share the basic premise that cognitions, emotions, physical sensations, and behavior are linked such that if one modality changes, the others will shift. There is also marked overlap between CBT and sex therapy – sex therapy provides the behavioral elements used in CBT for sexual dysfunction. The encouragement to stay present, attending to sensations, including sexual sensations, links MBCT to sex therapy (sensate focus in particular), but the sex therapy encourages evaluation and change, which is discouraged in MBCT.

and behavior in determining how and what a person feels. The underlying principle is fourfold: cognitions, emotions, sensations, and behavior are all interconnected (Fig. 24.4). In any given situation, including a sexual experience, one's thoughts and actions shape one's feelings – the latter including both emotions and physical sensations, sexual and non-sexual, and also including pain. In turn, what one feels influences thoughts and behaviors: if any of these components change, the others must also shift. Of the four possibilities, thoughts are the most amenable to change: thus a major component of CBT is cognitive therapy. This involves teaching the person to identify thoughts that, despite being believed, and possibly frequently entertained, may not be accurate. Thoughts are often exaggerated, even "catastrophic" i.e., maladaptive. Catastrophizing the sexual outcome (e.g., "the result will be a total disaster if I can't have an orgasm/keep an erection") is particularly common and is highly amenable to cognitive therapy. Skills are taught to allow individuals to critique recurrent negative thoughts, for example, about their sexual self-image and desirability, their ability to function as a sexual partner given their neurologic illness, the extent of the changes brought about by their illness, the severity of negative consequences of being sexual (e.g., sex causing worsening of neurologic symptoms), and assess whether these thoughts are accurate. The person is encouraged to create a thought record: to write down evidence for and against the accuracy of that thought. If the decision is that it is exaggerated/maladaptive (there is more contradictory than supportive evidence), then effort is required to construct a different thought that can now be believed to be true having considered the evidence for and against the former thought. Each time the old thought is entertained, the task is to pause and replace it with the new altered thought. Soon the new altered thought becomes automatic and in time the whole process can be done in the moment rather than at a later time by creating a formal thought record.

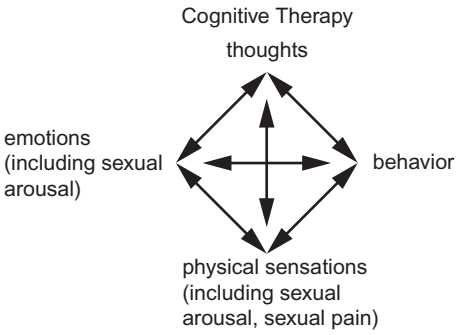

Fig. 24.4. Cognitive therapies rely on the principle that, as cognitions, emotions, physical sensations, and behavior are linked, deliberate change to one of the four (specifically to cognitions) will cause changes in the other three modalities.

It has been proposed that cognitive therapy helps patients learn to recruit prefrontal regulatory mechanisms to modulate emotional reactivity in the limbic system (DeRubeis et al., 2008). Thus cognitive therapy is thought to increase inhibitory executive control, helping to interrupt or dampen automatic limbic reactions. Functions of the prefrontal cortex (PFC), such as direction of attention (Ottowitz et al., 2002) and reappraisal (Ray, 2005), are addressed in cognitive therapy. Functional imaging studies have not been done in persons with sexual dysfunction treated with cognitive therapy but such studies in persons with depression have shown that cognitive therapy has been associated with decreased resting-state activity in the PFC, possibly allowing greater capacity for "top-down" emotion regulation when it is needed (DeRubeis et al., 2008).

CBT can increase patients' sense of control over their dysfunction by including an explanation of the many contributory factors, only some of which are due to their neurologic illness. This provides logic to patients' situation and opportunities for changes they can make. This is particularly helpful when there is sexual pain: some neurologic conditions can cause pain from genital touch, from heightened muscle tone of sexual arousal, from orgasm, from ejaculation, or from vaginal or anal penetration. Research has shown that perceived control of pain severity reduces its intensity under experimental conditions. Using functional magnetic resonance imaging, activation of the PFC, especially the right anterolateral PFC (i.e., high-level conscious appraisal), was shown to mediate the analgesic effect of perceived control (Wiech et al., 2006), interacting with the nucleus accumbens to suppress amygdala activation (Wager et al., 2008). Encouraging patients to decide if and when the difficult part of their sexual response is included in their sexual activity can capitalize on this finding: a woman for whom vaginal penetration can be painful can decide if penetration is to be included in a given experience and at what point during non-penetrative activities, as can a man with variable ED. Clearly both partners need to be involved in treatment so as to create a true sense of control for the patient.

Having anxious thoughts whilst being sexual underlies many sexual dysfunctions. CBT can target those anxious thoughts effectively. Similarly, anxiety can increase pain intensity. In the experimental situation pain in the presence of anxiety is perceived as more intense and associated with very different activation of the entorhinal hippocampal cortex compared to when pain-related anxiety is absent (Ploghaus et al., 2001). Often the sexual pain from the underlying neurologic condition cannot be directly improved – medications such as

gabapentin often are of limited benefit. Lessening the associated anxiety can indirectly lessen the pain intensity.

Having positive expectations is highly therapeutic for sexual dysfunctions: of note is the marked placebo effect of medication for sexual dysfunction (Bradford and Meston, 2011). Encouraging positive expectations about sexual interactions, including pain reduction, is a component of CBT. Imaging studies show that manipulating anticipated pain can lessen both the subjective experience of pain and the activation of pain-related brain areas, assuming those expectations are of reduced pain (Koyama et al., 2005).

A behavioral component of CBT is relaxation. Eliciting the relaxation response (RR), for instance, from a commonly prescribed practice of progressive muscle relaxation, has recently been investigated to determine underlying molecular mechanisms that might explain the clinical benefits seen in many conditions, including anxiety, hypertension, insomnia, and sexual dysfunctions. Relaxation response practice enhanced the expression of genes associated with energy metabolism, mitochondrial function, insulin secretion and telomere maintenance, and reduced expression of genes linked to inflammatory response and stress-related pathways (Bhasin et al., 2013). Other sexual behavioral components of CBT are chosen from those used in sex therapy.

Sex therapy

Although all treatment modalities used in sexual rehabilitation are sexual therapy, traditionally the term "sex therapy" has included the comprehensive evaluation of the biologic, interpersonal, sociocultural, and cognitive-emotional-behavioral aspects of the current difficulties along with specific treatments. The latter include education as well as communication training and behavioral interventions such as sensate focus practice, guided stimulation techniques, systemic desensitization, the "stop/start" and the "squeeze" techniques, and directed masturbation. These practices all aim at distracting the patient from excessive control, decreasing stress and increasing awareness for the necessary stimulation needed for rewarding sexual experiences (Leiblum, 2007). Sexual aids such as vibrators provide another aspect of sex therapy. The goal of sex therapy is to create or restore mutual sexual comfort, and increase satisfaction and pleasure, rather than perfect genital response (Leiblum and Wiegel, 2002). Sex therapy is particularly suited to the needs of persons with neurologic illness. Detailed information may be needed: for instance, knowing that the whole clitorourethral–vaginal complex is engorged during vaginal but not during direct clitoral stimulation (Buisson and Jannini, 2013) can prompt the suggestion to combine both methods in cases of reduced genital sensitivity from peripheral neuropathy. The act of intercourse, or the experience of orgasm, or the ability to effectively stimulate the partner or self may no longer be possible, such that assistance is needed to think "outside the box" to find new ways to have and enjoy sexual activity. Treatment may be conducted in an individual, couples, or group format.

Sensate focus

This term describes a series of planned progressive nondemand pleasuring exercises which involve each partner taking turns giving and receiving sensual and, later on, sexual touches, caresses, and kisses. Therapists tailor the sessions to the individual couple, guided by their being a heterosexual or same-sex couple, and by whether one or both partners have chronic disease or sexual hesitancies unrelated to the neurologic illness. Partners are invited to take turns touching and caressing each other and guiding verbally and non-verbally as to what feels most pleasurable. Partners learn to listen to their own feelings, discover their partner's preferences, and become accustomed to slowing down instead of rushing through a sexual experience. Initially, genital areas and breasts are off limits. The idea of any goal or expectation of arousal or orgasm is put aside. Usually, each session lasts 15–20 minutes and two or preferably three sessions should occur each week for 3–6 weeks. The couple together with the therapist decides as to when breasts and genital areas are included. As sessions are planned, touches may often be sensual rather than specifically sexual. However, when sexual touches are wanted, oral and manual genital stimulation or the use of a vibrator can be considered. Given possible problems with mobility, dyspareunia, and erection, exploring non- penetrative genital sexual stimulation may be particularly important. Ultimately, the act of intercourse (or vaginal penetration with dildo) may be included but is not the major focus. For some couples intercourse may prove to be less enjoyable, e.g., due to the need for intracavernosal injection or continued dyspareunia, or may not be possible at all, and the therapist then encourages more erotic and more various non-penetrative activities. Focusing away from intercourse can alleviate performance anxiety, and decrease self-monitoring and cognitive distractions, with benefit to all phases of sexual response.

Men and women with spinal cord injury can explore their pleasure–pain continuum, as the skin near their injury is hypersensitive to touch. Often painful and intensely aversive when touched, these sensations can become pleasant when stimulated the right way with a wanted partner. Sensate focus can explore the hypersensitive areas, and find how to create a pleasuring touch.

The emotions and thoughts elicited by the sensate focus experience can clarify conscious and unconscious conflicts that may be part of the sexual problem. Working with this information and addressing the underlying issues brought out by the sensate focus exercises can be the most powerful part of treatment. Therefore, it is important that the therapist links sensate focus exercises with regular psychosexual sessions, where couples can process, communicate, and understand these experiences.

Systemic desensitization

Systemic desensitization is used when severe anxiety or phobic response to sexual stimulus is evident, e.g., fears of penetration leading to vaginismus in a woman or performance anxiety underlying a man's inability to have orgasms with a partner. Such dysfunctions can occur after a neurologic insult as patients attempt to restart a sexual life. Initially relaxation skills are taught. Subsequently, the therapist helps the patient to identify the level of distress produced by various types of sexual situations. Then patients are encouraged to begin with the least distressing situations, and gradually expose themselves to more distressing ones. In the case of vaginismus, vaginal touch, followed by the use of gradually larger vaginal inserts, is helpful. At each step in the progression, the patients use relaxation skills and discuss their emotions and thoughts with the sex therapist. The fear gradually extinguishes by realizing that nothing bad is happening to them.

Physiotherapy of the pelvic floor

Physiotherapy of the pelvic floor, often involving electromyographic muscle biofeedback, is an important component of treatment for sexual hesitancy due to incontinence and for women with sexual pain disorders (e.g., vaginismus, dyspareunia, including vestibulodynia) and for men with painful ejaculation. Thus pelvic floor strengthening exercises may be the focus. Alternatively, pelvic floor relaxation, manual therapy such as introital stretching techniques and pelvic floor massage, and work with vaginal inserts may be needed, with collaboration between the clinician and physiotherapist to allow a simultaneous psychologic and behavioral approach (Rosenbaum, 2011).

The stop/start and the squeeze techniques for premature ejaculation

The "stop/start" and the "squeeze" techniques are behavioral interventions for premature ejaculation. Men learn how to focus on, rather than distract from, their arousal and to identify intermediate levels of sexual excitement. Men with premature ejaculation are typically sexually anxious, such that they fear focusing on their sexual excitement, believing it will cause them to ejaculate more quickly. They usually limit their sexual pleasure, and fail to focus on or remain in intermediate levels of sexual excitement. The prescribed exercises are tailored to the couple but can be adapted for the single man. The premise is that the sexual stimulation (manual touch, fantasy, touch using lubrication, oral penile stimulation) is introduced gradually over a number of sessions, progressing to more intensely erotic stimuli only when ejaculatory control at lower stages of arousal has been explored and achieved. Individual choices of both partners guide the treatment.

Positioning for sexual activity

Due to physical changes and limitation, counseling about positioning for sexual activity is frequently required. The couple's needs are discussed and they are encouraged to experiment, explore, and find positions that are comfortable, balanced, and safe. Consultation with an occupational therapist or physiotherapist can be helpful. Pillows behind the lower back and/or knees for support can reduce lower-back pain, alleviate spasm, and enable easier access to genitals. The "spoon" position, lying side to side, with both partners facing the same direction, can be useful for people who wear catheters. The "chair or wheelchair position" is possible when armrests are removed or another chair is used. During sex play or intercourse, one partner can sit on the other partner's lap face to face, facing away, or facing to the side. The person in the wheelchair can also be penetrated or receive oral sex by moving to the edge of the chair, while the partner kneels or sits in front. The "supportive rear position" for intercourse is when one partner is leaning on his/her stomach at the edge of a bed/table/couch (with a pillow under the hips or the belly). The other partner can stand or straddle behind. This position provides optimal balance for the disabled person and allows him/her to help more with the sexual movements.

Use of sexual devices and aids

There are devices designed to assist positioning (e.g., intimate rider, body bouncer, thigh sling to hold the thighs in an elevated and open position). Massagers and vibrators are used to enhance pleasure genitally and non-genitally to facilitate arousal and orgasm in women and men. Vibrostimulation is also used for sperm retrieval when the neurologic condition impairs ejaculation (Phillips et al., 2014). When there is reduced blood flow to the vulva, especially to the clitoris, mechanical vibration may not produce engorgement. A clitoral vacuum engorgement device uses a gentle vacuum to engorge the clitoris. Significant improvement in genital sensation,

vaginal lubrication, orgasm, and sexual satisfaction in women with arousal dysfunction unrelated to neurologic disease has been reported (Billups et al., 2001; Wilson et al., 2001). Vacuum erectile devices for men similarly draw venous blood back into the penis to cause a passive erection. The blood needs to be trapped by placing a tight band around the base of the penis, and only kept in place for up to 30 minutes. Devices with cuffs with elastic straps can hold a variety of objects, including dildos and vibrators. Realistic penetration devices can be found today in sex toy stores, and enable penetration when vaginally penetrating a partner is not possible.

Lubricants

Autonomic damage may impair lubrication, as may estrogen lack postmenopause. External lubrication is needed for anal penetration. A variety of external lubricants are available commercially, or vegetable oil can be used. Sensitivities to product ingredients are common: avoiding parabens, alcohol, perfume, silicone. and glycerin can be helpful. A "patch test" on the inner arm can be done. Water-based lubricants will dry out during use and some water or more lubricant should be added but they can be safely used with condoms and sex toys. Silicone-based lubricants last longer but cannot be used with silicone sex toys: the silicone in the lubricant may degrade the silicone toy. Oil-based lubricants deteriorate latex condoms or gloves.

Mindfulness and mindfulness-based cognitive therapy

Mindfulness is an ancient form of meditation recently adopted by western medicine and found to benefit stress, chronic pain, anxiety, depression, sexual dysfunction, and immune mechanisms. Mindfulness involves "deliberately and non-judgmentally paying attention to the present moment" (Kabat-Zinn, 1982). With ongoing meditation practice a heightened awareness and focus are accompanied by relaxation and non-reactivity: multiple thoughts that enter consciousness are noted, but not followed. A fundamental component of mindfulness is the non-judgmental accepting attitude. This enables individuals to observe, but not judge, their tendency to cling on to (attach) pleasant emotions and sensations and to avoid (find aversive) those that are unpleasant. Mindfulness practice leads to the realization that all thoughts and feelings and physical sensations are only temporary brain phenomena. This is specifically pertinent to the experience of pain: the physical sensation can be "uncoupled" from the emotional and cognitive experience (Kabat-Zinn, 1982), of relevance to both sexual pain and background pain from the neurologic condition. A recent review of the various theoretically reversible epigenetic mechanisms which regulate gene expression involved in pain highlights the therapeutic potential of altering the experience of pain (Seo et al., 2013). As with pain sensations, sexual sensations can be "uncoupled" from cognitive evaluation: a man can learn to experience his multiple sclerosis-altered sexual arousal and erections as sexual sensations, focusing on their sexual nature rather than on their evaluation and judgment. Thus acceptance of what is happening sexually in the moment, rather than anticipating possible performance failure, a major inhibitory factor for men's arousal, may be encouraged by mindfulness practice. Increased acceptance of the present sexual context may be especially relevant for women. Women's need to have many things in place before they can attend to sexual stimuli has been termed "arousal contingency" and is found to be a major factor determining a proneness to inhibition of women's arousal (Sanders et al., 2008).

Two styles of mindfulness practice are followed: focused attention or *shamatha*, an example being to direct attention to the sensations in a certain area of the body; and open monitoring or *vipassana*, where one learns to be aware of all sensory, emotional, or cognitive events occurring in the mind. Mindfulness practice was introduced to the western medical community some three decades ago mainly by the work of Jon Kabat-Zinn to develop a program of mindfulness-based stress reduction (MBSR). This is still widely used and mechanisms of change are now under investigation (Dobkin and Zhao, 2011). Mindfulness-based cognitive therapy (MBCT) is an adaptation of MBSR, originally developed to prevent relapse of major depression. In contrast to the objective to change maladaptive thoughts inherent in CBT, in MBCT, although there is similar encouragement to identify the negative and catastrophic thoughts, there is encouragement to view them as simply "mental events" that need not be believed or followed. Recently MBCT has been adapted for sexual dysfunction (Brotto et al., 2008a; Basson and Smith, 2014). Given the high prevalence of concerns regarding low self-image, increased numbers of depressive and anxious thoughts along with anxiety about sexual performance, fears of "not being normal," and tendency to distract during sexual activity, MBCT for sexual dysfunction appears to hold high therapeutic promise. Mindfulness practice, with its focus on a non-judgmental stance and acceptance of the present moment, can temper these distractions and self-criticisms. Research suggests that the power of anxiety to underlie sexual problems rests in its ability to distract from the erotic stimulus (Barlow, 1986). With MBCT, the person learns to notice distracting critical and anxious thoughts and becomes increasingly able to accept their presence for just that moment, but not follow them. The erotic stimulus can now be attended to.

Facets of mindfulness include the ability to describe, but be non-judgmental of, one's inner experience in the present moment (Baer et al., 2006). Thus MBCT may lead to: (1) more appreciation of sexual sensations and sexual arousal from those sensations even when there is some sensory loss; (2) more sexual arousal from sexual stimuli during the time in between sexual experiences to restore a sense of being a sexual person despite neurologic changes; and (3) less self-criticism of sexual response during sexual activity, i.e., less self-monitoring that typically compounds sexual dysfunctions.

Recent research identifies changes in brain structure with mindfulness training and relationships between brain structure and facets of mindfulness (Murakami et al., 2012). There are changes in gray-matter density in brain areas involved in the regulation of emotion, self-referential processing, and perspective taking associated with mindfulness practice. The "describing facet" (a domain on the Five Facet Mindfulness Questionnaire (Baer et al., 2006) which assesses the ability to find words to describe feelings and the ability to be non-judgmental) shows a positive association with gray-matter volume in the right anterior insula (Murakami et al., 2012). The researchers suggest that the increase in volume of the insula might reflect greater awareness of one's own stressed state and more ability to mitigate emotions cognitively. The research also demonstrated that higher scores on the "describing" facet (potentially reflecting the ability to exert cognitive control on emotional responses) was associated with lower amygdala activity. This could be interpreted as the potential of mindfulness practice to temper the anxiety, guilt, self-criticism, and frustration that can preclude subjective arousal from sexual stimuli.

It is important to note that, in both neurologic and non-neurologic disease, it is frequently comorbid depression that determines whether or not there is sexual dysfunction. This, together with the major role of anxiety underlying sexual dysfunction in both men and women, encourages the use of MBCT or CBT given their documented benefit for both depression and anxiety disorders.

Outcome data for psychologic therapies

Given that sexual medicine is highly interdisciplinary, a multidisciplinary and multimodal approach to treatment is often required, especially in the context of a chronic illness. Thus controlled trials of just one type of therapy, especially if there are exclusion factors such as comorbid depression, are of limited relevance for neurologic patients, but will be summarized. Outcome data on psychologic methods are incomplete due in part to past lack of funding for non-pharmacologic sexuality research but also due to lack of standard or common protocols such that studies can be compared. Recently introduced manualized therapy (where treatment is outlined in manuals for participants and expanded versions are created for clinicians to include rationale and detailed instructions on teaching the cognitive and mindfulness skills) holds promise (Brotto et al., 2008a). There are no studies focused on patients with neurologic disease.

A Cochrane review of five randomized trials determined that psychologic methods benefited ED (Melnik et al., 2007). Two systematic reviews and one meta-analysis of controlled clinical trials for female and male sexual dysfunction have been recently published (Gunzler and Berner, 2012a, b; Frühauf et al., 2013). The authors searched all relevant publications between 1985 and 2009. Studies lacking a control arm were excluded, given the well-recognized therapeutic effect arising from careful assessment, validation, and explanation of sexual difficulties. All noted the preponderance of sex therapy, the larger number of older trials (the emerging research on MBCT was too recent to be included), and low quality, as measured by indicators of internal validity. Summarizing the 2012 systematic reviews, 20 controlled trials for male and 15 for female sexual dysfunction were identified, plus two which included both male and female dysfunction in the same study. However, for women the majority of studies were on sexual pain, with just four on hypoactive sexual desire and three on orgasmic disorder. For men, only one study addressed low desire and only three included absent/delayed ejaculation. Although involving both partners in therapy is generally recommended, nine of the female studies and 12 of the male studies involved only the one partner. Most of the research involved small-group therapy. For female dysfunction, therapy included CBT (seven trials), sex therapy (three trials), or both (seven trials), while for male dysfunction, studies included CBT with psychotherapy (one trial), sex therapy (seven trials), or both (six trials), CBT plus medication (six trials), or hypnosis ± acupuncture (two trials). The overall conclusion was that psychosocial interventions for sexual dysfunction were effective.

The 2013 meta-analysis included 20 studies of intervention compared to waitlist. Only six focused on male dysfunction and none on male low desire (Frühauf et al., 2013). Quality of method, outcome measures, and reporting was seen to be highly variable. Psychologic treatments proved superior to waitlist for both sexual function and sexual satisfaction, with significant effect sizes of 0.58 and 0.47 respectively. There was clear evidence of benefit in both symptom severity and sexual satisfaction for women with orgasmic dysfunction and also in women with low desire. However, evidence was less clear for ED and premature ejaculation.

Research using psychologic and pharmacologic versus each alone has been unsatisfactory to date. In general, studies have found PDE5 inhibitors plus psychologic therapies to be more effective and with more lasting benefit than PDE5 inhibitors alone (Barnett et al., 2012). The 2013 meta-analysis determined that, for men with premature ejaculation or ED, combined treatment improved sexual satisfaction more than medication alone. This was also true for men with mixed sexual dysfunctions (Frühauf et al., 2013).

Outcome data for MBCT using manualized therapy are preliminary but encouraging. Benefit has been shown in gynecologic cancer survivors (Brotto et al., 2008b) and in otherwise healthy women with desire and arousal difficulties (Brotto et al., 2008a), including those with histories of sexual abuse. MBCT has also been adapted for women's sexual pain. Currently a program aligned with other established MBCT programs involves eight sessions 1 week apart and combines both *vipassana* and *shamatha* traditions (Basson and Smith, 2014). This evolved from a four-session program that was associated with benefit to sexual pain, associated self-efficacy, pain catastrophizing, hypervigilance, sexual distress, and comorbid symptoms of depression compared to waitlist (Brotto et al., 2014).

In clinical practice as opposed to research, a couple's sexual difficulties are typically complex. For the couple living with neurologic disease addressing the psychologic concerns of both partners, using various combinations of education, CBT, sex therapy, and mindfulness is frequently necessary, but outcome data are lacking.

MEDICATIONS

Medications for erectile dysfunction

Medications dependent upon nitric oxide production

Phosphodiesterase type 5 inhibitors

Penile erection results from increased blood accumulating within sponge-like cavernosal tissue that is enclosed by the tunica albuginea (capsule), thereby increasing intracavernosal volume and pressure to ultimately compress the subtunical venous plexus and trap the blood within the penis. The major neurotransmitter that modulates smooth-muscle relaxation to dilate the sponge-like (sinusoidal) spaces within the cavernosal tissue is nitric oxide (NO). Other vasodilators are involved, including vasoactive intestinal polypeptide, prostaglandins, and acetylcholine. The man's experience of sexual arousal from sexual stimulation signals alterations in the autonomic nervous system such that NO is released from the nerve endings in the sinusoidal smooth muscle and endothelium, stimulating the conversion of guanosine triphosphate into cyclic guanosine monophosphate (cGMP). The increased cGMP stimulates a further cascade of cellular reactions, resulting in dilatation of the smooth muscle surrounding the sinusoids. PDE5 is the rate-limiting enzyme degrading cGMP: inhibiting PDE5 prolongs the action of cGMP. Thus it is clear that PDE5 inhibitors are usually only useful if subjective sexual excitement/arousal is maintained. However, there is another situation which allows sinusoidal NO release from genital stimulation when the relevant spinal cord centers (T10–L1 and S2–4) are disconnected from the brain (as in spinal cord injury), namely a reflex erection that can occur and can be augmented by these drugs.

There are six commercially available oral PDE5 inhibitors: sildenafil, tadalafil, vardenafil and, most recently approved by the US Food and Drug Administration, avanafil, with udenafil and miradenafil available in South Korea. These medications differ in time of onset and duration of action and in side-effect profiles, but there are no data confirming that one is more efficacious than another. These medications can be taken daily or "on demand"; while the daily option is more expensive, it is less disruptive to sexual life. There is some evidence that in men without neurologic disorders, those generally unresponsive to PDE5 inhibitors may respond to daily tadalafil. Only tadalafil is approved for daily dosage, using 5 mg rather than the daily dose of 20 mg.

Studies suggest that many men discontinue the use of PDE5 inhibitors, one reason being lack of awareness that subjective sexual excitement needs to be present (other than the case of reflex erections). There is a learning curve and guidelines suggest that any one drug should be tried on at least four or five occasions before considering a switch to an alternative PDE5 inhibitor (Kendirci et al., 2006). When there is cognitive impairment, difficulty staying focused on the pleasure of sexual stimulation and arousal can limit efficacy (Basson, 2001). Importantly, PDE5 inhibitors are contraindicated in nitrate users owing to severe risk of hypotension. While not always definitely contraindicated, definite caution is needed when prescribing these medications to men with multiple systems atrophy. In addition to using the shortest-action inhibitor and warning of possible hypotension, first testing the smallest dose without any sexual activity is suggested. If the PDE5 inhibitor is tolerated, its subsequent use can be further safeguarded by using horizontal positions for sexual activity. Despite the general cardiovascular safety of these medications, caution should be taken if the patient has uncontrolled hypertension or unstable angina or is prescribed alpha-blockers. Other antihypertensives, including calcium channel blockers, are well tolerated despite the fact that PDE5 inhibitors are mildly hypotensive. Of note, vardenafil should not be taken by men prescribed type 1A or type

3 antiarrhythmics or in men with a congenital prolonged QT syndrome (Morganroth et al., 2004). There was concern regarding a possible link between PDE5 inhibitors and non-arteritic ischemic optic neuropathy, but this has not been confirmed (Tomsak, 2005). There is some possibility of a link between PDE5 inhibitor use, especially sildenafil, and hearing impairment (McGwin, 2010).

There are 11 types of PDE enzymes involved in the degradation of cyclic adenosine monophosphate (cAMP) to AMP and cGMP to GMP. PDE5 is found in skeletal muscle, vascular and visceral smooth muscle, brain, kidneys, platelets, lungs, as well as in the penile tissue. PDE1 is found in the heart and PDE6 in the retina and PDE11 in the skeletal muscles. Thus there are potential side-effects from lack of complete selectivity, e.g., the inhibition of PDE6 in the retina is responsible for the occasional blue vision, particularly with sildenafil. Headaches, flushing, dyspepsia, and nasal congestion are generally infrequent side-effects, headache being more common with neurologic disease. Back pain is most noticeable with tadalafil.

A recent review of PDE5 inhibitors for men with neurologic disease noted the good evidence of benefit in spinal cord injury, contrasting with sparse and insufficient data in other neurologic disorders (Lombardi et al., 2012). This insufficiency may be related to the high prevalence of comorbid low desire in men with certain pathologies, e.g., 80% in multiple sclerosis (Demirkiran et al., 2006) and 66% in PD (Kummer et al., 2009). Most of these studies involved sildenafil. None included additional or alternative psychologic treatment. No deaths, priapism, or autonomic dysreflexia were associated with medication use. Headache was the most common side-effect (up to 15% with vardenafil for men with spinal cord injury), but may lessen as treatment continues. The review confirmed statistically significant benefit in men with spinal cord injury, especially when the lesion is above T12, when there is some residual erection, and when the cord lesion is incomplete. Benefit was also demonstrated in three clinical studies of sildenafil for men with PD, even though depression and vascular disease were frequently comorbid in two of the studies: depression improved along with erectile function in one of the studies (Raffaele et al., 2002). In these three studies the men's Parkinson's symptom scores ranged between 1 and 3 on a 0–5 scale, where 0 indicated no symptoms. Problematic hypotension from the PDE5 inhibitors was not reported.

Two of three clinical studies of sildenafil in men with multiple sclerosis showed statistically significant benefit. Disability scores were less than 6 (range 0–10, where 0 is no disability). Preservation of reflex erections was associated with likely benefit. One small controlled study of young men with spina bifida (mostly with thoracic lesions) also showed benefit from sildenafil.

Medications independent of nitric oxide production

When there is insufficient neuronal and/or endothelial NO to allow the PDE5 inhibitors to be effective, prostaglandin E_1 can be injected directly into the cavernosal tissue to generate cAMP and thus vasodilatation. In this situation the erection is not dependent on the man's subjective arousal. This can be disconcerting and it is important to explain that this medication creates an erection but only sexual stimulation can create the subjective excitement and enjoyment. Mixing prostaglandin E_1 with papaverine, phentolamine, and/or vasoactive intestinal polypeptide can be effective when prostaglandin E_1 alone is not. However, with the mixtures, there is a risk of priapism and penile fibrosis. Careful patient education and monitoring can minimize this risk – patients must be seen to be able to give the injection correctly and educated not to increase dosage without supervision. Partners may need to assist in the man's self-injection. Prostaglandin E_1 is also available as a intraurethral pellet but has lower success rates and some risk of hypotension as the drug becomes systemic.

Whereas neurogenic ED typically requires very small doses of intracavernosal prostaglandin E_1 (e.g., just 1–2 μg in the 17-year-old man with spinal cord injury), when neurogenic ED is comorbid with endothelial dysfunction a higher dose (up to 40 μg) is necessary. Each patient's dosage requires individual incremental adjustment. Both partners often need help in adjusting to the creation of an erection that is independent of sexual excitement of either partner: thus follow-up visits are required to preclude early abandonment of the therapy and despair that the ED is untreatable.

PHARMACOLOGIC TREATMENT OF PREMATURE EJACULATION

Although neurologic dysfunction will more often delay ejaculation, premature ejaculation may occur, e.g., in PD or multiple sclerosis. Medication to slow down the ejaculatory reflex by increasing serotonergic transmission is commonly used. However, relapse is usual when medication is discontinued. Combining pharmacologic and behavioral techniques is recommended to prolong benefit to ultimately allow withdrawal of medication. Ejaculation may be delayed eightfold by paroxetine (10–40 mg daily) and four- to fivefold by clomipramine (12.5–50 mg daily), sertraline (50–200 mg daily), and fluoxetine (20–40 mg daily) (Waldinger et al., 2001, 2004). On-demand therapy 1–2 hours before sexual activity is an option but generally less effective. Most

common side-effects experienced with these agents include fatigue, nausea, diarrhea, decreased sexual desire, and ED. There is no clear evidence of benefit from PDE5 inhibitors but their combination with a rapid-acting SSRI may be more effective than the SSRI alone (Lee et al., 2013).

TESTOSTERONE REPLACEMENT

Comorbid hypogonadism can contribute to sexual dysfunction in the neurologic patient. A meta-analysis of 16 studies showed that testosterone replacement is useful in men with ED with confirmed low concentrations of bioavailable testosterone, although these studies did not focus on the neurologic patient (Jain et al., 2000). In practical terms, when the neurologic condition would be expected to be responsive to PDE5 inhibitor therapy but efficacy is lacking, and when the typical symptoms of low testosterone are clear (low desire, absent sleep-associated erections, and delayed ejaculation), serum testosterone levels are checked and replacement prescribed if morning levels are repeatedly low and there are no contraindications. These include prostate cancer, cardiac failure, breast cancer, general frailty in older men (Ruige et al., 2013), and a secondary hypogonadal state from additional pathology, e.g., pituitary tumor, hemochromatosis. Recent research warns against overly generous replacement given that both high and low endogenous testosterone levels are associated with increased risk of ischemic arterial disease (Soisson et al., 2013). Moreover there is now concern over the safety of testosterone replacement in men older than 65 years of age, both those with and without evidence of cardiovascular disease (Finkle et al., 2014). Occasionally central nervous system disease, e.g., brain injury (especially with basal skull fracture), can interrupt gonadotropin release, leading to secondary low testosterone state (Rees et al., 2007).

TREATMENT OF DISINHIBITED SEXUAL BEHAVIOR WITH ANTIANDROGENS

Patients with dementia may lose the normal inhibitory control of sexual behavior and, although such behavior is not usually dangerous, it can cause immense distress. Having confirmed that what appears to be inappropriate or disinhibited sexual behavior is not simply a result of frustration or lack of privacy to be alone to self-stimulate or to be with the intimate partner (Fig. 24.1), it is occasionally necessary to consider medication, including antiandrogen therapy. Spironolactone, medroxyprogesterone acetate, and gonadotropin-releasing hormone agonists may be of some benefit but research is lacking. Spironolactone can cause hyperkalemia and hypotension and gonadotropin-releasing hormone agonists will cause a brief increase in testosterone level before it declines, which may produce a temporary increase in sexual behaviors. Quetiapine has also been used with some benefit (Raja and Bentivoglio, 2012). All healthcare team and family members need to be included in any decision to use medication, and legal advice is occasionally necessary.

MEDICATIONS FOR FEMALE SEXUAL DYSFUNCTIONS

The only approved and available medication for female sexual dysfunction is local vaginal estrogen for the treatment of dyspareunia from vulvovaginal atrophy due to estrogen deficiency. A careful examination for atrophy must be made before attributing dyspareunia solely to neurologic disease such as multiple sclerosis or peripheral neuropathy. Guidelines suggest that any vaginal estrogen formulation is effective: included are estradiol, estriol, estrone, and conjugated equine estrogens dispensed as vaginal tablets, cream, suppositories, or, in the case of estradiol, there is available a vaginal ring which stays *in situ* for 12 weeks. Despite the intent to avoid systemic absorption, small amounts have been detected from some formulations. Although premenopausal levels are not reached from recommended doses, nevertheless, for women with a past history of breast cancer there is need for caution. There is recent evidence that very small doses of estriol (estriol, unlike estradiol, having minimal action on either endometrial or breast estrogen receptors) at 0.05 mg or even 0.03 mg daily for 3 weeks and then twice weekly thereafter is as effective as the former usual dose of 0.2–0.5 mg twice weekly (Griesser et al., 2012).

MEDICATIONS UNDER INVESTIGATION FOR FEMALE SEXUAL DYSFUNCTION

Intravaginal dehydroepiandrosterone (DHEA)

A study by Labrie et al. (2009) has shown that nightly intravaginal DHEA 13 mg in postmenopausal women without neurologic disease not only restored estrogen deficiency-associated dryness and discomfort but was associated with increased genital sexual sensitivity and ease of orgasm, with subsequent increase in sexual desire/interest. Systemic absorption of DHEA was modest (i.e., DHEA was not increased to the levels of women less than 40 years of age), and no systemic absorption of the testosterone or estrogen derived from the DHEA was detectable using mass spectrometry methods. For the older woman with neurologic disease complaining of lost genital sensitivity, consideration of a trial of

compounded intravaginal DHEA used investigationally may be worthwhile.

Benefit from the following medications has been marginal or absent and none has been studied in the neurologic patient.

Transdermal testosterone

Randomized controlled trials have yielded conflicting results: a number of large trials of surgically and naturally postmenopausal women by one sponsor showed statistical increase in the number of satisfactory sexual experiences (Wierman et al., 2006), whereas two large studies from a different sponsor were negative (Snabes et al., 2012), as were studies in premenopausal women (Davis et al., 2008). Criticisms of the trials include the following:

1. Many of the women would appear to have no sexual dysfunction (experiencing some two to three rewarding sexual experiences per month on average at baseline): this is not currently considered to indicate disorder according to the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (*DSM-5*: American Psychiatric Association, 2013).
2. There is no evidence that women's sexual dysfunction, specifically low sexual desire, correlates with low androgen activity using recent mass spectrometry measurements of androgen metabolites to include intra-cellular testosterone from adrenal precursors (Basson et al., 2010; Wahlin-Jacobsen et al., 2015).
3. There is a lack of long-term safety data given the knowledge that women's sexual life tends to continue unless there is no available sexual partner.
4. There is an absence of studies on the more common sexual dysfunction in women, namely the blunting of arousal, enjoyment, pleasure, and orgasm occurrence with associated lack of sexual motivation (American Psychiatric Association, 2013).
5. Depressive symptoms were an exclusion criterion in all trials –typically these are comorbid with complaints of low desire, even in women without clinical depression (Hartmann et al., 2004).

Transdermal testosterone for women with low sexual desire was approved in Europe but is no longer available due to low sales. Despite the scientific evidence of only marginal or no benefit from regulated transdermal formulations, compounded preparations of transdermal testosterone are prescribed in many countries.

Phosphodiesterase type 5 inhibitors

Although very small randomized controlled trials suggested some benefit to women with neurogenic deficit of genital vasocongestion (e.g., from spinal cord injury, diabetic neuropathy), a larger study has been negative (Alexander et al., 2011). This is in keeping with the clinical experience of lack of benefit from these agents for women with presumed neurogenic deficit of genital congestion. The repeatedly confirmed lack of correlation between women's subjective sexual excitement/arousal and degree of genital congestion may underlie a lack of benefit from these agents (Chivers et al., 2010). Moreover, the importance of feedback of pleasure from genital congestion to the brain to augment the subjective sexual experience is much reduced in women compared to men. Thus it would seem that some degree of reduced genital congestion is not sexually symptomatic (provided there is no comorbid estrogen deficiency).

Flibanserin

Flibanserin (a 5-HT_A agonist, 5-HT_{2A} antagonist, and weak D4 agonist), initially trialed as an antidepressant, has shown only marginal benefit (Katz et al., 2013) (again in women who could already have satisfactory sexual experiences but reported reduced sexual desire).

Bremelanotide

Bremelanotide is a melatonin agonist at MT1, MT3, and MT4 receptors. Given by injection or intranasal inhalation, this molecule was previously investigated and is again currently being trialed, again in women complaining of low desire but able to have satisfactory sexual experiences. Marginal benefit was shown previously (Diamond et al., 2006). Given the widespread distribution of melatonin receptors and only partial understanding of the associated physiology and pathophysiology, major caution is needed in consideration of this molecule for women's sexual dysfunction.

TREATMENT OF ANTICONVULSANT-ASSOCIATED SEXUAL DYSFUNCTION

Sexual symptoms in the neurologic patient may at least in part result from medication, including antiseizure drugs. There are some data supporting impairment of male sexuality from enzyme-inducing antiseizure, drugs including phenytoin, barbiturates, and carbamazepine (but not oxcarbazepine). These medications increase the level of sex hormone-binding globulin, thus reducing the level of free or bioavailable testosterone. Data on women are inconclusive. Theoretically, enzyme-neutral antiseizure drugs are less likely to cause sexual side-effects: these include oxcarbazepine, gabapentin, pregabalin, levetiracetam, and lamotrigine (Devinsky, 2005).

CONCLUSION

Despite their complexity, clinical experience confirms that the sexual difficulties of patients with neurologic disease are highly amenable to the standard modalities of treatment, including PDE5 inhibitors, SSRIs, CBT, sex therapy, and, more recently, MBCT. Outcome data, save for PDE5 inhibitors, in this population are scarce. Managing comorbid depression is crucial, choosing non-pharmacologic approaches when possible. Optimal management of hypersexuality is unclear but careful distinction between lack of opportunity for sexual expression and true hypersexuality must be made.

Commonly both partners have sexual difficulties: the importance of assessing and treating both partners is clear but often ignored. More interdisciplinary clinics or programs with clinicians having expertise both in sexual medicine and neurology are needed. Future research on sexual dysfunctions in neurologic patients, employing both pharmacologic and psychologic treatments focused on the couple rather than on the individual, is needed.

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 25

Management of male neurologic patients with infertility

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INTRODUCTION

Male sexuality and fertility rely heavily on the hypothalamus–pituitary–gonadal axis and on an intact neurologic function of the spinal cord and the pelvic floor. In a previous chapter it has already been described how erectile capacity is decreased or absent in men with neurologic injuries and how this can be treated (see Chapters 13 and 24). This chapter describes normal fertility and ejaculation and how these can be diminished by neurologic conditions. We will describe possible treatments for anejaculation and give recommendations for subsequent management in patients where an ejaculate cannot be obtained. Finally, we will discuss methods of assisted reproductive techniques (ART).

NORMAL FERTILITY AND EJACULATORY FUNCTION

Normal male fertility depends on sufficient sperm production and on delivery of this sperm into the uterus of the female partner. The testes are responsible for sperm production. This takes place in the seminiferous tubules, where immature germ cells develop into spermatozoa while moving from the basement membrane to the lumen of the tubules. The process of sperm maturation takes aproximatly 74 days.

Meanwhile Sertoli cells offer both protection and nourishment to the maturing germ cells. The Sertoli cells also contribute to the blood–testis barrier as tight junctions develop between these cells at the time of puberty. This is crucial because mature sperm, which are present after puberty, are potentially antigenic and may activate the immune system with resulting antisperm antibodies, should they come into contact with this. Meanwhile, Leydig cells in the intertubular connective tissue produce testosterone. Both spermatogenesis and testosterone production are controlled by the hypothalamic–pituitary–gonadal axis with gonadotropin-releasing hormone from the hypothalamus and follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland. The primary function of FSH is to induce production of paracrine growth factors and other factors supporting spermatogenesis from the Sertoli cells. Meanwhile, LH stimulates the Leydig cells to produce testosterone, which in turn supports spermatogenesis via the Sertoli cells.

Each testis is divided into lobules consisting of seminiferous tubules, which converge to form another network of larger tubules termed the rete testis. Following spermatogenesis the mature sperm are released to the lumina of the seminiferous tubule and from here they are transported through the network of tubuli, to the epididymis. During their epididymal transit, the sperm mature further and in a process that makes them capable of progressive movement. Finally the cells reach the cauda epididymis where they are stored until ejaculation. Sperm cells contribute about 1–2% of the ejaculatory volume. The rest stems from the accessory sex glands with the seminal vesicles producing about two-thirds of the combined volume (mainly fructose) and the prostate producing about one-third.

Antegrade ejaculation is a prerequisite for impregnating one's female partner through normal intercourse. The function is coordinated through a spinal reflex with afferent input from the dorsal penile nerve and efferent fibers originating in the spinal cord from the thoracolumbar sympathetic fibers from segments T10 to L2 and somatic fibers from segments S2–4 respectively. Neurons in the cortex, thalamus, hypothalamus, midbrain, and pons also contribute to the ejaculatory process, but the exact roles are not well described (Coolen et al., 2004; Giuliano and Clement, 2005). During normal intercourse, the dorsal penile nerve receives sensory input through sexual stimulation of the glans penis prior

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to ejaculation. Prior to ejaculation, sperm are transported from the cauda epididymis to the ampulla of the vas deferens by contractions of smooth-muscle tissue. When sufficient stimulation has been provided the result is activation of efferent sympathetic fibers from segments T10 to L2. These fibers innervate the smooth-muscle cells in the epididymis, vas deferens, prostate, and seminal vesicles and cause them to contract. The sum result is coordinated peristaltic contractions of these structures, which transport both sperm and ejaculatory fluids from the accessory glands into the posterior urethra – this process is termed seminal emission (Thomas, 1983; Maizels, 1998).

The next step in the process is contraction of the bladder neck which is also mediated by the sympathetic fibers (Thomas, 1983; Bohlen et al., 2000). Meanwhile the external urethral sphincter relaxes through the coordinated action of fibers from the spinal segments S2–4. This is important because it allows for antegrade ejaculation as opposed to flowing into the bladder as retrograde ejaculation. Following seminal emission, somatic fibers from S2 to S4 initiate rhythmic contractions of the periurethral and pelvic floor muscles through the pudendal nerve. Under normal conditions, these contractions result in pulsatile antegrade ejaculation as they push the ejaculate through the urethra and out through the meatus. It is important to note that erections and ejaculation are dependent on completely separate neurologic processes. This means that, although erections are necessary for normal vaginal intercourse, they are not a prerequisite for ejaculation and for fertility.

GENERAL CONSIDERATIONS WITH NEUROLOGIC DAMAGE

Any disruption of the hypothalamus–pituitary–gonadal axis can cause infertility. From a neurologic standpoint, this means that any brain trauma or focal lesions affecting the hypothalamus and/or the pituitary may adversely alter fertility. In practice the most common of such conditions are pituitary adenomas or tumors. Regarding the delivery of semen, ejaculation is based on finely tuned and highly coordinated neurologic reflexes, as described above. This means that any neurologic condition causing either peripheral or central dysfunction can disrupt the process. Overall, this can take the following forms.

Retrograde ejaculation

All or part of the ejaculate is propelled into the bladder instead of out of the urethral meatus. The malfunction arises when closure of the bladder neck during ejaculation is compromised. This can be caused by direct trauma to the muscles of the bladder neck, as seen with transurethral resection of the prostate, but in relation to neurologic disease it happens with disruption or dysfunction of the sympathetic nerves (Yavetz et al., 1994). Symptoms include a lack of antegrade ejaculate along with cloudy postejaculatory urine caused by the ejaculate. Ultimately the condition is diagnosed when sperm are identified within the bladder or in the urine following ejaculation (Colpi et al., 2004).

Anejaculation

Anejaculation is the complete absence of an ejaculate, both antegrade and retrograde. True anejaculation is always caused by central or peripheral neurologic dysfunction or by drugs, including antihypertensives, antipsychotics, anxiolytics, and antidepressants. Orgasm may be achieved in some patients. Spinal cord injuries are considered the most common neurologic cause of anejaculation (Ohl et al., 2008).

Delayed ejaculation

It takes an abnormal amount of stimulation during a prolonged period of time to produce an ejaculate. Delayed ejaculation is a less severe condition in which ejaculation can occur at a higher threshold of stimulation than normally needed (Colpi et al., 2004).

In addition to direct disruption of the ejaculatory reflex, neurologic conditions affecting the spinal cord may have an impact on semen quality. This issue is not well illuminated but especially in spinal cord-injured men, it has been shown that semen quality declines following the injury to the level that fertility is impaired based on this issue alone. The research focus on spinal cord-injured men is somewhat logical as such injuries mainly arise in men aged 16–45 years, which means that fertility is of major concern in the patient group. Below we describe some selected neurologic conditions and their effect on fertility. It should be mentioned that, in many neurologic conditions, there is limited research in the area of fertility, perhaps due to the relatively late age of onset of many of the conditions.

SPECIFIC NEUROLOGIC DEFECTS

Multiple sclerosis (MS)

MS is an autoimmune T-cell-mediated inflammatory disease of unknown etiology, which damages the myelin sheets of nerve fibers in the central nervous system, including the brain and the spinal cord (Olek, 1999). In most cases the disease has an overall steady progress over time, with intermittent episodes of worsening and partial remission of symptoms. The symptoms affecting individual patients vary with the location of affected areas in the central nervous system. Most often the disease first manifests around the age of 20–40 years and

the incidence in women is higher than in men (Duquette et al., 1992).

Not surprisingly, the risk of sexual dysfunction increases with the overall severity of the condition, but problems may well be present also in mild stages of the disease. Thus a small Norwegian study ($n = 194$) among men and women with MS found that 86% of patients with severe MS suffered from some kind of sexual dysfunction while the corresponding figure in patients with mild disease was 53% (Nortvedt et al., 2001). Due to the high dependence on spinal reflex centers, erectile and ejaculatory problems are common in male MS patients. Thus erectile dysfunction is seen in about 70% of men and retrograde, delayed, or absent ejaculation affects approximately 50% of male MS patients (Haensch and Jorg, 2006). In addition to these problems patients may struggle with reduced sexual desire (Haensch and Jorg, 2006).

Regarding effects on semen, little research has been conducted in MS patients. However, a study from 2008 showed reduced semen quality with reduced sperm counts, reduced sperm motility, and altered sperm morphology in MS patients compared to healthy men (Safarinejad, 2008). The semen quality was especially reduced in men with progressive disease. These problems may be due to a disturbed hypothalamus–pituitary–gonadal axis. Other possible explanations for reduced fertility may include reduced levels of sex hormones due to neurologic damage or chronic inflammation as well as direct effects of the autoimmune pathology on semen quality. To make matters worse in the patient group, both erectile and ejaculatory function may be further reduced by adverse effects of anxiolytics and antidepressants used for symptomatic relieve (Cavalla et al., 2006).

Epilepsy

It has been shown that men suffering from epilepsy may have reduced sperm counts, decreased sperm motility, as well as altered sperm motility resulting in an increased risk of infertility (Herzog et al., 1986; Schupf and Ottman, 1996; Isojarvi et al., 2004). However, as most evidence stems from small studies, the exact magnitude of the problem is not well illuminated.

The mechanism behind the disturbances in reproductive function is believed to be related to disruption of the endocrine balance due to effects from electric discharges, both interictal and during generalized and partial seizures on hypothalamic and pituitary function. Thus, disruption in gonadotropin-releasing hormone release along with increased levels of LH, FSH, and prolactin along with decreased levels of free testosterone has been observed in men suffering from epilepsy (Herzog et al., 1986; Murialdo et al., 1995; El-Khayat et al., 2003). According to current understanding, epilepsy-induced endocrine disturbances is most common in cases of temporal-lobe origin due to extensive connections between the limbic system and the hypothalamus (Verrotti et al., 2011). In addition to the direct effects of the disease, antiepileptic medications can adversely affect reproductive function through alterations in testosterone homeostasis as well as through direct effects on sperm cells (Verrotti et al., 2011).

Spinal cord injury (SCI)

In men with an SCI, both the nerves responsible for erections and those responsible for ejaculation are disrupted either partly or completely. Therefore sexual dysfunction and infertility are extremely common in male SCI patients. In women with an SCI, however, fertility is not significantly affected.

The occurrence and treatment of erectile dysfunction in SCI men are covered in Chapter 13. Regarding the ejaculatory function, approximately 90% of men with SCI are unable to ejaculate through masturbation or normal sexual intercourse (Brackett et al., 2010). This means that, although many SCI men can achieve reflex erections and thereby are able to engage in vaginal intercourse, they are not able to father children without medical assistance. In addition to ejaculatory dysfunction, many men with SCI have reduced semen quality, with low sperm motility and viability (Denil et al., 1992). In addition, semen from SCI men has been determined to have more DNA damage compared to that from fertile men; however, the clinical significance of this is unknown (Brackett et al., 2008).

Reductions in semen quality are most likely to affect SCI men with complete spinal cord lesions (Iremashvili et al., 2010). However, the abnormalities tend to be present regardless of level of injury, the time that has passed following the injury, and the age of the SCI patients. However, the exact reason for the poor sperm quality is unknown and has been the subject of much speculation.

Many intuitively sound suggestions have been posed as explanations. Thus elevated scrotal temperatures from time spent in a wheelchair, a lack of ejaculations, recurrent urinary tract infections, and endocrine disturbances have been investigated. However, none of these causes has been able to adequately account for the reduced semen quality. On the contrary, recent evidence points to etiologies related to sperm transportation and storage, seminal plasma factors, and the immune system (Aird et al., 1999; Brackett et al., 1996, 2000, 2007a; Ohl et al., 1999; Basu et al., 2002, 2004; Trabulsi et al., 2002; Cohen et al., 2004).

Thus, SCI men have been shown to have an abnormal pattern of transport of mature sperm cells, where the sperm tends to be stored in the seminal vesicles. In addition, the seminal plasma has been shown to contain several abnormalities which may be detrimental to semen quality. In one elegant study, researchers attempted to mix seminal fluids from SCI men with semen abnormalities with healthy sperm cells of fertile, normospermic men. Interestingly, this caused a significant decrease in semen motility (Brackett et al., 1996). In addition, the same group aspirated sperm directly from the vas deferens and were able to show that these sperm cells had greater motility compared to those in the ejaculate of the same men (Brackett et al., 2000). These findings were interpreted to conclude that the seminal plasma of SCI men exerts a toxic effect on their own sperm. It has been further hypothesized that the toxicity may be caused by disruption of the sympathetic nervous innervation of the seminal vesicles, although no conclusive evidence exists to confirm this theory. Another explanation relates to the immune system and revolves around the finding that most SCI men have an elevated number of T lymphocytes in their blood. Meanwhile, lymphocytes secrete cytokines which may be harmful to sperm cells and such cytokines have been identified in the seminal plasma of SCI men (Basu et al., 2004). Interestingly, and perhaps of future clinical importance, the motility of sperm from SCI men has been shown to improve when these cytokines are neutralized (Cohen et al., 2004; Brackett et al., 2007a).

Congenital abnormalities of the spinal cord

Neural tube defects are relatively common birth defects involving the spinal cord. Such defects most often involve the lumbar vertebrae and, among other problems, result in sexual dysfunction, including ejaculatory dysfunction and infertility (Decter et al., 1997). In fact, patients with lifelong ejaculatory dysfunction are sometimes diagnosed with occult congenital dysplasia of the lumbar spinal cord. To make matters worse, attempted surgical treatment of the conditions can result in further neurologic damage which in turn can create further sexual dysfunction (Boemers et al., 1995). Among patients with neural tube defects, those with lower and less severe damage have the greatest likelihood of parenting children by natural intercourse (Decter et al., 1997).

Diabetes

The topic of diabetes and infertility is a matter of debate and more research in the area is clearly needed. However, some studies have found that infertility may be more prevalent in diabetic men compared to non-diabetic controls (Bener et al., 2009) and the prevalence of subfertility in diabetic men may be as high as 50% (La Vignera et al., 2009). To explain these findings, it is important to know that diabetes delivers two devastating blows to male sexual function through autonomic neuropathy and comorbid vascular disease respectively. In combination, these two issues are responsible for a very high rate of erectile dysfunction in diabetic men. In addition the neurologic deficits may cause delayed ejaculation, retrograde ejaculation, and – with very pronounced dysfunction – frank anejaculation. Both erectile function and ejaculatory capacity show a gradual decline with autonomic neuropathy. With erections, this manifests in a progressive decline in hardness culminating in a total lack of erections. Regarding ejaculation, the typical clinical course may include, at first, an increased need for stimulation over a prolonged time period to induce ejaculation (delayed ejaculations). Over time, the problem may be attenuated by retrograde ejaculation. The final stage is total anejaculation with severe sympathetic autonomic neuropathy (Dunsmuir and Holmes, 1996; Sexton and Jarow, 1997). Depending on study populations and the exact methods used for evaluation, between 35% and 75% of diabetic men suffer from ED (Vinik et al., 2003). Similarly, some form of ejaculatory dysfunction is estimated to affect about 40% of diabetic men (Dunsmuir and Holmes, 1996). As with any long-term complication of diabetes, the occurrence of sexual dysfunction and ejaculatory problems is directly related to blood sugar control over time (Genuth, 2006).

When evaluating the semen quality in diabetic men, the results of the literature are somewhat conflicting and no strong evidence exists. However, several studies have shown that the semen volume is reduced in diabetic patients as compared to that in healthy men (Bartak et al., 1975; Padron et al., 1984; Ali et al., 1993; Niven et al., 1995; Agbaje et al., 2007; Delfino et al., 2007). In addition semen motility and/or semen morphology has been found to be negatively affected by the disease in most studies on the subject (Bartak et al., 1975; Padron et al., 1984; Ali et al., 1993; Delfino et al., 2007). Increased levels of sperm DNA damage have been identified in diabetic men, although the clinical significance of this finding is somewhat unclear (Agbaje et al., 2007).

Possible explanations for the reduced semen quality in at least some diabetic men include disruption of the hypothalamus–pituitary–testis axis with reduced testosterone production and perhaps an increase in peripheral estrogen levels. In addition, low-grade inflammation and chronic oxidative stress may disrupt sperm maturation and testosterone production in the testes (La Vignera et al., 2012). The most likely cause of the reduced semen volume seen in diabetic patients is unidentified partial retrograde ejaculation along with neurologically caused

atony of the accessory male sexual glands causing less seminal fluid to be excreted with ejaculation (La Vignera et al., 2011).

Nerve trauma and surgery

Naturally, the nerves of the pelvic floor can be damaged directly by mechanical trauma or surgery. As with all other neurologic damage this can result in diminished or abolished sexual and reproductive function. In men, the ejaculatory ducts and accessory ejaculatory glands are removed with radical surgery for bladder and prostate cancer. This means that, although the nerves responsible for ejaculation are likely not damaged during most surgeries, patients will with certainty suffer from complete and untreatable anejaculation following surgery. Due to the often advanced age of the patients, routine sperm banking is not offered in most centers but for men who wish to father children following surgery this should certainly be considered. In addition to ejaculatory dysfunction, both cystectomies and prostatectomies cause at least some degree of erectile dysfunction in the majority of patients. The exact reported numbers vary greatly depending on differences in patient populations, erectile function before surgery, surgical techniques, data collection, treatments for erectile dysfunction, and working definitions of potency; however at least 70% of patients are affected (Tal et al., 2009). Another type of surgery which may cause erectile dysfunction is rectal surgery. Overall, erectile dysfunction has been reported in 36–60% of men following such procedures (Rees et al., 2007). In addition to peripheral nerve damage caused by this type of surgery, the superior hypogastric plexus may be damaged, further contributing to sexual dysfunction and adding a risk of ejaculatory dysfunction with the surgery.

In addition, damage to the lumbar sympathetic ganglia and the superior hypogastric plexus or to the nerves originating from these structures may be damaged during aortic aneurysm repair or coronary bypass procedures as well as by trauma surgery and by any retroperitoneal lymph node dissections. In particular retroperitoneal lymph node dissection as an adjuvant therapy in testicular cancer poses a risk of such damage. Thus, postganglionic sympathetic nerves and the hypogastric plexus are both removed with the "classic" retroperitoneal lymph node dissection technique, meaning that normal ejaculation is abolished.

To ameliorate the problem, nerve-sparing alternatives have been developed and these have improved outcomes. However, even with these advances, the risk of retrograde ejaculation and anejaculation resulting from surgery is still present, and it is especially pronounced with high tumor burdens and surgery following chemotherapy (Ohl et al., 2008). As testicular cancer often affects young men, the practical consequence of ejaculatory dysfunction is of particular importance in this patient group. However, from a fertility standpoint, sperm banking is already recommended before any testicular cancer treatment, as the primary treatments themselves (surgery, chemotherapy, or radiation) can affect semen quality severely.

MANAGEMENT OF NEUROLOGICALLY INDUCED INFERTILITY

As of today, there are no clinically applicable methods of improving semen quality. Additionally, the greatest fertility-related problem with neurologic conditions tends to be ejaculatory dysfunction. The natural goal in the management of ejaculatory disorders is to obtain viable sperm cells which can be used to inseminate the female partner. The best situation is to re-establish antegrade ejaculation. If this is not possible the sperm cells must be collected either from the bladder (in retrograde ejaculation) or directly from the testes of ejaculatory ducts. It is very important to keep in mind that patients should always be offered the least invasive treatment option available.

MANAGEMENT OF RETROGRADE EJACULATION

In the management of retrograde ejaculation, the optimal outcome is to reverse the flow of semen so the patient is able to obtain an antegrade ejaculate. In mild cases of neurologic dysfunction the first simple step is for the clinician to consider if any medications the patient is taking may be contributing to the problem. Such medications most commonly include alpha-blockers and antidepressants and these drugs should be discontinued if possible. Next, some patients may benefit from simple sympathomimetic medications which can pharmacologically stimulate the contraction of the bladder neck in conjunction with ejaculations (Kamischke and Nieschlag, 2002). The principle is that the medications can induce contractions of the smooth musculature which is not being stimulated adequately by the sympathetic nerve fibers. Bladder neck contractions will then prevent the ejaculate from flowing back into the bladder just as in a normal healthy ejaculatory process. Possible medications include imipramine, ephedrine, pseudoephedrine, and phenylpropanolamine (Gilja et al., 1994; Kamischke and Nieschlag, 2002; Ohl et al., 2008). However, due to a lack of well-designed studies, the success rates of these treatments are unknown and none of the drugs have been approved for thetreatment of retrograde ejaculation by regulatory agencies. In addition, it is important to use caution with

these drugs in patients at risk for cardiovascular complications. Side-effects include dizziness, sleep disturbances, weakness, restlessness, dry mouth, nausea, or sweating. To reduce the occurrence of such unwanted effects, the drugs should be used strictly for fertility purposes and as such they should be administered around the time of the female partner's ovulation (Kamischke and Nieschlag, 2002). The drugs have the best results in patients who are not severely affected by their neurologic dysfunctions, such as men with limited peripheral nerve lesions from trauma or surgery or in the early stages of progressive disorders, such as diabetes or MS.

When antegrade ejaculation cannot be re-established, it becomes necessary to use more invasive methods of sperm retrieval. Here, sperm cells may be harvested from the bladder following ejaculation. When attempting this, it is important to note that both urine and the acidic environment naturally present in the bladder can damage sperm cells severely, rendering them incapable of fertilizing an oocyte (Crich and Jequier, 1978). To account for this, the bladder is emptied prior to ejaculation through catheterization with the use of a non-spermicidal lubricant. Following emptying, a sperm-friendly medium (e.g., sperm wash medium or Ham's F-10 medium) can be instilled into the bladder through the catheter (Suominen et al., 1991). Subsequently the man must be subjected to sexual stimulation, most commonly by masturbation. When he obtains a feeling of orgasm/ejaculation, the sperm cells must be collected immediately from the bladder, again by catheterization. Again a non-spermicidal lubricant is used and furthermore it is important to use a plastic catheter as sperm cells may adhere to silicone catheters. Following the "harvest" the sperm must be quickly processed for subsequent use in assisted reproduction (Braude et al., 1987; Shangold et al., 1990; Okada et al., 2004).

ANEJACULATION

The management of anejaculation parallels that of retrograde ejaculation in that mild cases may sometimes be reversed by a change in exacerbating medications and with the administration of sympathomimetic agents (Gilja et al., 1994; Kamischke and Nieschlag, 2002; Ohl et al., 2008). In anejaculation, a clinical effect may come from an increased contraction of the smooth muscles in the seminal ducts and in the accessory sex glands.

However, in most cases of neurologic anejaculation, assisted ejaculation consisting of penile vibratory stimulation (PVS) or electroejaculation (EEJ) must be used in order to obtain viable sperm cells. If this is unsuccessful then surgical sperm retrieval represents the final treatment option.

ASSISTED EJACULATION

Penile vibratory stimulation

As the name implies, the principle behind PVS is to induce erections by mechanical vibratory stimulation of the penis. The procedure was developed for SCI men and it is performed with specifically designed vibrators, which are able to deliver the sufficient stimulation. In this regard, it has been shown that optimal results are obtained with stimulation parameters consisting of an amplitude of 2.5 mm and a frequency of 100 Hz (Sonksen et al., 1994). When performing the procedure, the vibrating disc of the PVS device is placed on the glans penis, either on the dorsal surface at the frenulum or on the ventral surface. Depending on the hand function of the patient, this can be done either by a medical professional or by the patient himself. Alternatively the stimulation can be performed by the patient's partner in a home setting. When activated, the vibrating disc stimulates the Pacini bodies under the skin surface and through these the dorsal nerve of the penis is activated.

As described above, this nerve constitutes the afferent limb of the ejaculatory reflex. With sufficient stimulation, the ejaculatory reflex center will then be activated through connections to the spinal cord. Animal studies have shown that this function is completely reliant on an intact dorsal penile nerve as transection of this nerve eliminates the reflex response to PVS (Wieder et al., 2000). If the efferent limb of the reflex is also intact, activation of the ejaculatory center in the spinal cord will in turn then activate the ejaculatory reflex, with sympathetic outflow creating peristaltic contractions of the smooth muscles of the seminal ducts and accessory sex glands as well as contraction of the bladder neck. Meanwhile, somatic fibers from S2 to S4 are responsible for creating rhythmic contractions of the pelvic floor and a pulsatile antegrade ejaculation.

The efferent activation naturally requires intact sympathetic and somatic nerve fibers. Therefore, men with SCI above T10 (the level of the reflex) have a success rate of approximately 88% with PVS, while men with lower injuries below the level of the reflex achieve a successful ejaculatory response in approximately 15% of cases (Sonksen, 2003; Kafetsoulis et al., 2006a). The vibratory stimulation is applied to the glans for consecutive periods of about 2 minutes of stimulation, interrupted by breaks of approximately 30 seconds. There is no set upper limit to the number of stimulation periods but, when successful, PVS will usually induce an ejaculation within the first 2 minutes of stimulation (Brackett et al., 1998).

The clinician should take care that the penile skin is not damaged and should thus inspect the glans both before stimulation is begun and during each stimulation

Fig. 25.1. The FertiCare vibrator (Multicept, Frederiksberg, Denmark). The ejaculatory reflex is activated by mechanic stimulation delivered through the plastic plate seen at the bottom left of the picture. Optimal results are obtained with an amplitude of 2.5 mm and a frequency of 100 Hz. The device is especially effective in men with a spinal cord injury.

break. It must be noted that SCI patients have reduced or absent sensation of the glans. Therefore they cannot be expected to note abrasions and bruises from the stimulation. When successful, PVS will usually induce an ejaculation within the first 2 minutes of stimulation (Brackett et al., 1998). When PVS is successful it ultimately results in an antegrade ejaculate which can be collected in a non-spermicidal cup for further use in fertility treatment (see below) (Brackett, 1999; Sonksen and Ohl, 2002). Once the ejaculation is initiated, the PVS device is removed and turned off. To gather as much semen as possible, the urethra should be "milked" manually until all the ejaculate has been collected. The only device which is commercially licenced for the purpose is the FertiCare vibrator (Multicept, Frederiksberg, Denmark), which has been on the market since 1995 (Fig. 25.1).

It is important to realize that the ejaculatory reflex can be inhibited by cortical mechanisms, which means that PVS is not necessarily successful in non-SCI patients with neurologic anejaculation, even if the reflex arches are preserved. Cortical inhibition may naturally be especially pronounced in the clinic. This means that some patients may experience an improved response simply by bringing the PVS device home and performing the procedure themselves in a private setting. However, the best candidates for PVS remain SCI men and limited success should be expected in other patients.

If the first PVS treatment sequence is unable to induce an ejaculation, a subsequent attempt may be performed a few weeks later. If this is still unsuccessful, the patient is considered a non-responder and more invasive treatments will be necessary. Before abandoning PVS completely, however, there are a few ways of increasing the treatment response which should be attempted. Most simply, it has been shown that the use of two vibrators simultaneously will salvage some of the non-responders (Brackett et al., 2007b). With this method a vibrator is placed on the dorsal side of the glans while another is placed on the ventral side and they are activated simultaneously by the clinician. Another method employs the use of accessory abdominal electric stimulation together with PVS (Kafetsoulis et al., 2006b). Finally, oral administration of midodrine or a phosphodiesterase-5 inhibitor before PVS is attempted may also increase the response rate (Blanchard-Dauphin et al., 2005; Courtois et al., 2008; Giuliano et al., 2008). Although the exact mechanism of action is unknown and although the method is not well investigated, supplementary oral drugs may be worthwhile because of the non-invasiveness and the mild side-effect profile. Finally, it is important to note that the response to PVS may be reduced in the initial period following the injury. This is due to unresponsiveness of the reflex during the spinal shock phase. In such cases, additional PVS attempts should be made 1–6 months after the injury.

Side-effects to PVS are rare and usually of limited clinical significance. As described, the penile skin may be damaged. To limit this issue, PVS should be postponed or at least performed with caution where there is inflammation or irritation of the glans penis before treatment. Especial caution should be taken in patients with penile implants. In such men too vigorous stimulation may push the tip of the implant against the glans and there is a risk of perforation.

The final and most feared complications consist of increases in blood pressure and, in rare cases, an uninhibited sympathetic reflex response, termed autonomic dysreflexia (Courtois et al., 2008; Ekland et al., 2008). Patients at risk are SCI men with a SCI at or above the level of T6. In most cases patients who experience autonomic dysreflexia with PVS are used to unpleasant symptoms of headaches and flushing with stimulation below the level of the injury. Such stimuli can be everything from an ingrown nail to sensations during urination/catheterization and the response is caused by a rise in systemic blood pressure. As with other stimuli below the injury, initial symptoms of autonomic dysreflexia consist of rising blood pressure, headaches, and flushing. In addition bradycardia may be experienced. If the symptoms are not addressed, the situation can result in stroke, seizure, and in extreme cases, death. Patients prone to autonomic dysreflexia can be pretreated with the calcium channel blocker nifedipine prior to PVS. In such cases, 20 mg nifedipine should be administered sublingually about 15–20 minutes before PVS is initiated. This will limit the rise in blood pressure and thereby reduce the likelihood of complications. If several PVS attempts are made then the nifedipine dose can be adjusted based on the individual response (Steinberger et al., 1990; Sheel et al., 2005; Elliott and Krassioukov, 2006). The potential consequences of autonomic dysreflexia also mean that healthcare professionals performing PVS should always be aware of a fast and/or very steep rise in patient blood pressure during the vibratory

stimulation and that patients should be told to let the physician know if they experience headaches or other pre-symptoms. Naturally, this is especially important in those patients who are at specific risk. In all cases when pre-symptoms arise or a severe blood pressure increase is noted, PVS should be terminated immediately and the patient must be returned to an upright position if he was lying down during PVS.

Electroejaculation

An older method of assisted ejaculation, which is today the second choice to PVS, consists of EEJ with the Seager model 14 electroejaculator (Dalzell Medical Systems, The Plains, Virginia, USA) (Fig. 25.2). This method employs an electric current to activate the smooth musculature of the seminal ducts and accessory sex glands and it was originally invented for use in veterinary practices. In humans EEJ can be used in all cases of neurologic anejaculation but it is most commonly employed in SCI men. The method has a very high success rate, with more than 90% of patients reaching ejaculation upon stimulation. Thus, a large case series found that 897 of 953 EEJ trials in 210 SCI men resulted in ejaculation (94.1%) with viable sperm identified in the ejaculate in 90% of cases (Brackett et al., 2010). Prior to stimulation, the patient is placed in a lateral decubitus position and the probe of the device is placed in the rectum with the electrodes facing the seminal vesicles and the prostate. With most SCI men who have complete lesions the procedure can be performed without anesthesia. However, in men with other types of neurologic anejaculation and in SCI men with preserved sensation, must be done under general anesthesia (Perkash et al., 1985; Sarkarati et al., 1987). Once the probe is in place, the electric current is switched on and the stimulation is delivered in waves. Thus periods of 5 seconds of stimulation followed by approximately 20 seconds of pause are repeated until no more ejaculate is produced – this may take up to 20 waves of stimulation. Following each wave of stimulation the current should be terminated abruptly. Although the exact mechanism of action is unknown, this approach has been shown to increase the likelihood of antegrade ejaculation with EEJ (Sonksen et al., 2001; Brackett et al., 2002). The first electric wave is performed with 5 V and with the subsequent periods of stimulation the electric current is progressively increased by 1–5 V. If a patient is azoospermic with the first EEJ treatment, a second trial may be attempted, as sperm may sometimes be present in such cases.

Fig. 25.2. The Seager model 14 electroejaculator (Dalzell Medical Systems, USA). This device induces ejaculation by stimulating the ejaculatory ducts and accessory sexual glands directly with an electric current. The current is delivered through a rectal probe, as seen at the bottom of the picture. The method is almost always successful in inducing ejaculation if it can be accepted by patients.

Compared to PVS, EEJ is more invasive, more time consuming, and more expensive. In addition the procedure must always be performed by a physician and some patients require full anesthesia. This means that, in spite of the high success rate, EEJ is preferred less by patients (Ohl et al., 1997). More importantly, however, EEJ often results in at least partial retrograde ejaculation, following which sperm must be harvested from the bladder and ultimately the procedure yields fewer motile sperm than PVS (Brackett et al., 1997; Ohl et al., 1997).

EEJ is a safe procedure with few side-effects. As with PVS, the most common issue is local irritation at the place of stimulation. Therefore, rectoscopy should be performed prior to the procedure to rule out pre-existing mucosal lesions and to avoid harming the rectal mucosa the maximal stimulation current is 30 V. As an additional safety measure, the Seager electroejaculator probe has a thermometer and the current will be terminated automatically if the rectal mucosa reaches a temperature above 38.5 °C. Likewise, autonomic dysreflexia may arise with EEJ treatment in SCI patients with an injury at T6 or above. Regarding this issue, risk factors, precautions/prophylactic nifedipine treatment, and management are identical to that described above for PVS. For patients undergoing EEJ under general anesthesia, it is essential that the blood pressure is monitored continuously during the treatment as pre-symptoms cannot be noted in such patients.

EEJ is contraindicated in the presence of lesions or inflammation of the rectum, bleeding disorders, and ongoing treatment with anticoagulation therapy as the risk of local complications is deemed unacceptably high

in these cases. In addition, it is unknown if EEJ may interfere with pacemakers and therefore these are considered a relative contraindication. It should be noted that EEJ often results in at least partial retrograde ejaculation, following which sperm must be harvested from the bladder and ultimately the procedure yields fewer motile sperm than PVS (Brackett et al., 1997; Ohl et al., 1997).

Surgical sperm retrieval

When assisted ejaculation through both PVS and EEJ is either impossible or has failed, then the next choice consists of sperm retrieval directly from the epididymis or the testis, either by aspiration or surgically. Such procedures are far more invasive than assisted ejaculation and therefore they are also more expensive and associated with more side-effects. However, in some cases they may represent the only option in the treatment of male infertility. Mild and relatively frequent side-effects include small hematomas and transient pain. Severe complications are rare but may include injury to the arteries with partial testicular infarction or permanent devascularization as well as prolonged testicular pain (Schlegel and Su, 1997; Practice Committee of American Society for Reproductive Medicine, 2008). The sperm yield from surgical sperm retrieval is generally lower than from assisted ejaculation.

Epididymal sperm aspiration

Methods of epididymal sperm retrieval include percutaneous epididymal sperm aspiration and the more advanced technique of microsurgical epididymal sperm aspiration. The latter is usually performed in patients with congenital bilateral absence of the vas deferens or used in intraoperative sperm retrieval in conjunction with reconstruction of the seminal pathways (Matthews and Goldstein, 1996).

Percutaneous epididymal sperm aspiration avoids surgical exploration and is performed under local anesthesia. The procedure is performed by first finding and stabilizing the epididymis between the surgeon's fingers and then inserting a syringe into the caput. The syringe is then withdrawn until fluid is aspirated (Craft et al., 1995).

In microsurgical epididymal sperm aspiration the epididymal tunic is microsurgically incised and sperm is aspirated with a micropipette from a dilated tubule. If no satisfactory sperm samples can be obtained, a subsequent incision is made that is more proximal than the first one and new aspirations are attempted (Goldstein and Tanrikut, 2006).

Testicular sperm retrieval

Testicular sperm retrieval consists of percutaneous testicular fine-needle aspiration and percutaneous needle biopsy (both of which can be done using local anesthesia), as well as more invasive surgical methods.

In percutaneous testicular fine-needle aspiration, the testis is held between the surgeon's fingers and a needle is inserted into the testis. The needle is then redirected to disrupt tubules and aspirate sperm (Practice Committee of American Society for Reproductive Medicine, 2008). Percutaneous testis biopsy provides better sperm yield than fine-needle aspiration but is more invasive. Here, a 14-gauge biopsy gun is used to obtain a small portion of testicular tissue and multiple samples can be obtained through a single entry site (Practice Committee of American Society for Reproductive Medicine, 2008).

In the traditional open testis biopsy, an incision is made in the tunica albuginea and a biopsy of the testis is removed so that sperm can be extracted (Schoysman et al., 1993). In microsurgical testicular sperm extraction the biopsy is taken under an operating microscope. This enables the surgeon to identify seminiferous tubules in order to extract sperm from these. The microsurgical procedure allows for removal of a minimal amount of tissue with less damage to the testis than in the traditional open testis biopsy (Schlegel, 1999; Dardashti et al., 2000; Ramasamy et al., 2005; Goldstein and Tanrikut, 2006). When no spermatozoa are found in either procedure, the biopsy is repeated in a new area of the testis.

The surgical procedures are associated with longer recovery time than percutaneous testicular or epididymal sperm retrieval procedures and can result in hematomas and pain. Serious complications, which include injury to the arteries and partial testicular infarction or permanent testicular devascularization, are rare (Schlegel and Su, 1997; Practice Committee of American Society for Reproductive Medicine, 2008).

Sperm obtained from sperm retrieval methods are employed in ART. This can be done immediately after extraction or the sperm can be cryopreserved and used at a later time. The latter can potentially spare the patient from repeated surgeries and may avoid hormonal treatment of the female if no sperm can be retrieved.

Choice of assisted ejaculation/sperm retrieval technique

It is well established that the first choice in neurologic anejaculation should be PVS, with EEJ as a second choice in PVS failures. The main reason for attempting PVS as a first choice is the non-invasiveness of the procedure and the ease with which it can be carried out. In addition, PVS is cheaper than EEJ and can in some cases be carried out

by patients or their partners in their own homes, while EEJ must always be performed by a physician and some patients require full anesthesia. This means that, in spite of the high success rate, EEJ is preferred less by patients (Ohl et al., 1997). Finally, EEJ yields less motile sperm and a fraction of the ejaculate may be retrograde into the bladder. PVS is especially successful in SCI men, with about 90% success if the injury is above T10. Meanwhile, the success rates with other causes of neurologic anejaculation are not well studied and may be significantly lower due to cortical inhibition of the ejaculatory reflex. However, even in such patients, it may be worth attempting PVS before moving on to EEJ due to the non-invasiveness and low cost.

When comparing surgical sperm retrieval to PVS and EEJ, these methods are more invasive and more expensive. In addition, the results are generally less satisfying as the numbers of retrieved sperm are lower. In SCI men, it has even been shown that it can be beneficial to repeat the EEJ procedure if no sperm are found in the first ejaculate before proceeding to sperm retrieval. Thus it has been found that viable sperm are present in about one-third of such "second ejaculates" (Iremashvili et al., 2011). Thus surgical sperm retrieval is rarely necessary when fertility problems stem from neurologic anejaculation alone. This is well illustrated in an analysis of 3152 assisted ejaculation procedures performed in 500 SCI men. Here ejaculates were obtained in 97% of patients and the total motile sperm counts exceeded 5 million in 63% of cases (Brackett et al., 2010). In spite of these encouraging numbers, many centers neglect to offer assisted ejaculation to their patients with neurologic anejaculation and move straight to surgical sperm retrieval (Kafetsoulis et al., 2006a). The reason is likely a lack of knowledge about both the existence and use of PVS and EEJ. The increased costs of the fertility treatment with the surgical procedures is amplified by the fact that the low number of sperm obtained automatically commits the infertile couple to the most complicated and expensive of the ART, namely *in vitro* fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI).

Assisted reproductive techniques

Sperm obtained from both assisted ejaculation and from surgical sperm retrieval are used in ART. This can be done in conjunction with the sperm retrieval or sperm can be cryopreserved for later use. Of course, it is also possible to use some of the sperm immediately while saving another fraction for use at a later time. Saving part of the sample is especially useful if the sperm has been obtained by surgical sperm retrieval as the patient may then avoid repetition of the invasive procedure.

Methods of ART include intravaginal insemination (IVI), intrauterine insemination (IUI), and IVF/ICSI. The success of the procedures relies partly on the female partner and partly on the total motile sperm count obtained from the man. When taking this into account, it has been shown that couples with an SCI man can obtain the same pregnancy rates as other infertile couples when opting for ART (Kafetsoulis et al., 2006a). With a gynecologically healthy female partner with no fertility problems, the choice of ART is made based on the total motile sperm count obtained from the man. With more than 4 million viable sperm, the most simple and cheapest methods, IVI and IUI, can be attempted (Ohl et al., 2001; Van Voorhis et al., 2001). Meanwhile, lower sperm counts make IVF/ICSI necessary.

Intravaginal insemination

The simplest method of ART consists of IVI. As the name implies, the ejaculate is simply injected into the vagina of the female partner with this method and the sperm must make their way to fertilize the oocyte as with normal intercourse. The method has especially been used in SCI men with relatively high sperm counts and a good response to PVS who wish for a more natural pregnancy. Thus IVI is usually performed with self-insemination by couples in their own homes. The first step with IVI is to establish the male response to PVS. This must be done in the clinic. PVS should be performed by a healthcare professional to both access the ejaculatory response and to make sure that the patient is not prone to autonomic dysreflexia. After this, the man's and/or female partner's ability to perform PVS should be assessed. Sometimes the instruction may include methods to optimize the results, for example, with the use of two vibrators and/or oral medications, as described previously. If everything is satisfactory and the sperm count is acceptable, then the couple can bring home a PVS device for home insemination. In addition, the couple should be given non-spermicidal cups and needleless syringes to collect and inject the ejaculate into the female partner.

At home the time of ovulation should be monitored by the couple using, for example, basal body temperature or urinary LH excretion kits. Around the time of ovulation, IVI can then be performed (Brackett, 1999). In the largest case series published to date, 140 couples with SCI men attempting IVI were analyzed (Sonksen et al., 2012). The median total motile sperm count was 29 million (range, 1–92 million) and 60 of the couples achieved one or more pregnancies (43%). Altogether, 73 healthy babies were born as a result of the treatments, with a median time to first pregnancy of 22.8 months. No

complications were reported in the study. Other IVI studies have reported pregnancy rates of 25–65% per couple (Perkash et al., 1985; Dahlberg et al., 1995; Nehra et al., 1996; Lochner-Ernst et al., 1997; Sonksen et al., 1997; Rutkowski et al., 1999; Kathiresan et al., 2011).

Intrauterine insemination

IUI is another simple form of ART using the same basic principle as IVI, with injection of sperm into the female partner around the time of ovulation (most often induced by human chorionic gonadotropin to facilitate the timing of the procedure). However, with IUI, the ejaculate is first processed and the fraction which contains viable sperm cells is separated (Boomsma et al., 2007). The sperm is then injected into the uterine cavity in the clinic, bypassing the cervix and the initial obstacles. With a reasonable number of viable, motile sperm cells this ensures that a relatively high number of sperm will reach the oocytes (Duran et al., 2002). For IUI, the ejaculate can be collected by bladder harvest following retrograde ejaculation or by assisted ejaculation with PVS or EEJ.

To increase the chance of pregnancy, the number of available oocytes may be increased by stimulating the maturation process with antiestrogens or gonadotropins (Cantineau et al., 2007). Such stimulation is usually used if there is a female fertility problem. However, it is unclear if ovarian stimulation increases the chance of pregnancy if the problems are caused exclusively by a male factor (Goverde et al., 2005; Bensdorp et al., 2007). In this context, it is important to note that the stimulation sometimes results in ovarian hyperstimulation syndrome and that it increases the risk of multiple pregnancies, which are associated with an increase in perinatal and maternal morbidity as well as perinatal mortality (Yeh et al., 1990; Navot et al., 1992; Schenker and Ezra, 1994; Anonymous, 1999; Fauser et al., 2005).

We only have limited information on IUI success in patients with neurologic infertility. However, there is no reason to believe that this should be any different than success rates in couples with other forms of infertility, as it is mainly dependent on total motile sperm counts. When infertility is due to an SCI male partner, IUI is successful in about 30% (Nehra et al., 1996; Sonksen et al., 1997; Rutkowski et al., 1999; Ohl et al., 2001; Kathiresan et al., 2011).

In vitro fertilization/intracytoplasmic sperm injection

The final and most complicated forms of ART consist of IVF/ICSI. These procedures can be performed with very low numbers of sperm but are also significantly more expensive than IVI and IUI. In addition, IVF/ICSI is demanding on the female partner as they always require ovarian stimulation and as ovulation must be induced by human chorionic gonadotropin administration. Furthermore, the oocytes are retrieved from the female before fertilization under the guidance of transvaginal ultrasound.

In IVF, oocytes and sperm are simply mixed in Petri dishes. With functional sperm this allows for oocyte penetration and fertilization (Palermo et al., 1992; Cohen et al., 1997; Kupker et al., 2000). In ICSI, a sperm cell is injected directly into the oocyte to ensure fertilization. This means that ICSI can theoretically be performed with as little as one non-motile sperm cell. In both IVF with and without ICSI, the fertilized oocytes are allowed about 5 days of *in vitro* development before they are injected into the uterus (della et al., 2007). With injection of multiple developing embryos, the chance of achieving a pregnancy is increased. However, naturally, the risk of multiple pregnancies is also increased by such an approach and clinical practice on this issue varies widely.

As with IUI, the success rate of IVF/ICSI with neurologic infertility is only studied specifically for SCI men. Here studies have found pregnancy rates which vary between 38% and 100% per couple (Dahlberg et al., 1995; Hultling et al., 1997; Lochner-Ernst et al., 1997; Sonksen et al., 1997; Rutkowski et al., 1999; Heruti et al., 2001; Shieh et al., 2003).

CONCLUSION

Neurologic disorders can cause infertility, predominantly in male patients. The most common cause of neurologic infertility is ejaculatory dysfunction, although semen quality may also be diminished in some patients. Ejaculatory dysfunctions include retrograde ejaculation and anejaculation. With retrograde ejaculation, the problem may be temporarily reversed by oral medications or sperm may be harvested from the bladder following ejaculation. With anejaculation, assisted ejaculation with either PVS or EEJ may be used as a first choice. From these procedures it is often possible to obtain enough viable sperm cells to offer IVI or IUI to patients. If bladder harvest and/or assisted ejaculation fail, the next choice of treatment is surgical sperm retrieval. Such procedures are invasive and expensive and yield relatively few sperm. This necessitates the most complicated ART procedures, namely IVF with or without ICSI. Results of ART in neurologic patients are not well studied, but the success rates seem to be similar to those in patients with other forms of infertility.

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 26

Management and rehabilitation of neurologic patients with lower urinary tract dysfunction

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INTRODUCTION

Neurogenic lower urinary tract dysfunction (NLUTD) is a global term that signifies the diverse problems arising in neurologic disease. The complexity is evident when considering the contrasting nature of urine storage and voiding, and the various structures relevant, most notably the bladder and the sphincter complex. In the male, convergence of the urinary and genital tracts further increases physiologic complexity. The several central nervous system centers responsible for driving bladder or sphincter contraction, for coordinating their activity, for integrating with homeostatic and allostatic requirements, and for imposing appropriate activity in social context are present throughout the neuraxis (see Chapters 5 and 7). Thus, NLUTD is commonly a feature in neurologic disease. Furthermore, it is an aspect with potential impact on key health parameters, such as renal function, and has a considerable effect on quality of life for the patient.

Current practice benefits from better understanding of the complexities, and the ability to undertake individual assessment with a range of urodynamic tests. New treatments to improve storage function, recovery of bladder emptying using intermittent catheterization (IC), and multidisciplinary support are some key modern advances. However, research in NLUTD has not fully kept pace with the context of modern evidence-based practice of medicine, and this has hampered progress and introduction of new therapy.

The neurologic condition should be evaluated regarding parts of the nervous system affected, and potential for progressive deterioration. This can give a valuable indication of potential effects on the lower urinary tract (Birder et al., 2010; Drake et al., 2010) (Table 26.1). Sometimes, urinary tract evaluation is used to inform appreciation of the neurologic lesions.

CLINICAL EVALUATION (CHAPTER 9)

The evaluation should identify management priorities for the individual patient:

1. Does the patient have problems with urine storage function (urgency, increased daytime frequency, nocturia, or incontinence)?
2. Does the patient have problems with voiding function (hesitancy, poor stream, incomplete bladder emptying, and urinary retention)?
3. Which component of the genitourinary tract is affected in the presence of storage or voiding dysfunction?
4. Are there related issues that also need to be managed, for example, colorectal or sexual problems, or impaired pelvic floor support?
5. Is the patient at risk of complications, such as renal dysfunction, pressure sores, or recurrent urinary tract infections (UTIs)?
6. Are there factors that might limit treatment options, for example, impaired manual dexterity or cognitive dysfunction?
7. Are the mechanisms causing urinary tract problems neurogenic or coexisting issues, such as benign prostate enlargement, or postobstetric?

History and examination

The urinary tract is evaluated in detail. If appropriate, this information should be compared with the urinary

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Table 26.1

Possible neurogenic lower urinary tract dysfunctions (NLUTDs) resulting from lesions at specified levels of the neuraxis

Central nervous system region affected	Potential NLUTDs
Cerebrum	Urinary retention (inability to initiate voiding)
	Lack of conscious awareness of urinary sensations (e.g., state of bladder filling or feeling of urine flow along the urethra)
	Detrusor overactivity (loss of descending inhibition)
Brainstem/suprasacral spinal cord	Detrusor sphincter dyssynergia (unregulated simultaneous activity of parasympathetic and Onuf's nuclei)
	Detrusor overactivity
	Lack of conscious awareness of urinary sensations
Thoracolumbar spinal cord	Retrograde ejaculation in men (loss of sympathetic nucleus control of bladder neck)
Spinal cord above T6	Autonomic dysreflexia (unregulated activity of sympathetic nucleus)
Sacral spinal cord	Detrusor failure (non-function of parasympathetic nucleus) with poor bladder compliance during filling
	Stress incontinence (non-function of Onuf's nucleus)
	Lack of conscious awareness of urinary sensations (painful awareness of bladder distension may be preserved via hypogastric nerves)
Peripheral innervation	Detrusor failure (parasympathetic nucleus not communicating with bladder)
	Stress incontinence (Onuf's nucleus not communicating with sphincter complex)

function before the NLUTD developed. Symptoms can be categorized into those affecting the storage phase, and those affecting the voiding stage or arising immediately postmicturition (see Chapter 9). In order to facilitate professional communication, standardized terminology was developed by the International Continence Society (Abrams et al., 2002). This terminology should be used when establishing the symptomatic complaints of individual patients. Incontinence, i.e., failure of urine storage, can arise from various mechanisms. Stress urinary incontinence, which occurs with activity that raises the intra-abdominal pressure, can arise because neurologic disease may affect sphincter function ("intrinsic sphincter deficiency"). In women, it can also be a consequence of previous childbirth damaging the ligamentous support of the urethra ("urethral hypermobility"). Urgency urinary incontinence is also common in people with an upper motor neuron lesion, as the bladder develops unregulated contractility ("detrusor overactivity": DO). DO can cause urinary urgency, and will cause urgency urinary incontinence if the amplitude of the overactive contraction exceeds the outlet resistance. Usually the urgency gives people some warning of impending urgency urinary incontinence, but if they have impaired sensory function the warning time may be minimal. Alternatively, if their mobility is impaired, they may not have enough time to reach the toilet before incontinence occurs. Thus, the impact of the neurologic disease on sensory function and mobility is important.

Voiding dysfunction occurs as a result of loss of coordinated bladder contraction at the required time, or failure of synergic relaxation of the sphincter complex. This leads to voiding symptoms and incomplete bladder emptying. Where the bladder fails to empty completely, the postvoid residual (PVR) urine in the bladder may predispose the person to incontinence and also to UTIs. Managing the PVR may require IC. Thus, the impact of the neurologic disease on manual dexterity and cognition is important.

An assessment of medical risks is undertaken. Due to the potential adverse effect of NLUTD on renal function, specific aspects that may predispose to renal problems are assessed. These include recurrent UTIs, vesicoureteric reflux (VUR), PVR, kidney stones, and dyssynergic voiding for the lower urinary tract, and known chronic kidney disease, medical conditions, specific medications, and pressure sores in the wider context. A history of headaches potentially signifying autonomic dysreflexia should be considered in people with spinal cord injury (SCI) above T6 (see below). In neurologic disease in general, blood pressure control in regard to hypotension (including postural drop in blood pressure) and hypertension are assessed. Potential severe latex allergy should be considered in congenital conditions such as spina bifida.

Bowel function, sexual function, and the obstetric and gynecologic history are directly relevant aspects of assessing NLUTD. They have to be considered for identifying priority issues for the patient and potential impact of urinary tract management.

Physical examination

Mobility, balance (when walking, and when seated), spasticity, weakness, coordination, and cognition are evaluated, for example in regard to accessing and using toilet facilities, and potential ability to use specific treatment options. Hand function is a particular consideration, since the ability to hold a catheter and the genitals is a requirement for intermittent self-catheterization (ISC).

The physical examination evaluates the lower abdomen, external genital organs, and perineal skin. Rectal and vaginal examination is used to evaluate sphincter tone, and voluntary contraction strength (which is crucial for effective pelvic floor muscle exercises). Fecal loading of the large intestine and rectum should be noted. Pelvic organ prolapse and prostate disease are considered. Perineal sensation and skin quality are assessed, in view of increased risk of skin breakdown in insensate skin, notably where there is infection and chemical irritation from urinary or fecal incontinence. The bulbocavernosus/anal/cremaster reflexes can be assessed; their preservation indicates functioning reflex arcs and sacral spinal cord.

Based on the history and examination, supplemented as necessary by urodynamic tests, a simple way to view the LUT dysfunctions was presented by Madersbacher (1990), and supported by organizations such as the European Association of Urology Guidelines group (Stohrer et al., 2009). The approach is to catalog the behaviour of both the bladder and outlet as overactive, normal, or underactive. These can be considered both during storage and voiding. Thus, a practical and simple means of viewing the mechanisms is presented, which helps to guide subsequent therapy selection.

Basic investigations

A urinary diary is valuable, as it identifies polyuria, nocturnal polyuria, daytime and nighttime frequency, and incontinence episodes. Scales can be co-administered to gauge sensation. Optimal diary duration is 3 or 4 days in the general population, as a suitable compromise balancing information captured against inconvenience to the patient; studies on optimal duration have not been formally reported in NLUTD (Naoemova et al., 2008).

Urinalysis is a requirement, as people with NLUTD may be at risk of UTI, and bacterial colonization, potentially contributing to the clinical presentation. In many cases, symptoms may not reflect the presence of UTI (Linsenmeyer and Oakley, 2003). A dipstick urinalysis can be used to screen for hematuria, inflammation (leukocyturia), and bacteria (nitrites). Culture and sensitivity testing may be appropriate.

Renal assessments consider both function and structure. Serum tests of renal function are often quoted with normal ranges applicable for the general population. In neurologic disease, associated low muscle mass means that lower upper limits for normal range of creatinine values are appropriate. A renal ultrasound scan is commonly employed to look for scarring, hydronephrosis, stones, or structural change affecting the parenchyma. Renal function and structure may be checked at baseline and repeated during follow-up in those forms of NLUTD at risk of affecting the upper urinary tract, with regularity of assessment reflecting the perceived risk of the situation.

URODYNAMIC TESTS

The nature and severity of NLUTD can be difficult to appreciate from clinical assessment alone, and urodynamic techniques evaluate multiple functional parameters in NLUTD (Wyndaele, 1984). Key to urodynamic assessment is deciding on the issues to be evaluated, referred to by investigators as "formulating the urodynamic questions." Of greatest importance is often the identification of factors that could risk patient safety (notably lower urinary tract risk factors that may come to endanger renal function). Of slightly less overall importance (but still very important to the patient) is understanding mechanisms underlying LUT symptoms, for selecting treatment options. The urodynamic questions are influenced by the disease context. For example, in SCI, the International Urodynamic Basic data set includes bladder sensation, detrusor function, and compliance during filling cystometry, detrusor function during voiding, detrusor leak point pressure, maximum detrusor pressure, cystometric bladder capacity, and PVR (Biering-Sorensen et al., 2008).

The fundamental urodynamic tests are free flow rate (FFR) testing with PVR measurement, and filling and voiding cystometry. Videourodynamics, where filling and voiding cystometry use X-ray contrast medium to enable imaging at key points in the cystometry, is the more informative approach, recommended in the relevant guidelines (Abrams et al., 2010). Technical points on how to undertake urodynamic testing have been set out by the International Continence Society in their "Good urodynamic practices" document (Schafer et al., 2002), which was undergoing revision in 2014. This indicates that initial filling rates for people with NLUTD should be slow (a pump should infuse body-warm saline at 10 mL/min, in addition to the natural bladder filling with physiologic urine production). This is to gain a clear appreciation of the pressure change with increasing volume (compliance).

Free flow rate testing with PVR measurement

A FFR test is a simple test of rate of flow over time. The maximum flow rate (Q_{max}) and pattern of flow can give some useful information (Fig. 26.1). Voided volume (VV) during the FFR test is compared with typical VV on the patient's bladder diary, since FFR results may otherwise give unrepresentative information. In addition, PVR is measured (usually with an ultrasound-based bladder scanner), since PVR is relevant for LUT symptoms, UTIs, and risk of renal dysfunction. If Q_{max} appears to be low, the investigator should check that

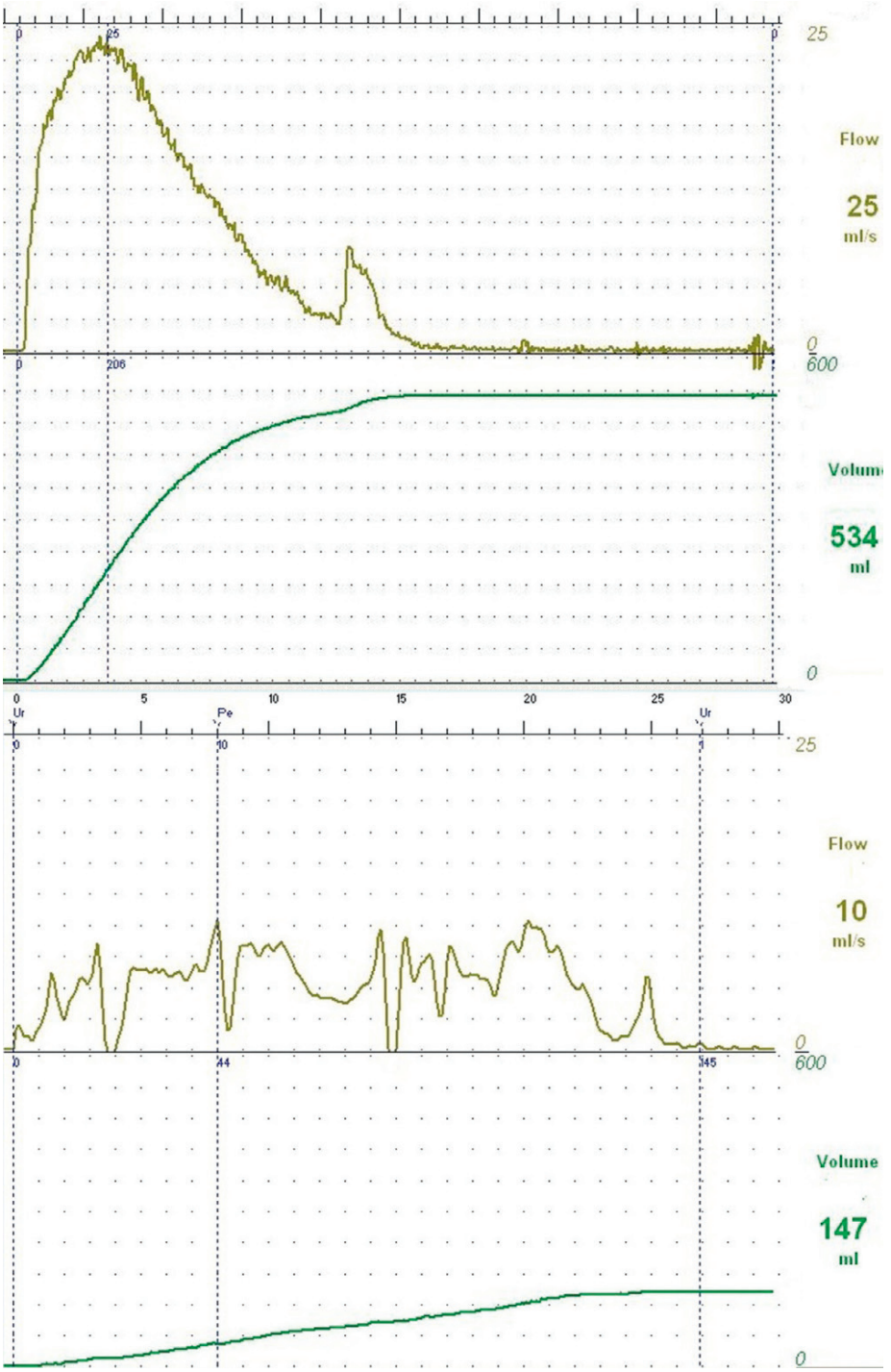

Fig. 26.1. Free flow rate tests from a healthy person (above) and a person with neurogenic lower urinary tract dysfunction (below). The normal pattern and high maximum flow rate are clearly lost in the lower trace.

the bladder was adequately filled (i.e., that the sum of VV and PVR is greater than 150 mL), since underfilling can impair voiding contractility.

FFR is often done at initial assessment, and especially before cystometry, since the presence of a catheter during voiding cystometry can influence Q_{max}, and comparison of Q_{max} obtained with FFR provides a check on whether voiding cystometry is adequately representative. FFR is also widely used during follow-up.

Filling cystometry

Bladder properties are assessed over the course of filling from empty to capacity, evaluating sensation, bladder compliance, and continence (see Table 26.2 for definitions of some of the key urodynamic terms). Usually the bladder will be emptied with a catheter prior to filling. However, it may be appropriate in some cases to fill on top of the PVR, particularly in those patients where IC is unlikely to be feasible as a management option. A pump is typically used for bladder filling, with fluid instilled at a rate of 10 mL/min, increasing the filling rate if bladder compliance is satisfactory. In SCI patients, filling using diuretics for "natural filling" has been tested in comparison with conventional urodynamics, with clear demonstration that pressures and compliance differ (Ko et al., 2002). However, the clinical implications of these differences are not certain. "Provocation tests" during filling can be undertaken in order to elicit problems such as incontinence or DO:

1. During filling cystometry, various urodynamic observations may be made.
2. Reduced bladder sensation: inability to discern the conventional filling sensations is strongly suggestive of neurologic dysfunction (Wyndaele, 1993). Nonetheless, many patients do report some degree of bladder filling sensation despite neurologic disease.
3. Urodynamic stress incontinence: the patient is asked to do a series of strong coughs, to see whether the resulting rise in abdominal pressure causes urinary

Table 26.2

Terminology of urodynamic testing

Term	Abbreviation	Definition
Detrusor overactivity	DO	A urodynamic observation characterized by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked
Detrusor leak point pressure	DLPP	The lowest detrusor pressure at which urine leakage occurs in the absence of either a detrusor contraction or increased abdominal pressure
Abdominal leak point pressure	ALPP	The intravesical pressure at which urine leakage occurs due to increased abdominal pressure in the absence of a detrusor contraction
Compliance		Compliance describes the relationship between change in bladder volume and change in detrusor pressure*
First sensation of filling	FSF	The feeling the patient has, during filling cystometry, when he/she first becomes aware of the bladder filling
Normal desire to void	NDV	The feeling, during filling cystometry, that would lead the patient to pass urine at the next convenient moment, but voiding can be delayed if necessary
Strong desire to void	SDV	Strong desire to void is defined, during filling cystometry, as a persistent desire to void without the fear of leakage
Cystometric capacity		Cystometric capacity is the bladder volume at the end of the filling cystometrogram, when "permission to void" is usually given. The end point should be specified, for example, if filling is stopped when the patient has a normal desire to void. The cystometric capacity is the volume voided together with any residual urine
Bladder outlet obstruction	BOO	The generic term for obstruction during voiding; it is characterized by increased detrusor pressure and reduced urine flow rate. It is usually diagnosed by studying the synchronous values of flow rate and detrusor pressure
Detrusor underactivity	DUA	A contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span
Detrusor sphincter dyssynergia	DSD	A detrusor contraction concurrent with an involuntary contraction of the urethral and/or periurethral striated muscle. Occasionally, flow may be prevented altogether

*Compliance is calculated by dividing the volume change by the change in detrusor pressure during that change in bladder volume (units mL/cm H_2O).

Reproduced from Abrams et al. (2002).

leakage. If coughing fails to elicit any leakage, a series of Valsalva strains can also be used to attempt to provoke incontinence. If urodynamic stress incontinence is observed, video imaging can be used to see whether it is a consequence of urethral hypermobility (resulting from a poorly supported pelvic floor in women), or intrinsic sphincter deficiency.

4. DO and DO incontinence (Fig. 26.2): bladder contractions during the filling phase are clearly counterproductive to the bladder's reservoir function. DO may arise spontaneously, or may be provoked, e.g., by a short phase of increased bladder filling rate, or the sound of running water (turning on the taps). If the amplitude of DO is sufficient, especially where sphincter function is impaired, the consequence may be DO incontinence.
5. Poor bladder compliance (Fig. 26.2), signifying a rise in pressure with ongoing bladder filling, which can be particularly exaggerated if filling rate is accelerated. Mechanisms which can cause this may be

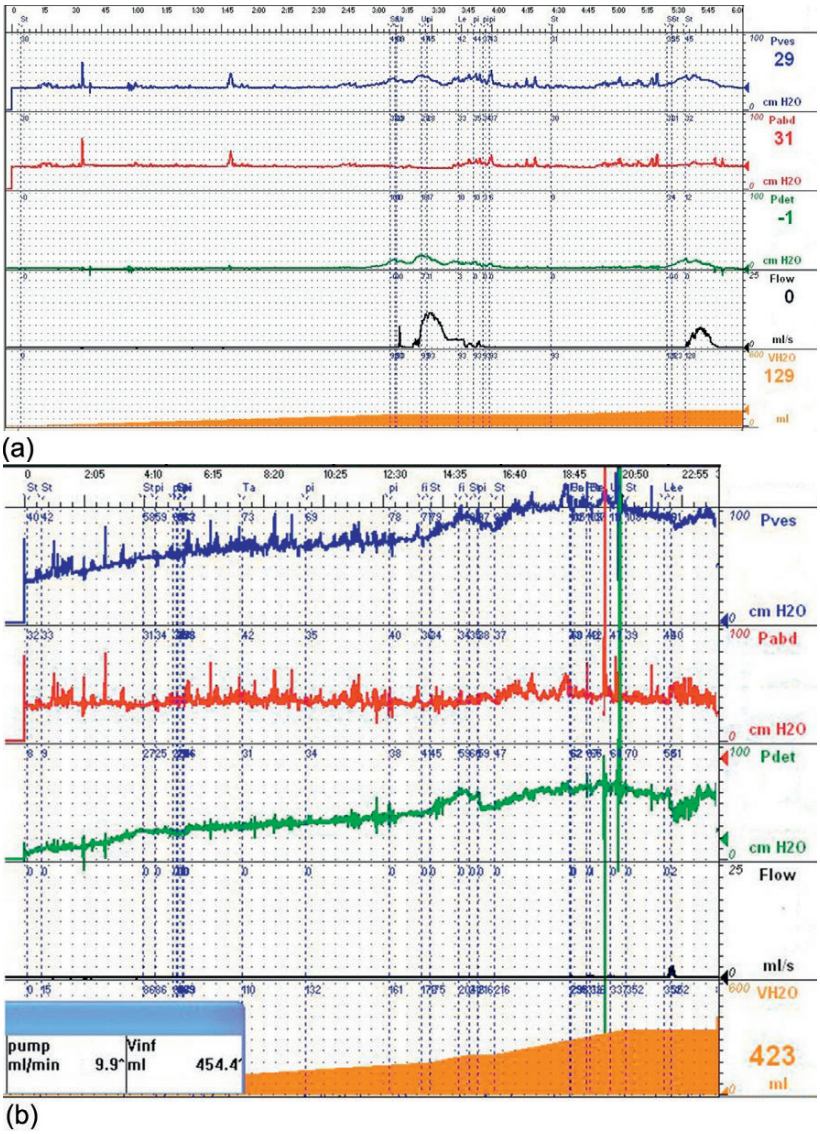

Fig. 26.2. Filling phase of urodynamics in two patients with neurogenic lower urinary tract dysfunction. Above, detrusor overactivity incontinence in a female patient with multiple sclerosis affecting the spine. On two occasions, a rise in detrusor pressure can be seen (detrusor overactivity), associated with urine flow (incontinence). Below, a poorly compliant bladder in a male patient with myelomeningocoele. The detrusor pressure climbs throughout filling. At around 22:00 minutes on the time scale marked at the top of the trace, a very small leakage occurs, seen as a small flow. This is the detrusor leak point pressure; for this man the detrusor leak point pressure was a dangerously high 61 cm H_2O. For both traces, bladder pressure (P_{ves}) is given in blue, abdominal pressure (P_{abd}) is given in red, computed detrusor pressure (P_{det}) is in green, flow in black, and filled volume (V_{H2O}) in orange.

functional (for example, disease affecting the sacral part of the spinal cord), or structural (connective tissue scarring of the bladder wall resulting from chronic catheterization or chronic UTI). Compliance can be highly problematic for renal function, due to implications for ability of urine emptying from the renal pelvis.

In videourodynamics, the following additional aspects can be discerned;

1. Open bladder neck seen on video imaging. In men, the bladder neck is usually shut at rest; if open (in a man who has not previously had prostate surgery), it may indicate problems with the sympathetic nervous system supply to the LUT. It is worth checking for a history of retrograde ejaculation (dry orgasm) if this is seen.
2. VUR (Fig. 26.3): the abnormal retrograde flow of urine from the LUT to the upper urinary tract due to failure of the valve mechanism of the ureterovesical junction (UVJ). VUR may signify a functional or structural problem; for example, high pressures during bladder filling or voiding, or trauma to the ureterovesical junction. In theory, denervation of the bladder base could impair muscle tension in the trigone, which is thought to maintain the slit-like ureterovesical junction configuration.

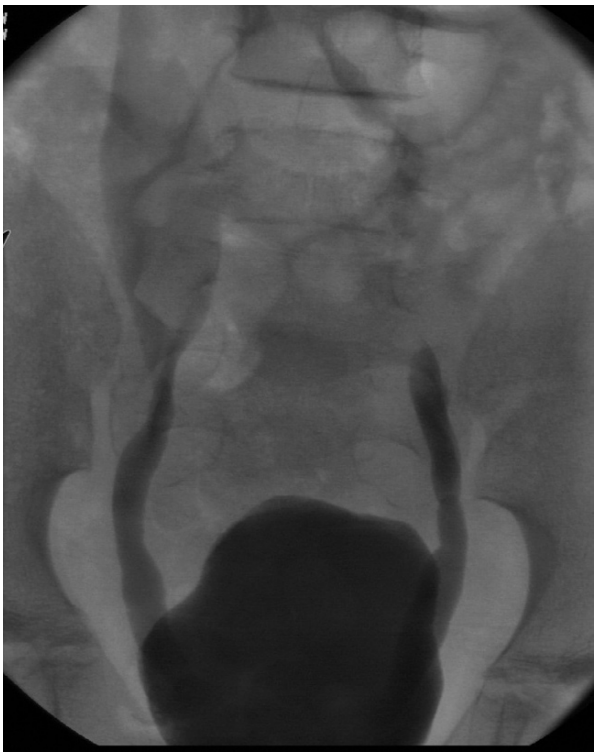

Fig. 26.3. Bilateral vesicoureteric reflux in a child with neurogenic lower urinary tract dysfunction.

3. Impaired pelvic floor support: normally the base of the bladder lies level with the pubic symphysis, but in women it may drop below this where there is impairment of pelvic floor innervation, or loss of ligamentous support (due to previous pregnancy and childbirth)

Pressure–flow studies (voiding cystometry)

"Cystometric capacity" is defined as the volume at which the patient has a strong desire to void, incontinence/leakage, or a substantial involuntary detrusor contraction. It is rather a subjective parameter. At this point, the patient is given "permission to void," which represents the start of the voiding phase. If urine flow does not result relatively soon, it is termed "hesitancy," and this may reflect an abnormality, or may simply represent the natural reticence people have when passing urine in a public or uncomfortable setting.

Measurement of detrusor pressure synchronous with flow rate during voiding is used to evaluate several parameters. These include the ability of the patient to initiate voiding voluntarily, the bladder contraction strength, the caliber of the outlet in allowing flow, and the coordination of the LUT elements. There are many clinically relevant urodynamic observations which the investigator may discern during the course of a study. Non-voluntary initiation is a situation in which people with DO incontinence experience urine flow without voluntary initiation, and may not have the facility to initiate voiding in the absence of DO, or to inhibit voiding when requested by the urodynamic tester. Absence of bladder contraction means there is a lack of change in detrusor pressure when attempting to pass urine. This often results in "straining," which is a process of raising abdominal pressure, which raises the bladder pressure (since it is an intra-abdominal organ) and this provides the force to expel the urine. It implies some degree of outlet impairment or relaxation, since people do not normally pass urine simply as a consequence of increased abdominal pressure due to the presence of a "guarding reflex." Detrusor underactivity (DUA) is a less severe version, indicating weak bladder contractility, such that the bladder does not empty completely, or in a normal timeframe. This will usually cause hesitancy, weak stream, and dribbling, often with a PVR. On urodynamic testing, this is seen as low maximum flow rate with low detrusor pressure, and fluctuating poorly sustained detrusor contraction.

Bladder outlet obstruction (BOO) is a key issue, indicated by the presence of high bladder pressures in association with a weak stream. Symptomatically, the patient will often report hesitancy and dribbling, and a PVR may

be evident. Since clinical features of BOO are very similar to those in DUA, urodynamics is needed to discern whether either DUA, or BOO, or both is present. The pressure–flow relation indicates whether BOO is present, but the actual location of obstruction may best be ascertained with synchronous imaging (videourodynamics) to visualize the site of obstruction (Madersbacher, 1977; Sakakibara et al., 2001).

Dyssynergia is a particular form of BOO, in which impairment of the upper motor neuron control of the LUT results in impaired coordination, such that both bladder and outlet can contract simultaneously. The main form of dyssynergia is detrusor sphincter dyssynergia (DSD), where video imaging shows contrast being held up at the external urethral sphincter (in men, the high pressures in the proximal urethra may lead to contrast highlighting the prostate gland). DSD is typically associated with intermittent urine flow and a substantial PVR, perhaps with VUR. It can readily be identified by the relationship between pressure and flow, and additional use of sphincter electromyography (EMG) can reinforce the confidence with which its presence can be concluded; phasic detrusor contractions with associated increase in EMG activity on attempted voiding are seen in DSD (Perkash, 1978). A separate entity of bladder neck dyssynergia is also described by some investigators, though it is a less clear-cut urodynamic entity.

Other forms of neurogenic mechanisms may impair outlet opening and cause BOO, such as bradykinesia of the sphincter and urethral relaxation failure (Nitti et al., 1996; Sakakibara et al., 2000). Non-neurogenic BOO should also be considered; everyone, whether or not they have neurologic disease, can get BOO. In older men, this can be due to benign prostate hyperplasia causing intrusive enlargement into the urethral lumen, or a stricture of the urethra. In women, it can result from pelvic organ prolapse or previous pelvic surgery.

Indications for urodynamic testing

Clinical, urodynamic, and imaging evaluation of the upper and lower urinary tract is required in specific neurologic scenarios, for example myelomeningocoele patients, where urodynamic data correlate with risk of deterioration in the upper urinary tract (Bruschini et al., 2006). In this setting, a detrusor leak point pressure over 40 cm H_2O was associated with upper urinary tract damage (Bruschini et al., 2006) (accordingly, the case illustrated in Figure 26.2 is at risk). Thus, most centers will consider videourodynamic testing in the context of impaired renal function, structural change in the upper urinary tract (especially hydronephrosis or scarring), high PVR (though professional consensus has not been achieved on an acceptable range of PVR), and for assessment of refractory symptoms. Tests will be done at baseline and may be incorporated into follow-up for individual cases.

Complications

Complications of cystometry include traumatic hematuria and UTI. Due to potential for UTI in a group that may have a higher risk of adverse consequences, and who may not present in a timely manner consequent upon impaired bladder sensation, antibiotic prophylaxis should be considered (Pannek and Nehiba, 2007).

Special tests in urodynamics

Various modifications have been evaluated in the context of urodynamic testing for NLUTD, and new modifications are researched regularly to refine further key aspects for developing urodynamic insights. EMG can offer additional insights into the synergic behavior of the LUT elements. In particular, recording from the external sphincter during voiding should show reduced EMG activity, but in patients with upper motor neuron lesions, increased activity in the sphincter during voiding indicates DSD. EMG can be used to categorize DSD into three types according to the pattern of electric activity (Blaivas et al., 1981). The methodology of EMG in urodynamics has long been debated (Wein and Barrett, 1982). Surface patch electrodes are more convenient than concentric needle electrodes but less reliable (Mahajan et al., 2006). Anal sphincter EMG has been used as a proxy for sphincter EMG in patients with suspected NLUTD, but is probably unreliable (Nordling and Meyhoff, 1979). The presence of a urethral catheter (Aoki et al., 1985) or abdominal straining may influence EMG behavior. Refinements of EMG recording may bring further benefits in facilitating the neurourologic appreciation (Fowler et al., 1984; Vodusek, 1989), for example in identifying patients with parkinsonism who have multiple system atrophy (Fowler, 1998).

Nerve conduction studies have been evaluated in small studies, though they are not a routine component in urodynamic studies. Bladder filling may moderate the excitability of somatic spinal motor neurons in DO (Carbone et al., 2002). Urethral and anal responses produced by electric stimulation of penis, bladder neck, and anus may be delayed and the duration reduced (Vereecken et al., 1982). Techniques were described for recording somatosensory evoked potentials with stimulation of the human urinary bladder (Badr et al., 1982). More recently, somatosensory evoked potentials were used as a means to predict efficacy of tibial nerve stimulation therapy (Mazo et al., 2005). Loss of

sympathetic skin responses may be used in assessing NLUTD (Rodic et al., 2000).

Instillation of cooled saline into the bladder (the ice-water test) detects a proposed spinal reflex, in which detrusor contraction is elicited by temperature stimulation, suggesting loss of inhibition by supraspinal centers. Thus, a positive test may suggest a spinal lesion, for example in multiple sclerosis (Ismael et al., 2000). However, there are problems with the sensitivity and specificity of this test (Chancellor et al., 1998).

Bethanechol supersensitivity was proposed as an approach to deciding whether a non-contractile bladder was due to a neurogenic or myogenic defect (Lapides et al., 1962). However, doubts about the observations (Blaivas et al., 1980) mean the test is not standard current practice.

TREATMENT

The two key priorities are to protect life expectancy and improve quality of life. A holistic approach is taken, since bowel function, sexual function, and fertility often have to be managed in addition to NLUTD. Thus a multidisciplinary setting, with easy access to expert support and advice, is essential. The changing picture of NLUTD in each individual also needs to anticipated, as a consequence of neurologic disease progression, aging, and comorbid disorders. For many patients with significant NLUTD, ongoing surveillance and follow-up will be required.

Consideration is needed for surveillance of renal function, and whether the patient is at risk of UTIs. Options that may improve urine storage function and/or bladder emptying should be weighed up.

Conservative measures

For each patient, advice regarding volume and type of fluid intake is needed. This is individualized according to numerous influences. High volume intake is often self-initiated by patients to try to counteract UTIs, but in reality this is unlikely to be beneficial in people with a PVR, and will increase the number of catheterizations needed, hence may be counterproductive.

Containment is a crucial aspect of achieving acceptable quality of life, and is also an essential aspect of preventing or treating sacral sores. A range of pads and protective products is available; the advisor needs to be well informed about the options available (Fader et al., 2008a, b). Male patients with NLUTD can be candidates for a condom catheter connected to a collection bag. Problems can arise with this approach in men with penile atrophy, penile retraction, or obesity.

Recurrent UTIs can result from a range of predisposing factors (e.g., PVR, catheter use, anatomic abnormalities, urolithiasis), which often require urologic assessment. Febrile UTIs (which need treatment) must be distinguished from bacteriuria (which often does not), so formal microbiology information is required. Recurrent confirmed UTIs may benefit from cautious use of antibiotic prophylaxis.

Autonomic dysreflexia (Khastgir et al., 2007) is specifically a problem where the sacral nucleus below spinal cord level T6 is intact and unregulated by higher centers, most typically as a consequence of SCI. The consequence is severe life-threatening hypertension elicited by a noxious stimulus below the SCI level, caused by severe vasoconstriction. The body makes some compensatory responses, including bradycardia (since the vagus nerve is usually still intact), but if the stimulus persists, there is a risk of death due to cerebral hemorrhage. Prevention requires avoidance of stimuli, and a crucial point is to make all carers and the patient aware that a blocked catheter could easily trigger a dysreflexic episode. Once an episode has started, the cause must be reversed, antihypertensives administered, and subsequent monitoring may be needed until the labile blood pressure has stabilized.

Non-surgical interventions to improve urine storage (continence)

These are typically aimed at reducing storage pressures and improving filling compliance, with the management of symptoms. Antimuscarinic medications are widely used in the treatment of neurogenic DO. Justification for their use largely relies on research on treatment of overactive bladder in people without neurologic disease. The evidence base for their use in NLUTD is rather limited. For example, a Cochrane systematic review for antimuscarinic treatment in multiple sclerosis was unable to reach a conclusion (Nicholas et al., 2009).

Oxybutynin hydrochloride has been studied for people with NLUTD caused by various conditions (Gajewski and Awad, 1986; Bennett et al., 2004). While oxybutynin is widely used in NLUTD, it may be less well tolerated than other antimuscarinics. Other agents studied in NLUTD include propiverine (Stohrer et al., 2007b), solifenacin (van Rey and Heesakkers, 2011), tolterodine (Ethans et al., 2004), and trospium (Mazo and Babanina, 2007). It seems that larger doses of antimuscarinics are needed to achieve best effect on neurogenic bladder (Ethans et al., 2004; Horstmann et al., 2006). Some clinicians use doses or combinations outside the regulatory licenses for overactive bladder (Bennett et al., 2004; Amend et al., 2008). Antimuscarinic side-effects may include dry mouth, visual disturbance, constipation, and cognitive impairment, which can be problematic in people with neurologic disease. Intravesical administration of antimuscarinic medication

(specifically oxybutynin) can be beneficial (Evans, 2005), but there is no standard instillation protocol and the treatment is not licenced.

Bladder injection with botulinum neurotoxin type A in the onabotulinumtoxinA (Botox) formulation is now a recognized treatment for DO refractory to antimuscarinic medications, and is licenced in several countries for use in specific populations of patients with multiple sclerosis or SCI. This is based on extensive level 1 evidence, demonstrating improvement in symptomatic and urodynamic parameters (Schurch et al., 2005; Karsenty et al., 2008; Apostolidis et al., 2009; Cruz et al., 2011; Duthie et al., 2011; Herschorn et al., 2011; Mangera et al., 2011). The majority of the studies recruited patients with NLUTD caused by SCI or multiple sclerosis. Some case series have reported outcomes for other conditions, such as cerebrovascular accident, Parkinson's disease, and multiple system atrophy (Kuo, 2006; Giannantoni et al., 2009; Kulaksizoglu and Parman, 2010). AbobotulinumtoxinA (Dysport) has been studied (Mangera et al., 2011), but less extensively, and does not as yet have regulatory approval for neurogenic DO. It should be noted that the doses used for the two preparations are not the same, and that 200 U of onabotulinumtoxinA is the licenced dose in neurogenic DO in the specific indications. Mean duration of effect is approximately 42 weeks for onabotulinumtoxinA, as compared to 13 weeks for placebo (Cruz et al., 2011). Several studies have shown ongoing symptomatic response with repeat treatment (Reitz et al., 2007; Game et al., 2011; Khan et al., 2011), though it is clear that indefinite benefit cannot be anticipated for all recipients. Patients remaining on antimuscarinic drugs do not appear to derive additional benefit.

Botox bladder injections are a minimally invasive intervention, and can readily be done under local anesthesia through a flexible cystoscope. Antibiotic prophylaxis is needed, and there remains some discussion on practical aspects, such as dose and volume of diluent, along with number/location of sites, and volume at each site. In reality, these aspects may actually have little impact on outcome. There is some research into means of delivering the toxin that do not rely on injections, such as using liposomes (Chuang et al., 2009) or via electromotive drug administration (Kajbafzadeh et al., 2011). Patients need to be willing and able to use clean intermittent self-catheterization (or potentially accept an indwelling catheter), as there is an increase in PVR and a risk of acute urinary retention after injections. UTIs can be problematic. The most serious adverse event is generalized weakness, occurring in up to 0.02% of recipients (Mangera et al., 2011).

Peripheral nerve stimulation can employ various nerves deriving from the relevant spinal segments. Percutaneous tibial nerve stimulation (was described some time ago as a treatment for neurogenic DO in SCI, and can improve NLUTD in various neurologic diseases (Andrews and Reynard, 2003; Kabay et al., 2009; Gobbi et al., 2011), though it is still debated regarding genuine influence on NLUTD (Rijkhoff, 2008). Electric stimulation using alternative approaches has been used in attempts to ameliorate bladder storage dysfunction. Anogenital stimulation has been used to treat overactive bladder symptoms (Gladh et al., 2001). Direct pudendal nerve stimulation can be undertaken via differing anatomic and technical approaches (Spinelli et al., 2005). Conditional peripheral nerve stimulation, in which electric stimulation is only delivered at the time of onset of an overactive bladder contraction, has been researched (Dalmose et al., 2003; Hansen et al., 2005), though it presents many technical challenges. Dorsal genital nerve stimulation is another option for electric stimulation with potential to moderate NLUTD, using continuous or conditional stimulation (Horvath et al., 2010), and this may work by improving outlet function alongside reducing DO (Reitz et al., 2003).

Intravesical instillation of vanilloid agonists (MacDonald et al., 2008) exploits expression of transient receptor potential (trp) channels on the bladder urothelium and afferent nerves, including the trp-V1 channel. Vanilloid agonists, capsaicin and resiniferatoxin, desensitize afferent nerves by binding trp-V1. Capsaicin has been evaluated in patients with SCI and multiple sclerosis, and appears to counteract aspects of NLUTD, but problematically causes initial excitation of afferent nerves. Resiniferatoxin does not cause the initial excitation. The long-term safety of vanilloid agents, including potential carcinogenic effects, is not known. They are not currently in standard clinical use. Trp channel antagonists, such as piperine, may offer another potential strategy (Gevaert et al., 2007).

The identification of functional cannabinoid receptors in the human bladder urothelium (Tyagi et al., 2009) has intensified interest in intravesical cannabinoid agonists for bladder dysfunctions, but clinical testing has thus far been limited.

Stimulation of cranial centers appears to have potential application in NLUTD. Transcranial magnetic stimulation of the motor cortex can influence spinal cord excitability and NLUTD (Centonze et al., 2007). Deep-brain stimulation of the subthalamic nucleus can influence NLUTD in Parkinson's disease (Herzog et al., 2006). Some indicators suggest that thalamic deep-brain stimulation may also influence bladder parameters (Kessler et al., 2008).

The beta-3 adrenergic agonist mirabegron is licenced for idiopathic overactive bladder syndrome; at the time of writing, no studies had reported on its use in NLUTD, but clinical and urodynamic studies have been initiated.

Non-surgical interventions to improve bladder emptying

IC is increasingly used as a key means of bladder emptying. IC can be done either by a carer or by the patient (ISC). IC requires several factors for successful use. Firstly, bladder capacity needs to be sufficient that catheterization does not have to be done excessively frequently. More than six catheterizations daily is usually considered excessive; high urine volumes in polyuric patients can make this harder to achieve. Some sphincter function is needed so that leakage is absent or manageable. Secondly, storage pressures in the bladder need to be low, in respect of protecting renal function. Thirdly, the urethral meatus needs to be accessible. The urethra may be difficult to catheterize if it is very sensitive, or if there is distortion, constriction, kinking, or a false passage. Fourthly, access to supplies of catheters has to be reliable and affordable. For ISC, the patient needs adequate cognitive function, manual dexterity, and mobility. Generally "clean" IC is used, but sometimes a sterile non-touch technique is recommended; a systematic Cochrane review on strategies for catheter use emphasized that the evidence base is weak (Jamison et al., 2011b).

Indwelling catheterization may be necessary in more severe NLUTD, and it can improve quality of life (Bothig et al., 2012). There is a risk of complications and problems (Cameron et al., 2011). Crucially, indwelling catheters may stabilize chronic renal dysfunction caused by inadequately managed NLUTD (Drake et al., 2005). Bacterial colonization in chronic use is unavoidable, and can lead to recurrent blockage and systemic infection. Attempts at eliminating bacteriuria associated with indwelling or intermittent catheters are generally unsuccessful. Catheter-induced trauma to the urethra can be considerable, especially where there is sensory nerve impairment, so suprapubic catheters (SPC) are generally preferred, though comparative evidence is lacking (Jamison et al., 2011a). If the urethra is severely nonfunctional, urethral leakage can occur in patients with an SPC (Colli and Lloyd, 2011).

Oral medications have limited utility in this context. Alpha-adrenergic antagonists can decrease urethral resistance during voiding. Tamsulosin improves voiding in SCI (Abrams et al., 2003). The cholinomimetic agent, bethanechol chloride, seems to be of limited benefit for detrusor areflexia and for elevated residual urine volume.

Triggered reflex voiding (Fig. 26.4) is an option in SCI patients (after recovery from spinal shock) with preserved sacral cord function, and uses stimulation such as suprapubic percussion to provoke a bladder contraction at a time chosen by the patient. The aim is "balanced voiding," indicating the attainment of adequate continence and urine storage under safe pressures. Most centers tend to initiate IC in preference to triggered reflex voiding in current practice.

Bladder expression involves raising the abdominal pressure by Valsalva, or direct manual suprapubic pressure (Credé), and can be used to increase the bladder pressure above outlet resistance, leading to emptying. This can be an option where outlet resistance is weak (due to the NLUTD, or using sphincterotomy). However,

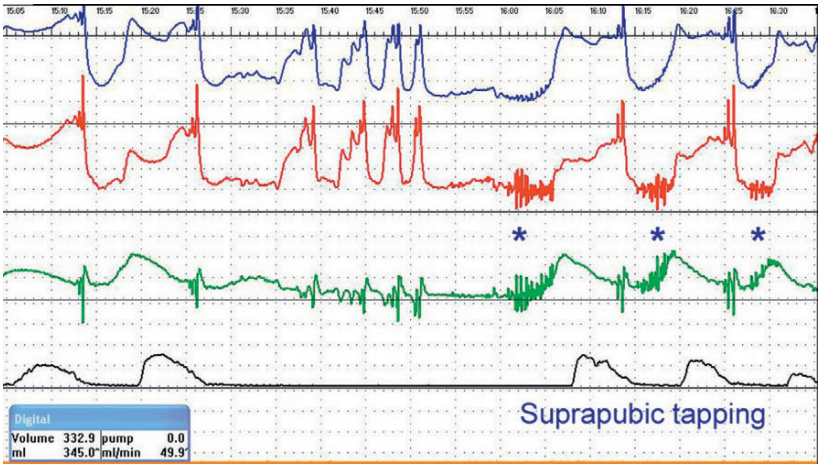

Fig. 26.4. The "voiding phase" in a suprasacral spinal cord injury paraplegic patient. He had some detrusor overactivity (DO) incontinence (two episodes seen to the left of the picture). He deliberately enhanced these by raising his abdominal pressure, and hence his bladder pressure ("straining"), in order to maximize expulsion of urine. On the right of the picture are three episodes of "suprapubic tapping" (marked by *), in which he percussed over his bladder several times with his wrist to provoke a DO contraction, then recommenced straining as soon as he felt the onset of DO. Between the times when flow was achieved there were four strains that failed to elicit any flow, indicating his need to exploit DO to achieve emptying by triggered reflex voiding.

there is a recognized risk of incomplete bladder emptying, UTIs, VUR, and anal prolapse. Thus, bladder expression is no longer recommended for general use.

Botulinum neurotoxin type A was first employed in NLUTD for sphincter injections as a means to improve bladder emptying (Dykstra et al., 1988). Usually 100 U onabotulinumtoxinA or 150 U abobotulinumtoxinA has been delivered transperineally or transurethrally (de Seze et al., 2002; Chen et al., 2011). This approach has not become established, as demonstrable improvement in clinically relevant parameters is lacking (Gallien et al., 2005).

Surgical options to improve urine storage

Preoperative urodynamic evaluation of bladder function is needed to appreciate the mechanisms of incontinence, and also to ensure that any procedure aiming to improve outlet resistance will not increase LUT storage pressures, such that renal function could be endangered. If this is considered likely, a strategy to reduce urine storage pressure may be needed, and close follow-up is mandatory.

Sacral neuromodulation (SNM) can be used to reduce DO (Fig. 26.5). The evidence base regarding SNM in NLUTD is limited, and sometimes reports do not clearly distinguish use of SNM in DO from voiding dysfunction. The procedure can be done with a test phase, or using two-stage implantation. SNM is an option used selectively in specialized centers, and neurogenic DO does sometimes respond (Spinelli et al., 2003a, b). In neurologic diseases at risk of progression, such as multiple sclerosis, it appears appropriate to consider the behavior of the underlying condition as part of patient selection. Benefits may be seen in patients with incomplete medullary lesions (Bosch and Groen, 1998; Chartier-Kastler et al., 2000; Hohenfellner et al., 2001). Furthermore, clinical benefits do not necessarily correspond with the associated urodynamic changes (Bosch and Groen, 1998; Chartier-Kastler et al., 2000, 2001). Initial response does not necessarily yield long-term benefit (Hohenfellner et al., 2001).

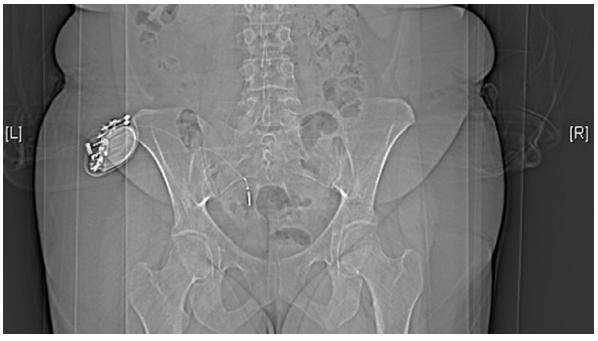

Fig. 26.5. A young woman with multiple sclerosis and a sacral neuromodulation device, showing the battery pack under the abdominal skin, connected to the multipolar electrode in the relevant sacral foramen.

Some benefit for urodynamic parameters has been reported with SNM applied during the spinal shock phase of SCI (Sievert et al., 2010). One publication reported correspondence between urodynamic test data and clinical data (Chartier-Kastler et al., 2000).

Bladder denervation has been attempted, in the assumption that this might reduce DO. In theory, denervation would render the bladder acontractile and thereby improve storage. In reality, the autonomous activity of the denervated bladder nullifies this concept (Drake, 2007). Thus, attempts to denervate the bladder at a peripheral level, as used in the past, including prolonged hydrostatic distension or bladder transection, are no longer supported. Selective dorsal sacral rhizotomy to target relevant innervation has been attempted (Rockswold et al., 1973), but response does not appear to be well sustained (Lucas et al., 1988). An implanted stimulator to induce micturition in paraplegic SCI patients has been developed by Brindley, and sacral rhizotomy during implant surgery substantially counteracts DO (Tanagho et al., 1989). Outcomes have been reported for a large series (Brindley, 1994).

Bladder augmentation can be used for treating DO or poor bladder compliance. Augmentation cystoplasty involves hemisection of the bladder and closure of the resulting defect with a detubularized segment of intestine. The effect is to increase bladder capacity and reduce the amplitude of overactive bladder contractions, and improved quality of life is often achieved (Hasan et al., 1995; Herschorn and Hewitt, 1998). Since voiding is rendered less efficient as well, patients need to be willing and able to undertake clean intermittent self-catheterization. This is a major operation with substantial long-term sequelae, so all alternative options should have been considered (Stohrer et al., 2007a). It is contraindicated if there is a history of urinary tract malignancy, stones, or gastrointestinal disease. If there is VUR, ureteric reimplantation may be considered as a means of protecting renal function (Hayashi et al., 2007), but it remains unclear whether reimplantation is beneficial (Misseri et al., 2008). Complications of augmentation cystoplasty include perioperative mortality, prolonged postoperative ileus, febrile UTI, intestinal transit disorders (Somani et al., 2007), fluid and electrolyte disorders (notably hyperchloremic acidosis), and malignancy (Higuchi et al., 2010). An important emergency complication to be aware of is cystoplasty rupture (DeFoor et al., 2003) due to overdistension or catheterization trauma (Blok et al., 2007). Autoaugmentation, in which the bladder is left intact and the bulk of the detrusor

muscle is excised, does not appear to achieve good results in NLUTD (Kumar and Abrams, 2005).

Bulking injections occasionally are used to treat stress urinary incontinence due to sphincteric incompetence. Various substances can be injected under the urethral epithelium, to cause an inward bulge to enhance coaptation of the outlet. The procedure is minimally invasive, but reaction to the injected substance, infections, low response rates, and poorly sustained efficacy are problematic.

Autologous fascial sling is used to treat stress urinary incontinence in women. In women, a strip of muscle sheath (usually from the rectus abdominis) can be passed around the urethra retropubically for a compressive effect. Good continence rates can be achieved, but there is a high chance of subsequent reliance on catheterization for bladder emptying. Use of autologous fascia is necessary, as there is a high risk of urethral erosion if artificial materials are used. Midurethral tapes are not widely supported for this reason, though small studies have been reported (Hamid et al., 2003).

Artificial urinary sphincter is a mainstream approach to treating severe stress urinary incontinence. The device comprises a compressive urethral cuff, an intra-abdominal pressure-regulating balloon, and a component (intrascrotal or labial) to enable patients to deflate the cuff when they wish to void. Sufficient manual dexterity and cognitive function is needed for the patient to be able to use the device successfully. In men, the cuff can be placed around the urethra in either the perineum or the abdomen. Continence rates are approximately 85%. The main serious complication is the possibility of infection, which is likely to cause device extrusion and damage to the tissues, and requires urgent device removal. Complications with artificial urinary sphincter appear to be higher in NLUTD (Sidi et al., 1987) than in men with postprostatectomy incontinence (Van der Aa et al., 2013). Since people with NLUTD are often comparatively young, it is relatively likely that AUS replacement will be needed, as the longevity of the device is not indefinite.

Bladder neck reconstruction aims to achieve a continent proximal urethra. Various approaches have been reported to reconfigure an abnormal bladder neck and have been adapted for carefully selected situations in NLUTD (Tanagho, 1981; Kropp and Angwafo, 1986; Sidi et al., 1987; Jones et al., 1993; Salle et al., 1994). Published evidence is limited, and subsequent procedures, including cystoscopy and clean intermittent self-catheterization, are rendered difficult. Bladder neck or urethral closure for intractable severe incontinence is only undertaken in severe cases, and has to be combined with an SPC or a reconstruction to enable catheterization through a new channel (Mitrofanoff).

Surgical options to improve voiding

SNM to improve voiding has been described by only one small study reporting specific results for neurogenic urinary retention (Hohenfellner et al., 2001), and response rate was low.

Sphincterotomy or sphincter stenting aims to prevent detrusor external sphincter dyssynergia. Endoscopic sphincterotomy was a widespread approach prior to the introduction of IC. It is irreversible and it is inappropriate if containment will be problematic. Complications can include hemorrhage (Reynard et al., 2003), autonomic dysreflexia, encrustation, and recurrence of outlet obstruction (Vapnek et al., 1994; Juma et al., 1995); consequently these patients should remain under follow-up. Sphincterotomy using laser has been reported (Rivas et al., 1995). Various stents have been tried to achieve a similar effect, and a temporary stent placement can be used to assess the clinical appropriateness of subsequent sphincterotomy (Game et al., 2008; Pannek et al., 2011). Permanent stents have also been designed, but substantial complications can occur with long-term use (Badlani, 1997; Corujo and Badlani, 1997; Wilson et al., 2002).

Mypolasty techniques to enhance detrusor contractility have been described. Transposition of the latissimus dorsi muscle to the vicinity of the bladder, with adapted stimulation methods, has been reported (Gakis et al., 2011).

Urinary diversion

In severe NLUTD, consideration may need to be given to bringing the urinary drainage to another anatomic site. This is particularly the case if there are major difficulties with catheterizing or mobility, and in severe NLUTD. Substantial care must be taken with patient selection. Note must be taken of surgical risk, potential impact on bowel and renal function, and likely effectiveness of containment (for example, extensive abdominal scarring or distortion will make stoma bag attachment problematic).

A continent cystostomy (replacement of the bladder outlet) retains the bladder as the reservoir, and an alternative route of catheterization is introduced. Most commonly this is the appendix (Mitrofanoff procedure) or a tube reconfigured from a short section of ileum (Monti et al., 1997). Complications are very common, including stenosis of the channel, difficulty catheterizing, and leakage.

Continent diversion (replacement of the bladder and outlet) is a major reconstructive procedure, in which a new reservoir is fashioned from a bowel segment, and an alternative route of catheterization is introduced. Several approaches have been described (Moreno et al., 1995; Watanabe et al., 1996; Plancke et al., 1999; Stein et al., 2005).

Incontinent diversion most commonly constructs an ileal conduit urinary diversion (urostomy), in which the ureters are anastomosed to a bowel segment brought out as a continuously draining stoma, with no reservoir component. The potential stoma site must be identified preoperatively in order to match location with the patient's daily needs, e.g., wheelchair use. Complications are common (Legrand et al., 2011), but quality of life is often improved for appropriately selected patients. Potential effects on intestinal function need to be considered (Somani et al., 2007), and a range of complications is recognized, such as stenosis of the ureteroileal anastomosis and stoma problems (Kato et al., 2002). Where the bladder is not removed, additional complications can occur (e.g., pyocystis, the accumulation of pus in the defunctioned bladder). Ileovesicostomy means an ileal segment is joined to the dome of the bladder, and the other end brought out as a stoma. This may be the preferred option in some cases (Sorokin and De, 2013). For female patients, additional surgery may be needed to counteract potential urethral leakage. Complications are common (Tan et al., 2008; Vanni and Stoffel, 2011), particularly related to poor drainage.

In a vesicostomy, a bladder tube is anastomosed directly to the skin. This is comparatively simple to undertake, but stenosis at the skin level is common. The procedure can be reversible, notably in children, and is a suitable option in well-selected cases (Morrisroe et al., 2005). In cutaneous ureterostomy, the ureters are anastomosed directly to the skin. This is only possible if there is substantial ureteric dilation, and risk of stenosis of the anastomosis and containment difficulties is high (Sarduy et al., 1982; Lindstedt and Mansson, 1983).

CONCLUSIONS

Neurourology is a challenging area, which has to work in a multidisciplinary context. Assessment is comprehensive and needs to factor in the neurologic condition, the component organs of the LUT, effects on both storage and voiding, UTIs, and how renal function may be impaired, along with bowel and sexual function. Treatment selection has to account for physical and cognitive limitations, availability of carers and support, and the range of other treatments the person affected is likely to require. Life-threatening problems include autonomic dysreflexia and chronic renal disease, and safe care requires ongoing follow-up and reassessment accordingly.

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Handbook of Clinical Neurology, Vol. 130 (3rd series)
Neurology of Sexual and Bladder Disorders
D.B. Vodušek and F. Boller, Editors

Chapter 27

Psychiatric disorders and sexual dysfunction

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INTRODUCTION

Although sexology is historically rooted in psychiatry, since the 1970s psychiatrists in general had lost their interest in treating patients with sexual dysfunction. What led psychiatrists to abandon sexology has never been investigated but may be related to the prevailing behavioristic and non-medical view sexologists held at that time. The prevailing thought was that sexual dysfunctions are mainly related to relationship difficulties and self-learned behavior, and that the use of medication to treat sexual disorders is only a symptomatic treatment and does not cure the patient. In the 1970s and 1980s, there was a strong but erroneous belief among many psychologists and psychiatrists that only psychotherapy could cure mental and sexual problems (Zegerius and Waldinger, 2000). However, things could now be starting to change, judging by the slowly increasing number of psychiatrists who again attend symposia on sexual medicine. Nevertheless, nowadays only a very small percentage of psychiatrists actively treat sexual disorders such as erectile disorder, ejaculatory disorders, and female sexual disorders. In contrast, the clinical importance of drug-induced sexual side-effects has become well known among psychiatrists and a substantial number of psychiatrists actively inquire about their occurrence. This is probably because, in the last two decades, human and animal sexual pharmacologic research has mainly been performed on antidepressant and antipsychotic drug-induced sexual side-effects (Olivier et al., 2006). Moreover, in psychiatric literature quite a lot of attention has been given to antidepressant-induced sexual side-effects (Baldwin, 2004; Balon and Segraves, 2008).

In general medicine, much less attention has been given to research into sexual side-effects induced by other drugs, such as cardiovascular drugs or cytotoxic agents. Compared to the attention given to psychotropic drug-induced sexual side-effects, only a limited number of studies have been performed on how patients with psychiatric disorders cope with sexual problems. Notably, a serious methodologic limitation of most studies into sexual complaints of patients with psychiatric disorders is the absence of baseline assessment of sexual functioning, the retrospective method, and the lack of studies using objective tools to (prospectively) assess sexual (dys)functioning. Although various methods using objective measurements and tools to study sexual functioning exist, for example, the use of a stopwatch to assess intravaginal ejaculation latency time (IELT) (Waldinger et al., 1994, 2004), studies of sexual functioning in psychiatric disorders have been mainly conducted with subjective questionnaires and retrospective assessments. Because of these methodologic limitations, together with the paucity of such studies in general, there is still a severe lack of hard information on sexual (dys) functioning in patients with psychiatric disorders.

In the current chapter, sexual dysfunction in the major psychiatric disorders will be discussed. Much of this information has recently been reviewed in three detailed review articles by Zemishlany and Weizman (2008), Knegtering and de Boer (2012), and Jonusiene and Griffioen (2013).

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SCHIZOPHRENIA AND SEXUAL DYSFUNCTION

In the early 20th century schizophrenia was thought to develop because of deficiencies in sex hormones (Jacobs and Bobek, 1991; Knegtering and de Boer, 2012). Later psychoanalytic theories suggested that psychosis might derive from unconscious homosexual tendencies (Norman, 1948). Erotic sexual behaviors were also seen as possible causal factors in schizophrenia in pre-schizophrenic patients (Ariety, 1967; Jacobs and Bobek, 1991). Mainly theory-driven and not based on any empiric research, these ideas have been abandoned in modern research (Knegtering and de Boer, 2012). According to case reports, schizophrenic patients sometimes do experience cenesthetic hallucinations of a sexual nature, erotomanic delusions, delusions related to sexual identity, and hypersexuality during an acute psychotic episode (Connolly and Gittleson, 1971; Akhtar and Thomson, 1980; Jacobs and Bobek, 1991). But such psychotic manifestations are uncommon and usually disappear after the start of antipsychotic medication (Fortier et al., 2000).

In their book on schizophrenia and sexual functioning, Knegtering and de Boer (2012) pointed out the historic sexual restrictions amongst patients with schizophrenia that often existed before mid 20th century. Sexual inactivity was typical within institutions as extramarital sexual intercourse was socially frowned upon. They noted this from the reports by Hilger et al. (1983). Institutionalization reinforced sexual inactivity by discouraging or even prohibiting sexual relationships. Interestingly, as pointed out by Wignall and Meredith (1968), there were illegitimate pregnancies in psychiatric facilities, but the incidence was much lower than that of the population overall – as low as one-fifth.

Mid 20th century things began to change for psychiatric inpatients due to the availability of oral contraceptives. These patients were trusted to take part in mixed social gatherings and allowed home visits (Wignall and Meredith, 1968). At the same time the relative fertility of women suffering major mental disorders also grew as social contact with men began to take place (Nicholson et al., 1996).

In the 1980s, it was thought by Skopec et al. (1976) that schizophrenic patients do not generally exhibit any differences in their sexual behavior compared to controls. It is quite rare that schizophrenic patients produce a lack of sexual inhibition directly related to their psychotic symptomatology. Knegtering and de Boer (2012) mention that some patients with schizophrenia have distorted and bizarre preoccupations with sex. As explained by Jacobs and Bobek (1991), their delusions remain as such and are rarely acted upon. It goes no further than an expression of sexual activity through fantasy or masturbation. Skopec et al. (1976) had found that male schizophrenic patients found masturbation less pleasurable even when practicing it several times more frequently than the population as a whole. Lyketsos et al. (1983) reported that it seems that both male and female chronic schizophrenic inpatients are less interested in sexual activity, engage in it less often, and derive a lower degree of satisfaction from sexual encounters. The higher level of severity of their psychopathology and time spent as inpatients were directly related to the lesser frequency of sexual activity and level of satisfaction derived from it.

In later reseach at the start of this century (McEvoy et al., 1983; McCann, 2010; Knegtering and de Boer, 2012) it was found that dreams and fantasies amongst such patients were no different from those in a control group. McEvoy et al. (1983) in particular found that chronically institutionalized women did have a continuing interest in sex and were indeed sexually active. This was confirmed in a study by McCann (2010). In that study, 30 schizophrenic patients were asked about their sexual experiences. The result showed that as many as 83% had ongoing sexual feelings and needs for intimacy.

In 1984 Raboch reported that schizophrenic patients felt their institutionalization got in the way of sexuality – they began to date, kiss, have first coitus or even marriage later than other people. However Raboch also reported how the sex life of schizophrenic patients who did have a relationship and a steady partner was the same as the norm.

Various researchers suggest there could be differences in the way schizophrenia affects the sexual behavior of males and females (McGlashan and Bardenstein, 1990). These authors observed that women are more likely to go out socially on dates and have sex, and to marry and have families. Some of the women studied were found to experience polarity in their sexual activity – from high to low levels of sexual activity (McEvoy et al., 1983). However, there was a degree of negativity in their sexual experience as women tended to have partners they did not think as desirable as they would like. And both male and female patients reported feeling guilty about their sexual preoccupations. Despite such negative feelings about having sex most women with chronic schizophrenia felt a strong urge to have children without any awareness of difficulties in their competence as mothers given their chronic schizophrenia.

An earlier study of Buddeberg et al. (1988) looked at the differences between non-institutionalized male and female schizophrenics and showed a high level of interest in sexual activity. Sexuality was important to 80% of respondents, 68% wanted to have sexual relations, and more than one-third of them did experience sexual

activity. However, it wasn't always easy as many men experienced erectile problems, and the women also said they suffered sexual impairment. The authors of the study concluded that sexual problems were likely to be the result of the antipsychotic treatment itself as well as of difficulties in actually relating interpersonally.

While schizophrenia itself may be a causal factor in sexual complaints, one must add in the negative sexual side-effects of antipsychotic medication. One must take into account also that many psychiatrists and physicians hesitate to discuss sexual topics with their patients and thus do not hear about any severe sexual side-effects that schizophrenic patients experience after taking this medication. Currently this attitude of avoiding talking about sex seems less prevalent among psychiatrists than it was a few decades ago.

In 1990, Finn et al. conducted a study in which 41 schizophrenic patients were asked ro rate and compare the burden of their psychotic symptoms with other symptoms they experienced. The scale was from 1 (mild) to 5 (most serious). In their study, 66% of respondents said they experienced persecutory hallucinations and 34% reported impotence as a problem. However, although less frequently, the burden of impotence was rated on a similar level of severity: hallucinations were rated as 4.34 and impotence even higher, as 4.5. A larger-scale survey 12 years later by the English National Schizophrenia Fellowship further confirmed these findings (Smith et al., 2002). In this case over 2000 mental health service users were surveyed and a high number of them on antipsychotic medication experienced perceived difficulties with sexual side-effects. In addition to the Finn study of 1990, Haddad and Sharma (2007) and Baggaley (2008) found a reduction in therapy compliance that could be linked to patients' dislike of sexual side-effects. Quite simply, they could not accept how the therapy adversely lessened their quality of life.

The view of psychiatrists in the 1980s is mirrored by the study of Strauss and Gross (1984). In this study among 86 psychiatrists, the psychiatrists said they found the drug-induced sexual side-effects clinically relevant in as many as two out of three patients and that this was likely to interfere with adherence by patients to their drug regime. The psychiatrists thought almost universally that patients would not be willing to spontaneously talk about sex. Notably, only 10% had actually asked their patients if they had any kind of sexual side-effects from medication. In contrast to the 1980s, it is currently known that patients are more willing to give feedback on sexual side-effects when answering specific questionnaires on sexual behavior, or in response to direct questioning (Knegtering et al., 2004; Dossenbach et al., 2005). Knegtering and de Boer (2012) pointed out the importance, therefore, of focused questioning of patients to avoid underestimating the impact of drugs on sexual activity by patients with schizophrenia and related psychotic disorders.

DEPRESSION AND SEXUAL DYSFUNCTION

Between 10 and 16% of the general population had been through an episode of depression (Kessler and Walters, 1998; Kessler et al., 2003; Zemishlany and Weizman, 2008). Depression is indeed a major worldwide cause of disability (Murray and Lopez, 1997). It is known that depressive disorders express themselves through reduced mood, loss of interest or pleasure, anhedonia, decreased activity, and difficulty concentrating. These symptoms are often accompanied by a reduction in sexual desire. Moreover, cultural, religious, and personal histories might be causally related to sexual dysfunction of patients and of their partners (Jonusiene and Griffioen, 2013). These could include their partner's sexual problems as well as their own shortcomings in sexual stimulation, medical conditions, medications, or even substance abuse. On a personal basis patients might have been subjected to difficulties in their upbringing, maybe personal loss and trauma of physical, emotional, as well as sexual nature.

Prevalence of sexual dysfunction

Sexual dysfunction is higher in patients with major depressive disorder than in the general population. Its prevalence ranges from 40% to 65% prior to antidepressant treatment (Mathew and Weinman, 1982; Casper et al., 1985; Angst, 1998; Derogatis and Burnett, 2008; Hayes et al., 2008; Chen et al., 2009; Lewis et al., 2010; Lee et al., 2013). The longitudinal epidemiologic Zurich study has shown that sexual problems in depressed patients (including those with major depression, dysthymia, and recurrent brief depression) are approximately twice as frequent as in control subjects (Angst, 1998). Depressive symptoms often coexist with anxiety symptoms, which are also associated with sexual problems (Mitchell et al., 1998; Rosen et al., 2006; Williams and Reynolds, 2006; Laurent and Simons, 2009; Quinta Gomes and Nobre, 2011; Lin et al., 2012).

Reduced sexual desire and arousal

In 1985, Casper et al. quantified a cohort of moderate to severe hospitalized drug-free patients with major affective disorder (132 patients with major depressive disorder and 80 normal controls) as having loss of sexual interest. The percentage was high (72% with unipolar and 77% bipolar depression). Their data suggested that, as their depression and anxiety increased, so their libido

weakened. Depressed patients with increased appetite were more sensitive in personal relationships, more hostile, and reported a greater decrease in libido than age-matched and sex-matched depressed patients without increased appetite. Depressed persons may also experience diminished ability to maintain sexual arousal or achieve orgasm.

In a later study by Kennedy et al. (1999), the prevalence of sexual dysfunction was investigated in 134 drug-free patients with major depression (55 male and 79 females). The study showed that only 50% of women and 75% of men reported sexual activity during the preceding month. Over 40% of men and 50% of women reported decreased sexual interest. Reduced levels of arousal were more common in both men and women (40–50%) than orgasm difficulties (15–20%). In women, problems with arousal and orgasm correlated with higher neuroticism and lower extraversion.

Erectile dysfunction

Various studies have shown that depressive and anxiety symptoms are highly associated with erectile dysfunction (Laumann et al., 1999; Ponholzer et al., 2005; Araujo et al., 1998; Williams and Reynolds, 2006; Mialon et al., 2012). Men with high depression scores are almost twice as likely to report erectile disorder compared to men with low depression scores (Perelman, 2011). Particularly in older men with severe depression, erectile dysfunction could be as high as 90% (Feldman et al., 1994). A study by Thase et al. (1988) involving a sample of 34 male outpatients with major depression matched against 28 healthy men found that in men from the same age group, diminished nocturnal penile tumescence, an objective measure of erectile capacity, was present in about 40% of the depressed men. These findings were confirmed in a later study among 51 outpatients with depression (Thase et al., 1992).

Neuroimaging studies

Neuroimaging studies show changes in brain activity relating to sexual function in both male and female depressed patients (Yang, 2004; Yang et al., 2008; Kennedy and Rizvi, 2009). For example, in a functional magnetic resonance imaging study by Yang et al. (2008), nine healthy women (mean age: 40.3 years) and seven depressive women (mean age: 41.7 years) were sexually visually stimulated by an erotic video film. It was found that healthy women were significantly ($P < 0.05$) activated in various regions of the brain (e.g., middle occipital gyrus, middle temporal gyrus, inferior frontal gyrus, insula, hypothalamus, septal area, anterior cingulate gyrus, parahippocampal gyrus, thalamus, and amygdala). In comparison with the healthy women, the depressive women showed lower activity, especially in the brain regions of hypothalamus, septal area, anterior cingulate gyrus, and parahippocampal gyrus.

Sexual activity

In 2004, Cyranowski et al. examined the association between a history of lifetime depression and sexual function in a community-based sample of middle-aged women. Specifically, 914 women, aged 42–52 years, completed a self-report assessment of their sexual behaviors, sexual desire, sexual arousal, and sexual satisfaction over the past 6 months. On the basis of the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) (American Psychiatric Association, 1994), subjects were categorized into one of three lifetime major depressive disorder (MDD) history groups: (1) no MDD history; (2) single-episode MDD; and (3) recurrent MDD. Women with a history of recurrent MDD reported experiencing less frequent sexual arousal, less physical pleasure, and less emotional satisfaction within their current sexual relationships. Although the groups did not differ in their reported frequency of sexual desire or partnered sexual behaviors, lifetime depression history was associated with increased rates of self-stimulation (masturbation). It was found that depressed women do continue to be be sexually active at the level of their partner's libido or according to the frequency established between them, rather than reducing their actual sexual activity in line with their loss of interest.

ANXIETY DISORDERS AND SEXUAL DYSFUNCTION

According to DSM-5, anxiety disorders include disorders that share features of excessive fear and anxiety and related behavioral disturbances (American Psychiatric Association, 2013). Fear is the emotional response to a real or perceived imminent threat, whereas anxiety is anticipation of future threat (American Psychiatric Association, 2013). Apart from (performance) anxiety that originates from well-known sexual dysfunctions, men and women in the general population may suffer from a number of anxiety disorders, such as separation anxiety disorder, selective mutism, specific phobias, social anxiety disorder (social phobia), panic disorder, agoraphobia, generalized anxiety disorder, and substance/medication-induced anxiety disorder (American Psychiatric Association, 2013), as well as obsessive-compulsive disorder (OCD), body dysmorphic disorder, and posttraumatic stress disorder (PTSD).

Panic attacks

Anxiety is a major factor in the etiology of sexual dysfunction (Kaplan, 1988). Anxiety concerning sexual performance or relationship issues, such as intimacy and partner rejection, is also the critical element in sexual avoidance patterns. In susceptible patients the intensity of sexual anxiety can reach panic proportions. According to Kaplan (1988), patients with sexual aversion disorder and phobic avoidance of sex have a high incidence of panic disorders. Kaplan argued that some of the patients experienced panic about their loss of control during arousal and orgasm. In extreme circumstances patients fear they could die during such a panic attack. According to Jonusiene and Griffioen (2013), it is the increased heart rate of sexual arousal that could produce this fear and panic. In one study, van Minnen and Kampman (2000) reported that women with panic disorder suffered more from sexual desire disorder.

Social phobia

Social phobia is a type of performance and interpersonal anxiety disorder and as such may be associated with sexual dysfunction and avoidance (Bodinger et al., 2002). Figueira et al. (2001) conducted a retrospective study into the sexual function of social-phobic patients in comparison with a panic disorder sample (30 patients with social phobia and 28 patients with panic disorder). Their study showed that panic disorder patients reported a significantly greater proportion of sexual disorders compared with social phobics: 75% vs 33.3% ($P = 0.0034$). Sexual aversion disorder was the most common sexual dysfunction in both male (35.7%) and female (50%) panic disorder patients, and premature ejaculation was the most common sexual dysfunction in male social-phobic patients (47.4%). These results suggest that sexual dysfunctions are frequent and neglected complications of social phobia and panic disorder. Further data are provided by the study of Bodinger et al. (2002), who investigated sexual function and behavior in 40 drug-free outpatients with social phobia compared with 40 mentally healthy subjects. The results showed that men with social phobia had more sexual problems than those without. Men with social phobia suffered mainly moderate impairment in arousal, orgasm, sexual enjoyment, and subjective satisfaction domains. Their performance problems occurred more often and their first sexual experience was at a later age. Women with social phobia reported severe impairment in their desire, arousal, sexual activity, and subjective satisfaction. In addition, compared with controls, women with social phobia had a significant paucity of sexual partners ($P < 0.05$) compared to the healthy control group (44% had only one partner or even none in their life compared with 6% in the control group). The authors concluded that patients with social phobia exhibit a wide range of sexual dysfunctions. Men have mainly performance problems, and women have a more pervasive disorder. Patients of both genders show difficulties in sexual interaction.

Obsessive-compulsive disorder

Several studies have shown that sexual dysfunction is rather common in OCD (Monteiro et al., 1987; Freund and Steketee, 1989; Staebler and Pollard, 1993; Aksaray and Yelken, 2001). However, Aksoy et al. (2012) note conflicting reports in the literature regarding the association between sexual dysfunction and OCD. They point to the study of Steketee (1997) showing a lower rate of marriage, sexual intercourse difficulties, and reduced sexual experience in OCD patients that may be related to sexual dissatisfaction encountered during the disease process. In addition, a study by Monteiro et al. (1987) showed that approximately 9% of female patients with OCD had anorgasmia and 22% had sexual arousal problems, whereas 25% of males had lower sexual arousal, 12% had premature ejaculation, and 6% had erectile disorder, with 39% of the patients displaying sexual dissatisfaction. Orgasm disorder was found in 12% of cases in another study by Freund and Steketee (1989). Aksaray and Yelken (2001) reported a higher incidence of anorgasmia, sexual arousal disorder, and sexual avoidance in OCD patients compared to patients with generalized anxiety disorder. In addition, Van Minnen and Kampman (2000) reported that women with panic disorder and those with OCD have lower sexual desire and lower frequency of sexual contact than controls. Vulink et al. (2006), who examined sexual satisfaction in women with OCD, reported that 62% of patients experienced reduced sexual desire, 29% had reduced sexual arousal, 33% had orgasmic-phase dysfunction, 25% had problems regarding physiologic arousal, and 10% had lack of sexual pleasure. The authors found no change in the frequency of sexual intercourse among the OCD patients, although they seemed to avoid sexual intercourse. Fontenelle et al. (2007) compared the presence of sexual difficulties in 31 patients with OCD with that in 26 patients with social anxiety disorder. According to their study, patients with OCD reported more difficulties in reaching orgasm ($P = 0.009$), less frequent effective erections ($P = 0.05$), and a positive history of sexual abuse ($P = 0.006$) significantly more often than patients with social anxiety disorder. Aksoy et al. (2012) investigated 40 drug-free patients (aged 20–60 years) with OCD, 40 patients with panic disorder, and 40 healthy controls. Males with OCD had a lower age of first masturbation and first

nocturnal ejaculation. Infrequency problem among female and male patients with OCD occurred in 63.6% and 57.1%, respectively. Corresponding figures for patients with panic disorder were 36% and 38%. Sexual avoidance was found in 60.6% of female OCD patients and in 64% of female panic disorder patients. Anorgasmia was detected in 24.2% of the female subjects with OCD.

Posttraumatic stress disorder

In women PTSD is often secondary to sexual trauma (Moser et al., 2014). In contrast, PTSD in men is frequently due to physical trauma and, for soldiers, to combat-related events. In their article on PTSD and sexual dysfunction, Kotler et al. (2000) note that exposure to extreme traumatic events may lead to behavioral and physiologic abnormalities which at times persist long after the precipitating stressor has been removed, leading to the clinical syndrome of PTSD, and may also significantly affect emotional, social, professional, and sexual functioning.

In 1988, Kaplan also reported on sexual problems among PTSD patients. About 10 years later, Letourneau et al. (1997) reported that over 80% of PTSD patients studied were experiencing clinically relevant sexual difficulties. Most frequently reported problems were erectile dysfunction and premature ejaculation. This research emphasized the risk of sexual problems from PTSD. Kotler et al. (2000) compared various components of sexual functioning among three groups of males: (1) untreated PTSD patients ($n = 15$); (2) PTSD patients currently treated with selective serotonin reuptake inhibitor (SSRI) agents ($n = 27$); and (3) a group of normal controls ($n = 49$). Their study showed that untreated and treated PTSD patients had significantly poorer sexual functioning in all domains (desire, arousal, orgasm, activity, and satisfaction) as compared to normal controls. Those treated with SSRI had greater impairment in desire, arousal, and frequency of sexual activity with a partner. The authors concluded that PTSD is associated with pervasive sexual dysfunction that is exacerbated by treatment with SSRIs. They also noted that patients with PTSD have a high rate of comorbid panic disorder, major depression, and anxiety, and it could thus be argued that these comorbid disorders, rather than PTSD, accounted for their observed results. Sexual dysfunction in PTSD may have several causes. It may be a symptom of PTSD itself. For example, it may be due to a numbing of responsiveness. But it may also be related to comorbid depressive and anxiety disorders. In addition, it may be caused by the use of antidepressants.

EATING DISORDER AND SEXUAL DYSFUNCTION

Anorexia nervosa patients often suffer from sexual dysfunction and immaturity (Zemishlany and Weizman, 2008). Low sexual interest, inhibited sexual behavior, disgust towards sex, and fear of intimacy have been reported in a number of studies (Raboch, 1984; Raboch and Faltus, 1991; Simpson and Ramberg, 1992). This is not a surprise as patients with anorexia nervosa usually have a profound disturbance of body image and feel overweight or misshapen (Zemishlany and Weizman, 2008). Anorexia nervosa is more prevalent in females than in males and its onset is usually in adolescence. Most research on eating disorders and sexuality has been done on women.

In a study by Raboch and Faltus (1991) of the sexual development and life of 30 adult women with anorexia nervosa and of 50 control women, it was found that 63% had irregular menstruation or secondary amenorrhea. The women (average age 24 years) were mostly unmarried and were often without a satisfactory partner relationship. Heterosexual development was found to be normal in the initial stages, but psychosexual adaptation in adulthood was impaired; 20% of patients had no coital experience and 80% were found to have sexual disturbances. In comparison, 92% of the control group reported having a satisfactory partner relationship.

This study and the study of Tuiten et al. (1993) showed that, during adolescence, prior to becoming anorexic, the sexual development of anorexia nervosa patients was normal (Tuiten et al., 1993 or even accelerated (Raboch, 1984). Tuiten et al. (1993) postulated that the sexual problems of anorexic females arise only after the emergence of hypogonadism, as a consequence of emaciation. Their study showed that patients, before they became anorexic, were indeed rather similar to normal subjects with respect to sexual attitude. Moreover, patients reported a considerably decreased sexual interest during their anorexic period when compared with normal controls.

In a follow-up study using a questionnaire, Morgan et al. (1995) investigated sexual functioning in 42 women who had been treated for either anorexia nervosa (restricting type) or bulimia nervosa (purging type). It was found that in formerly anorexic women there was a trend of being less likely to be in a romantic/erotic relationship. Almost all of the women had engaged in sexual intercourse, and formerly anorexic patients did not differ from bulimics with regard to age at first coitus. Anorexics were less likely than bulimics to have engaged in masturbation and also scored lower on a measure of sexual esteem. Although there were no differences between the two groups with regard to current level of

sexual functioning, erotophobia/erotophilia, or sexual satisfaction, the women in this study exhibited less sexual interest and more negative affect during sex than did a normative sample. In addition, nearly 40% of the women indicated clinically significant levels of sexual discord with their current partner. According to Zemishlany and Weizman (2008), eating disorder patients, even after recovery, struggle with acceptance of their sexuality and have high rates of inhibited sexual desire, sexual aversion, and anorgasmia. Moreover, they point to the fact that eating disorder patients often exhibit problematic personality characteristics, with a high frequency of secondary diagnoses of borderline or narcissistic personality disorders as well as depressive states.

PERSONALITY DISORDERS AND SEXUAL DYSFUNCTION

Patients with a personality disorder show an enduring pattern of inner experience and behavior that deviates markedly from the expectations of the individual's culture with regard to appropriateness of emotional response, interpersonal functioning, impulse control and perceiving and interpreting self, other people, and events. In addition, they have an enduring pattern that is inflexible and pervasive across a broad range of personal and social situations, leading to clinically significant distress or impairment in social, occupational, or other important areas of functioning (American Psychiatric Association, 2013).

These disturbed relationship traits may interfere with sexual functioning and the capacity for intimacy. There are, however, very few studies that address specifically the sexual relationships of patients with personality disorders.

Patients with personality disorders can experience various sexual difficulties, ranging from promiscuity to avoidance. However, the role of personality dimensions in the etiology and maintenance of sexual dysfunction has not been systematically studied in sex research (Quinta Gomes and Nobre, 2011).

Histrionic personality disorder

Jonusiene and Griffioen (2013) described the personality of patients with histrionic disorder as needing continual reassurance and ego gratification, and being self-centered. This is seen in their helplessness and dependency. So they would be sensitive to any criticism in regard to perceived sexual performance expectations, physical appearance, attractiveness, and sex appeal. Persons with histrionic personality disorder are deeply concerned that their appearance is attractive and sexually appealing (Gorton and Akhtar, 1990). According to O'Neill and Kempler (1969), sexual maladjustment is not uncommon among patients with histrionic personality disorder. In a study by Raboch (1984) of 30 inpatient females averaging 34 years in age suffering from decompensation of ICD-9 "hysterical psychopathic personality (World Health Organization, 1978)," it was found by a questionnaire that these women showed a disrupted history of sexual development and experienced lower levels of sexual activity and ability to experience orgasm. In a later study by Gorton and Akhtar (1990), it was reported that these women are often preoccupied with appearing attractive and sexually seductive. They tend to have fantasies about sex, are impulsive, and express dissatisfaction about their sexual relationships (Jonusiene and Griffioen, 2013).

According to a study by Hurlbert and Apt (1991), women with this disorder may show elements of sexual narcissism, which according to the authors is an egocentric pattern of sexual behavior. Apt and Hurlbert (1994) compared a sample of women with histrionic personality disorder to an adequately matched sample of women without personality disorders (aged 24–31 years) using various measures. As compared to the control group, women with histrionic personality were found to have significantly lower sexual assertiveness, greater erotophobic attitudes toward sex, lower self-esteem, and greater marital dissatisfaction. Women in the histrionic group were also found to evidence significantly greater sexual preoccupation, lower sexual desire, more sexual boredom, and greater orgasmic dysfunction, and were more likely to enter into an extramarital affair than their counterparts. Despite these findings, a higher sexual esteem was noted among the histrionic group. This pattern of sexual behavior noted among histrionic women appears consistent with those behaviors exhibited in sexual narcissism.

Interestingly, Bandini et al. (2009) investigated testosterone plasma levels in a consecutive series of 2042 heterosexual male patients (mean age 51.8 ± 13) consulting an outpatient clinic for sexual dysfunction. This retrospective study showed that testosterone levels were negatively correlated with depressive and anxiety symptoms. However, men with histrionic traits were strongly and positively associated with elevated testosterone. Men with histrionic traits had higher androgenization, as suggested by both higher total and free testosterone and higher testis volume. They were also characterized by better self-reported sexual functioning and a higher penile blood flow and had a more satisfying sexual relationship. These men were less likely to report orgasm difficulties of their partner and were more often engaged in extramarital affairs.

Borderline personality disorder

Patients with borderline personality disorder suffer from different degrees of maladaptive patterns of relating to the environment. Their relationships are often characterized as intense and unstable, fear of abandonment, and idealization and devaluation. Moreover identity disturbance, impulsivity and inappropriate intense anger are by definition part of its symptomatology. Presumably, these characteristics may interfere with sexuality and the capacity of being intimate with a partner. Patients with borderline personality disorder have reported a higher number of different sexual partners, higher likelihood of having been raped, and to have experienced sexual aggression in adulthood (Zanarini et al., 1999; Sansone and Wiederman, 2009; Sansone et al., 2011a, b). In addition, impulsive sexual behavior and unstable relationships my give rise to hyper- as well as hyposexual desire disorders, leading to either sexual avoidance or promiscuity (Schulte-Herbruggen et al., 2009).

A few studies (Hurlbert et al., 1992; Hull et al., 1993; Schulte-Herbruggen et al., 2009; Sansone et al., 2011a) have shown indications that women with borderline personality disorder are more likely to show high-risk sexual behavior, and to have higher levels of sexual assertiveness, greater erotophilic attitudes, higher sexual esteem, and greater sexual preoccupation. In a prospective study (Zanarini et al., 2003), patients with borderline personality disorders – 290 well-defined patients and 72 non-borderline in the control group – were tracked over a 6-year period. It was found that 61% in the borderline group had reported some type of sexual relationship problems compared with 19% in other personality disorder patients, and that these problems were more present amongst the females studied. Indeed, 65% of women and 43% of men reported having symptoms like feelings and thoughts of dissociation, becoming suicidal or harming themself when they engaged in sexual activities. Fear of experiencing such feelings and thoughts could put them off sex altogether. Over time these behavioral patterns would to a great extent decline.

A study in 2009 (Schulte-Herbruggen et al., 2009) has shown that, in sexually active women, borderline personality disorder with a history of sexual traumatization, rather than borderline personality disorder alone, is crucial for sexual difficulties in these women, whereas co-diagnoses such as PTSD and major depression, as well as use of antiopsychotics or SSRIs do not have a comparable impact (Schulte-Herbruggen et al., 2009). Notably, women with borderline personality disorder show a trend for describing themselves as more bisexually oriented (Reich and Zanarini, 2008; Schulte-Herbruggen et al., 2009) or even revealed significantly more as homosexual-oriented (Reich and Zanarini, 2008).

Among borderline patients with sexual relationship difficulties, a higher percentage report childhood sexual abuse (76.8%) than patients without such abuse (39.8%). This pattern of behavior is echoed amongst patients with a history of rape (42.9% compared with 13.3%) According to Reich and Zanarini, given these findings, borderline patients would be likely to avoid sexual activity for fear of bringing back memories of these childhood and abuse traumas, and for fear of sparking off borderline personality symptoms. The male versus female differences in rates of childhood abuse and adult rape experiences found in this study may explain why there is a parallel gap in the presence of sexual relationship difficulties with borderline personality disorder sufferers.

PSYCHOTROPIC DRUG-INDUCED SEXUAL SIDE-EFFECTS

In the US general population, sexual dysfunction affects about 43% of women and 31% of men (Laumann et al., 1999). In women, reduced libido is the most prevalent disorder, reported by approximately a third of women (Laumann et al., 1999). In men erectile dysfunction and premature ejaculation are most prevalent. The prevalence of erectile disorder is higher in older age whereas the prevalence of premature ejaculation does not significantly change with age (McMahon et al., 2008; Serefoglu et al., 2014). In patients with mental disorders, the prevalence of sexual dysfunctions is higher than in the general population, particularly in patients treated with psychotropic drugs. For example, sexual dysfunction occurs in 30–60% of patients with schizophrenia who use antipsychotic medication (Peuskens et al., 1998). In patients with depression and anxiety disorders about 80% suffer from sexual side-effects (Letourneau et al., 1997; Rosen et al., 1999; Clayton et al., 2002; Osvath et al., 2003). Notably, sexual dysfunctions in patients with mental disorders are not only due to their psychotropic medication. Sexual dysfunction may also be related to their premorbid sexual function, to the psychiatric disorder itself, to comorbid psychiatric disorders, to comorbid physical illnesses or concomitant medications (Zemishlany and Weizman, 2008). Obviously, treatment of sexual side-effects or at least talking about the burden of sexual side-effects may result in better medication compliance.

Neurotransmitters and sexual functioning

A basic understanding of the neurophysiology of sexual function is necessary in order to understand the mechanisms by which psychotropic drugs might influence sexual function and may help the clinician to explain to patients why it is often inevitable that a psychotropic

drug has negative effects on sexual performance and a concurrent positive effect on disturbing mental phenomena. This patient understanding may perhaps contribute to treatment compliance.

Sexual function may be subdivided into sexual desire (libido), sexual excitement (arousal), penile erection, lubrication, ejaculation, orgasm, and sexual satisfaction.

Sexual desire

Sexual desire or libido may be defined as a person's interest in initiating or having sexual intimacy. For the maintenance of libido, a certain amount of plasma testosterone is necessary in men and women. It primes specific brain areas to become sensitive to internal and external erotic or sexual cues (Bloemers et al., 2013; Poels et al., 2013; van Rooij et al., 2013). In women, libido is inhibited by activation of a center in the left forebrain which is influenced by 5-HT_{1A} receptors (van Rooij et al., 2013). The production and release of testosterone are dependent on the plasma level of prolactin. Hyperprolactinemia decreases testosterone release and, therefore, is associated with reduced libido. Hypothalamic dopamine inhibits the release of pituitary prolactin and, as a result, influences the libido positively. Serotonin, on the other hand, increases the release of prolactin and may cause diminished libido (Perryman and Thorner, 1981; Wein and van Arsdalen, 1988).

Drugs that stimulate the release of prolactin and decrease sexual desire include antipsychotics (e.g., phenothiazines and butyrophenones), tricyclic antidepressants (TCAs: e.g., imipramine), antihypertensives (e.g., reserpine), and opiates (e.g., morphine). Conversely, drugs that inhibit prolactin release, such as levodopa and dopamine receptor agonists (e.g., bromocriptine) may increase sexual desire (Zemishlany and Weizman, 2008). Indeed, data from animal research indicate that brain dopamine plays a stimulatory role in male sexual behavior (Gessa and Tagliamonte, 1974). It is known that in male patients with Parkinson's disease who are treated with levodopa, an increased sexual interest may appear (Hyppa et al., 1970). Furthermore, it has been demonstrated that reductions in sexual desire in hyperprolactinemic women can be restored by treatment with bromocriptine (Sobrinho et al., 1987).

Penile erection

Erection of the penis may result from stimulation of the peripheral nervous system and/or central nervous system. Stimulation of, mainly, the parasympathetic (cholinergic) system results in vasodilation by which the erectile tissues with the corpora cavernosa become filled with blood and an erection is produced. Sympathetic stimulation (mediated by α_1-adrenergic receptors), on the other hand, produces vasoconstriction and thus leads to an inhibition of erection. Animal research has shown that erection in the male rat may be triggered centrally by stimulation of 5-HT_{2C} receptors (Berendsen and Broekkamp, 1990).

Ejaculation

Ejaculation has a peripheral and central nervous system component (Segraves, 1989). Generally, stimulation of sympathetic neurons results in rhythmic contractions of the epididymis, vas deferens, and seminal vesicles, which results in the seminal fluid being expelled into the posterior urethra. Excretion of seminal fluid from the wall of the vesica seminalis is the only activity of parasympathetic neurons during the ejaculation process. Once the seminal fluid with spermatozoa has arrived in the posterior part of the urethra, contractions of the surrounding muscles then propel the seminal fluid from the urethra. Studies of the male rat have shown that ejaculation is influenced centrally by the 5-HT_{1A} receptor subtype (Ahlenius et al., 1981).

Orgasm

In the female, the feeling of orgasm is expressed by rhythmic contractions of vaginal muscles. In the male, orgasm is usually accompanied by ejaculation. In males, it has been shown that at orgasm oxytocin release takes place (Ogawa et al., 1980). This release can be inhibited by naloxone, an opioid recept antagonist (Murphy et al., 1990). Therefore, it may be postulated that the pleasant feelings during orgasm might be a result of the central effects of oxytocin.

Neuroanatomy and sexual side-effects

There are two brain areas which play an important role in the ejaculation process. The first is located in the medial preoptic area of the hypothalamus (Rodgriguez et al., 1984) and promotes ejaculation (MacLean, 1975). The other area, the paragigantocellular reticular nucleus, is located in the brainstem and inhibits ejaculation (Marson and McKenna, 1990). A third important center mediating ejaculation is the so-called "spinal ejaculation generator" (Marberger, 1974; McKenna et al., 1991; Carro-Juarez and Rodriguez-Manzo, 2008), which is located in the spinal cord and coordinates sympathetic, parasympathetic, and motor outflows with inputs from the genitals to trigger ejaculation (Truitt and Coolen, 2002; Coolen et al., 2004). The lumbar spinothalamic cells, located lateral to the central canal in lamina X and in the medial portion of lamina VII of L3 and L4 of the lumbar spinal cord, play a fundamental role

in the generation of ejaculation and are part of spinal ejaculation generation (Truitt and Coolen, 2002; Coolen et al., 2004).

Dopamine and serotonin

Sexual functioning is mediated by the central and peripheral nervous system. Various neurotransmitters, neuropeptides, and hormones, including androgens, estrogens, progesterone, prolactin, and oxytocin, are related to specific (dys)functions. With regard to psychotropic drug-induced sexual side-effects, it should be realized that the neurotransmitters involved in sexual functioning, e.g., mainly dopamine, serotonin, and epinephrine, are also involved in the pathophysiology and pharmacologic treatment of mental disorders (Zemishlany and Weizman, 2008).

Dopamine

The central dopaminergic system plays a role in all components of male sexual activity: desire, erection, orgasm, ejaculation, and satisfaction (Pfaus and Everitt, 1995; Meston and Frohlich, 2000). Dopaminergic drugs such as L-dopa, apomorphine, bupropion, and amphetamines may stimulate sexual functioning, e.g., may give rise to a better erection or may facilitate ejaculation. On the other hand, central dopaminergic blockers, such as antipsychotics, inhibit sexual function, e.g., may give rise to erectile dysfunction and delayed ejaculation.

Serotonin

Serotonin (5-hydroxytryptamine: 5-HT) may facilitate or inhibit sexual functioning (Olivier et al., 1998, 2011). The effect depends on the amount of serotonin neurotransmission in the synapse of serotonergic neurons in the central nervous system, e.g., the brain, brainstem, and spinal cord. Its effect is also dependent on the the serotonin receptor subtype that is affected (Snoeren et al., 2014). For example, activation of 5-HT_{1A} receptors may faciliate ejaculation, whereas inhibition of 5-HT_{2C} or 5-HT_{2A} receptors may increase sexual desire.

Animal research of sexual behavior

Most knowledge of the fundamental mechanisms of human sexual functions is derived from animal research, particularly psychopharmacologic research of *in vivo* animal sexual behavior (Olivier et al., 1998, 2006, 2011; Pattij et al., 2005; de Jong et al., 2006a; Bijlsma et al., 2014; Snoeren et al., 2014) and anatomic animal research (Veening and Coolen, 1998, 2014; Veening et al., 2014). Olivier et al. (2011) note that serotonin plays an important role in both male and female sexual behavior, e.g., that reduction of serotonin function facilitates, whereas enhancement inhibits, sexual behavior. In rats the SSRIs have comparable effects on male and female sexual behavior; they inhibit it, but only after chronic administration. Activation of the 5-HT_{1A} receptor facilitates sexual behavior in male rats but inhibits sexual behavior in female rats, suggesting a differential role for 5-HT_{1A} receptors in male and female rats (Olivier et al., 2011). Research on sexual behaviour in rats with null mutations in the serotonin transporter indicated also a differential role for 5-HT_{1A} receptors in male and female sexual behavior. Evidence exists that different pools of 5-HT_{1A} receptors have differential roles in various parts of the cascade of sexual events occurring during sexual interactions. Roles for other serotonin receptors are less well defined, although 5-HT_{1B}, 5-$HT_{2A/B}$, and 5-HT_7 receptors seem to be involved (Olivier et al., 2011).

Bijlsma et al. (2014) add that animal models are also suitable for examining potential sexual side-effects of novel drugs. Important for such research are the stability and reproducibility of a standardized test procedure that assesses the acute, subchronic, and chronic effects of psychoactive compounds in a 30-minute mating test (Pattij et al., 2005). Bijlsma et al. (2014) postulate that the sexual side-effects of SSRIs may be mediated by their inhibitory effects on dopamine signaling in sex brain circuits. According to this theory, clinical development of novel antidepressants should focus on compounds that simultaneously increase both serotonin and dopamine signaling.

ANTIDEPRESSANT-INDUCED SEXUAL SIDE-EFFECTS

Most antidepressants affect sexual functioning in a negative way. They may give rise to decreased sexual desire, erectile difficulties, delayed ejaculation, female anorgasmia, and, rarely, retrograde ejaculation, painful ejaculation, priapism, and vaginal or penile anesthesia (Balon et al., 1980; Segraves, 1992). These adverse effects often affect patient compliance.

Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs)

Until the 1990s, the sexual side-effects of TCAs were attributed to their anticholinergic and sympatholytic properties. However, this anticholinergic hypothesis has been disputed because atropine and other anticholinergic compounds do not appear to cause sexual disturbances with any great frequency (Smith, 1980). Futhermore, the SSRIs lack the anticholinergic and sympatholytic properties of the TCAs, yet also induce sexual side-effects. These findings and those from animal research suggested during the start of the 1990s that the sexual side-effects of SSRIs are associated with

effects on central serotonergic function. Therefore, with regard to the pathogenesis of sexual dysfunction, attention in those years has shifted from the peripheral neurons towards the brain itself (Waldinger, 1996).

Throughout the years in which one could only prescribe TCAs and irreversible MAOIs, e.g., the 1970s and 1980s, to psychiatric patients, there was hardly any interest among clinicians in antidepressant-induced sexual side-effects. Therefore, research on sexual side-effects induced by these antidepressants mainly consists of case reports and small clinical series (Segraves and Balon, 2014). There were two placebo-controlled trials with these drugs. One of these trials reported that delayed orgasm occurred in 20–30% of patients on imipramine and in 30–37% of patients on phenelzine (Harrison et al., 1986). Another controlled study showed that more than 90% of patients taking clomipramine for OCD suffered from severe delayed orgasm (Monteiro et al., 1987). TCAs and MAOIs affect various neurotransmitters and have various side-effects. This complicates fundamental research of their sexual side-effects. Therefore, although TCAs tend to cause reduced libido and erectile dysfunction, their exact mechanism of action on sexual functioning has never been elucidated by evidence-based research strategies.

Selective serotonin reuptake inhibitors

SSRI treatment of premature ejaculation

In the first years after their introduction on the market in the mid-1980s, it was said that SSRIs had hardly any sexual side-effects. Soon, however, case reports started to be published on their disturbing effects on sexual functioning. It appeared that SSRIs particularly delay ejaculation in men and orgasm in females. But they also may negatively interfere with erectile function and sexual desire. Interestingly, their ejaculation-delaying effect became very suitable for the treatment of premature ejaculation. In 1994, Waldinger et al. published the first double-blind, randomized, and placebo-controlled study on paroxetine treatment of premature ejaculation. Within a few years, various other randomized double-blind studies with all SSRIs and some other antidepressants followed. Notably, these studies were performed in mentally and physically healthy men with lifelong and/or acquired premature ejaculation, and a stopwatch was used to prospectively measure their IELT both in a baseline period, and during the SSRI treatment period. A meta-analysis of these studies showed not only that, of all SSRIs, paroxetine exerts the strongest ejaculation delay, but also that prospective studies using a stopwatch produce more reliable outcome data than retrospective questionnaire studies (Waldinger et al., 2004).

Using a stopwatch and the IELT, it became possible to express the extent of SSRI-induced ejaculation delay in a standard measure, e.g.. in the fold increase (fold increase (FI) = IELT value at end of SSRI treatment/IELT value at baseline). Using statistics, ejaculation delay at various intercourses within a certain time period is expressed as the fold increase of the geometric mean IELT (Waldinger et al., 2008). This method enabled a comparison of the extent of ejaculation induced by various SSRIs.

The meta-analysis of daily SSRI treatment studies of premature ejaculation (Waldinger et al., 2004) revealed a low placebo effect in men with premature ejaculation, e.g., a geometric mean 1.4-fold IELT increase (95% confidence interval (CI): 1.2–1.7). The meta-analysis also demonstrated a rank order of efficacy: (1) paroxetine exerted an 8.8 FI (95% CI: 5.9–13.2); (2) clomipramine a 4.6 FI (3.0–7.4); (3) sertraline a 4.1 FI (2.6–7.0); and (4) fluoxetine a 3.9 FI (3.0–5.4) (Waldinger et al., 2004). Thus, in general, daily SSRI treatment studies generate a 2.6–13.2 geometric mean IELT fold increase, dependent on the type of SSRI (Waldinger et al., 2004). Moreover, of all SSRIs, daily use of 20 mg paroxetine exerts the strongest ejaculation delay in the investigated males. The meta-analysis also demonstrated that, compared to stopwatch studies measuring the IELT, open and single-blind studies led to exaggerated IELT values and that retrospective assessment of the IELT by a questionnaire or subjective report led to far more variability in IELTs (Waldinger et al., 2004).

Interestingly, although it was generally believed in the mid-1990s that all SSRIs exerted the same extent of ejaculation delay, the use of a stopwatch and prospective measurement of the IELT showed that SSRIs do differ in the extent of delaying ejaculation. As such, it was shown in 1998 in a head-to-head study of SSRI treatment of lifelong premature ejaculation that the defined daily dosage of fluvoxamine (e.g., 100 mg/day) exerted significantly less ejaculation delay than paroxetine 20 mg/day, sertraline 50 mg/day, and fluoxetine 20 mg/day (Waldinger et al., 1998). The rather small ejaculation-delaying effect of fluvoxamine compared to paroxetine was confirmed in a placebo-controlled male Wistar rat study (Mos et al., 1999; Waldinger et al., 2002; de Jong et al., 2006b). However, although this prospective, randomized, placebo-controlled, double-blind study with an objective tool was conducted in mentally healthy non-depressed individuals, it was argued in psychiatry that these results could not be generalized to depressed patients.

It took another decade before the low prevalence of fluvoxamine-induced sexual side-effects was confirmed by Serretti and Chiesa (2009) in a meta-analysis of antidepressant-induced sexual side-effects in patients with depressive and anxiety disorders.

SSRI treatment research of mood and anxiety disorders

In contrast to the evidence-based research of SSRI-induced ejaculation delay in men with premature ejaculation, most studies of SSRI-induced ejaculation delay in psychiatric patients are characterized by poor methodology, e.g., retrospective design, use of questionnaire, no baseline measurement, no measurement of the IELT, no use of a stopwatch, no use of the fold increase, no head-to-head studies of strictly defined daily dosages.

The meta-analysis by Serretti and Chiesa (2009) of all studies of antidepressant-induced sexual side-effects included double-blind, cross-sectional, and retrospective studies in which sexual side-effects were directly assessed. It showed that sertraline, venlafaxine, citalopram, paroxetine, and fluoxetine had the highest rate of sexual side-effects. Imipramine, duloxetine, escitalopram, and fluvoxamine had lower rates of sexual side-effects. No difference with placebo was found for agomelatine, amineptine, bupropion, moclobemide, mirtazapine, and nefazodone. Not included in this meta-analysis was vortioxetine, a novel antidepressant for the treatment of major depression, which appears to have a low incidence of sexual side-effects (Sanchez et al., 2014).

In their critical review of studies investigating antidepressant-induced sexual side-effects, Segraves and Balon (2014) point to the fact that a large number of these studies have been financed by pharmaceutical companies and that the efficacy and side-effect profile of the drug manufactured by the company financing the study are compared to a competitive drug. In other words, in case of a low rate of sexual side-effects, its profile was not investigated in comparison with another drug with a well-known low rate of sexual side-effects. For example, bupropion, an agent with adrenergic and dopaminergic activity, has been compared with SSRIs, which are known to negatively interfere with sexual functioning. All these studies have shown a statistically significant difference between SSRIs and bupropion with regard to their induced sexual side-effects (LaTorre et al., 2013). As expected, the SSRIs had a higher incidence of sexual dysfunction than bupropion.

Similarly, in a placebo-controlled study of 456 patients, Coleman et al. (2001) found that 30% of patients on fluoxetine reported difficulties with orgasm and ejaculation as compared to 10% of patients using placebo or bupropion. Nearly the same result was found by Segraves et al. (2000) in a study comparing bupropion with sertraline in patients with major depression: 52% of patients using sertraline had problems with orgasm and ejaculation compared to 8% using bupropion. Similar lower sexual side-effects of bupropion were also found in other studies comparing bupropion with paroxetine (Kennedy et al., 2006), escitalopram (Clayton et al., 2006), and venlafaxine (Thase et al., 2006).

Interestingly, there is some preliminary evidence that vilazodone, an SSRI with 5-HT_{1A} agonist activity, has a low rate of sexual side-effects. This was found in pooled data from three randomized, double-blind, placebo-controlled studies of 481 patients with major depression. The sexual side-effects of vilazodone were mainly reduced sexual desire (Khan et al., 2011; Clayton et al., 2013). Duloxetine is a reuptake inhibitor of serotonin and norepinephrine. Compared to paroxetine treatment, a lower rate of duloxetine-induced sexual side-effects was only present in the first 8 weeks of treatment but disappeared after 26 weeks of treatment (Delgrado et al., 2005; Nelson et al., 2006).

A similar result was found in a study comparing duloxetine with escitalopram. At 8 weeks, patients on escitalopram had more sexual difficulties than those using duloxetine. This difference had disappeared after 12 weeks of treatment (Delgrado et al., 2005; Nelson et al., 2006).

Reboxetine is a selective norepinephrine reuptake inhibitor. In two controlled studies, it was found that reboxetine duloxetine had fewer sexual side-effects compared to fluoxetine and citalopram (Clayton et al., 2003; Langworth et al., 2006). Agomelatine is a melanonergic agonist. Studies have shown that agomelatine has fewer sexual side-effects than paroxetine (Montejo et al., 2011) and venlafaxine (Kennedy et al., 2008).

Rare and very rare SSRI-induced sexual side-effects

The most well-known SSRI-induced sexual side-effects are delayed or absent ejaculation and/or orgasm, erectile difficulties, and reduced sexual desire (Waldinger, 1996). Much less prevalent are priapism and penile or vaginal anesthesia. Notably, the SSRI-induced sexual side-effects are dose-dependent and reversible, e.g., they diminish and disappear soon after dose reduction or discontinuation of treatment. However, in very rare cases, the sexual side-effects do not disappear after their discontinuation. Recently, this has been called post-SSRI sexual dysfunction (PSSD) (Csoka et al., 2008). Another sexual side-effect that occurs during the start or discontinuation of SSRI treatment and may persist long after SSRI discontinuation has been called restless genital syndrome (ReGS) (Waldinger and Schweitzer, 2009; Waldinger et al., 2009).

Priapism

It is rather well known among psychiatrists that trazodone treatment may cause priapism (Kem et al.,

2002). Rather unknown is that, in very rare cases, SSRIs may also cause priapism (Ahmad, 1995; Rand, 1998; Dent et al., 2002; Bonnot et al., 2007). Priapism requires immediate medical treatment.

Penile and vaginal anesthesia

There is a clear absence of research into antidepressant-induced genital anesthesia, which manifests as a numb feeling of the penis, scrotal area, vaginal, clitoris, and labia. As there are only a few case reports of SSRI-induced genital anesthesia (Neill, 1991; Measom, 1992; King and Horowitz, 1993; Ellison and DeLuca, 1998; Deissenhammer and Trawoger, 1999; Michael and Mayer, 2000; Michael and Andrews, 2002), it seems that its incidence is rather low. However, as genital anesthesia may be a manifestation of PSSD, its occurrence demands the immediate attention of the clinician.

Post-SSRI sexual dysfunction

It is only recently that attention has been paid to a rather dangerous SSRI-induced sexual side-effect, which has been called PSSD (Csoka et al., 2008). So far only nine case reports in PSSD have been published (Bolton et al., 2006; Csoka and Shipko, 2006; Csoka et al., 2008; Farnsworth and Dinsmore, 2009; Waldinger et al., 2014). This very low incidence of PSSD contrasts sharply with the very high and well-known incidence of SSRI-induced sexual side-effects. Remarkably, there seems to be a rather high incidence of genital anesthesia or hypesthesia in the few published reports on PSSD (Bolton et al., 2006; Csoka and Shipko, 2006; Csoka et al., 2008; Farnsworth and Dinsmore, 2009; Waldinger et al., 2014). Of the nine case reports on PSSD, eight were reported to suffer from genital anesthesia, reduced tactile sensation, or genital numbness, including one woman with reduced genital and nipple sensitivity (Bolton et al., 2006; Csoka and Shipko, 2006; Csoka et al., 2008; Farnsworth and Dinsmore, 2009; Waldinger et al., 2014). Recently, Waldinger et al. (2014) postulated that, at least in one patient with PSSD, the genital anesthesia is associated with a dysfunction of transient receptor potential ion channels of sensory peripheral receptors related to peripheral serotonin neurotransmission. In addition, Waldinger et al. (2014) postulated the existence of two PSSD subtypes. Type 1 emerges soon after the start of SSRI treatment with rather acute severe penile anesthesia, anejaculation, erectile dysfunction, disappearance of libido, persisting in the same extent after SSRI discontinuation. Type 2 develops with rather moderate sexual side-effects during SSRI treatment but becoming more severe after SSRI discontinuation (Waldinger et al., 2014). Currently, a curable treatment of PSSD does not exist. More systematic research in PSSD is warranted.

Restless genital syndrome

ReGS is characterized by unwanted, restless, irritable, preorgasmic genital sensations that are intruding and persistent. It may be concurrent with restless legs and/or complaints of an overactive bladder (e.g., urge to urinate with low volumes) (Waldinger et al., 2009, 2010; Waldinger and Schweitzer, 2009). It mostly affects women, but it may also affect men (Waldinger et al., 2011). ReGS in males is characterized by persistent sensations of pre-ejaculation in the absence of an erection (Waldinger et al., 2011).

ReGS has several causes. One of these causes is the use of a serotonergic antidepressant or particularly discontinuation of an SSRI. ReGS may persist long after SSRI discontinuation (Waldinger et al., 2009, 2010; Waldinger and Schweitzer, 2009). There is some preliminary evidence that ReGS is the manifestation of a small-fiber sensory neuropathy of the dorsal nerve of the clitoris and the dorsal nerve of the penis, which are end branches of the pudendal nerve (Waldinger et al., 2010). The genital sensations of dysesthesias and hyperesthesia are mainly localized in the pudendal dermatome. Although some treatments are effective in reducing the unwanted sensations, for example the use of clonazepam 0.5 mg/day (Waldinger and Schweitzer, 2009), more systematic research into the treatment of PSSD is warranted.

Genetics of antidepressant-induced sexual side-effects

Genetics and sexual side-effects

A few studies have investigated whether there is a genetic susceptibility to antidepressant-induced sexual side-effects (Clark et al., 2012; Liang et al., 2012; Masiran et al., 2013). These studies used a questionnaire to detect antidepressant-induced sexual side-effects. By using a genome-wide association study in 1439 patients with depression and four questions on sexual functioning, Clark et al. (2012) found indications that the gene *SACM1L* mediated the effects of bupropion on sexual side-effects. This gene encodes SAC1, which is a membrane protein of the endoplasmic reticulum and the Golgi apparatus. A similar but much smaller study using a questionnaire for the detection of sexual side-effects was performed by Liang et al. (2012), who found some indication that the AA genotype of the 5-HT_{2A} receptor −1438 G/A polymorphism is in some way involved in antidepressant-induced sexual side-effects. On the other hand, in a study of 95 women treated with SSRIs for

major depression, Masiran et al. (2013) did not find any association between sexual desire disorder and the 5-HT_{2A} (rs6311) polymorphism.

Genetics and the intravaginal ejaculation latency time

Another way to investigate potential associations between genetic polymorphisms and sexual dysfunction is by using an objective tool to measure sexual function in a mentally healthy (e.g., non-depressed) population. Using a stopwatch to measure the duration of the IELT in men with lifelong premature ejaculation who ejaculate within 1 minute after vaginal penetration, Janssen et al. (2009, 2014a, b) found that the duration of the IELT is associated with the serotonergic gene polymorphisms. It was found that Dutch men with lifelong premature ejaculation and with the 5HTTLPR LL genotype ejaculated 100% faster than men with the 5HTTLPR SS genotype (Janssen et al., 2009). Notably, the genotype distribution of these men did not differ from the genotype distribution of the general male population in the Netherlands (Janssen et al., 2009). In addition, it was found that Dutch men with lifelong premature ejaculation and with the 5-HT_{1A} CC genotype ejaculated 250% faster than men with the 5-HT_{1A} GG genotype (Janssen et al., 2014a), and that those with the 5-HT_{2C} CysCys genotype ejaculated 79% faster than men with the monozygote mutant 5-HT_{2C} (SerSer) genotype (Janssen et al., 2014b). However, using the same stopwatch method, an association between paroxetine-induced ejaculation dalay and 5HTTLPR gene polymorphism has not been found (Janssen et al., 2014c).

Brain imaging of antidepressant-induced sexual side-effects

The first neuroimaging study on antidepressant-induced sexual side-effects was conducted by Kim et al. (2009). Using erotic visual stimuli in 19 patients taking SSRIs or mirtazapine and 10 controls they found in the control group an activation in the occipitotemporal area, anterior cingulate gyrus, insula, orbitofrontal cortex, and caudate nucleus. In patients using SSRIs, the intensity of activity in these regions was much lower compared to the control group (Kim et al., 2009). Notably, the intensity of activation in the group treated with mirtazapine was less than the control group but greater than those treated with SSRIs. It was found that those using SSRIs showed significantly lower activation than the mirtazapine group in the anterior cingulate gyrus and the caudate nucleus. The authors suggested that the different rates of sexual side-effects between the patients in the SSRI-treated group and the mirtazapine-treated group may be due to different effects on brain activation. In their review of a number of neuroimaging studies of antidepressant-induced sexual side-effects, Graf et al. (2014) conclude that these studies have shown that SSRIs lead to decreased activation in reward and emotional networks whereas dopaminergic medications lead to enhanced activation within these brain regions. They note that neuroimaging studies could link clinically observed antidepressant-related sexual dysfunction to a plausible explanatory neurobiologic model.

NEUROLEPTIC-INDUCED SEXUAL SIDE-EFFECTS

The negative symptoms of schizophrenia, including anhedonia, avolition, and blunted affect, are related to hypodopaminergic activity in the frontal cortex of these patients. This may also affect sexual functioning as it hampers interpersonal relationships and may lead to a lack of sexual experience.

Typical antipsychotics block postsynaptic D2 dopaminergic receptors. This may give rise to erectile dysfunction, delayed ejaculation, and decreased libido (Zemishlany and Weizman, 2008). The prevalence of sexual dysfunction in schizophrenia patients using typical antipsychotics is about 37–54% (Ghadirian et al., 1982; Smith et al., 2002). In a study by Aizenberg et al. (1995) it was found that treated and untreated male schizophrenia patients have a higher prevalence of sexual dysfunction compared to healthy controls. Untreated patients reported reduced sexual desire. Antipsychotic treatment gave rise to further difficulties of erection, orgasm, and sexual satisfaction. In another study (MacDonald et al., 2003) in both male and female patients with schizophrenia, male patients reported less libido compared to males in the general population (52% vs 12%) and more erectile dysfunction (52% vs 9%). They also more often reported having no intercourse or masturbation (27% vs 0%). Female patients reported less pleasure than controls (46% vs 5%). Notably, in this study most of the schizophrenic patients had no partner, whereas most of the controls did have a partner.

As dopaminergic drugs may sometimes increase sexual desire, these drugs have been prescribed to treat antipsychotic-induced sexual side-effects, but their use in patients with schizophrenia is limited (Valevski et al., 1998). Indeed, co-administration of dopaminergic drugs may exacerbate psychotic symptoms (Angrist and Gershon, 1977) or may cause nausea (Schiavi and Segraves, 1995).

Compared to typical antipsychotics, atypical antipsychotics exert a stronger 5-HT_{2A} receptor affinity relative to D2 receptor affinity and have a lower risk of increasing plasma prolactin (Zemishlany and Weizman, 2008). Atypical antipsychotics have less effect on peripheral

cholinergic and α_1-adrenergic receptors involved in sexual function (Cutler, 2003). Moreover, the occurrence of fewer extrapyramidal effects are probably beneficial for sexual performance. In a study comparing the sexual side-effects of clozapine and haloperidol in schizophrenic patients, Hummer et al. (1999) did not find statistically significant differences in sexual side-effects. In contrast, in a similar study, Aizenberg et al. (2001) showed that clozapine may be associated with better orgasmic function and sexual satisfaction compared to first-generation antipsychotics.

Among the atypical antipsychotics, risperidone is associated with a high dose-dependent serum prolactin concentration (Peuskens, 1995; Kleinberg et al., 1999). In recent years, it has been shown that the atypical antipsychotics olanzapine, quetiapine, and ziprasidone exert fewer sexual side-effects than the typical antipsychotics and risperidone (Hammer, 2002; Bitter et al., 2005; Dossenbach et al., 2006).

CONCLUSION

Reliable research into human sexual (dys)function is complicated as the researcher is dependent on the observations or measurements of the couple at home. Nevertheless, in the last two decades, in sexual medicine a lot of progress has been made in the investigation of nearly all well-known sexual dysfunctions. However, although substantial research has been done into the sexual side-effects of psychotropic drugs, clinical and psychopharmacologic sexual research into psychiatric patients is still in its infancy. Overall, it still shows rather severe limitations in methodology and design. First of all, it is still completely dependent on questionnaires. In psychiatric patients objective tools have not been used to measure the sexual dysfunction, there are hardly any studies with baseline measurements (for example, in drug-free patient samples), and above all, most studies compare different populations and different drug dosages. It should be noted that genetic research into the sexual side-effects of psychotropic drugs will only be successful when performed by objective tools, such as, for example, the stopwatch. Genetic research performed with only questionnaires is deemed to fail. The discrepancy between the increasingly evidence-based methodology applied by clinicians specialized in sexual medicine and the limited evidence-based methodology applied by researchers in psychiatry may be partly due to the fact that psychiatrists in general have missed the opportunity to become involved in sexual medicine practice.

It is a misunderstanding that sexual problems in patients with mental disorders are only due to their use of psychotropic drugs. With regard to sexual medicine, there still is a lot of work to do in research into how patients with mood and anxiety disorders, OCD, schizophrenia and other psychotic disorders, eating disorders, PTSD, and personality disorders cope with sexual problems and which sexual dysfunctions are particularly related to these disorders. More knowledge and understanding of these items is essential for better treatment approaches of sexual dysfunctions experienced by patients with mental disorders.

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