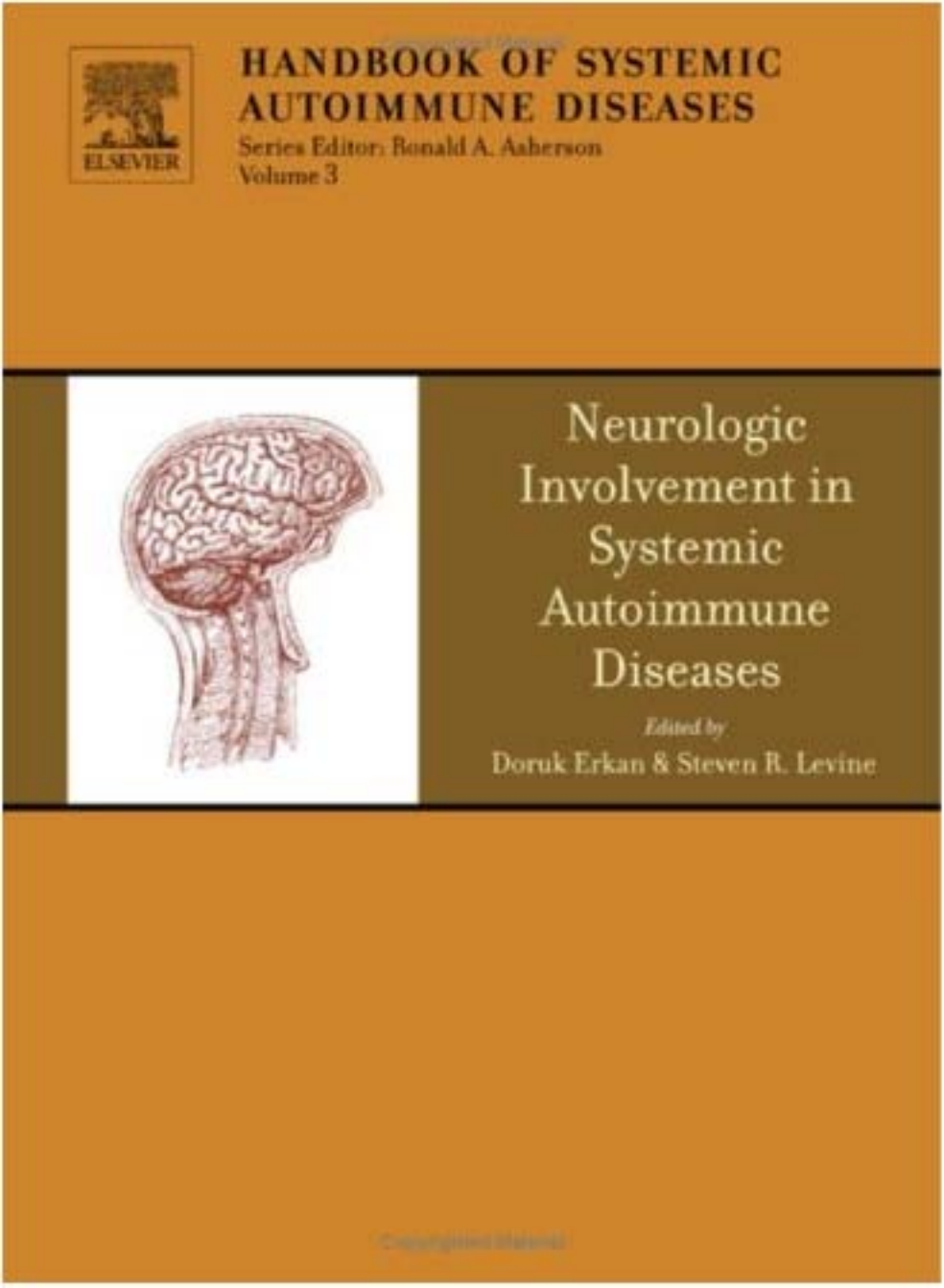
HANDBOOK OF SYSTEMIC AUTOIMMUNE DISEASES
Series Editor: Ronald A. Asherson
Volume 3
Neurologic Involvement in Systemic Autoimmune Diseases
Edited by
Doruk Erkan & Steven R. Levine

Handbook of
Systemic Autoimmune Diseases

Volume 3

Neurologic Involvement in Systemic Autoimmune Diseases

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Series Editor: Ronald A. Asherson

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Neurologic Involvement in Systemic Autoimmune Diseases

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Series Editor

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Preface

Systemic autoimmune diseases can affect both the central and peripheral nervous systems in a myriad of ways and through a heterogeneous number of mechanisms leading to many different clinical manifestations. As a result, neurological complications of these disorders can result in significant morbidity and mortality. Advances in the diagnosis, laboratory investigations, and management of these conditions has placed an increasing burden on the practicing clinician to correctly assess and treat these patients.

This volume of the "Handbook of the Systemic Autoimmune Diseases" will help the clinician and researcher better understand the current concepts of nervous system involvement from systemic autoimmune disorders, recognize current approaches to diagnosis and treatment, current controversies, and areas that need significant research efforts. We believe that providing this approach in a single volume will facilitate its use as a frequent resource for all those caring for or investigating these patients and their diseases.

Each chapter follows a consistent outline to provide the reader with important and useful information in an easy-to-navigate manner. Each chapter is also liberally referenced to provide more primary source material for further consideration. The standardized approach to each chapter will allow the reader to be able to compare and contrast more efficiently the neurological complications of the autoimmune diseases discussed.

We would like to thank the contributing authors for their expertise in the following chapters.

Doruk Erkan, M.D.
Steven R. Levine, M.D.

New York, 2004

Series Editor

Ronald A. Asherson

Dr. Ronald A. Asherson, MD. FACP, MD (Hon) (London), FCP (SA), FACR, is Honorary Consultant Physician at the Rheumatic Disease Unit, Department of Medicine, University of Cape Town Health Sciences Centre in Cape Town, as well as being Consultant Rheumatologist at the Rosebank Clinic in Johannesburg, South Africa. He is also a Visiting Professor at the Systemic Autoimmune Diseases Unit at the Hospital Clinic, Barcelona, Spain where he regularly visits and coordinates research projects.

Dr. Asherson qualified in Medicine at the University of Cape Town in 1957 and, after completing his internship, became H/P to Prof. Sir Christopher Booth at the Hammersmith Hospital, London, in 1960. In 1961 he accepted a Fellowship at the Columbia Presbyterian Hospital in New York, returning in 1962 to become Registrar and then Senior Registrar at Groote Schuur Hospital in Cape Town to 1964. After 10 years as a Clinical Tutor in the Department of Medicine, he returned to the United States and was appointed as Assistant Clinical Professor of Medicine at the New York Hospital — Cornell Medical Centre under the late Professor Henry Heineman. From 1981 to 1986 he was associated with the Rheumatology Department at the Royal Postgraduate Medical School of London. It was at that time that he developed his interest in Connective Tissue Diseases and Antiphospholipid Antibodies.

In 1986 he moved to the Rayne Institute and St. Thomas' Hospital in London, where he was appointed Honorary Consultant Physician and Senior Research Fellow. In 1991 he took a sabbatical at St Luke's Roosevelt Hospital Centre in New York, working with Prof. Robert Lahita. In 1992 he returned to South Africa to private practice in Johannesburg.

In 1998 he was elected as Fellow of the American College of Physicians (FACP) as well as a Founding Fellow of the American College of Rheumatology (FACR). From 1988 to 1991 he served on the Council of the Royal Society of Medicine in London. In 1992 he was co-winner of the European League Against Rheumatism (EULAR) Prize and in 1993 was the co-recipient of the International League Against Rheumatism (ILAR) Prize, both for his research on antiphospholipid antibodies. In 1994 he was elected as a Fellow of the Royal College of Physicians (FRCP) of London. In 2002 he was awarded an Honorary Doctorate in Medicine from the University of Pleven in Bulgaria.

Dr. Asherson has been an invited speaker at many universities and International conferences both in the USA and in Europe. He is the author of more than 280 papers on connective tissue diseases and has contributed to more than 30 textbooks of medicine, rheumatology and surgery as well as having co-edited "*Problems in the Rheumatic Diseases*", the "*Phospholipid Binding Antibodies*", two editions of "*The Antiphospholipid Syndrome*" and "*Vascular Manifestations of the Systemic Autoimmune Diseases*". He is currently engaged in research on connective tissue diseases, particularly on the antiphospholipid syndrome and is involved in clinical practice in South Africa. In 1999, he was the co-recipient of the Juan Vivancos Prize in Spain and in 2003 was the co-recipient of the Abbott Prize, awarded at the European League Against Rheumatism (EULAR) International Meeting, held in Lisbon, Portugal.

His original description of the "Catastrophic Antiphospholipid Syndrome" and the publishing of more than 40 papers on this new disease was rewarded by the attachment of the eponym "Asherson's Syndrome" to this condition at the November 2002 International Phospholipid Conference held in Sicily.

He is currently editing a series of 12 volumes entitled. "The Handbook of Systemic Autoimmune Disease" (Elsevier, Holland) and in September of 2003 was Co-Chairman of the First Latin American Congress on Autoimmunity, held in the Galapagos Islands, Ecuador. He co-chaired a Session at the Milan Conference on "Heart, Rheumatism and Autoimmunity" held in February 2004.

He was appointed to the International Advisory Board of the International Conference on Systemic Lupus Erythematosus held in New York in May of 2004.

Volume Editors

Doruk Erkan

Dr. Doruk Erkan is an Assistant Attending Rheumatologist and the Clinical Director of the international Lupus Clinical Trials Consortium (LCTC) at the Hospital for Special Surgery, Weill Medical College of Cornell University in New York. Dr. Erkan is one of the leading researchers in the field of autoimmune diseases, with particular focus on the Antiphospholipid Syndrome and Systemic Lupus Erythematosus. Dr. Erkan has received several honors and awards from the American College of Rheumatology and the Arthritis Foundation for his research in autoimmune diseases, is an accomplished member of several international scientific organizations and committees, and has lectured internationally on Autoimmune Diseases and the Antiphospholipid Syndrome. Dr. Erkan has published extensively on Rheumatologic Diseases including numerous invited editorials, reviews, book chapters, and research papers. His current research interests are the primary and secondary prevention of thrombosis and other complications in the Antiphospholipid Syndrome.

The Co-editorship of the Neurology Volume of the Handbook of the Systemic Autoimmune Diseases combined Dr. Erkan's clinical expertise with his research interests to bring this book to fruition.

Steven R. Levine

Dr. Levine, a professor of Neurology within the Stroke Program at The Mount Sinai School of Medicine in New York has had a long-standing interest in cerebrovascular disease associated with antiphospholipid antibodies and auto-immune diseases. He was a founding member of the Antiphospholipid Antibodies and Stroke Study (APASS) Group, has received NIH grant support for work in this field and has published numerous original scientific reports, book chapters, invited reviews, and editorials in this field. He has lectured internationally on this topic. He serves on several editorial boards including *Stroke, Clinical Neuropharmacology*, and *Seminars in Cerebrovascular Diseases and Stroke*. He has been listed as one of the *Best Doctors in America* (2003-2004) among other awards. He has published over 120 peer-reviewed articles, 44 review/invited articles, 9 editorials, 58 books chapters, 16 case reports, and over 200 abstracts.

Dr. Levine has grappled with the challenges of trying to diagnose, treat, and manage patients with the antiphospholipid syndrome, as well as other neurological manifestations of systemic autoimmune disorders – a formidable task for all neurologists. His impetus for editing this volume was to have a single, cohesive, and comprehensive volume of state-of-the-art reviews of neurological complications from systemic auto-immune disorders. This will allow clinicians and researcher easy access to the current understanding and concepts in the field.

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Contents

PART I

Systemic Lupus Erythematosus

Handbook of Systemic Autoimmune Diseases, Volume 3
Neurologic Involvement in Systemic Autoimmune Diseases
D. Erkan and S.R. Levine, editors

CHAPTER 1

Neuropsychiatric Lupus: Pathogenesis and Clinical Features

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1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder affecting the central (CNS) and peripheral nervous systems (PNS) as well as other organs. CNS involvement in SLE is complex because of its multiple clinical presentations. The American College of Rheumatology (ACR ad hoc committee, 1999) established case definitions and diagnostic criteria for 19 CNS and PNS syndromes observed in SLE patients, which collectively are referred to as neuropsychiatric systemic lupus erythematosus (NPSLE) syndromes (Table 1).

The new ACR (ACR ad hoc committee, 1999) guidelines for NPSLE eliminate the frequently used term 'lupus cerebritis'. Although cutaneous and visceral vasculitis is not unusual in SLE (Drenkard et al., 1997), true cerebral vasculitis is rarely found in SLE despite its popular use as a clinical diagnosis (Liem et al., 1996; Moore, 1998; De Marcaida and Reik, 1999).

2. Prevalence

SLE is a disease with a fluctuating course. Neuropsychiatric SLE manifestations can occur as single or multiple events at any time during the course of the disease, even during periods in which no non-nervous system SLE disease activity is detected (Sibbitt, 1999a,b; Rivest et al., 2000). Approximately 40% of the NPSLE manifestations develop before the onset of SLE or at the time of diagnosis and 63% within the first year after diagnosis (Rivest et al., 2000).

Estimates of the prevalence of NPSLE have ranged from 14% to over 80% (ACR ad hoc committee, 1999; Futrell et al., 1992; Kaell et al., 1986; McNicholl et al., 1994; West et al., 1995; Ainiala et al., 2001; Brey et al., 2002; Costallat et al., 2001). Most are based on research conducted before the introduction of the ACR criteria for NPSLE. Three studies (Ainiala et al., 2001; Brey et al., 2002; Costallat et al., 2001) have reported prevalence of NPSLE based on the ACR 1999 criteria. The three detected the presence of 14–17 of the 19 syndromes described by the ACR (ACR ad hoc committee, 1999) and report identical prevalence of cranial neuropathy (1.5%) and chorea (1%). These studies also report very similar prevalence of four other syndromes: total spectrum of headache (56–61%), total spectrum of mood disturbances (69–74%), psychosis (5%), and total range of cognitive disorders (75–80%).

3. Epidemiology

There are no definitive data to date to suggest that NPSLE manifestations are more frequent or severe in different ethnic groups. A number of clinical and serological parameters have been suggested as risk factors for CNS involvement in SLE. The presence of

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Table 1
Neuropsychiatric syndromes associated with SLE

NPSLE associated with central nervous system
Aseptic meningitis
Cerebrovascular disease
Stroke
Transient ischemic attack
Cerebral venous sinus thrombosis
Cognitive disorders
Delirium (acute confusional state)
Dementia
Mild cognitive impairment
Demyelinating syndromes
Headaches
Tension headaches
Migraine headaches
Movement disorders (chorea)
Psychiatric disorders
Psychosis
Mood disorders
Anxiety disorder
Seizure disorders
Transverse myelopathy
NPSLE associated with peripheral nervous system
Autonomic neuropathy
Myasthenia gravis
Peripheral neuropathy
Sensorineural hearing loss
Sudden onset
Progressive
Cranial neuropathy

Modified from Sibbitt et al. (1999a,b) and ACR ad hoc committee (1999).

discoid and articular manifestations is thought to associate with a more benign course and less likelihood of NPSLE (Karassa et al., 2000). Their absence at onset, or during flares, seems to bestow a higher risk of CNS involvement, primarily cerebrovascular disease and seizures, and also psychosis, acute confusional state and isolated cognitive dysfunction (Karassa et al., 2000). Other associations with high likelihood of NPSLE are low serum levels of C_3, and especially C_4, high-titer anticardiolipin antibodies (aCL) (IgG) and cutaneous vasculitic lesions (Karassa et al., 2000).

When age at disease onset is factored in, the predictive clinical value of cutaneous and articular features for NPSLE is less clear. There is a higher prevalence of discoid lesions, malar rash, cutaneous vasculitis, and neurologic involvement at SLE onset and during the course of the disease in juvenile-onset SLE relative to adult-, and elderly-onset SLE (Formiga et al., 1999; Carreño et al., 1999; Font et al., 1998; Antolin et al., 1995). Furthermore, hypocomplementemia (C_3 and C_4) and higher anti-DNA and aCL IgG antibody levels also are more prevalent in early/juvenile-onset SLE (Formiga et al., 1999; Carreño et al., 1999; Font et al., 1998). Hence, the risk for CNS involvement in SLE may be more related to a particular serologic profile at the onset of SLE and/or during the course of the disease.

4. Etiology/pathogenesis

The pathogenic etiology of NPSLE is likely to be multifactorial and may involve autoantibody production, microangiopathy, and intrathecal production of pro-inflammatory cytokines (Hanly, 2001). Histopathologic studies reveal a wide range of brain abnormalities caused by multifocal microinfarcts, cortical atrophy, gross infarcts, hemorrhage, ischemic demyelination and patchy multiple-sclerosis-like demyelination (Hanly, 2001), but these are not diagnostic for NPSLE (Sibbitt, 1999a,b). Bland microvasculopathy (characterized by vessel tortuosity, cuffing of small vessels, vascular hyalinization, endothelial proliferation, and perivascular gliosis), formerly attributed to deposition of immune complexes, but now suspected to arise from activation of complement, appears to be the most common microscopic finding (Hanly et al., 1992; Belmont et al., 1996). However, this too is a non-specific finding as patients without NPSLE also show these changes (Hanly, 2001). A histologically normal brain with no specific pathognomic brain lesions is also a common finding in NPSLE (Hanly et al., 1992).

Autoantibody production has been implicated in vasculopathic and autoantibody-mediated neuronal injury mechanisms. Anti-ribosomal P antibodies (anti-P) have been linked to diffuse CNS involvement in NPSLE (Isshi and Hirohata, 1996, 1998). Antiphospholipid antibodies (aPL), detected by immunoreactivity to aCL assays and/or their ability to prolong phospholipid-dependent coagulation assays (lupus anticoagulant [LA]), are implicated in the microvascular thrombo/embolitic and endothelial damage found in the brain of NPSLE patients (Sibbitt, 1999a,b).

4.1. Vasculopathy in SLE

Neuropathologic studies in SLE patients have frequently found a small vessel vasculopathy consisting of proliferative changes of the intima, vascular hyalinization and perivascular lymphocytosis. This small vessel vasculopathy has been seen both in SLE patients with only psychiatric symptoms as well as those with focal NS manifestations (Hanly, 2001). Interestingly, SPECT and MR spectroscopy studies suggest that both cerebral atrophy and cognitive decline in SLE patients may be related to chronic cerebral ischemia (Karassa et al., 2000; Sibbitt, 1999a,b; Gonzalez-Crespo et al., 1995). It is possible that SPECT and MR spectroscopy studies represent a functional image correlate for cerebral vasculopathic change.

4.2. Cytokines

Cytokines appear to have regulatory roles in mediating SLE-disease activity and inflammation in target organs (Kelley and Wuthrich, 1999; Kirou and Crow, 1999). Recent work has highlighted the importance of SLE monocytes in the generation of potentially pathogenic cytokines, particularly IL-6 and IL-10 (Jara et al., 1998). The balance between pro-inflammatory and anti-inflammatory cytokines and the degree and extent of inflammation appear to profoundly influence SLE-mediated disease manifestations (Kelley and Wuthrich, 1999).

Several, largely cross-sectional, studies in SLE have suggested that IL-6 is a marker of disease activity (Alcocer-Varela et al., 1992; Isshi et al., 1994; Kozora et al., 2001). There are multiple other mechanisms whereby SLE patients might have higher IL-6 levels. The C5b-9 complex stimulates IL-6 (Viedt et al., 2000). Diabetes, which is increased in SLE patients taking prednisone, is associated with higher IL-6 levels (Shikano et al., 2000; Kado et al., 1999). Homocysteine, which is elevated in 30% of SLE patients, leads to higher IL-6 levels (van Aken et al., 2000). Over 33% of SLE patients are morbidly obese, another associate of IL-6 levels (Yudkin et al., 2000). Finally, dehydroepiandrosterone (DHEA) is low in SLE; a low level of DHEA could increase IL-6 secretion (Young et al., 1999; Straub et al., 1998).

Few studies have investigated the role of cytokine abnormalities in NPSLE patients. Cerebrospinal fluid (CSF) IL-1 and IL-6 levels are increased in SLE patients with CNS involvement compared with non-SLE neurological controls (Jara et al., 1998; Alcocer-Varela et al., 1992). Both serum and CSF IL-6 levels are elevated in NPSLE patients vs. non-NPSLE patients or healthy controls (Jara et al., 1998; Alcocer-Varela et al., 1992). In one study, however, there was no difference in serum IL-6 levels between NPSLE patients and CNS infection control patients (Jara et al., 1998). In another study, CSF IL-6 activity paralleled NPSLE disease activity most consistently (Isshi et al., 1994). In a study of 15 SLE patients without overt CNS disease (vs. rheumatoid and healthy controls), regression analysis showed that serum DHEA-s and IL-6 accounted for unique portions of the variance in measures of learning and attention, after controlling for depression and corticosteroid treatment (Kozora et al., 2001).

4.3. Adhesion molecules

Other processes leading to immune-mediated brain dysfunction in SLE probably involve abnormal endothelial–white blood cell interactions that allow proteins or cells' access to the CNS. The expression of adhesion proteins on endothelial cells appears to be up-regulated in SLE, and facilitates lymphocyte entry in CNS disease (Hickey, 1991; Raine et al., 1990; Rossler et al., 1992; Savage and Cooke, 1993; Zabry et al., 1992; Dopp et al., 1994; Wong and Dorovini-Zis, 1992; Belmont et al., 1994; Sharief et al., 1993; Janssen et al., 1994). Shedding of the active form of these molecules occurs, and soluble levels can be measured in both serum and CSF (Sharief et al., 1993; Janssen et al., 1994).

Studies of circulating soluble adhesion molecules in SLE have yielded contradictory results (Horwitz et al., 1998; Barcellini et al., 1996; Dinarello, 1999). In addition, there is disagreement as to whether soluble adhesion molecules are an accurate reflection of membrane bound proteins. Soluble serum levels of ICAM-1 increase with systemic disease activity in

patients with SLE (Sfikakis et al., 1994; Matsuda et al., 1994). Wellicome et al. (1993) evaluated soluble serum levels of VCAM-1 in patients with rheumatoid arthritis and SLE, and found elevations in both groups as compared to normal controls. Janssen et al. (1994) studied soluble serum levels of ICAM-1, VCAM-1 and E-selectin in SLE and found that soluble VCAM-1 levels were elevated during active disease, and normalized with remission in SLE. These findings were replicated by Spronk et al. (1994) who also described an elevation of soluble VCAM-1 levels with disease activity and a fall with clinical remission in SLE, but no difference in ICAM-1 and E-selectin levels between SLE patients and controls at any time point. Machold et al. (1993) likewise failed to find a difference in mean ICAM-1 levels between SLE patients, rheumatoid arthritis patients, and normal controls, however, within the patient groups, soluble serum ICAM-1 levels correlated with other markers of disease activity, e.g. sedimentation rates and clinical findings. Levels of sICAM-1, but not E-selectin, may have decreased after corticosteroid therapy (Wong et al., 2000), although this is controversial (Fehniger et al., 1999; Dao et al., 1997). In one study, only combined elevation of three adhesion molecules (solubleCD14, solubleICAM-1 and solubleE-selectin) correlated with SLE prognosis (Egerer et al., 2000).

4.4. Autoantibodies and NPSLE

Autoantibody production has been implicated in vasculopathic and autoantibody-mediated neuronal injury mechanisms. Anti-ribosomal P antibodies have been linked to diffuse CNS involvement in NPSLE (Isshi and Hirohata, 1996, 1998).

Antiphospholipid antibodies are a family of antibodies directed against plasma proteins bound to negatively charged phospholipids that lead to hypercoagulability through effects on the protein C/protein S system, platelets, endothelial cells and complement activation (Roubey, 1996; Giaradi et al., 2001). Antiphospholipid antibodies defined as positive LA test, aCL, and anti-β_2 glycoprotein 1 (anti-β2GP1), are strongly associated with localized NPSLE, including TIA, stroke, seizure, and cerebral vein thrombosis (Brey and Escalante, 1998).

Multiple studies have also shown an association of aPL with cognitive dysfunction in SLE (Hanly et al., 1999; Denburg et al., 1997; Menon et al., 1999). Denburg et al. (Maeshima et al., 1993) found, in a cross-sectional study, that LA-positive patients were 2–3 times more likely than LA-negative patients to be cognitively impaired, primarily on tasks of verbal memory, cognitive flexibility, and psychomotor speed. In a 5-year prospective study, Hanly et al. found that patients who had persistent IgG aCL positivity had a reduction in psychomotor speed, and patients who had persistent IgA positivity had a reduction in conceptual reasoning and executive ability (Hanly et al., 1999). In a study of 45 SLE patients assessed twice, persistently elevated aCL levels were associated with poorer cognitive function, particularly speed of attention and concentration (Menon et al., 1999). High titers of CSF IgG aCL have been detected in SLE patients (vs. controls) with lupus headache, acute psychosis, cognitive dysfunction, higher cortical dysfunction, and altered consciousness (Lai and Lan, 2000). LA, but not IgG aCL, was associated with reduced regional cerebral blood flow in a SPECT study (Maeshima et al., 1993). However, one comparative study of PET, HMPAO-SPECT and MRI scans did not find any abnormalities that correlated with aCL (Kao et al., 1999). Antiphospholipid antibodies are also implicated in both microvascular thrombo/embolic episodes and endothelial damage.

4.5. Non-immune-mediated mechanisms

Neurologic complications of SLE may result from abnormalities, either not directly related to the primary disease, or as an effect of non-nervous system organ involvement. Many of these processes result in neurologic dysfunction, including confusion and seizures, which are indistinguishable from primary immune-mediated damage. The major etiologies in this group are infections, toxins (including medications), and metabolic derangements. Although survival in SLE has improved over the years, infection remains a leading cause of morbidity and mortality in the disease (Futrell et al., 1992). Meningitis from both bacterial pathogens such as *Neisseria* and

opportunistic infections including *Candida* and *Cryptococcus* occur (Mitchell et al., 1990). The spectrum of infections includes bacterial, viral, fungal, and parasitic organisms (Iliopoulos and Tsokos, 1996). Septic emboli continue to be a cause for concern in patients with fever. The high frequency of infections is due to diminished immunocompetence resulting from both medication and the underlying disease. The importance of identifying CNS infections is underscored by studies showing that patients on high-dose corticosteroids for NPSLE have a higher mortality rate than those on lower doses (Wysenbeek et al., 1990).

The toxins most often causing neurologic abnormalities in SLE are medications. Corticosteroids and antihypertensive medications can produce neurologic and psychiatric symptoms (Wolkowitz, 1994; Wolkowitz et al., 1993; Newcomer et al., 1994). Metabolic abnormalities likely to affect the nervous system include uremia, as well as disorders of calcium, sodium, and magnesium. The rapid reversibility of abnormalities on some neurodiagnostic studies may well reflect transient metabolic abnormalities (Shak, 1996; Yaffe et al., 1995).

5. Clinical manifestations

An important consideration in the diagnostic approach to a patient with possible NPSLE manifestations is whether the particular clinical syndrome is due to SLE-mediated organ dysfunction, a secondary phenomenon related to infection, medication side-effects or metabolic abnormalities (e.g. uremia), or is due to an unrelated condition. For each NPSLE syndrome, the ACR case definitions give clear guidance regarding the differential diagnosis and evaluation that is required to make a diagnosis of a primary NPSLE syndrome. It cannot be stressed enough that infection is a major cause of CNS syndromes in hospitalized SLE patients (Futrell et al., 1992). Appropriately, the exclusion of infection plays a prominent role in the differential diagnosis of CNS NPSLE syndromes in the ACR guidelines. The appendix can be found on the ACR website at www.rheumatology.org/publications/ar/1999/aprilappendix.asp (Appendix). This is a tremendous resource for all clinicians who care for SLE patients when faced with the possibility of evaluating a patient for an NPSLE syndrome (Table 1).

6. Diagnosis and management of individual syndromes

6.1. Acute inflammatory demyelinating polyradiculoneuropathy (Guillain–Barré syndrome)

Polyradiculoneuropathy is a rare and potentially severe manifestation of NPSLE (Lesprit et al., 1996). Acute inflammatory demyelinating polyradiculoneuropathy is a demyelinating syndrome of the spinal roots, peripheral, and occasionally cranial nerves. The onset of the disease may precede, coincide, or follow the diagnosis of SLE (Lesprit et al., 1996). The disease may follow a monophasic course, follow a relapsing–remitting pattern, or in the protracted form of the disease, a chronic course with episodic flares (Rechthand et al., 1984; Millette et al., 1986).

The diagnostic criteria include clinical features of progressive polyradiculoneuropathy that is usually symmetric and ascending and predominantly motor, and may be associated with arreflexia. It usually peaks within 21 days of onset, and may have an acute or insidious onset with an acute, subacute or chronic course (Appendix).

Other investigations advocated are CSF analysis, which typically shows elevated protein without pleocytosis, and nerve conduction studies (NCS). Electrodiagnostic findings supportive of polyradiculoneuropathy are one or more of the following abnormalities in three or more nerves tested: (a) conduction block with decreasing compound muscle action potential with more proximal testing; (b) absence or prolonged F waves, c) conduction velocity slowing; and (d) prolonged distal latencies. Since abnormalities may be subtle early in the course of the disease, NCS may need to be repeated.

The differential diagnosis includes acute spinal cord disease, botulism, poliomyelitis and other infections, and acute myasthenia gravis (MG). If the CSF evaluation shows increased white cells in

addition to high protein levels, human immunodeficiency virus-1 infection should be suspected.

6.2. Aseptic meningitis

This is a syndrome of acute or subacute onset characterized by headache, fever, and meningeal irritation, with CSF findings of pleocytosis and negative cultures. Typical CSF findings are mild pleocytosis (usually in the 200–300 cells/mm^3; this may be much higher in the severely ill) with lymphocytic predominance and mildly elevated protein (Kovacs et al., 1993; West, 1994).

Aseptic meningitis is one of the most infrequent manifestations of NPSLE, occurring in up to 1% (Kovacs et al., 1993; Mok et al., 2001; Canoso and Cohen, 1975). The onset is usually early in the course of SLE and may actually precede the diagnosis (Harris et al., 1984; Lancman et al., 1989). Most cases of aseptic meningitis are associated with NSAID intake and other drugs like trimethoprim/sulfamethoxazole (Kovacs et al., 1993), and recurrent episodes temporally related to azathioprine (Sands et al., 1988) have been reported.

The differential diagnosis includes infectious processes (bacterial, mycobacterial, viral, fungal, and parasitic), subarachnoid hemorrhage, malignancy (leukemia, lymphoma or carcinoma), granulomatous disease (sarcoidosis), and medications like NSAIDs, intravenous immunoglobulin (IVIg) and azathioprine. NPSLE-related aseptic meningitis is responsive to steroid therapy (West, 1994). The clinical course is usually benign (Sands et al., 1988), but chronic cases have been described (Lancman et al., 1989).

6.3. Autonomic disorder

Autonomic dysfunction is characterized by sympathetic and or parasympathetic impairment with sparring of the somatic sensorimotor function (Hoyle et al., 1985). It is a disorder of the autonomic nervous system with orthostatic hypotension, sphincteric erectile/ejaculatory dysfunction, anhidrosis, heat intolerance, constipation.

The reported prevalence of autonomic disorders varies from no difference vs. controls, to as high as 88% (Gamez-Nava et al., 1998), and no association with aCL was found (Liote and Osterland, 1994). Although it can occur in isolation, approximately one-half of the cases reported in the literature were associated with other neurological deficits (Hoyle et al., 1985). There are no studies investigating whether autonomic dysfunction carries prognostic significance in SLE as it does in diabetes mellitus (Altomonte et al., 1997; Straub et al., 1996).

Non-invasive cardiovascular testing is the mode of choice to investigate for the presence of autonomic disorders (Gamez-Nava et al., 1998; Mathias, 1997). The heart rate response to postural changes and breathing evaluates parasympathetic function, whereas blood pressure response to sustained hand grips is a test of sympathetic efferent function (Hoyle et al., 1985; Gamez-Nava et al., 1998).

The differential diagnoses include Lambert–Eaton-related autonomic dysfunction, medications (tricyclic antidepressants), organophosphate toxicity, Shy–Drager syndrome, and other neuropathic processes (i.e. elderly, diabetics).

6.4. Cerebrovascular disease

Cerebrovascular disease is defined as neurological deficits due to arterial insufficiency or occlusion, venous occlusive disease, or hemorrhage. Focal deficits may be multifocal in recurrent disease.

Cerebral ischemic events may occur early in the course of SLE, or may precede the diagnosis. This may provide a diagnostic clue of underlying SLE in young patients with stroke that would be otherwise unsuspected (Haas, 1982). The frequency of cerebrovascular disease as a whole has been reported as ranging from 5.3 (Kovacs et al., 1993) to 19% (Mok et al., 2001). Venous thrombosis, specifically, is a rare complication of SLE, and may be seen as the presenting manifestation of the disease (Vidailhet et al., 1990). Hemorrhagic stroke may also occur—both intracerebral and subarachnoid hemorrhage.

The association between aPL and venous/arterial thrombotic events has been described both in primary antiphospholipid syndrome and secondary to SLE (Harris et al., 1984). The pathogenesis of aPL is not fully understood, but may include endothelial activation and injury and alteration of the levels and/or function of coagulation proteins (Brey et al., 1990).

There is also an association with Libman–Sacks endocarditis (Tsokos et al., 1986), which is a known source of embolic phenomena. Furthermore, in patients with a first stroke and aPL, the risk of recurrence is high and usually occurs within the first year (Tsokos et al., 1986).

The evaluation should include obtaining information regarding potential precipitants and stroke risk factors (i.e. cocaine or amphetamine use, atrial fibrillation, septal defects, hypertension, diabetes, cigarette smoking, and lipid status). Imaging studies include CNS imaging (MRI or CT and angiogram if indicated) and cardiovascular evaluation (EKG, carotid Doppler US, and echocardiogram).

The differential diagnosis includes space-occupying lesions of the brain (infections, tumor), trauma, vascular malformation and hypoglycemia.

6.5. Cranial and peripheral neuropathies

A variety of neuropathic processes of the PNS have been described. The ACR nomenclature recognizes cranial, mono and polyneuropathies, as well as plexopathies (Appendix; Sivri et al., 1995), which may be sensory or sensorimotor (Omdal et al., 1991), and axonal or demyelinating (Appendix; Sivri et al., 1995; Huynh et al., 1999). Peripheral sensorimotor neuropathy (PN) is the most common, and mononeuritis multiplex (Scott et al., 1994), cranial neuropathies and plexopathies (Bloch, 1979; Rolak, 1996) are progressively less frequent (Omdal et al., 2001a,b). The onset of peripheral neuropathies usually follows the diagnosis of SLE, but it may actually precede it (Sivri et al., 1995; Huynh et al., 1999). Peripheral neuropathy has been linked to cutaneous vasculitis, is common among NPSLE patients with renal failure, and may be an important prognostic factor for mortality in SLE (McNicholl et al., 1994; Harel et al., 2002; Matsuki et al., 1999; Fierro et al., 1999; Sabbadini et al., 1999a,b).

Distal PN tends to affect the longer nerves first, hence the earlier involvement of the lower extremities (Huynh et al., 1999). Neurologic exam may reveal hypesthesia to pinprick and light touch testing, impaired temperature and vibratory perception (Omdal et al., 2002). Clinical and subclinical cranial and peripheral neuropathies are detected in 12–47% of unselected outpatient SLE referrals by electromyography and nerve conduction velocity studies (McNicholl et al., 1994; Harel et al., 2002; Matsuki et al., 1999; Fierro et al., 1999; Sabbadini et al., 1999a,b). However, clinical correlation with electrophysiologic testing is equivocal (Sivri et al., 1995; Omdal et al., 1991, 1993; Huynh et al., 1999), and may underestimate the true prevalence (Huynh et al., 1999). Even different modalities of electrophysiologic testing yield diverse findings (Omdal et al., 1991). The clinical manifestations of PN are not fixed and the course is not of inexorable progression, instead fluctuating over time (Omdal et al., 1993). Other causes of neuropathy, including vitamin deficiencies, diabetes mellitus, leprosy, etc should be excluded.

Histopathology data are scarce (Huynh et al., 1999). Studies of sural nerve biopsies showed predominantly axonal degeneration with loss of myelinated and unmyelinated fibers with occasional perivascular inflammatory infiltrates (Huynh et al., 1999; Hughes et al., 1982; McCombe et al., 1987). Scheinberg describes the occurrence of vasculopathic changes in the vasa nervorum, and demyelination (Scheinberg, 1956). Immune complex, complement, IgG and C1q deposition have been seen in the vasa nervorum and basement membrane of Schwann cells (Bódi et al., 1998).

Cranial neuropathies most commonly involve CNII–VII, with ocular manifestations, either as internuclear ophthalmoplegia or isolated II, IV or VI palsy (Genevay et al., 2002; Lee et al., 2000; Sedwick and Burde, 1983; Rosenstein et al., 1989; Friedman et al., 1995; Keane, 1995), facial palsy (Blaustein and Blaustein, 1998), and trigeminal neuralgia (Lundberg and Werner, 1972) being the most common. Even though audiovestibular involvement is considered rare (Vyse et al., 1994), subclinical involvement may be much more common by audiometric studies independent of hydroxychoroquine treatment (Andonopoulos et al., 1995). Other reported cranial neuropathies include X (Vaile and Davis, 1998) or its branches (Saluja et al., 1989; Gordon and Dunn, 1990) and XII (Chan et al., 1989).

The differential diagnosis includes vitamin deficiencies (B_{12}, niacin, thiamine), and hypothyroidism for peripheral neuropathy; and skull fracture, tumor (meningioma, carcinomatous meningitis), aneurysm, infection (herpes zoster, neuroborreliosis,

syphilis, mucormycosis), and Miller Fisher syndrome for cranial neuropathies.

6.6. Demyelinating syndrome

A demyelinating syndrome is defined as an acute or relapsing demyelinating encephalomyelitis with evidence of discrete neurologic lesions distributed in place and time (Appendix). The diagnostic criteria require the occurrence of two or more manifestations or recurrence of at least one manifestation on distinctly separate occasions. The manifestations include (a) multiple areas of damage to white matter within the CNS, causing one or more limbs to become weak with sensory loss; (b) transverse myelopathy; (c) optic neuropathy; (d) diplopia due to isolated nerve palsies or internuclear ophthalmoplegia; (e) brain stem disease with vertigo, vomiting, ataxia, dysarthria, or dysphagia; and (f) other cranial nerve palsies (Appendix).

Transverse myelitis (TM), optic neuropathy and cranial neuropathies are distinct demyelinating syndromes. Studies recommended in the evaluation of all patients with possible demyelinating syndrome include CSF evaluation for cell count, protein, oligoclonal bands, IgG index, culture and cytology, MRI and, if indicated, evoked potentials (Appendix).

The differential diagnosis includes: structural lesions, familial disorders like ataxia and leukodystrophies, sarcoidosis, Behçet's syndrome and multiple sclerosis (MS), and the exclusion of infectious (TB, HIV, syphilis, etc.) and nutritional (vitamin B_{12} deficiency) causes.

6.7. Lupoid sclerosis

The association of SLE and MS has been described (Sloan et al., 1987; Kaplan and Betts, 1977; Kinnunen et al., 1993; McCombe et al., 1990). The syndrome of Lupoid Sclerosis is so named to illustrate the clinical overlap that exists between the two. There is still debate on whether this represents coexistence of two separate illnesses (Kinnunen et al., 1993). However, as mentioned above, the Ad Hoc committee recognizes this as a distinct manifestation of NPSLE.

The onset of demyelinating syndrome may precede the diagnosis of SLE (Kinnunen et al., 1993; Scott et al., 1994) making the distinction from MS in some cases difficult (West, 1994; Kaplan and Betts, 1977; Kinnunen et al., 1993). Adding to the confusion are the high prevalence of positive anti-nuclear antibodies (ANA) in MS (about 81%, typically of low titer), the frequent finding of oligoclonal bands in about 50% of cases of NPSLE, and MRI findings that may often be indistinguishable (Rolak, 1996). The presence of other systemic features of SLE like arthritis, rash or alopecia, the presence of extractable nuclear antibodies, an elevated ESR or CSF findings of pleocytosis or elevated protein may be valuable diagnostic clues (Rolak, 1996).

Antiphospholipid syndrome may sometimes mimic demyelinating syndrome, as they can both present in young females with multifocal relapsing symptoms, visual disturbances and high T2-weighted signal in CNS MRI. Visual disturbances of retrobulbar neuritis may last days to weeks and may be bilateral whereas amaurosis fugax is brief and unilateral. Disseminated CNS involvement, relapsing–remitting course, white matter or spinal cord, oligoclonal bands in the CSF and abnormal evoked potentials all favor demyelinating syndrome. A history of recurrent thrombosis or miscarriages and the presence of abnormal coagulation studies are suggestive of antiphospholipid syndrome (Scott et al., 1994).

6.8. Optic neuritis

Optic neuritis is one important cause of neurologic visual loss in SLE (Giorgi and Balacco Gabrieli, 1999; Giorgi et al., 1999). It has been associated with aPL (Levine et al., 1988; Oppenheimer and Hoffbrand, 1986; Galindo-Rodriguez et al., 1999) and with TM (Levine et al., 1988; Galindo-Rodriguez, 1999; April and Vansonnenberg, 1976; Rosenbaum et al., 1997). In fact, out of 51 cases of SLE-related optic neuropathy reported in the literature by 1997, 41% had signs of spinal cord disease (Giorgi and Balacco Gabrieli, 1999; Giorgi et al., 1999), and Jabs et al. found to be as high as 54% (Jabs et al., 1986). The coexistence of optic neuropathy and transverse myelopathy in non-SLE patients is denominated Devic's syndrome (Giorgi and Balacco Gabrieli, 1999; Giorgi et al., 1999; Bonnet et al., 1999), and it is considered to be a variant of MS.

Clinical presentation of optic neuritis is acute visual loss that may be painful or painless. Physical examination reveals an afferent pupillary defect evidenced by an escape phenomenon on the swinging light test, known as Marcus–Gunn pupil. Fundoscopic examination often is normal, as the involvement is frequently retrobulbar. As gliosis occurs, central disc pallor, particularly in the temporal side, may later become evident (Giorgi and Balacco Gabrieli, 1999; Giorgi et al., 1999; Cinefro and Frenkel, 1978; Smith and Pinals, 1982).

Optic neuropathy may be the presenting manifestation of SLE in some cases (Giorgi and Balacco Gabrieli, 1999; Giorgi et al., 1999; Smith and Pinals, 1982). Since it is most commonly associated with MS (Rosenbaum et al., 1997), this may lead to confusion in previously undiagnosed patients. Findings suggestive of NPSLE are bilateral involvement (sometimes not suspected clinically, but unmasked by visual evoked potentials (VEP) or visual field testing) (Giorgi and Balacco Gabrieli, 1999; Giorgi et al., 1999), bilateral, dense, central scotomata (up to 70% of cases) (Giorgi and Balacco Gabrieli, 1999; Giorgi et al., 1999; Smith and Pinals, 1982), and severe, persistent visual defects after the first attack, rare findings in MS (Oppenheimer and Hoffbrand, 1986). Other diagnostic clues are the absence of oligoclonal bands in the CSF and typical VEP findings of markedly decreased or absent responses with little or no conduction delay (Oppenheimer and Hoffbrand, 1986).

6.9. Transverse myelitis

TM is a rare but serious complication of NPSLE that may occur at any point of the disease (Kovacs et al., 1993, 2000; Andrianakos et al., 1975; Hachen and Chantraine, 1979; Mok et al., 1998). Thoracic involvement is most common, with associated optic neuritis in almost half (Kovacs et al., 2000). Some postulate the cause of the susceptibility of this region is an anatomical disadvantage in its blood supply taxed by the vasculopathic changes often seen in autopsy (Andrianakos et al., 1975; Kovacs et al., 2000). The reported association with aPL could also play a role (Kovacs et al., 2000; Schantz et al., 1998; Barile and Lavalle, 1992). The evolution is rapid and often complete within a few hours (Warren and Kredich, 1984). Prognosis has always been viewed as dismal (Kovacs et al., 1993). However, Kovacs et al. reviewed the 105 cases reported in the literature and found favorable outcomes in most, pondering whether the introduction of early, more aggressive treatment may be the cause (Kovacs et al., 2000).

The diagnosis of TM is made clinically, which may be supported by serological tests, CSF analysis and imaging studies (Marabani et al., 1989). Physical examination typically reveals paraparesis or paraplegia and a sensory level. Sphincter involvement, manifested as urinary retention or fecal incontinence, invariably occurs (Andrianakos et al., 1975; Marabani et al., 1989; Provenzale and Bouldin, 1992), and fever is very often present at the onset (Andrianakos et al., 1975). Deep tendon reflexes are most commonly absent, but they may be hyperactive (Andrianakos et al., 1975; Provenzale and Bouldin, 1992). Other presenting symptoms include low back, mid-scapular or abdominal pain, and lower extremity paresthesia (Andrianakos et al., 1975).

Cerebrospinal fluid abnormalities are common but non-specific and often mild (Provenzale and Bouldin, 1992). They include elevated protein, pleocytosis, and hypoglycorrhachia (Andrianakos et al., 1975; Warren and Kredich, 1984). The latter has been described as a finding typical of SLE-related TM, as it does not occur in idiopathic TM (Propper and Bucknall, 1989) and may be a clue in undiagnosed SLE. MRI is abnormal in about 70% of the cases (Wolf and Barrows, 1966), which may show high T2 signal, spinal cord enlargement and contrast enhancement. These last two findings have been reported to correlate with the clinical course on serial imaging (Provenzale et al., 1994). An additional and very important role of MRI is to help exclude space-occupying lesions that may have the same clinical manifestations (Provenzale and Bouldin, 1992).

The differential diagnosis includes structural lesions, infections, (TB, HTLV-I, HIV, CMV, Borrelia), CNS Whipple's disease, progressive multifocal leukoencephalopathy, syphilis and vitamin B_{12} deficiency.

6.10. Headache

The inclusion of headache as a manifestation of NPSLE is a matter of controversy. With a few exceptions (Sfikakis et al., 1998; Fernández-Nebro et al., 1999), most authors agree there is a higher prevalence of headache and its subtypes in SLE vs. controls or population estimates (Ainiala et al., 2001; Brey et al., 2002; Glanz et al., 2001; Atkinson and Appenzeller, 1975; Isenberg et al., 1982; Vázquez-Cruz et al., 1990; Rozell et al., 1998). The dispute arises from lack of correlation with clinical, neuropsychiatric and laboratory features of SLE, as well as imaging and neurochemical abnormalities (Sfikakis et al., 1998; Fernández-Nebro et al., 1999; Glanz et al., 2001; Atkinson and Appenzeller, 1975; Isenberg et al., 1982; Rozell et al., 1998; Markus and Hopkinson, 1992; Brandt and Lessell, 1978; Montalban et al., 1992), raising the question of whether headache or its subtypes even represent active NPSLE. Previous associations with aCL and Raynaud's phenomenon that would seem to make sense pathophysiologically in vascular-type headaches have not been found in a number of studies (Sfikakis et al., 1998; Fernández--Nebro et al., 1999; Glanz et al., 2001; Isenberg et al., 1982; Markus and Hopkinson, 1992; Montalban et al., 1992).

The definition of headache in SLE is also a matter of controversy. The work of Atkinson and Appenzeller (1975) and Brandt and Lessell (1978) described a severe, disabling, persistent headache, not responsive to narcotics that followed disease activity and would subside with corticosteroids that was later deemed 'lupus headache' (Sfikakis et al., 1998; Omdal et al., 2001a,b). This term is part of the SLEDAI, but was deemed too non-specific for the ACR NPSLE nomenclature. They instead describe migraine with and without aura, tension headache, cluster headache, intracranial hypertension-related, including pseudotumor cerebri, and non-specific intractable headache, with strict inclusion parameters (Appendix).

The evaluation of headache in SLE is difficult and has a vast differential diagnosis. These include brain abscess, infectious meningitis, NSAID-induced, cerebral venous thrombosis, hypertension, acute or chronic sinusitis and intracranial hemorrhage, tumor, seizures, aseptic meningitis, sepsis, low intracranial pressure and metabolic reversible causes like carbon monoxide exposure and caffeine withdrawal.

6.11. Movement disorders

Chorea is an uncommon clinical manifestation of SLE, characterized by random, irregular and jerky movements that may occur in any part of the body. Two-thirds of the cases have a single episode and over one-half have bilateral symptoms (Cervera et al., 1997). Prevalence is about 1–4% of SLE (Brey et al., 2002; Cervera et al., 1997; Khamashta et al., 1988) and is the only movement disorder included in the ACR nomenclature. It is the most common movement disorder, but reports of tremor mimicking essential tremor exist (Venegoni et al., 1994). Estrogen-containing oral contraceptives and pregnancy have been known to precipitate attacks (Cervera et al., 1997; Wolf and McBeath, 1985). Chorea has been associated with aPL and antiphospholipid syndrome (Cervera et al., 1993, 1997; Khamashta et al., 1988; Asherson et al., 1986, 1987; Hatron et al., 1986).

The diagnosis is clinical, but supplemented by studies aiding in the differential diagnosis, which includes Wilson's disease, drugs (illicit or prescription), hyperthyroidism, as well a Huntington's and Sydenham's chorea. Since chorea may precede the onset of other SLE manifestations and is clinically indistinguishable from Sydenham's and Huntington's (Cervera et al., 1997; Asherson et al., 1987; Lusins and Szilagyi, 1975; Olsen, 1968), clinical suspicion is of utmost importance. Neuropathologic studies have revealed basal ganglia abnormalities in the minority of patients (Lusins and Szilagyi, 1975; Bryun and Padberg, 1984), and imaging studies are non-specific except in aiding in the differential diagnosis.

6.12. Myasthenia gravis

MG is an autoimmune disorder characterized by antibodies against acetylcholine receptors inducing muscle weakness and fatigability commonly affecting bulbar and other voluntary muscles. It is a purely motor disorder and tendon reflexes are spared. Clinical manifestations include ptosis, diplopia, masticatory weakness, dysphagia, and weakness of

the extremity and less commonly of the trunk and neck musculature. History in undiagnosed patients may reveal symptoms occurring in the evening, reflecting the accentuation of symptoms with repeat use typical of the disorder.

The association of MG with SLE has been reported in more than 50 cases (Wolf and Barrows, 1966; Petersen and Lund, 1969; Abbruzzese et al., 1979; Chan and Britton, 1980; Killian and Hoffman, 1980; Vaiopoulos et al., 1994; Meloni et al., 1996; Barbosa et al., 2000; Mevorach et al., 1995). Muscle weakness in SLE is often a diagnostic problem; given this known association, MG should be included in the differential diagnosis (Killian and Hoffman, 1980; Vaiopoulos et al., 1994). MG may either precede or follow the diagnosis of SLE (Wolf and Barrows, 1966). The development of SLE produces variable impact in the severity of MG and vice versa (Wolf and Barrows, 1966; Chan and Britton, 1980). Thirty percent of patients with MG have a positive ANA, increasing to 50% in those with thymoma (Killian and Hoffman, 1980). Interestingly, homology in a sequence segment of U1 RNP and the main immunogenic region of the acetylcholine receptor has been reported (Vaiopoulos et al., 1994).

Diagnosis is made by compatible clinical history in association with the presence of anti-acetylcholine receptor antibodies and/or fatigability evidenced by electrophysiological testing (EMG). A trial of edrophonium (Tensilon®) or neostigmine should reversibly eliminate the patient's symptoms.

The differential diagnosis includes Lambert–Eaton syndrome, MS, GBS and its Miller Fisher variant, corticosteroids, congenital and inflammatory myopathies, motor neuron disease, medications (neuromuscular blocking agents, aminoglycosides, penicillamine, antimalarial drugs, colistin, streptomycin, polymyxin B, tetracycline, hypokalemia, hypophosphatemia, organophosphate toxicity, botulism, black widow spider venom and stroke).

6.13. Seizures

Seizures are defined as spells of brief, involuntary, paroxysmal alterations of behavior lasting seconds to several minutes and associated with a transient hypersynchronous discharge of cortical neurons. The behavioral alterations may or may not include convulsions. Recovery after a seizure is typically rapid and complete. It is important to differentiate seizures from spells that may mimic them such as breath-holding spells, migraine, convulsive syncope narcolepsy with cataplexy and psychogenic spells (Scheuer and Pedley, 1990). Next it is important to distinguish between isolated seizures and epilepsy, a disorder characterized by recurrent, unprovoked seizures. Provoked seizures are seen in SLE patients with systemic or CNS infection, renal failure, electrolyte balances, drug toxicity or hypertension (Herranz et al., 1994). Two-thirds to three-fourths of the seizures in SLE patients are generalized tonic/clonic seizures. These tend to occur for the first time during a disease flare and often do not recur until another flare. If residual cerebral injury is sustained during the flare, the patient might develop epilepsy.

Seizures account for 9–58% of NPSLE manifestations reported in clinical series (reviewed in Viedt et al., 2000; Vyse et al., 1994; Ward et al., 1996; Warren and Kredich, 1984). Seizures in SLE patients tend to appear early in the disease course (Mackworth-Young and Hughes, 1985; Feinglass et al., 1997; McCure and Globus, 1988), and may be the presenting feature of SLE (Mackworth-Young and Hughes, 1985). The frequency varies widely, however, depending on the specific SLE population studied. For example, in studies that include an unselected, primarily outpatient population, the frequency of seizures ranges from 9–20% (Ainiala et al., 2001; Brey et al., 2002; Costallat et al., 2001; Herranz et al., 1994; Mackworth-Young and Hughes, 1985; Feinglass et al., 1997). When the study population includes only hospitalized SLE patients, the reported frequency is higher, as is the proportion of patients with conditions that could provoke seizures (Futrell et al., 1992).

The clinical approach to the evaluation of seizures in any SLE patient is to look for those conditions that could provoke seizures listed above. In a hospitalized patient, this must include a thorough evaluation for infection. A brain MRI scan is done to evaluate for focal cerebral lesions, and an EEG is done to evaluate for epileptiform activity. A lumbar puncture should be performed after brain imaging is obtained in any patient in whom encephalitis or meningitis is suspected, but does not need to be performed routinely.

The differential diagnosis includes seizure-like signs or symptoms or seizure from vasovagal syncope, cardiac syncope, hysteria, hyperventilation, tics, narcolepsy and cataplexy, labyrinthitis, alcohol and drug withdrawal, medications (quinolones, imipenem), subarachnoid hemorrhage, trauma, hypoglycemia, panic attacks, conversion disorders, and malingering.

6.14. Cognitive dysfunction

The etiology of cognitive dysfunction in SLE remains an active research question, but it is clear that it cannot be fully accounted for by past or current corticosteroid treatment, disease duration, disease activity (SLEDAI) or its associated psychological/emotional distress, or sociodemographic factors (Rivest et al., 2000; Brey et al., 2002; Tzioufas et al., 2000). The detection of cognitive disorders has been regarded as time-consuming and therefore impractical for routine testing (Ainiala et al., 2001; Brey et al., 2002), and yet mild to severe cognitive dysfunction remains the most common type of NPSLE manifestation with a prevalence of up to 75% (Ainiala et al., 2001; Brey et al., 2002; Costallat et al., 2001). It is most reliably detected and monitored through neuropsychological examination, often revealing a subcortical cognitive syndrome with most prominent compromise in the areas of processing efficiency/speed and attention/concentration, memory function, conceptual reasoning and cognitive flexibility, approaching dementia in 15–25% of NPSLE cases (Ainiala et al., 2001; Brey et al., 2002).

Cognitive impairment in SLE is not consistently related to psychiatric manifestations and can be detected even in the absence of other current or past overt CNS manifestations (Ainiala et al., 2001; Tzioufas et al., 2000). It appears to be selectively linked to aCL but not to anti-P antibodies (Brey et al., 2002). History of persistently elevated aCL over a period of 1–5 years has been linked to greater and sustained cognitive impairment and may be responsible for the long-term subtle deterioration in cognitive function in SLE (Hanly et al., 1999; Menon et al., 1999). Specifically, reduced psychomotor speed has been selectively linked to persistent IgG aCL positivity, and reduced conceptual reasoning and executive function to IgA aCL positivity (Menon et al., 1999). Cognitive dysfunction in some studies appears to be a relatively stable feature of CNS involvement in SLE (Waterloo et al., 2001), although in others impairment waxes and wanes over time (Hanly et al., 1999; Menon et al., 1999). This may be because aCL levels fluctuate in SLE patients, albeit not always with disease activity. Continued observation with serum samples every 3–4 months may help assess risk for cognitive impairment in the SLE patient and give insights into the nature of some of the patient's complaints.

The differential diagnosis includes primary mental/neurologic disorder not related to SLE, metabolic disturbances (including glucose, electrolytes, fluid, osmolarity), substance or drug-induced delirium (including withdrawal), cerebral infections.

A full discussion of cognitive dysfunction and evaluation in patients with SLE can be found in Chapter 3.

6.15. Psychiatric disorders

The range of mood disorders in SLE is wide (major depressive episode, mood disorder with depressive, manic or mixed features) and is estimated to affect 69–75% of SLE patients, if standardized examination instruments are used (Ainiala et al., 2001; Brey et al., 2002). The prevalence of anxiety disorders ranges from 7 to 70% (Ainiala et al., 2001; Brey et al., 2002). Psychosis and depression are two specific psychiatric disorders affecting 5–40% of SLE cases, not always in the context of exacerbated disease activity (Ainiala et al., 2001; Brey et al., 2002; Sabbadini et al., 1999a,b).

Psychiatric disorders in SLE have been linked to anti-ribosomal P, but not aCL (Roubey, 1996; Tzioufas et al., 2000; Yalaoui et al., 2002; Arnett et al., 1996). Anti-ribosomal P antibodies are specific to SLE and their prevalence varies across ethnic groups. Serum, but not CSF, anti-ribosomal P antibodies are strongly associated with the development of psychosis and depression in SLE, but are not implicated in coexisting cognitive dysfunction (Font et al., 1998; Arnett et al., 1996).

It can be difficult to distinguish between the presence of acute confusional state, SLE-mediated psychosis and corticosteroid-induced psychosis

in some SLE patients. Acute confusional state is equivalent to 'delirium' defined in DSM-IV as an observable state of impaired consciousness, cognition, mood, affect and behavior (Appendix). The term 'organic brain syndrome' is not recommended for general use as 'acute confusional state' is more precise with a validated definition. Acute confusional states are often accompanied by cognitive deficits, however, if only cognitive deficits present and not other features described above, the syndrome should be diagnosed as 'cognitive dysfunction'.

Psychosis is defined as a severe disturbance in the perception of reality characterized by delusions and/or hallucinations. If psychosis occurs exclusively during times when an impaired level of consciousness is present, the syndrome should be diagnosed as 'acute confusional state'. If the onset of psychosis is accompanied by the presence of anti-ribosomal P antibodies or other evidence of systemic SLE-related organ involvement, the syndrome is most likely related to a direct SLE-related CNS effect. If, however, psychosis occurs as corticosteroids are administered, or the corticosteroid dose is escalated for the treatment of SLE-related disease activity, psychosis as a side-effect of corticosteroid therapy should be strongly suspected. This is particularly true if anti-ribosomal P antibody levels are also not elevated.

The differential diagnosis includes adjustment disorder with anxiety (e.g. maladaptive response to stress of having SLE, substance- or drug-induced anxiety, anxiety occurring exclusively during the course of an acute confusional state, a mood disorder, or psychosis for anxiety disorders; primary mental disorders, substance-induced mood disorder, adjustment disorder with depressed mood for mood disorders; and primary psychotic disorder unrelated to SLE (e.g. schizophrenia), substance- or drug-induced psychotic disorder (including NSAIDs, antimalarials), psychologically mediated reaction to SLE (brief reactive psychosis with major stressor) for psychosis.

7. Diagnostic investigations

7.1. Imaging

There is no single diagnostic test sensitive and specific for NPSLE. The assessment of individual patients is based on clinical neurologic and rheumatologic evaluation, immunoserologic testing, brain imaging, and psychiatric and neuropsychologic assessment. These examinations are used to support or refute the clinical diagnostic impression and rule out alternative explanations, and form the basis for prospective monitoring of clinical evolution and response to treatment interventions. Neuroimaging techniques have been used to help identify, locate and hopefully differentiate the pathophysiological mechanisms that give rise to the wide range of clinical NPSLE manifestations.

Focal neurological symptoms of NPSLE correlate with structural (MRI) abnormalities, and in fact MRI is usually normal in NPSLE patients with diffuse psychiatric (depression, psychosis) and no other CNS manifestations (Karassa et al., 2000; Sibbitt, 1999a,b). However, when diffuse manifestations are also accompanied by generalized seizures, MRI shows multiple small, high intensity lesions that often resolve with treatment (Karassa et al., 2000; Sibbitt, 1999a,b). In general, diffuse psychiatric manifestations are more easily detected with functional neuroimaging (SPECT, PET). A full discussion of anatomic and functional brain imaging in patients with SLE can be found in Chapter 3.

7.2. Electroencephalography

The electroencephalography (EEG) is commonly abnormal in any patient with a condition known to cause an encephalopathy. The abnormality is characterized by diffuse slowing (frequencies of less than 8 Hz) and can occur in the setting of many of the conditions that lower seizure threshold (Scheuer and Pedley, 1990). No study has specifically correlated focal or generalized EEG abnormalities with seizure type in SLE patients. However, about 75% of EEG's in SLE patients with seizures demonstrate diffuse abnormalities and 25% focal abnormalities (Omdal et al., 1989).

7.3. Cerebrospinal fluid evaluation

Cerebrospinal fluid analysis is recommended in the diagnostic evaluation of some patients with CNS NPSLE manifestations. A lumbar puncture cannot be

performed in the following situations: (a) anticoagulated patients, (b) patients with fewer than 20,000 platelets/mm^3, (c) patients with a focal mass lesion or edema that would increase risk for herniation. The CSF analysis is essential to the diagnosis of CNS infection, but in the absence of infection may also be helpful in suggesting a CNS SLE flare. When immune-mediated CNS damage is ongoing during an SLE flare, the CSF IgG index or synthesis rate is often elevated and an oligoclonal banding pattern is seen (West et al., 1995). In many patients these abnormalities normalize when the flare resolves. Findings of pleocytosis, elevated protein or hypoglycorrhachia are non-specific and seen in only about one-third of patients (West et al., 1995).

7.4. Autoantibody testing

Autoantibodies with association to NPSLE include aPL, anti-ribosomal P antibody (anti-P) (West, 1994), and antineuronal antibody (West, 1994). With the exception of aPL, they are of limited availability and applicability in the general clinical setting, but may help distinguish diffuse vs. focal CNS involvement in active NPSLE (West et al., 1995; West, 1994; Tzioufas et al., 2000; Ward et al., 1996).

8. Treatment

The management of patients with NPSLE includes symptomatic and immunosuppressive therapies, but evidence for the efficacy of the treatment modalities commonly used is largely limited to uncontrolled clinical trials and anecdotal experience (Table 2). The key to treatment is to establish the correct diagnosis first by carefully following the guidelines set forth for the diagnosis of NPSLE syndromes by the ACR. It is also important to remember that for many NPSLE syndromes, symptomatic treatment may also be needed in addition to immuno-modulatory therapy. As mentioned above, very few controlled trials specifically addressing any treatment modality for a specific NPSLE syndromes exist (Navarrete and Brey, 2000).

Low endogenous levels of DHEA and other androgens are typical for patients with autoimmune diseases such as SLE, and augmentation of androgen levels has been suggested as a treatment (Strand, 2000). A number of small controlled and uncontrolled clinical trials with SLE patients suggests that DHEA contributes to amelioration of disease activity, decreasing corticosteroid requirements, diminished flares, and improved cognition (van Vollenhoven, 2000). A short-term (1 month) course of DHEA under double-blinded placebo-controlled conditions demonstrated significant therapeutic effects on cognitive dysfunction in mild to moderate SLE (van Vollenhoven et al., 2001). Attention/concentration and learning/memory deficits were the most responsive to DHEA and treatment benefits were unrelated to depression or SLE disease activity. There is no approved standardized therapeutic regime of DHEA for SLE, but is widely used by SLE patients as a food supplement. Unfortunately, the Federal Drug Administration did not approve the use of DHEA to treat active disease in patients with SLE. More double-blinded placebo-controlled clinical trials are needed to assess the long-term benefits of this agent and its potential risks, which include possible lowering of HDL cholesterol and hormonal dysregulation (with potential adverse consequences for coagulation, atherosclerosis or development of neoplasms) (van Vollenhoven, 2000).

Cyclophosphamide is a cytotoxic immunosuppressive treatment option with documented therapeutic benefits in the management of severe NPSLE manifestations unresponsive to other treatment modalities (e.g. cerebral vasculopathy), and is an effective adjunctive agent when used with glucocorticoids for the treatment of transverse myelopathy (Swaak et al., 2001). A recent randomized controlled clinical trial comparing long-term use of cyclophosphamide and methylprednisolone reported better overall therapeutic control of SLE-related neurological manifestations (refractory seizures, peripheral and cranial neuropathy, and optic neuritis) with monthly intravenous cyclophosphamide (Barile et al., 2001). Larger number of improved cases (95 vs. 63%) and lower longitudinal levels of disease activity were also observed under cyclophosphamide; the two medications showed relatively equal incidence of new infections (52 vs. 63%). However, other studies with SLE report an increased dose-dependent risk of infection and sepsis (fatal in 18%

Table 2
Treatment of various manifestations of neuropsychiatric SLE

Neuropsychiatric manifestations	Symptomatic treatment[a]	Immune-modulating treatment
Aseptic meningitis	Withdrawal and avoidance of offending drugs	Corticosteroids
Autonomic neuropathy	Secretagogues, mineralocorticoids	Azathiaprine, corticosteroids
Cerebrovascular disease	Anticoagulation, anti-platelet agents, stroke risk factor identification and treatment (i.e. statins)	High-dose corticosteroids, IVIG, cytotoxic immunosuppressives or both
Cognitive dysfunction	None	Treatment of extra-neural disease activity
Demyelinating syndromes		
Lupoid sclerosis	Physical therapy	None
Optic neuritis	None	Corticosteroids, pulse cytoxan (monthly), plasmaphoresis
Transverse myelitis	None	High-dose corticosteroids, cytotoxic immunosuppressives, combination of both
Delirium	None	Treatment of extra-neural disease activity
Headaches	Migraine treatments, anti-platelet agents	Treatment of extra-neural disease activity
Idiopathic pseudotumor cerebri	Carbonic anhydrase inhibitors, repeated lumbar punctures, optic nerve decompression	High-dose corticosteroids
Movement disorders	Dopamine antagonists	High-dose corticosteroids, anticoagulation if related to antiphospholipid antibodies
Myasthenia gravis	Oral anticholinesterase inhibitors	Corticosteroids, plasmaphoresis, IVIG, thymectomy
Peripheral or cranial neuropathy	Tricyclic antidepressants, gabapentin	Corticosteroids
Psychiatric disorders		
Anxiety and depression	Psychotherapy	Effective treatment of extra-neural disease

[a] Includes treatment of secondary causes such as drugs, infections and metabolic problems related to kidney and liver dysfunction, and electrolyte disturbances.

of cases) with intravenous cyclophosphamide (Bellomio et al., 2001). Some (Trevisani et al., 2000) have pointed out that the question of efficacy and safety of cyclophosphamide as an alternative to methylprednisolone remains largely unanswered, as it has not been thoroughly assessed by randomized controlled clinical trials.

High-dose chemotherapy combined with autologous hematopoietic stem cell transplantation recently showed remarkable therapeutic benefits in cases of severe, life-threatening SLE with neuropsychiatric manifestations (and other organ involvement) that had been unresponsive to multiple monthly cycles of intravenous cyclophosphamide (Traynor et al., 2000). Within months, stem cell transplantation resulted in clinical remission of SLE, significant decline in anti-dsDNA antibody titers, normalization of serum complement levels, reduction and even discontinuation of glucocorticoids, and normalization of the T-cell receptor repertoire (Traynor, 2000).

Key points

- Guidelines exist for the diagnosis of 19 different NPSLE syndromes and are available at www.rheumatology.org/publications/ar/1999/aprilappendix.asp. Clinicians faced with an SLE patient with peripheral or CNS

manifestations should consult these guidelines for information about diagnostic criteria and differential diagnosis.
- NPSLE syndromes are common in patients with SLE and frequently occur within the first year of SLE diagnosis.
- Cognitive dysfunction is the most common NPSLE manifestation and is often a source of decreased quality of life for patients with SLE.
- There are very few controlled treatment trials for any of the NPSLE manifestations. These are sorely needed.

References

Abbruzzese, G., Abbruzzese, M., Bacigalupo, A., Ratto, S. 1979. Systemic lupus erythematosus after thymectomy in a patient with myasthenia gravis (letter). Neurology 29, 1436–1437.

Ainiala, H., Loukkola, J., Peltola, J., Korpela, M., Hietaharju, A. 2001. The prevalence of neuropsychiatric syndromes in systemic lupus erythematosus. Neurology 57, 496–499.
The study evaluates a population of SLE patients from Finland using the recently established ACR case definitions.

Alcocer-Varela, J., Aleman-Hoey, D., Alarcon-Segovia, D. 1992. Interleukin-1 and interleukin-6 activities are increased in the cerebrospinal fluid of patients with CNS lupus erythematosus and correlate with local late T-cell activation markers. Lupus 1 (2), 111–117.

Altomonte, L., Mirone, L., Zoli, A., Magaro, M. 1997. Autonomic nerve dysfunction in systemic lupus erythematosus: evidence for a mild involvement. Lupus 6 (5), 441–444.

American College of Rheumatology (ACR) ad hoc committee on neuropsychiatric lupus, 1999. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndrome. Arthritis Rheum. 42, 599–608.
Describes the case definitions for 19 NPSLE syndromes. The appendix (see below) gives further details for each manifestation.

Andonopoulos, A.P., Naxakis, S., Goumas, P., Lygatsikas, C. 1995. Sensorineural hearing disorders in systemic lupus erythematosus. A controlled study. Clin. Exp. Rheumatol. 13 (2), 137–141.

Andrianakos, A.A., Duffy, J., Suzuki, M., Sharp, J.T. 1975. Transverse myelopathy in systemic lupus erythematosus. Report of three cases and review of the literature. Ann. Int. Med. 83 (5), 616–624.

Antolin, J., Amerigo, M.J., Cantabrana, A., Roces, A., Jimenez, P. 1995. Systemic lupus erythematosus: clinical manifestations and immunological parameters in 194 patients. Subgroup classification of SLE. Clin. Rheumatol. 14 (6), 678–685.

Appendix **www.rheumatology.org/publications/ar/1999/aprilappendix.asp.**

April, R.S., Vansonnenberg, E. 1976. A case of neuromyelitis optica (Devic's syndrome) in systemic lupus erythematosus. Clinopathologic report and review of the literature. Neurology 26, 1066–1070.

Arnett, F.C., Reveille, J.D., Moutsopoulos, H.M., et al. 1996. Ribosomal P antibodies in systemic lupus erythematosus. Arthritis Rheum. 39, 1833–1839.

Asherson, R.A., Harris, N.E., Gharavi, A.E., Hughes, G.R.V. 1986. Systemic lupus erythematosus, antiphospholipid antibodies, chorea, and oral contraceptives (letter). Arthritis Rheum. 29 (12), 1535–1536.

Asherson, R.A., Derksen, R.H.W.M., Harris, E.N., Bouma, B.N., Gharavi, A.E., Kater, L., Hughes, G.R.V. 1987. Chorea in systemic lupus erythematosus and 'lupus-like' disease: association with antiphospholipid antibodies. Semin. Arthritis Rheum. 16 (4), 253–259.

Atkinson, R.A., Appenzeller, O. 1975. Headache in small vessel disease of the brain: a study of patients with systemic lupus erythematosus. Headache 15 (3), 198–201.

Barbosa, R.E., Cordova, S., Cajigas, J.C. 2000. Coexistence of systemic lupus erythematosus and myasthenia gravis (letter). Lupus 9 (2), 156–157.

Barcellini, W., Rizzardi, G.P., Borghi, M.O., et al. 1996. In vitro type-1 and type-2 cytokine production in systemic lupus erythematosus: lack of relationship with clinical disease activity. Lupus 5, 139–145.

Barile, L., Lavalle, C. 1992. Transverse myelitis in systemic lupus erythematosus—the effect of IV pulse methylprednisolone and cyclophosphamide. J. Rheumatol. 19 (3), 370–372.

Barile, L., Olguin, L., Ariza, R., et al. 2001. Controlled clinical trial of cyclophosphamide vs. methylprednisolone in severe neurologic manifestations in SLE. Lupus 10 (S1), S34.

Bellomio, V., Spindler, A., Cunio, S. 2001. Cyclophosphamide in systemic lupus erythematosus: Cumulative dose and adverse events. Lupus 10 (S1), s104.

Belmont, H.M., Buyon, J., Giorno, R., Abramson, S. 1994. Upregulation of endothelial cell adhesion molecules characterized disease activity in systemic lupus erythematosus. Arthritis Rheum. 37, 376–383.

Belmont, H.M., Abramson, S.B., Lie, J.T. 1996. Pathology and pathogenesis of vascular injury in systemic lupus erythematosus: interactions of inflammatory cells and activated endothelium. Arthritis Rheum. 39, 9–22.

Blaustein, D.A., Blaustein, S.A. 1998. Antinuclear antibody negative systemic lupus erythematosus presenting as bilateral facial paralysis. J. Rheumatol. 25 (4), 798–800.

Bloch, S.L., Jarrett, M.P., Swerdlow, M., Grayzel, A.I. 1979. Brachial plexus neuropathy as the initial presentation of systemic lupus erythematosus. Neurology 29, 1633–1634.

Bódi, I., Váradi, P., Pokorny, G., Engelhardt, J., Dibó, G., Vécsei, L., Miko, T.L. 1998. Polyneuropathy with endoneurial immune complex deposition as the first manifestation of systemic lupus erythematosus. Acta Neuropathol. 96, 297–300.

Bonnet, F., Mercie, P., Morlat, P., Hocke, C., Vergnes, C., Ellie, E., Viallard, J.F., Faure, I., Pellegrin, J.L., Beylot, J., Leng, B. 1999. Devic's neuromyelitis optica during pregnancy in a patient with systemic lupus erythematosus. Lupus 8 (3), 244–247.

Brandt, K.D., Lessell, S. 1978. Migrainous phenomena in systemic lupus erythematosus. Arthritis Rheum. 21 (1), 7–16.

Brey, R.L., Escalante, A. 1998. Neurological manifestations of antiphospholipid antibody syndrome. Lupus 7 (Suppl. 2), S67–S74.

Brey, R.L., Gharavi, A.E., Lockshin, M.D. 1990. Neurologic complications of antiphospholipid antibodies. Rheum. Dis. Clin. North Am. 19, 833–850.

Brey, R.L., Holliday, S.L., Saklad, A.R., Navarrete, M.G., Hermosillo-Romo, D., Stallworth, C.L., et al. 2002. Neuropsychiatric syndromes in SLE: prevalence using standardized definitions in the San Antonio Study of Neuropsychiatric Disease Cohort. Neurology 58, 1214–1220.
The study evaluates a population of predominantly Mexican American SLE patients using the recently established ACR case definitions.

Bryun, G.W., Padberg, G. 1984. Chorea and systemic lupus erythematosus. A critical review. Eur. Neurol. 23, 278–290.

Canoso, J.J., Cohen, A.S. 1975. Aspectic meningitis in systemic lupus erythematosus. Report of three cases. Arthritis Rheum. 18 (4), 369–374.

Carreño, L., Lopez-Longo, F.J., Monteagudo, I., et al. 1999. Immunological and clinical differences between juvenile and adult onset of systemic lupus erythematosus. Lupus 8, 287–292.

Cervera, R., Khamashta, M.A., Font, J., Sebastiani, G.D., Gil, A., Lavilla, P., Domenech, I., Aydintug, A.O., Jedryka-Goral, A., de Ramon, E., et al. 1993. Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. The European Working Party on Systemic Lupus Erythematosus. Medicine 72 (2), 113–124.

Cervera, R., Asherson, R.A., Font, J., Tikly, M., Pallares, L., Chamorro, A., Ingelmo, M. 1997. Chorea in the antiphospholipid syndrome: clinical, radiologic, and immunologic characteristics of 50 patients from our clinics and the recent literature. Medicine 76 (3), 203–212.

Chan, M.K.L., Britton, M. 1980. Comparative clinical features in patients with myasthenia gravis with systemic lupus erythematosus. J. Rheumatol. 7 (6), 838–842.

Chan, C.N., Li, E., Lai, F.M., Pang, J.A. 1989. An unusual case of systemic lupus erythematosus with isolated hypoglossal nerve palsy, fulminant acute pneumonitis, and pulmonary amyloidosis. Ann. Rheum. Dis. 48 (3), 236–239.

Cinefro, R.J., Frenkel, M. 1978. Systemic lupus erythematosus presenting as optic neuritis. Ann. Ophthalmol. 10 (5), 559–563.

Costallat, L., Bertolo, M., Appenzeller, S. 2001. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes: analysis of 527 patients. Lupus 10 (S1), S32.

Dao, T., Ohashi, K., Kayano, T., et al. 1997. Interferon g-inducing factor, a novel cytokine, enhances Fas ligand-mediated cytotoxicity of muring T helper cells. Cell Immunol. 173, 230–235.

De Marcaida, J.A., Reik, L. 1999. Central nervous system infections: disorders that mimic central nervous system infections. Neurol. Clin. 17, 901–915.

Denburg, S.D., Carbotte, R.M., Ginsberg, J.S., Denburg, J.A. 1997. The relationship of antiphospholipid antibodies to cognitive function in patients with systemic lupus erythematosus. J. Int. Neuropsychol. Soc. 3 (4), 377–386.

Dinarello, C.A. 1999. IL-18: a Th1-inducing, proinflammatory cytokine and new member of the IL-1 family. J. Allergy Clin. Immunol. 103, 11–24.

Dopp, J.M., Breneman, S.M., Oschowka, J.A. 1994. Expression of ICAM-1, VCAM-1, L-selectin, and leukosialin in the mouse central nervous system during the induction and remission stages of experimental allergic encephalomyelitis. J. Neuroimmunol. 54, 129–144.

Drenkard, C., Villa, A.R., Reyes, E., et al. 1997. Vasculitis in systemic lupus erythematosus. Lupus 6, 235–242.

Egerer, K., Feist, E., Rohr, U., Pruss, A., Burmester, G.-R., Dörner, T. 2000. Increased serum soluble CD14, ICAM-1 and E-selectin correlate with disease activity and prognosis in systemic lupus erythematosus. Lupus 9, 614–621.

Fehniger, T.A., Shah, M.H., Turner, M.J., et al. 1999. Differential cytokine and chemokine gene expression by human NK cells following activation with IL-18 or IL-15 in combination with IL-12: implications for the innate immune response. J. Immunol. 162, 4511–4520.

Feinglass, R.J., Arnett, F.C., Dorsch, C.A., Zizic, T.M., Stevens, M.B. 1997. Neurological manifestations of systemic lupus erythematosus: diagnosis, clinical spectrum, and relationship to other features of the disease. Medicine 55, 323–339.

Fernández-Nebro, A., Palacios-Muñoz, R., Gordillo, J., Abarca-Costalago, M., De Haro-Liger, M., Rodríguez-Andreu, J., González-Santos, P. 1999. Chronic or recurrent headache in patients with systemic lupus erythematosus: a case control study. Lupus 8, 151–156.

Fierro, B., Brighina, F., Amico, L., et al. 1999. Evoked potential study and radiological findings in patients with systemic lupus erythematosus. Electromyogr. Clin. Neurophysiol. 39, 305–313.

Font, J., Cervera, R., Espinosa, G., et al. 1998. Systemic lupus erythematosus in childhood: analysis of clinical and immunological findings in 34 patients and comparison with SLE characteristics in adults. Ann. Rheum. Dis. 57, 456–459.

Formiga, F., Moga, I., Pac, M., et al. 1999. Mild presentation of systemic lupus erythematosus in elderly patients assessed by SLEDAI. Lupus 8, 462–465.

Friedman, A.S., Folkert, V., Khan, G.A. 1995. Recurrence of systemic lupus erythematosus in a hemodialysis patient presenting as a unilateral abducens nerve palsy. Clin. Nephrol. 44 (5), 338–339.

Futrell, N., Schultz, L.R., Millikan, C. 1992. Central nervous system disease in patients with systemic lupus erythematosus. Neurology 42, 1649–1657.

Galindo-Rodriguez, G., Avina-Zubieta, J.A., Pizarro, S., Diaz de Leon, V., Saucedo, N., Fuentes, M., Lavalle, C. 1999. Cyclophosphamide pulse therapy in optic neuritis due to systemic lupus erythematosus: an open trial. Am. J. Med. 106 (1), 65–69.

Gamez-Nava, J.I., González-Lopez, L., Ramos-Remus, C., Fonseca-Gomez, M.M., Cardona-Muñoz, E.G., Suárez-Almazor, M.E. 1998. Autonomic dysfunction in patients with systemic lupus erythematosus. J. Rheumatol. 25 (6), 1092–1096.

Genevay, S., Hayem, G., Hamza, S., Palazzo, E., Meyer, O., Kahn, M.F. 2002. Oculomotor palsy in six patients with systemic lupus erythematosus. A possible role of antiphospholipid syndrome. Lupus 11 (5), 313–316.

Giaradi, G., Pierangeli, S., Holers, V.M., Espinola, R., Lui, X., Harris, N., Salmon, J.E. 2001. Complement activation is required for antiphospholipid antibody induced thrombosis. Arthritis Rheum. 44, S162.

Giorgi, D., Balacco Gabrieli, C. 1999. Optic neuropathy in systemic lupus erythematosus and antiphospholipid syndrome (APS): clinical features, pathogenesis, review of the literature and proposed ophthalmological criteria for APS diagnosis. Clin. Rheumatol. 18 (2), 124–131.

Giorgi, D., Balacco Gabrieli, C., Bonomo, L. 1999. The association of optic neuropathy with transverse myelitis in systemic lupus erythematosus (letter). Rheumatology 38 (2), 191–192.

Glanz, B.I., Venkatesan, A., Schur, P.H., Lew, R.A., Khoshbin, S. 2001. Prevalence of migraine in patients with systemic lupus erythematosus. Headache 41, 285–289.

Gonzalez-Crespo, M.R., Blanco, F.J., Ramos, A., et al. 1995. Magnetic resonance of the brain in systemic lupus erythematosus. Br. J. Rheumatol. 34, 1055–1060.

Gordon, T., Dunn, E.C. 1990. Systemic lupus erythematosus and right recurrent laryngeal nerve palsy. Br. J. Rheumatol. 29 (4), 308–309.

Haas, L.F. 1982. Stroke as an early manifestation of systemic lupus erythematosus. J. Neurol. Neurosurg. Psychiatry 45, 554–556.

Hachen, H.J., Chantraine, A. 1979. Spinal cord involvement in systemic lupus erythematosus. Paraplegia 17 (3), 337–346.

Hanly, J.G. 2001. Neuropsychiatric lupus. Curr. Rheumatol. Rep. 3 (3), 205–212.

Hanly, J.G., Walsh, N.M.G., Sangalang, V. 1992. Brain pathology in systemic lupus erythematosus. J. Rheumatol. 19, 732–741.

Hanly, J.G., Hong, C., Smith, S., Fisk, J.D. 1999. A prospective analysis of cognitive function and anticardiolipin antibodies in systemic lupus erythematosus. Arthritis Rheum. 42 (4), 728–734.

Harel, L., Mukamel, M., Brik, R., Blau, H., Straussberg, R. 2002. Peripheral neuropathy in pediatric systemic lupus erythematosus. Pediatr. Neurol. 27 (1), 53–56.

Harris, E.N., Gharavi, A.E., Asherson, R.A., Boey, M.L., Hughes, G.R. 1984. Cerebral infarction in systemic lupus: association with anticardiolipin antibodies. Clin. Exp. Rheumatol. 2, 47–51.

Hatron, P.Y., Bouchez, B., Wattel, A., Arnott, G., Devulder, B. 1986. Chorea, systemic lupus, circulating lupus anticoagulant (letter). J. Rheumatol. 13 (5), 991–993.

Herranz, M.T., Rivier, G., Khanashta, M.A., Blaser, K.U., Hughes, G.R.V. 1994. Association between antiphospholipid antibodies and epilepsy in patients with systemic lupus erythematosus. Arthritis Rheum. 37, 568–571.

Hickey, W.F. 1991. T-lymphocyte entry into the central nervous system. J. Neurosci. Res. 28, 254–260.

Horwitz, D.A., Gray, J.D., Behrendsen, S.C., et al. 1998. Decreased production of interleukin-12 and other Th1-type cytokines in patients with recent-onset systemic lupus erythematosus. Arthritis Rheum. 41, 838–844.

Hoyle, C., Ewing, D.J., Parker, A.C. 1985. Acute autonomic neuropathy in association with systemic lupus erythematosus. Ann. Rheum. Dis. 44, 420–424.

Hughes, R.A.C., Cameron, J.S., Hall, S.M., Heaton, J., Payan, J., Teoh, R. 1982. Multiple mononeuropathy as the initial presentation of systemic lupus erythematosus—nerve biopsy and response to plasma exchange. J. Neurol. 228, 239–247.

Huynh, C., Ho, S.L., Fong, K.Y., Cheung, R.T.F., Mok, C.C., Lau, C.S. 1999. Peripheral neuropathy in systemic lupus erythematosus. J. Clin. Neurophysiol. 16 (2), 164–168.

Iliopoulos, A.G., Tsokos, G.C. 1996. Immunopathogenesis and spectrum of infections in systemic lupus erythematosus. Semin. Arthritis Rheum. 25, 318–336.

Isenberg, D.A., Meyrick-Thomas, D., Snaith, M.L., McKeran, R.O., Royston, J.P. 1982. A study of migraine in systemic lupus erythematosus. Ann. Rheum. Dis. 41, 30–32.

Isshi, K., Hirihata, S. 1996. Association of anti-ribosomal P protein antibodies with neuropsychiatric systemic lupus erythematosus. Arthritis Rheum. 39 (9), 1483–1490.

Isshi, K., Hirohata, S. 1998. Differential roles of the anti-ribosomal P antibody and antineuronal antibody in the pathogenesis of central nervous system involvement in systemic lupus erythematosus. Arthritis Rheum. 41, 1819–1827.

Isshi, K., Hirohata, S., Hashimoto, T., Miyashita, H. 1994. Systemic lupus erythematosus presenting with diffuse low density lesions in the cerebral white matter on computed axial tomography scans: its implication in the pathogenesis of diffuse central nervous system lupus. J. Rheumatol. 21 (9), 1758–1762.

Jabs, D.A., Miller, N.R., Newman, S.A., Johnson, M.A., Stevens, M.B. 1986. Optic neuropathy in systemic lupus erythematosus. Arch. Ophtalmol. 104 (4), 564–568.

Janssen, B.A., Luqmani, R.A., Gordon, C., Hemingway, I.H., Bacon, P.A., Gearing, A.J., et al. 1994. Correlation of blood levels of soluble vascular cell adhesion molecule-1 with disease activity in systemic lupus erythematosus and vasculitis. Br. J. Rheumatol. 33, 1112–1116.

Jara, L.J., Irigoyen, L., Ortiz, M.J., Zazueta, B., Bravo, G., Espinoza, L.R. 1998. Prolactin and interleukin 6 in neuropsychiatric lupus erythematosus. Clin. Rheumatol. 17, 110–114.

Kado, S., Nagase, T., Nagata, N. 1999. Circulating levels of interleukin-6, its soluble receptor and interleukin-6/interleukin-6 receptor complexes in patients with type 2 diabetes mellitus. Acta Diabetol. 36 (1–2), 67–72.

Kaell, A.T., Shetty, M., Lee, B.C.P., Lockshin, M.D. 1986. The diversity of neurologic events in systemic lupus erythematosus. Arch. Neurol. 43, 273–276.

Kao, C.H., Lan, J.L., ChangLai, S.P., Liao, K.K., Yen, R.F., Chieng, P.U. 1999. The role of FDG-PET, HMPAO-SPET and MRI in the detection of brain involvement in patients with systemic lupus erythematosus. Eur. J. Nucl. Med. 26 (2), 129–134.

Kaplan, P.E., Betts, H.B. 1977. Lupoid sclerosis: evaluation and treatment. Arch. Phys. Med. Rehabil. 58, 24–28.

Karassa, F., Ioannidis, J.P., Boki, K., et al. 2000. Predictors of clinical outcome and radiologic progression in patients with

neuropsychiatric manifestations of systemic lupus erythematosus. Am. J. Med. 109, 628–634.

Keane, J.R. 1995. Eye movement abnormalities in systemic lupus erythematosus. Arch. Neurol. 52 (12), 1145–1149.

Kelley, V.R., Wuthrich, R.P. 1999. Cytokines in the pathogenesis of systemic lupus erythematosus. Semin. Nephrol. 19, 57–66.

Khamashta, M.A., Gil, A., Anciones, B., Lavilla, P., Valencia, M.E., Pintado, V., Vázquez, J.J. 1988. Chorea in systemic lupus erythematosus: association with antiphospholipid antibodies. Ann. Rheum. Dis. 47, 681–683.

Killian, P.J., Hoffman, G.S. 1980. Coexistence of systemic lupus erythematosus and myasthenia gravis. South Med. J. 73 (2), 244–246.

Kinnunen, E., Muller, K., Keto, P., Ketonen, L., Helve, T., Sepponen, R. 1993. Cerbrospinal fluid and MRI findings in three patients with multiple sclerosis and systemic lupus erythematosus. Acta Neurol. Scand. 78, 356–360.

Kirou, K.A., Crow, M.K. 1999. New pieces to the SLE cytokine puzzle. Clin. Immunol. 91, 1–5.

Kovacs, J.A.J., Urowitz, M.B., Gladman, D.D. 1993. Dilemmas in neuropsychiatric lupus. Rheum. Dis. Clin. North Am. 19 (4), 795–813.

Kovacs, B., Lafferty, T.L., Brent, L.H., DeHoratius, R.J. 2000. Transverse myelopathy in systemic lupus erythematosus: an analysis of 14 cases and review of the literature. Ann. Rheum. Dis. 59 (2), 120–124.

Kozora, E., Laudenslager, M., Lemieux, A., West, S.G. 2001. Inflammatory and hormonal measures predict neuropsychological functioning in systemic lupus erythematosus and rheumatoid arthritis patients. J. Int. Neuropsychol. Soc. 7 (6), 745–754.

Lai, N.S., Lan, J.L. 2000. Evaluation of cerebrospinal anticardiolipin antibodies in lupus patients with neuropsychiatric manifestations. Lupus 9 (5), 353–357.

Lancman, M.E., Mesropian, H., Granillo, R.J. 1989. Chronic aseptic meningitis in a patient with systemic lupus erythematosus. Can. J. Neurol. Sci. 16 (3), 354–356.

Lee, J.S., Roh, Y.B., Oum, B.S., Kwak, I.S. 2000. Isolated oculomotor nerve palsy with pupillary abnormality in systemic lupus erythematosus. J. Pediatr. Ophthalmol. Strabismus 37 (4), 241–243.

Lesprit, P., Mouloud, F., Bierling, P., Schaffer, A., Cesaro, P., Brun-Buisson, C., Godeau, B. 1996. Prolonged remission of SLE-associated polyradiculoneuropathy after a single course of intravenous immunoglobulin. Scand. J. Rheumatol. 25, 177–179.

Levine, S.R., Crofts, J.W., Lesser, G.R., Floberg, J., Welch, K.M. 1988. Visual symptoms associated with the presence of a lupus anticoagulant. Ophthalmology 95 (5), 686–692.

Liem, M.D., Gzesh, D.J., Flanders, A.E. 1996. MRI and angiographic diagnosis of lupus cerebral vasculitis. Neuroradiology 38, 134–136.

Liote, F., Osterland, C.K. 1994. Autonomic neuropathy in systemic lupus erythematosus: cardiovascular autonomic function assessment. Ann. Rheum. Dis. 53 (10), 671–674.

Lundberg, P.O., Werner, I. 1972. Trigeminal sensory neuropathy in systemic lupus erythematosus. Acta Neurol. Scand. 48 (3), 330–340.

Lusins, J.O., Szilagyi, P.A. 1975. Clinical features of chorea associated with systemic lupus erythematosus. Am. J. Med. 58, 857–861.

Machold, K.P., Kiener, H.P., Graninger, W.B., et al. 1993. Soluble ICAM-1 in patients with rheumatoid arthritis and SLE. Clin. Immunol. Immunopathol. 68, 74–78.

Mackworth-Young, C.G., Hughes, G.R.V. 1985. Epilepsy: an early symptom of systemic lupus erythematosus. J. Neurol. Neurosurg. Psychiatry 48, 185–192.

Maeshima, E., Maeshima, S., Yamada, Y., Yukawa, S. 1993. Antiphospholipid antibodies and regional cerebral blood flow in systemic lupus erythematosus. Ryumachi 33 (2), 125–130.

Marabani, M., Zoma, A., Hadley, D., Sturrock, R.D. 1989. Transverse myelitis occurring during pregnancy in a patient with systemic lupus erythematosus. Ann. Rheum. Dis. 48 (2), 160–162.

Markus, H.S., Hopkinson, N. 1992. Migraine and headache in systemic lupus erythematosus and their relationship with antibodies against phospholipids. J. Neurol. 239, 39–42.

Mathias, C.J. 1997. Autonomic disorders ad their recognition. N. Engl. J. Med. 336, 721–724.

Matsuda, J., Gohchi, K., Gotoh, M., Tsukamoto, M., Saitoh, N. 1994. Circulation intercellular adhesion molecule-1 and soluble interleukin 2-receptor in patients with systemic lupus erythematosus. Eur. J. Haematol. 52, 302–303.

Matsuki, Y., Hidaka, T., Matsumoto, M., et al. 1999. Systemic lupus erythematosus demonstrating serum anti-GM1 antibody with sudden onset of drop foot as the initial presentation. Intern. Med. 38, 729–732.

McCombe, P.A., McLeod, J.G., Pollard, J.D., Guo, Y.-P., Ingall, T.J. 1987. Peripheral sensorimotor and autonomic neuropathy associated with systemic lupus erythematosus. Brain 110, 533–549.

McCombe, P.A., Chalk, J.B., Pender, M.P. 1990. Familial occurrence of multiple sclerosis, thyroid disease and systemic lupus erythematosus. J. Neurol. Sci. 97, 163–171.

McCure, W.J., Globus, J. 1988. Neuropsychiatric lupus. Rheum. Dis. Clin. North Am. 14, 149–167.

McNicholl, J., Glynn, D., Mongey, A., Hutchinson, M., Bresnihan, B. 1994. A prospective study of neurophysiologic, neurologic and immunologic abnormalities in systemic lupus erythematosus. J. Rheumatol. 21, 1061–1066.

Meloni, F., Gueli, N., Villatico Campbell, S., Di Maio, F., Di Bernardo, M.G., Di Nuzzo, M., Carmenini, G. 1996. A case of systemic lupus erythematosus (SLE) and myasthenia gravis (MG). Allergy 51 (5), 362–363.

Menon, S., Jameson-Shortall, E., Newman, S.P., Hall-Craggs, M.R., Chinn, R., Isenberg, D.A. 1999. A longitudinal study of anticardiolipin antibody levels and cognitive functioning in systemic lupus erythematosus. Arthritis Rheum. 42 (4), 735–741.

Mevorach, D., Perrot, S., Buchanan, N.M., Khamashta, M., Laoussadi, S., Hughes, G.R., Menkes, C.J. 1995. Appearance of systemic lupus erythematosus after thymectomy: four case reports and review of the literature. Lupus 4 (1), 33–37.

Millette, T.J., Subramony, S.H., Wee, A.S., Harisdangkul, V. 1986. Systemic lupus erythematosus presenting with recurrent acute demyelinating polyneuropathy. Eur. Neurol. 25, 397–402.

Mitchell, S.R., Nguyen, P.Q., Katz, P. 1990. Increased risk of neisserial infections in systemic lupus erythematosus. Semin. Arthritis Rheum. 20 (3), 174–184.

Mok, C.C., Lau, C.S., Chan, E.Y., Wong, R.W. 1998. Acute transverse myelopathy in systemic lupus erythematosus: clinical presentation, treatment, and outcome. J. Rheumatol. 25 (3), 467–473.

Mok, C.C., Lau, C.S., Wong, R.W.S. 2001. Neuropsychiatric manifestations and their clinical associations in southern Chinese patients with systemic lupus erythematosus. J. Rheumatol. 28, 766–771.

Montalban, J., Cervera, R., Font, J., Ordi, J., Vianna, J., Haga, H.J., Tintore, M., Khamashta, M.A., Hughes, G.R.V. 1992. Lack of association between anticardiolipin antibodies and migraine in systemic lupus erythematosus. Neurology 42, 681–682.

Moore, P.M. 1998. Immune-mediated vasculopathies of the central nervous system. In: J.M. Gilchrist (Ed.), Prognosis in Neurology. Butterworth-Heinemann, Melbourne, pp. 117–122.

Navarrete, G., Brey, R.L. 2000. Neuropsychiatric systemic lupus erythematosus. Curr. Treat. Options Neurol. 2 (5), 473–485. A review of current treatment options for NPSLE syndromes.

Newcomer, J.W., Craft, S., Hershey, T., Askins, K., Bardgett, M.E. 1994. Glucocorticoid-induced impairment in declarative memory performance in adult humans. J. Neurosci. 14, 2047–2053.

Olsen, J.E. 1968. Chorea minor associated with systemic lupus erythematosus. Report of a case. Acta Med. Scand. 183, 127–129.

Omdal, R., Selseth, B., Klow, N.E., Husby, G., Mellgren, S.I. 1989. Clinical neurological, electrophysiological and cerebral CT scans findings in systemic lupus erythematosus. Scand. J. Rheumatol. 18, 283–289.

Omdal, R., Henriksen, O.A., Mellgren, S.I., Husby, G. 1991. Peripheral neuropathy in systemic lupus erythematosus. Neurology 41, 808–811.

Omdal, R., Mellgren, S.I., Husby, G., Salvesen, R., Henriksen, O.A., Torbergsen, T. 1993. A controlled study of peripheral neuropathy in systemic lupus erythematosus. Acta Neurol. Scand. 88, 41–46.

Omdal, R., Løseth, S., Torbergsen, T., Koldingsnes, W., Husby, G., Mellgren, S.I. 2001a. Peripheral neuropathy in systemic lupus erythematosus—a longitudinal study. Acta Neurol. Scand. 103, 386–391.

Omdal, R., Waterloo, K., Koldingsnes, W., Husby, G., Mellgren, S.I. 2001b. Somatic and psychological features of headache in systemic lupus erythematosus. J. Rheumatol. 28, 772–779.

Omdal, R., Mellgren, S.I., Gøransson, L., Skjesol, A., Lindal, S., Koldingsnes, W., Husby, G. 2002. Small nerve fiber involvement in systemic lupus erythematosus. A controlled study. Arthritis Rheum. 46 (5), 1228–1232.

Oppenheimer, S., Hoffbrand, B.I. 1986. Optic neuritis and myelopathy in systemic lupus erythematosus. Can. J. Neurol. Sci. 13 (2), 129–132.

Petersen, P., Lund, J. 1969. Systemic lupus erythematosus following thymectomy for myasthenia gravis. Danish Med. Bull. 16 (6), 179–181.

Propper, D.J., Bucknall, R.C. 1989. Acute transverse myelopathy complicating systemic lupus erythematosus. Ann. Rheum. Dis. 48 (6), 512–515.

Provenzale, J., Bouldin, T.W. 1992. Lupus-related myelopathy: report of three cases and review of the literature. J. Neurol. Neurosurg. Psychiatry 55 (9), 830–835.

Provenzale, J.M., Barboriak, D.P., Gaensler, E.H.L., Robertson, R.L., Mercer, B. 1994. Lupus-related myelitis: serial MR findings. Am. J. Neuroradiol. 15 (10), 1911–1917.

Raine, C.S., Cannella, B., Duijvestijn, A.M., Cross, A.H. 1990. Homing to the central nervous system vasculature by antigen-specific lymphocytes. II lymphocyte/endothelial cell adhesion during the initial stages of autoimmune demyelination. Lab. Invest. 63, 476–489.

Rechthand, E., Cornblath, D.R., Stern, B.J., Meyerhoff, J.O. 1984. Chronic demyelinating polyneuropathy in systemic lupus erythematosus. Neurology 34, 1375–1377.

Rivest, C., Lew, R., Welsing, P., et al. 2000. Association between clinical factors, socio-economic status, and organ damage in recent onset systemic lupus erythematosus. J. Rheumatol. 27, 680–684.

Rolak, L.A. 1996. The diagnosis of multilple sclerosis. Neurol. Clin. 14, 27–43.

Rosenbaum, J.T., Simpson, J., Neuwelt, C.M. 1997. Successful treatment of optic neuropathy in association with systemic lupus erythematosus using intravenous cyclophosphamide. Br. J. Ophthalmol. 81 (2), 130–132.

Rosenstein, E.D., Sobelman, J., Kramer, N. 1989. Isolated, pupil-sparing third nerve palsy as initial manifestation of systemic lupus erythematosus. J. Clin. Neuro-Ophthalmol. 9 (4), 285–288.

Rossler, K., Neuchrist, C., Kitz, O., Kraft, D., Lassmann, H. 1992. Expression of leukocyte adhesion molecules at the human blood–brain-barrier. J. Neurosci. Res. 31, 365–374.

Roubey, R.A. 1996. Immunology of the antiphospholipid antibody syndrome. Arthritis Rheum. 39 (9), 1444–1454.

Rozell, C.L., Sibbitt, W.L. Jr., Brooks, W.M. 1998. Structural and neurochemical markers of brain injury in the migraine diathesis of systemic lupus erythematosus. Cephalalgia 18, 209–215.

Sabbadini, M.G., Manfredi, A.A., Bozzolo, E., et al. 1999a. Central nervous system involvement in systemic lupus erythematosus patients without overt neuropsychiatric manifestations. Lupus 8, 11–19.

Sabbadini, M.G., Manfredi, A.A., Bozzolo, E., et al. 1999b. Central nervous system involvement in SLE patients without overt neuropsychiatric manifestations. Lupus 8, 11–19.

Saluja, S., Singh, R.R., Misra, A., Gairola, A.K., Prasad, K., Ahuja, G.K., Malaviya, A.N. 1989. Bilateral recurrent laryngeal nerve palsy in systemic lupus erythematosus. Clin. Exp. Rheumatol. 7 (1), 81–83.

Sands, M.L., Ryczak, M., Brown, R.B. 1988. Recurrent aseptic meningitis followed by transverse myelitis as a presentation of systemic lupus erythematosus. J. Rheumatol. 15 (5), 862–864.

Savage, C.O.S., Cooke, S.P. 1993. The role of the endotheliumin system vasculitis. J. Autoimmun. 6, 237–249.

Schantz, V., Oestergaard, L.L., Junker, P. 1998. Shrinking spinal cord following transverse myelopathy in a patient with systemic

lupus erythematosus and the phospholipid antibody syndrome. J. Rheumatol. 25 (7), 1425–1428.

Scheinberg, L. 1956. Polyneuritis in systemic lupus erythematosus. Review of the literature and report of a case. N. Engl. J. Med. 255 (9), 416–421.

Scheuer, M.L., Pedley, T.A. 1990. The evaluation and treatment of seizures. N. Engl. J. Med. 323, 1468–1472.

Scott, T.F., Hess, D., Brillman, J. 1994. Antiphospholipid antibody syndrome mimicking multiple sclerosis and systemic lupus erythematosus clinically and by magnetic resonance imaging. Arch. Int. Med. 154, 917–920.

Sedwick, L.A., Burde, R.M. 1983. Isolated sixth nerve palsy as initial manifestation of systemic lupus erythematosus. A case report. J. Clin. Neuro-Ophthalmol. 3 (2), 109–110.

Sfikakis, P.P., Charalambopoulos, D., Vayoipoulos, G., Oglesby, R., Sfikakis, P., Tsokos, G.C. 1994. Increased levels of intercellular adhesion molecule-1 in the serum of patients with SLE. Clin. Exp. Rheumatol. 12, 5–9.

Sfikakis, P.P., Mitsikostas, D.D., Manoussakis, M.N., Foukaneli, D., Moutsopoulos, H.M. 1998. Headache in systemic lupus erythematosus: a controlled study. Br. J. Rheumatol. 37, 300–303.

Shak, A.K. 1996. Reversible MRI lesions (letter). Neurology 46, 1188–1189.

Sharief, M.K., Noori, M.A., Ciardi, M., Cirelli, A., Thompson, E.J. 1993. Increased levels of circulating ICAM-1 in serum and cerebrospinal fluid of patients with active multiple sclerosis. Correlation with TNF-alpha and blood–brain barrier damage. J. Neuroimmunol. 43, 15–21.

Shikano, M., Sobajima, H., Yoshikawa, H., Toba, T., Kushimoto, H., Katsumata, H., et al. 2000. Usefulness of a highly sensitive urinary and serum IL-6 assay in patients with diabetic nephropathy. Nephron 85 (1), 81–85.

Sibbitt, W.L., Sibbitt, R.R., Brooks, W.M. 1999a. Neuroimaging in neuropsychiatric systemic lupus erythematosus. Arthritis Rheum. 42, 2026–2038.

Sibbitt, W.L., Sibbitt, R.R., Brooks, W.M. 1999b. Neuroimaging in neuropsychiatric systemic lupus erythematosus. Arthritis Rheum. 42, 2026–2038.

Sivri, A., Hasçelik, Z., Çeliker, R., Basgöze, O. 1995. Early detection of neurological involvement in systemic lupus erythematosus. Electromyogr. Clin. Neurophysiol. 35, 195–199.

Sloan, J.B., Berk, M.A., Gebel, H.M., Fretzin, D.F. 1987. Multiple sclerosis and systemic lupus erythematosus: occurrence in two generations of the same family. Arch. Intern. Med. 147, 1317–1320.

Smith, C.A., Pinals, R.S. 1982. Optic neuritis in systemic lupus erythematosus. J. Rheumatol. 9 (6), 963–966.

Spronk, P.E., Bootsma, H., Huitema, M.G., et al. 1994. Levels of soluble VCAM-1, ICAM-1 and E-Selectin during disease exacerbations in patients with SLE. Clin. Exp. Immunol. 97, 439–444.

Strand, V. 2000. New therapies for systemic lupus erythematosus. Rheum. Dis. Clin. North Am. 26 (2), 1–16.

Straub, R.H., Zeuner, M., Lock, G., Rath, H., Hein, R., Scholmerich, J., Lang, B. 1996. Autonomic and sensorimotor neuropathy in patients with systemic lupus erythematosus and systemic sclerosis. J. Rheumatol. 23 (1), 87–92.

Straub, R.H., Konecna, L., Hrach, S., Rothe, G., Kreutz, M., Scholmerich, J., et al. 1998. Serum dehydroepiandrosterone (DHEA) and DHEA sulfate are negatively correlated with serum interleukin-6 (IL-6), and DHEA inhibits IL-6 secretion from mononuclear cells in man in vitro: possible link between endocrinosenescence and immunosenescence. J. Clin. Endocrinol. Metab. 83 (6), 2012–2017.

Swaak, A.J., van den Brink, H.G., Smeenk, R.J., et al. 2001. Systemic lupus erythematosus. Disease outcome in patients with disease duration of at least 10 years: second evaluation. Lupus 10 (1), 51–58.

Traynor, A.E., Schroeder, J., Rosa, R., et al. 2000. Treatment of severe systemic lupus erythematosus with high-dose chemotherapy and hematopoietic stem-cell transplantation: a phase I study. Lancet 356, 701–707.

Trevisani, V.F., Castro, A.A., Neves-Neto, J.F., Atallah, A.N. 2000. Cyclophosphamide versus methylprednisolone for the treatment of neuropsychiatric involvement in systemic lupus erythematosus. Cochrane Database Syst. Rev. (3), CD002265.

Tsokos, G.C., Tsokos, M., leRiche, N.G.H., Klippel, J.H. 1986. A clinical and pathologic study of cerebrovascular disease in patients with systemic lupus erythematosus. Semin. Arthritis Rheum. 16 (1), 70–78.

Tzioufas, A.G., Tzortzakis, N.G., Panou-Pomonis, E., et al. 2000. The clinical relevance of antibodies to ribosomal-P common epitope in two targeted systemic lupus erythematosus populations: a large cohort of consecutive patients and patients with active central nervous system disease. Ann. Rheum. Dis. 59, 99–104.

Vaile, J.H., Davis, P. 1998. Isolated unilateral vagus nerve palsy in systemic lupus erythematosus (letter). J. Rheumatol. 25 (11), 2287–2288.

Vaiopoulos, G., Sfikakis, P.P., Kapsimali, V., Boki, K., Panayiotidis, P., Aessopos, A., Tsokos, G.C., Kaklamanis, P. 1994. The association of systemic lupus erythematosus and myasthenia gravis. Postgrad. Med. J. 70, 741–745.

van Aken, B.E., Jansen, J., van Deventer, S.J., Reitsma, P.H. 2000. Elevated levels of homocysteine increase IL-6 production in monocytic Mono Mac 6 cells. Blood Coagul. Fibrinolysis 11 (2), 159–164.

van Vollenhoven, R.F. 2000. Dehydroepiandrosterone in systemic lupus erythematosus. Rheum. Dis. Clin. North Am. 26 (2), 135–145.

van Vollenhoven, R.F., Elliot, D., Powell, M., et al. 2001. Dehydroepiandrosterone improves cognitive function in patients with systemic lupus erythematosus: results of a double-blinded, placebo controlled pilot study. Lupus 10 (S1), s51.

Vázquez-Cruz, J., Traboulssi, H., Rodriquez-De la Serna, A., Geli, C., Roig, C., Díaz, C. 1990. A prospective study of chronic or recurrent headache in systemic lupus erythematosus. Headache 30, 232–235.

Venegoni, E., Biasioli, R., Lamperti, E., Rinaldi, E., Salmaggi, A., Novi, C. 1994. Tremor as an early manifestation of systemic lupus erythematosus. Clin. Exp. Rheumatol. 12, 199–201.

Vidailhet, M., Piette, J.C., Wechsler, B., Bousser, M.G., Brunet, P. 1990. Cerebral venous thrombosis in systemic lupus erythematosus. Stroke 21, 1226–1231.

Viedt, C., Hansch, G.M., Brandes, R.P., Kubler, W., Kreuzer, J. 2000. The terminal complement complex C5b-9 stimulates interleukin-6 production in human smooth muscle cells through activation of transcription factors NF-{kappa} B and AP-1. FASEB J. 14 (15), 2370–2372.

Vyse, T., Luxon, L.M., Walport, M.J. 1994. Audiovestibular manifestations of the antiphospholipid syndrome. J. Laryngol. Otol. 108 (1), 57–59.

Ward, M.M., Pyun, E., Studenski, S. 1996. Mortality risks associated with specific clinical manifestations of systemic lupus erythematosus. Arch. Intern. Med. 156 (12), 1337–1344.

Warren, R.W., Kredich, D.W. 1984. Transverse myelitis and acute central nervous system manifestations of systemic lupus erythematosus. Arthritis Rheum. 27, 1058–1060.

Waterloo, K., Omdal, R., Husby, G., et al. 2001. Neuropsychological function in SLE: a five year longitudinal study. Lupus 10 (S1), 35.

Wellicome, S.M., Kapahi, P., Mason, J.C., Lebranchu, Y., Yarwood, H., Haskard, D.O. 1993. Detection of a circulating form of vascular cell adhesion molecule-1: raised levels in rheumatoid arthritis and systemic lupus erythematosus. Clin. Exp. Immunol. 92, 412–418.

West, S.G. 1994. Neuropsychiatric lupus. Rheum. Dis. Clin. North Am. 20 (1), 129–158.

West, S.G., Emlen, W., Wener, M.H., Kotzin, B.L. 1995. Neuropsychiatric lupus erythematosus: a 10-year prospective study on the value of diagnostic tests. Am. J. Med. 99, 153–163.

Wolf, S.M., Barrows, H.S. 1966. Myasthenia gravis and systemic lupus erythematosus. Arch. Neurol. 14, 254–258.

Wolf, R.E., McBeath, J.G. 1985. Chorea gravidarum in systemic lupus erythematosus. J. Rheumatol. 12 (5), 992–993.

Wolkowitz, O.M. 1994. Prospective controlled studies of the behavioral and biological effects of exogenous corticosteroids. Psychoneuroendocrinology 19, 233–255.

Wolkowitz, O.M., Weingartner, H., Rubinow, D.R., et al. 1993. Steroid modulation of human memory: biochemical correlates. Biol. Psychiatry 33, 744–746.

Wong, D., Dorovini-Zis, K. 1992. Upregulation of intercellular adhesion moleculte-1 (ICAM-1) expression in primary cultures of human brain microvascular endothelial cells by cytokines and lipopolysaccharide. J. Neuroimmunol. 39, 11–22.

Wong, C.K., Ho, C.Y., Li, E.K., Lam, C.W.K. 2000. Elevation of proinflammatory cytokine (IL-18, IL-17, IL-12) and Th2 cytokine (IL-4) concentrations in patients with systemic lupus erythematosus. Lupus 9, 589–593.

Wysenbeek, A.J., Leibovici, L., Zoldan, J. 1990. Acute central nervous system complications after pulse steroid therapy in patients with systemic lupus erythematosus. J. Rheumatol. 17, 1695–1696.

Yaffe, K., Ferriero, D., Barkovich, A.J., Rowley, H. 1995. Reversible MRI abnormalities following seizures. Neurology 45, 104–108.

Yalaoui, S., Gorgi, Y., Hajri, R., Goucha, R., Chaabouni, L., Kooli, C., Ayed, K. 2002. Autoantibodies to ribosomal P proteins in systemic lupus erythematosus. Joint Bone Spine 69 (2), 173–176.

Young, D.G., Skibinski, G., Mason, J.I., James, K. 1999. The influence of age and gender on serum dehydroepiandrosterone sulphate (DHEA-S), IL-6, IL-6 soluble receptor (IL-6 sR) and transforming growth factor beta 1 (TGF-beta1) levels in normal healthy blood donors. Clin. Exp. Immunol. 117 (3), 476–481.

Yudkin, J.S., Kumari, M., Humphries, S.E., Mohamed-Ali, V. 2000. Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? Atherosclerosis 148 (2), 209–214.

Zabry, Z., Waldschmidt, M.M., Hendrickson, D., Keiner, J., Love-Homan, L., Takei, F., et al. 1992. Adhesion molecules on muring brain microvascular endothelial cells: expression and regulation of ICAM-1 and Lgp 55. J. Neuroimmunol. 36, 1–11.

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CHAPTER 2

Systemic Lupus Erythematosus: Cognitive Evaluation and Dysfunction

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1. Introduction

Nervous system or 'neuropsychiatric' (NP) involvement in systemic lupus erythematosus (SLE) occurs in a high proportion of patients. Estimates of the prevalence of NP involvement vary widely, ranging from 14 to 75%, reflecting variable diagnostic methodologies and criteria (McCune and Golbus, 1988; Bluestein, 1992; Denburg et al., 1993a; West, 1996; Hermosillo-Romo and Brey, 2002). While NP involvement is typically diagnosed on the basis of clinical neurologic or psychiatric events and syndromes (e.g. seizures, neuropathies, hemiparesis, organic brain syndrome, psychosis, depression), SLE patients also frequently experience a wide variety of 'soft' neurologic and psychiatric problems, including paraethesias, headaches, anxiety, mood swings and reported difficulties in concentration, memory and word finding (Denburg et al., 2003). The absence of an acceptable gold standard has made it difficult to establish diagnostic criteria for NPSLE. Several attempts at classifying NP symptomatology have been made (Kassan and Lockshin, 1979; Yancey et al., 1981; Carbotte et al., 1986; Denburg et al., 1987a; Singer et al., 1990) culminating in an American College of Rheumatology (ACR)-sponsored workshop organized for the purpose of developing a standardized nomenclature system for the NP syndromes of NPSLE (ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature, 1999), for which revisions have subsequently been suggested (Jennekens and Kater, 2002a). Through these consensus processes, cognitive dysfunction, which is typically assessed using neuropsychological test procedures, has been given further definition and clinical importance, both as an independent NPSLE syndrome and in association with other NPSLE syndromes. The documented sensitivity of neuropsychological procedures to subclinical nervous system disturbance in a variety of clinical populations (Tarter et al., 1988) suggests that neuropsychological studies of SLE patients have the potential to contribute substantially, not only to the redefinition of central nervous system (CNS) diagnostic criteria, but also to the evaluation of more subtle symptoms and complaints of SLE patients.

The systematic study of cognitive function in patients diagnosed with SLE began in the 1980s (Bresnihan and O'Connell, 1982; Sonies et al., 1982; Carbotte et al., 1986) and continues to the present time, with at least 30 studies published to date (see below). Most investigators have reported that lupus is attended by significant impairment in a number of cognitive domains, even in the absence of overt NP manifestations, and there is now a fair degree of

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consensus that cognitive status can provide an index of nervous system functioning in SLE. This chapter provides an introduction to neuropsychological assessment methods. It then reviews findings regarding the prevalence, type, and course of cognitive deficits in SLE, cites the evidence for the role of confounding factors on the manifestation of cognitive dysfunction in SLE and relates cognitive dysfunction to potential pathogenetic mechanisms. Finally the clinical implications for documenting cognitive deficits are reviewed.

2. Prevalence of cognitive deficits

2.1. Overview of neuropsychological assessment approaches

Clinical neuropsychology is an approach to studying the functional integrity of the CNS (Lezak, 1995). Neuropsychological assessment includes the administration of a variety of tests found to be sensitive to brain abnormalities and for which there are normative data from healthy individuals. Diverse approaches are taken to neuropsychological assessment, some stemming from empirical and others from more theoretical bases. In the former, tests are used because they have been shown to be sensitive to the presence of brain lesions, while the functions tapped may not be well characterized; in the latter, tests are selected because they measure well-articulated cognitive processes and documented brain-behavior relationships. Approaches range from the administration of a fixed battery of tests with very specific criteria for identifying impaired nervous system function, to a more eclectic and flexible approach which may also incorporate procedures from experimental neuropsychological literature and the analysis of a patient's test-taking strategies ('qualitative' assessment) (Spreen and Strauss, 1998; Vanderploeg, 2000; Hebben and Milberg, 2002). Commonly, a wide range of functions is assessed, including attention, memory, language, concept formation, visuospatial abilities, executive functions, and motor skills. Tests are administered and scored in a standardized manner, and results are analyzed with reference to expected levels of performance, typically expressed as normative data, and which may also include an estimate of an individual's pre-morbid level of functioning. Test selection should reflect consideration of the reliability and validity of the test instruments and their appropriateness for the questions being posed. Batteries must be sufficiently broad-based to ensure coverage of important areas of function, but sufficiently focused to thoroughly assess areas of particular interest (e.g. memory) that have emerged as relevant to the individual patient and the particular patient population.

While a broad-based battery of neuropsychological tests is preferred in order to ascertain the type and extent of cognitive impairment in an individual or in a patient group, the time required for administration of these batteries can be extensive. As a result, there has been increasing demand for abbreviated neuropsychological test batteries, which have now been developed for diverse populations, including multiple sclerosis (MS) (Benedict et al., 2002), schizophrenia (Gur et al., 2001a), and SLE. The latter, termed the 'ACR Neurocognitive Battery', emanates from the above-noted consensus conference and is a collaboratively developed 1 h test battery composed of measures found to be most sensitive to deficits in SLE patients (ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature, 1999). In addition to abbreviated test batteries, alternate forms of neuropsychological assessment are also being developed. For example, computerized neuropsychological assessment has evolved to address a number of issues including the precision of administration, the ease with which different indices of performance can be obtained (e.g. accuracy, reaction time, variability), and their adaptability for repeated administration over short time intervals with only limited practice effects. Although they hold significant promise, particularly for following patients' cognitive status over time, there is some evidence that as computer-related anxiety increases in patients, performance on computer-administered measures tends to decrease (Browndyke et al., 2002; Weber et al., 2002). Computerized testing can consist of computerized administration of standard neuropsychological tests, or new batteries developed for computer administration (e.g. Gur et al., 2001b). In both cases, comparability of results with standardized neuropsychological test batteries must be determined (Feldstein et al., 1999). One newly developed battery,

the Automated Neuropsychology Assessment Metrics (ANAM), developed by the US military to assess the effects of chemical agents, extreme environments and fatigue on cognitive processing speed and efficiency (Bleiberg et al., 2000), has been found to correlate well with traditional neuropsychological measures (Wilken et al., 2003). The ANAM, together with the ACR Neurocognitive Battery, is currently included in a prospective longitudinal study of cognitive function in SLE (Petri et al., 2002).

2.2. Purpose of neuropsychological assessment

Neuropsychological assessment provides a detailed description of an individual's cognitive strengths and weaknesses and can be undertaken for a variety of reasons (see Fig. 1). Goals of neuropsychological assessment can include diagnosis of brain involvement, prediction of the effects of impairment on daily functioning, prescription of compensatory or rehabilitative strategies, and tracking the course of disease-related brain dysfunction over time or in response to intervention. The inclusion of measures of emotional status in a comprehensive assessment allows for the identification of possible changes in emotions which frequently occur, either primarily or secondarily, in association with brain damage, and which have implications for rehabilitation and recovery. It should be noted that the relationship between deficits elicited during formal neuropsychological assessment and 'real life' abilities is imperfect (Heinrichs, 1990; Goodman and Zarit, 1995; Burgess et al., 1998; Silver, 2000; Goldberg and Podell, 2000; Ready et al., 2001). There can also be limited concordance between subjective report and objective assessment of cognitive function (Zelinski et al., 1990) and further, perception and report of poor cognitive function can be influenced by depressed mood or anxiety (Cull et al., 1996; Gass and Apple, 1997). Nevertheless, it is clinically important to include measures that objectively tap areas of function cited by patients as problematic, both to confirm or disconfirm such complaints but also because the 'face validity' of these measures facilitates communication with patients and clinical management.

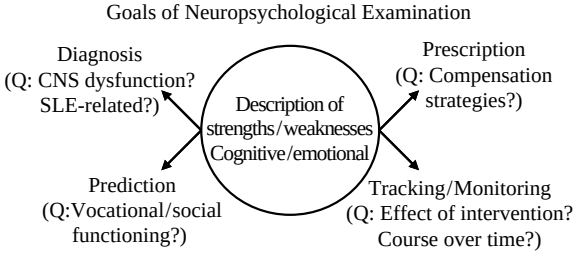

Figure 1. Goals of neuropsychological assessment. Neuropsychological assessment provides a detailed description of an individual's strengths and weaknesses. This description facilitates diagnosis, predicts daily functioning, allows the physician to prescribe compensatory or rehabilitative strategies to counteract deficits, and tracks cognitive function over time. Such an evaluation not only monitors the course of disease but can also assess the effects of treatment. (From J. Musculoskelet. Med. 16, 356, 1999, with permission.)

2.3. Prevalence of cognitive impairment in SLE

Since the first published results of cognitive dysfunction in SLE reported by our laboratory (Carbotte et al., 1986), a large number of studies have been undertaken to assess the prevalence of cognitive impairment in SLE (Carbotte et al., 1986; Koffler, 1987; Kutner et al., 1988; Papero et al., 1990; Wekking et al., 1991; Hay et al., 1992; Hanly et al., 1992; Kozora et al., 1996; Sailer et al., 1997; Denburg et al., 1997a; Breitbach et al., 1998; Sabbadini et al., 1999; Gladman et al., 2000; Carlomagno et al., 2000; Leritz et al., 2000; Monastero et al., 2001; Brey et al., 2002). Estimates have ranged from 17 to 79% (see Fig. 2), with the wide variability accounted for on the basis of several methodologic factors. First, studies have included fairly diverse patient samples, with differing proportions of patients who manifest current, previous or no NP involvement. Second, different sets of neuropsychological tests measuring different cognitive skills have been used, including, most recently, the use of a computerized test battery (Brey et al., 2002). Third, studies have differed in their use of premorbid level of function and/or appropriate normative data. Fourth, studies have differed in their inclusion of an appropriate control group. Finally, and most importantly, different criteria for defining impairment

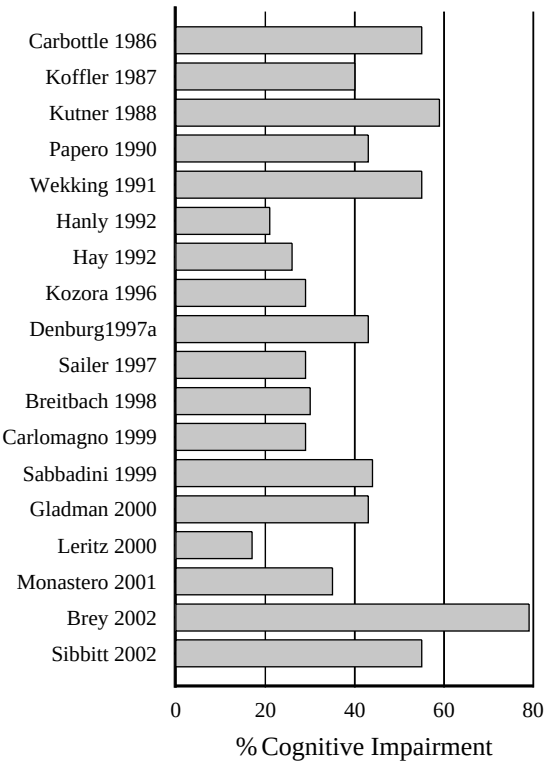

Figure 2. Summary of prevalence estimates for cognitive impairment in SLE. Overall impairment rates for studies of cognitive function in SLE are presented. Sample size ranged from *N* of 20 to *N* of 169. Studies vary in proportion of NP and non-NP patients within study sample, test battery used, and criteria applied to define impairment.

have been adopted, often with limited attention paid to the sensitivity and specificity of the chosen criterion. Nevertheless, despite widely divergent estimates, there are substantial converging data to suggest that even in the absence of current or previous NP symptoms, a significant proportion of SLE patients can reliably be shown to have cognitive problems.

3. Course of cognitive function in SLE

A significant early finding in studies of cognitive function in SLE was the high prevalence of cognitive impairment in NPSLE patients whose NP symptomatology had been quiescent for months or years and yet whose documented impairment was as severe as that of patients with active NP symptoms (Carbotte et al., 1986). While clinical experience suggests that cognitive functioning does appear to improve over time in many individuals who have had an NP event, this finding from objective neuropsychological assessment suggested *residual* cognitive compromise in these patients. This, together with the other striking finding that a high proportion of patients with *no* history of clinically significant NP symptomatology were demonstrating significant cognitive dysfunction, highlighted the importance of following cognitive function over time in SLE.

Data on the natural history of cognitive deficits in SLE remain limited. Studies, following patients over periods of 2–5 year periods, have reported both fluctuation (Hay et al., 1994; Hanly et al., 1997) and relative stability (Carlomagno et al., 2000; Waterloo et al., 2002) in cognitive impairment over time, with type and extent of change related to NP status (Denburg et al., 1997a). It is important to consider that NPSLE and its associated cognitive problems may represent a range of reversible and non-reversible brain-related abnormalities, as has been observed in MS (Bernard et al., 1995). The well-documented fluctuations in other systemic manifestations, serological measures, and overall disease activity scores in SLE suggest that cognitive function need not demonstrate an inexorable deterioration in order to serve as an index of current CNS status, and possibly, as a risk factor for further CNS complications (Denburg et al., 1997a).

4. Etiology/Pathogenesis of cognitive deficits in SLE

A number of different potential pathogenetic mechanisms have been proposed in relation to NPSLE more generally, and to cognitive deficits in particular. The type of cognitive deficit demonstrated by SLE patients has been noted to be wide-ranging and variable (see Section 5 below). In order to prove causality of any given pathogenetic mechanism, procedures which would allow us to define more homogeneous groups of SLE patients (e.g. those with deficits in particular cognitive areas) would be essential.

4.1. Common lymphocyte/brain antigens

The biological underpinnings of a relationship between autoimmunity, as manifested clinically in SLE, and nervous system disease rest historically on observations of antigens common to the lymphoid and nervous systems (Reif and Allen, 1964; Wernet and Kunkel, 1973; Bluestein and Zvaifler, 1976; Bresnihan et al., 1977). The notion has been advanced that lymphocyte antigens, shared with brain tissue, become targets of the autoimmune response in SLE, thus leading to a 'cross-reaction' of the immune response with elements of the nervous system. Such autoantibody-mediated neuronal dysfunction or cytotoxicity could lead to subclinical or clinical NP disease, including cognitive dysfunction (Bluestein, 1978; Temesvari et al., 1983; Denburg et al., 1988; Long et al., 1990). Whether or not antibodies directed against common lymphocyte/brain antigens can account for more than a limited number of clinical NPSLE manifestations/syndromes remains controversial (Bell et al., 1991; Denburg et al., 1993b; West et al., 1995). Since lymphocytotoxic antibodies (LCA) are common in SLE (Bluestein, 1978; Winfield, 1985), it has been suggested that some cases of NPSLE, including neurocognitive disorder, may be due to T-cell/brain cross-reactive autoimmune responses, resulting in neuronal or glial cell loss, demyelination and/or inflammation in the brain. For example, certain surface proteins on $CD4^+$ lymphocytes have been shown to be targeted by a large majority of lupus sera with autolymphocytotoxic activity (Long et al., 1990). These reactivities correlate positively with the presence of NPSLE and/or cognitive impairment, suggesting (but not proving) a causal role in certain individuals with SLE (Denburg et al., 1994a). The possibility that these antigens are specifically expressed in certain areas of the CNS has been raised on the basis of the patterns of serology and cognitive dysfunction observed (Denburg et al., 1988, 1994a) (see below). However, because of advancing knowledge on the existence of multiple autoantigen–autoantibody reactions, and even of several, alternative (non-antibody) mechanisms, the pre-eminence of cross-reactive lymphocyte–brain autoantibodies in the pathogenesis of NPSLE, and its attendant cognitive and behavioral problems, has receded recently.

4.2. Phospholipid and other non-protein antigens

An interesting class of non-protein antigens, which may be present on formed elements of the blood (including lymphocytes), as well as in the brain, include phospholipids. Antiphospholipid antibodies (aPL) represent the targeting by the immune response of a very important antigenic family in SLE, presumably leading to vasculopathy, thrombosis and/or infarction with focal NP deficits (extensively reviewed as 'Antiphospholipid Syndrome') (Asherson et al., 1989; Wang et al., 1990). Some of these antibodies may be directed at endothelial antigens and thus putatively eventuate in vasculopathy (Belmont et al., 1996), leading to cognitive dysfunction (see below).

4.3. Specific antigens on neuroglia

Many SLE patients have significant elevations of autoantibodies which bind to neuroblastoma cells (How et al., 1985; Hanly et al., 1988); the nature of the surface antigens against which IgG antibodies are directed in sera and in cerebrospinal fluid of SLE patients has been explored, but without final identification of these moieties (How et al., 1985; Kelly and Denburg, 1987; Denburg et al., 1987a; Hanly et al., 1988; Denburg, 1990; Hanson et al., 1992). One report of a specific mouse brain autoantigen identified through cloning, and distributed in the hippocampus, hypothalamus, and cingulate gyrus (Moore et al., 1998) has not been further confirmed.

4.4. Brain cross-reactive antigens in other diseases

More cogency for the argument of antigenic localization and autoantibody-mediated disease comes from elegant studies done by Posner and Furneaux (1990) on the pathogenesis of paraneoplastic syndromes. Autoantibodies present in serum and CSF of patients with subacute cerebellar degeneration associated with gynecological carcinomas (Posner and Furneaux, 1990) show specificity for both the primary tumor and for Purkinje cells in the cerebellum; another antibody is found in patients with oat cell carcinoma and a syndrome of limbic encephalitis (Posner and

Furneaux, 1990), and is also described in a patient with SLE (Schnider et al., 1995). The concept that a distinct NP syndrome and cognitive dysfunction can eventuate from specific autoantibody responses, localizable to some but not all areas of the brain, is attractive.

4.5. Other mechanisms: apoptosis

Disordered apoptosis occurs in the MRL-lpr mouse, an animal model of SLE, in which a mutated Fas receptor leads to lymphoproliferation and manifestations of autoimmunity. Great interest has recently developed in apoptosis as a mechanism in human SLE in studies by Rosen et al. (Casciola-Rosen et al., 1994, 1995) in which it has been demonstrated that autoantibodies in SLE can target nuclear antigens on the cell surface, leading to apoptosis. Thus, anti-DNA and anti-ribosomal antibodies in SLE are potentially pathogenic and could be implicated in depression and psychosis (P antigens) (Bonfa and Elkon, 1986; Bonfa et al., 1987; Schneebaum et al., 1991), although negative findings have been reported (Gerli et al., 2002). However, there is still no direct evidence *causally* relating disordered apoptosis in the development of NPSLE or of cognitive dysfunction in SLE patients. This area is worthy of further investigation.

4.6. Behavioral abnormalities in lupus-prone mice

In spontaneous SLE syndromes in mice, including the NZB/W, MRL/lpr, and BXSB strains, there is not only a high prevalence of behavioral abnormalities but also of antibodies directed against brain extracts, homogenates or tissue (Forster et al., 1988), along with an upregulation of pro-inflammatory cytokines such as interleukin (IL)-1 and IL-6 (Sakic et al., 1997b). The presence of brain-reactive antibodies, brain leukocyte infiltrates, and/or upregulated cytokines can be shown to be related to learning deficits in aging and/or autoimmunity (Forster et al., 1988; Hoffman et al., 1988; Farrell et al., 1997; Sakic et al., 1997b). Avoidance learning, for example, has been shown to be defective in murine lupus, and this is associated with the presence of brain-reactive antibodies (Forster et al., 1988; Schwegler et al., 1988). Anxiety-like behavior in NZB/W mice has likewise been related to upregulated cytokines, possibly interferons (Dunn and Crnic, 1993), and not simply a result of neuronal ectopies (Schrott et al., 1992, 1993). Some of the latter behavioral abnormalities can, in fact, be ameliorated by chronic, soluble interferon-γ receptor treatment (Schrott and Crnic, 1998). To what extent brain autoantibodies and cytokines interact to cause (or ameliorate) learning and behavioral abnormalities in lupus-prone mice is the subject of active investigation (Sakic et al., 1997b, 1998; Maric et al., 2001; Ballok et al., 2003).

Studies using the MRL/lpr murine model have demonstrated the co-emergence of autoantibodies against nuclear antigens and specific behavioral disturbances including perseveration, motor incoordination, disruption of nocturnal/diurnal rhythms, and hesitancy or 'emotionality' (Sakic et al., 1992, 1994a,b, 1996a,b, 1997b). These abnormalities, collectively termed Autoimmunity-Associated Behavioral Syndrome (AABS), appear before the onset of overt manifestations of lupus such as lymphadenopathy, arthritis, renal disease, or anemia (Sakic et al., 1992, 1994a,b). The animals have high systemic levels of brain-reactive antibodies and pro-inflammatory cytokines; however, the higher antibody titers in the MRL/lpr compared to the congenic MRL/$^{++}$ strain are not sufficient to account for the wide range of behavioral and learning abnormalities. Recent findings suggest that the development of depressive-like symptomatology and other illness behaviors in MRL-lpr mice can be reproduced in MRL^{++} and control mice by transgenic upregulation of IL-6 expression (Sakic et al., 1996a, 1997a). Furthermore, reductions in neuronal cell mass and dendritic arborization of neurites and changes in neurotransmitter profiles are observed in MRL-lpr mice; these changes are associated with infiltrations of T- and B-cells in the brain and with both T-cell and, to a larger extent, neuronal apoptosis (Farrell et al., 1997; Szechtman et al., 1997; Sakic et al., 1998, 2000, 2002; Maric et al., 2001; Ballok et al., 2003) in these animals. Treatment with the immunosuppressive drug, cyclophosphamide, or with an IL-6 receptor antagonist can reverse the dendritic changes and improve some of the abnormal behavior in the MRL-lpr mouse model

(Sakic et al., 1995; Farrell et al., 1997). Thus, multiple mechanisms may be involved in the development of AABS.

4.7. Relationship of cognitive measures to potential pathogenetic mechanisms

A large number of studies have examined the relationship between potential pathogenetic factors and nervous system involvement in SLE. Most of these studies have defined nervous system involvement on the basis of clinically diagnosed NP syndromes (reviewed in Denburg et al., 1995; West, 1996). In contrast, a relatively small number of studies have used cognitive status as a marker of nervous system involvement. These studies have revealed significant associations between an overall designation of cognitive impairment and the presence of neuronal antibodies (NA) (Denburg et al., 1987a) as well as between NA and sequential changes in cognitive function (Hanly et al., 1989). Associations have also been reported between cognitive function and both LCA (Long et al., 1990) and aPL, even in patients with no NP involvement (Denburg et al., 1997c). Negative findings have also been reported (Papero et al., 1990; Hanly et al., 1993). In addition to examining a global designation of impairment, associations between antibodies and specific cognitive areas have also been reported, including the association between LCA positivity and visuospatial deficits (Denburg et al., 1988, 1994a) and aPL positivity and difficulties with verbal memory, productivity, and speeded output (Denburg et al., 1997c; Whitelaw et al., 1999; Menon et al., 1999; Hanly et al., 1999; Leritz et al., 2002). Further, the role of other immunologic factors has also begun to be investigated. For example, the pro-inflammatory cytokine, IL-6, has recently been shown to contribute uniquely to measures of learning beyond the effects of depression, prednisone therapy and hormonal measures (Kozora et al., 2001). To date, the most robust findings have involved aPL. The fact that aPL has been associated with cognitive deficits in both cross-sectional and longitudinal studies (Denburg et al., 1997c; Hanly et al., 1999) highlights its potential relevance in the pathogenesis of cognitive dysfunction in at least a subset of SLE patients.

5. Clinical manifestations—type of cognitive deficits in SLE

In addition to an overall diagnosis of cognitive impairment, many reports of cognitive function in SLE have described the types of cognitive deficits manifested by SLE patients. These studies have utilized very different approaches to deficit specification, ranging from decline from estimated pre-morbid functioning and/or significant departure from normative data, to significant group differences between SLE patients and controls. Irrespective of the approach, the data suggest that cognitive deficits manifested in SLE are fairly wide-ranging (e.g. Denburg et al., 1987b). This is in keeping with the heterogeneity of clinical NP presentation in SLE and the likelihood of multiple pathogenetic mechanisms underlying NPSLE (Bluestein, 1992; Denburg et al., 1993a; West, 1996). Early unpublished studies of cognitive function in selected groups of SLE patients who were referred for suspected nervous system involvement (Bresnihan and O'Connell, 1982; Sonies et al., 1982) suggested group deficits in motor speed, new learning and concentration. Published studies of more representative patient samples have reported problems in attention and concentration, various aspects of verbal and non-verbal memory including working memory, verbal fluency/productivity, visual spatial skills, psychomotor speed, and cognitive flexibility (Denburg et al., 1987b, 1997a; Papero et al., 1990; Rummelt et al., 1991; Wekking et al., 1991; Hay et al., 1992; Ginsburg et al., 1992; Hanly et al., 1992; Ferstl et al., 1992; Fisk et al., 1993; Kerr et al., 1994; Beers et al., 1996; Kozora et al., 1996; Holliday et al., 1997; Sailer et al., 1997; Glanz et al., 1997; Waterloo et al., 1997; Skeel and Johnstone, 2000; Monastero et al., 2001; Ainiala et al., 2001; Brey et al., 2002; Loukkola et al., 2003). In order to facilitate a summary of the results of these diverse studies, cognitive functions have been grouped according to a factor analytic model proposed in a study of occupational exposure (Ryan et al., 1987) that utilized a test battery very similar to that applied to SLE patients (Denburg et al., 1997c). Results from studies that presented data about the type of cognitive deficits in their patient samples were grouped under these five cognitive headings according to similarity

Table 1
Type of cognitive deficits in SLE: an overview

	General intelligence	Area of cognitive function			
		Verbal learning and memory	Visuospatial skills (including memory)	Psychomotor speed and manual dexterity	Attention and mental flexibility
Denburg et al. (1987b)	✓	✓	✓	✓	✓
Ginsburg et al. (1992)	–	–	✓	–	✓
Hanly et al. (1992)	–	✓	✓	✓	✓
Hay et al. (1992)	–	–	✓	–	✓
Kozora et al. (1996)	✓	✓	–	–	✓
Denburg et al. (1997a)	✓	✓	✓	✓	–
Glanz et al. (1997)	–	✓	✓	✓	–
Holliday et al. (1997)	✓	–	–	✓	✓
Sailer et al. (1997)	–	✓	✓	✓	✓
Waterloo et al. (1997)	✓	✓	✓	✓	✓
Skeel and Johnstone (2000)	–	–	–	–	✓
Ainiala et al. (2001)	–	✓	✓	✓	✓
Monastero et al. (2001)	n/a	✓	✓	–	–
Brey et al. (2002)	n/a	✓	✓	✓	✓
Loukkola et al. (2003)	–	✓	–	✓	✓
Percentage of studies finding deficit in cognitive areas	38% (5/13)	73% (11/15)	73% (11/15)	67% (10/15)	80% (12/15)

Groupings for type taken from Ryan et al., 1987. Criteria for impaired cognitive function differed across studies. –: cognitive area not impaired; ✓: cognitive area impaired; n/a: cognitive area not assessed.

of tests used to those in the original Ryan battery. The majority of studies reviewed included tests representing these cognitive areas (Table 1). Except for measures of general intelligence, which were impaired in 38% of the studies where this was assessed, deficits in all other cognitive areas were documented in 67–80% of the studies represented. While not depicted in the table, NP status did not determine the type of deficit, which was manifested significantly more frequently in SLE patients than in healthy controls. Interestingly, even when they did not meet criteria for a global designation of impairment, one study reported a pattern of cognitive function consistent with patients with subcortical brain damage (Leritz et al., 2000), not inconsistent with many of the deficits noted above. In summary, attempts to consolidate the literature on type of deficit manifested in SLE have yielded a pattern of wide-ranging deficits irrespective of NP involvement. A specific pattern of cognitive dysfunction in SLE has not clearly emerged. The possibility that such a pattern exists in subsets of SLE patients defined on the basis of very specific clinical presentations (e.g. stroke, depression), or in association with potential pathogenetic factors (e.g. aPL) is currently being pursued. Table 2 presents the data from studies reporting a consistent association between aPL and particular areas of cognitive function, including psychomotor speed and attention, with somewhat less consistency in the areas of memory and visuospatial skills.

6. Diagnostic investigations—brain imaging and neuropsychological assessment in SLE

The general neuropsychological literature is replete with studies relating the results of neuropsychological assessment and brain imaging techniques. Correlations between neuropsychological assessment and findings from brain imaging technology, both structural [e.g. computed tomography (CT), magnetic

Table 2
Relationship between antiphospholipid antibody positivity and areas of cognitive deficit

	General intelligence	Verbal learning and memory	Visuospatial skills (including memory)	Psychomotor speed and manual dexterity	Attention and mental flexibility
Denburg et al. (1997c)	–	✓	–	✓	✓
Hanly et al. (1999)[a]	–	–	–	✓	✓
Menon et al. (1999)[a]	–	–	–	✓	✓
Whitelaw et al. (1999)	✓	✓	✓	n/a	✓
Leritz et al. (2002)[a]	n/a	✓	✓	✓	✓

Groupings for areas taken from Ryan et al., 1987. Criteria for impaired cognitive function differed across studies. –: cognitive area not impaired; ✓: cognitive area impaired; n/a: cognitive area not assessed.
[a] Longitudinal study: data reported for time 1 and/or time 2.

resonance imaging (MRI)] and functional [e.g. positron emission tomography (PET), quantified electroencephalogram (QEEG), single photon emission computed tomography (SPECT), functional MRI (fMRI)], have been repeatedly demonstrated (e.g. De Leon et al., 1986; Albert et al., 1986; Levin et al., 1992; Kesler et al., 2000). In SLE, both structural and functional brain imaging techniques have yielded positive findings in the presence of clinically active NP syndromes (Hiraiwa et al., 1983; McCune et al., 1988; Volkow et al., 1988; Sibbitt et al., 1989, 1995; Stoppe et al., 1990; Bell et al., 1991; Nossent et al., 1991; Ritchlin et al., 1992; Kovacs et al., 1995; Otte et al., 1998). Some imaging techniques have also been sensitive to subclinical brain involvement (Pinching et al., 1978; Awada et al., 1987; Kushner et al., 1987; Nossent et al., 1991; Ritchlin et al., 1992). A small number of studies have utilized neuroimaging approaches together with neuropsychological assessment and have yielded variable results. Case reports of three SLE patients with well-defined neurologic syndromes found good concordance between PET and neuropsychological assessment at two points in time, highlighting the usefulness of neuropsychological data to delineate the behavioral problems associated with the lesions uncovered by functional scanning (Carbotte et al., 1992). Subcortical dysfunction suggested by the use of a brief cognitive screening tool (Leritz et al., 2000) is consistent with previous imaging studies in SLE (Emmi et al., 1993; Chinn et al., 1997).

Correlations between results of proton magnetic resonance spectroscopic imaging and neurocognitive testing have also been reported (Sibbitt et al., 1999). In contrast, routine investigative methods such as CT and conventional EEG have not generally yielded findings that correlate with neuropsychological results in NP and non-NPSLE patients (Waterloo et al., 1999). Similarly, MRI abnormalities were not associated with neurocognitive findings in patients with non-NPSLE (Kozora et al., 1998). Irrespective of the results of studies correlating brain imaging and neuropsychological assessment, it is important to note that the extent of cognitive/cognitive dysfunction that may accompany a brain lesion cannot be directly assessed with the use of imaging techniques. Even minimal findings on neuroimaging do not preclude the existence of significant cognitive problems that can be objectively assessed using neuropsychological methodology.

7. Differential diagnosis

When medically ill patients are assessed neuropsychologically, the contribution of a number of confounding factors must be considered before impaired test performance can be attributed to the disease process itself. Interpretation of neuropsychological test performance in SLE must take into account the effects of medication, emotional distress, and medical illness and/or constitutional symptoms at the time of testing. Most studies of cognitive function

in SLE have addressed some or all of these potentially confounding factors.

7.1. Corticosteroid use

There is good reason to suspect that corticosteroid therapy could contribute to cognitive impairment in SLE patients. For example, corticosteroids have been associated with psychosis (Ling et al., 1981; Perry et al., 1984) and discontinuation of steroid therapy has resulted in improvement of cognitive function in some medically ill patients (Varney et al., 1984). In addition, acute administration of corticosteroids in animals and humans has resulted in cognitive deficits (Lupien and McEwen, 1997), and corticosteroids have been shown to target hippocampal neurons (Sapolsky et al., 1984; Woolley et al., 1990; Wolkowitz et al., 1997). In SLE, the vast majority of studies have found no significant association between cognitive impairment and either corticosteroid use per se (Carbotte et al., 1986; Papero et al., 1990; Hay et al., 1992; Ginsburg et al., 1992; Hanly et al., 1997; Waterloo et al., 1997, 1999; Sabbadini et al., 1999; Gladman et al., 2000; Carlomagno et al., 2000; Monastero et al., 2001; Kozora et al., 2001) or steroid dose (Carbotte et al., 1986; Hanly et al., 1992; Kozora et al., 1996; Holliday et al., 1997; Sabbadini et al., 1999; Waterloo et al., 1999; Carlomagno et al., 2000). Exceptions to this negative finding do exist (Hanly et al., 1992, 1994; Waterloo et al., 1997; Zonana-Nacach et al., 2000; Brey et al., 2002); however, the bulk of the evidence is negative and consistent with similar conclusions reached in the context of neuropsychological research in other diseases (e.g. Grafman et al., 1990).

Based on retrospective data suggesting improved cognitive performance in association with steroid use (Denburg et al., 1987c), a series of *N*-of-1 drug/placebo trials using relatively low dose steroids (0.5 mg/kg) was undertaken in patients who had cognitive complaints in the absence of active NPSLE. Significant gains in cognitive function, mood and disease-related symptomatology were documented in five of eight patients completing a 6-month trial; two patients manifested no change and one patient with a fixed neurologic lesion showed significant decline (Denburg et al., 1994b). These data, together with the finding that immunosuppression with cyclophosphamide in an animal model of NPSLE attenuates leukocyte infiltration in the brain and reduces levels of autoantibodies, while improving cognitive abnormalities (Sakic et al., 1995; Farrell et al., 1997), suggest that variable response to steroid medication in SLE patients may reflect a variable neural substrate, with positive drug effects occurring in the context of an underlying inflammatory process.

7.2. Physical status

Almost all studies of cognitive function in SLE have examined the contribution of chronic disease and/or constitutional symptoms to the demonstration of cognitive deficits. The majority of studies have reported no association between cognitive dysfunction and disease activity, irrespective of the disease activity index applied (Hay et al., 1992; Ginsburg et al., 1992; Hanly et al., 1992; Beers et al., 1996; Kozora et al., 1996; Holliday et al., 1997; Sailer et al., 1997; Waterloo et al., 1997, 1999, 2002; Carlomagno et al., 2000; Monastero et al., 2001). This negative finding pertains as well to specific areas of cognitive impairment and activity of specific organ systems (Carbotte et al., 1995). Exceptions to this general consensus have been reported (Sibbitt et al., 2002), and it remains possible that more sensitive indices of disease activity, such as subjective measure of pain or fatigue (Krupp et al., 1989), may correlate with cognitive dysfunction in SLE. However, the lack of association documented to date suggests that non-specific inflammatory mechanisms are not sufficient causes of cognitive impairment in SLE.

7.3. Emotional status

The presence of clinically significant emotional distress is frequently accompanied by neuropsychological deficits (Caine, 1986; Grant and Adams, 1986; Cassens et al., 1990; Lezak, 1995; Burt et al., 1995). Given that such distress, with or without clinically diagnosed psychiatric syndromes, occurs commonly in chronic rheumatologic diseases (Katz and Yelin, 1993; DeVellis, 1993; Denburg et al., 1997b) and has been documented in many SLE patients (Kremer et al., 1981; Liang et al., 1984; Carbotte et al., 1986;

Wekking et al., 1991; Shortall et al., 1995; Kozora et al., 1996), emotional distress warrants study in relation to cognitive deficit in SLE. With few exceptions (Da Costa et al., 1999; Monastero et al., 2001; Brey et al., 2002), the majority of studies of cognition in SLE that have included measures of emotional status have found no significant association between cognitive dysfunction and psychological distress (e.g. Denburg et al., 1987b; Beers et al., 1995; Holliday et al., 1997; Hanly et al., 1997; Sailer et al., 1997; Gladman et al., 2000; Carlomagno et al., 2000; Kozora et al., 2001).This is consistent with findings in other medical disorders that have major neurologic involvement, such as AIDS (Grant et al., 1993) and MS (Minden et al., 1990; Rao et al., 1991a). Comparison of SLE patients to patients with rheumatoid arthritis (Kozora et al., 1996) and whiplash (Waterloo et al., 1997) has reinforced the finding that emotional distress is not sufficient to account for cognitive dysfunction.

In summary, the evidence to date suggests that objectively documented cognitive deficits in SLE cannot be accounted for on the basis of confounding factors such as the adverse side effects of medication, emotional distress or the non-specific effects of medical illness and/or constitutional symptoms at the time of testing.

8. Treatment

CNS manifestations in SLE that cannot be explained on the basis of toxic, metabolic, infectious or other causes are typically treated with corticosteroids. There are no controlled trials of corticosteroid therapy in NPSLE. The likelihood of multiple pathogenetic mechanisms (Bluestein, 1992; Denburg et al., 1993a; West, 1996) suggests that patients may vary in response to corticosteroid treatment, as has been demonstrated in a prospective, single-patient (*N*-of-1) trial of relatively low dose corticosteroids on cognitive and mood status in SLE (Denburg et al., 1994b). Information suggestive of a particular pathogenetic mechanism is desirable in order to rationalize an approach to therapy (Jennekens and Kater, 2002b). For example, a pattern of clinical and/or cognitive findings suggesting vasculopathy and/or focal abnormalities, in the presence of aPL, could suggest anticoagulation and/or anti-platelet drugs. Alternately, psychiatric and/or cognitive disturbances, coupled with cognitive abnormalities in the presence of NA or LCA or elevated cytokine levels, might suggest treatment with corticosteroids and/or immunosuppressives. In the absence of definitive data regarding an autoimmune/inflammatory mechanism, particular clinical NP manifestations might warrant the use of anticonvulsants, neuroleptics or antidepressants. Studies that have reported beneficial effects of pulse doses of cyclophosphamides or intrathecal immunosuppressives (Barile and Lavalle, 1992; Valesini et al., 1994; Neuwelt et al., 1995) have not assessed their effects on cognitive function; this can best be addressed through the inclusion of cognitive endpoints in prospective multi-center clinical trials of corticosteroids, immunosuppressives and/or anticoagulants in patients with SLE.

In addition to consideration in respect to medical intervention, cognitive deficits can present a significant challenge to the clinical management of chronic illness. Subjective complaints of cognitive problems may or may not be confirmed by objective testing (Zelinski et al., 1990; Gass and Apple, 1997; Denburg et al., 1997b, 2003) and should be considered in assessing the impact of chronic illness on the patient's functional competence. Even subtly diminished attention and memory skills can compromise the patient's compliance with treatment strategies, and when coupled with general reduction in mental efficiency, can have a significant impact on occupational functioning (Rao et al., 1991b; Heaton et al., 1994). Future studies of cognitive function in SLE should include well-validated measures of daily function. In the meantime, consideration should be given to modifying expectations in the home and work environments for SLE patients with documented cognitive problems, and where these are extensive, cognitive rehabilitation techniques (Sohlberg and Mateer, 1989) may be appropriate. In general, most patients and family members respond positively to having specific deficits defined and discussed, and their impact on daily life explored (Lezak, 1988). Therapeutic implications of identifying chronic or transient CNS dysfunction are as important for SLE patients as for any other patient group with CNS compromise (Levin et al., 1989; Rao, 1990).

Key points

- Neuropsychological assessment provides a detailed description of an individual's cognitive strengths and weaknesses. It is clinically important to include measures that objectively tap areas of function cited by patients as problematic.
- Imaging techniques cannot directly assess the extent of cognition/cognitive dysfunction—even minimal findings on neuroimaging do not preclude the existence of significant cognitive problems that can be objectively assessed using neuropsychological methodology.
- Neuropsychological studies of SLE patients can contribute substantially to the redefinition of CNS diagnostic criteria, and to the evaluation of more subtle symptoms and complaints.
- Even in the absence of current or previous NP symptoms, a significant proportion of SLE patients can reliably be shown to have cognitive problems.
- Objectively documented cognitive deficits in SLE cannot be accounted for on the basis of confounding factors such as the adverse side effects of medication, emotional distress or the non-specific effects of medical illness and/or constitutional symptoms.
- Attempts to consolidate the literature on type of deficit manifested in SLE have yielded a pattern of wide-ranging deficits irrespective of NP involvement—a specific pattern of cognitive dysfunction in SLE has not emerged.
- The course of cognitive function is variable, with deterioration most reliably associated with NP events and/or antiphospholipid antibody positivity.
- Cognitive function has implications for clinical management of SLE patients.
- Animal models are relevant to understanding cognitive deficits and their pathogenesis in SLE.

References

ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature, 1999. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum. 42, 599.
This report describes a collaborative effort to develop a standardized nomenclature system for NP-SLE and includes the proposal for a short neuropsychological test battery for the diagnosis of cognitive deficits.

Ainiala, H., Loukkola, J., Peltola, J., Korpela, M., Hietaharju, A. 2001. The prevalence of neuropsychiatric syndromes in systemic lupus erythematosus. Neurology 57, 496.

Albert, M.S., Naeser, M.A., Duffy, F.H., McAnulty, G. 1986. CT and EEG validators for Alzheimer's Disease. In: L.W. Poon (Ed.), Handbook for Clinical Memory Assessment of Older Adults. American Psychological Association, Washington, p. 383.

Asherson, R.A., Khamashta, M.A., Gil, A., Vazquez, J.-J., Chan, O., Baguley, E., Hughes, G.R.V. 1989. Cerebrovascular disease and antiphospholipid antibodies in systemic lupus erythematosus, lupus-like disease, and the primary antiphospholipid syndrome. Am. J. Med. 86, 391.

Awada, H.H., Mamo, H.L., Luft, A.G., Ponsin, J.C., Kahn, M.F. 1987. Cerebral blood flow in systemic lupus with and without central nervous system involvement. J. Neurol. Neurosurg. Psychiatry 50, 1597.

Ballok, D., Millward, J.M., Sakic, B. 2003. Neurodegeneration in autoimmune MRL-lpr mice as revealed by Fluoro Jade B staining. Brain Res. 964, 200.

Barile, L., Lavalle, C. 1992. Transverse myelitis in systemic lupus erythematosus—the effect of IV pulse methylprednisolone and cyclophosphamide. J. Rheumatol. 19, 370.

Beers, S.R., Morrow, L.A., Morgan, M.C., Manzi, S. 1995. Cognitive function in systemic lupus erythematosus (SLE): relationship to mood state [abstract]. J. Int. Neuropsychol. Soc. 1, 137.

Beers, S.R., Morrow, L., Ryan, C.M., Wasko, M.C., Rarie, J., Manzi, S. 1996. The use of information processing measures to detect cognitive deficits in systemic lupus erythematosus. J. Int. Neuropsychol. Soc. 2, 15.

Bell, C.L., Partington, C., Robbins, M., Graziano, F., Turski, P., Kornguth, S. 1991. Magnetic resonance imaging of central nervous system lesions in patients with lupus erythematosus: correlation with clinical remission and antineurofilament and anticardiolipin antibody titers. Arthritis Rheum. 34, 432.

Belmont, H.M., Abramson, S.B., Lie, J.T. 1996. Pathology and pathogenesis of vascular injury in systemic lupus erythematosus. Interactions of inflammatory cells and activated endothelium. Arthritis Rheum. 39, 9.

Benedict, R.H.B., Fischer, J.S., Archibald, C.J., Arnett, P.A., Beatty, W.W., Bobholz, J., Chelune, G.J., Fisk, J.D., Langdon, D.W., Caruso, L., Foley, F., LaRocca, N.G., Vowels, L., Weinstein, A., DeLuca, J., Rao, S.M., Munschauer, F. 2002. Minimal neuropsychological assessment of MS patients: a consensus approach. Clin. Neuropsychol. 16, 381.

Bernard, I., Le Gall, D., Truelle, J.L., Joseph, P.A., Emile, J. 1995. Cognitive disturbances in multiple sclerosis: a ten year follow-up study [abstract]. J. Int. Neuropsychol. Soc. 1, 201.

Bleiberg, J., Kane, R.L., Reeves, D.L., Garmoe, W.S., Halpern, E. 2000. Factor analysis of computerized and traditional

tests used in mild brain injury research. Clin. Neuropsychol. 14, 287.

Bluestein, H.G. 1978. Autoantibodies to lymphocyte membrane antigens: pathogenetic implications. Clin. Rheum. Dis. 4, 643.

Bluestein, H.G. 1992. The central nervous system in systemic lupus erythematosus. In: R.G. Lahita (Ed.), Systemic Lupus Erythematosus. Churchill Livingstone, New York, p. 639.

Bluestein, H.G., Zvaifler, N.J. 1976. Brain-reactive lymphocytotoxic antibodies in the serum of patients with systemic lupus erythematosus. J. Clin. Invest. 57, 509.
This seminal article was the first to introduce the concept, and provide evidence for the antibody-mediated hypothesis in the pathogenesis of NP-SLE. Further, it includes data on cross-reactivity between brain tissue and lymphocytes, lending plausibility to a connection between an autoimmune response targeting lymphocytes and 'spillover' effects on the brain.

Bonfa, E., Elkon, K.B. 1986. Clinical and serologic associations of the antiribosomal P protein antibody. Arthritis Rheum. 29, 981.

Bonfa, E., Golombek, S.J., Kaufman, L.D., Skelly, S., Weissbach, H., Brot, N., Elkon, K.B. 1987. Association between lupus psychosis and anti-ribosomal P protein antibodies. N. Engl. J. Med. 317, 265.

Breitbach, S.A., Alexander, R.W., Daltroy, L.H., Liang, M.H., Boll, T.J., Karlson, E.W., Partiridge, A.J., Roberts, W.N., Stern, S.H., Wacholtz, M.C., Straaton, K.V. 1998. Determinants of cognitive performance in systemic lupus erythematosus. J. Clin. Exp. Neuropsychol. 20, 157.

Bresnihan, B., O'Connell, A. 1982. Systemic lupus erythematosus, cerebral disease and intellectual function [abstract]. Arthritis Rheum. 25, 580.

Bresnihan, B., Oliver, M., Grigor, R., Hughes, G.R.V. 1977. Brain reactivity of lymphocytotoxic antibodies in systemic lupus erythematosus with and without cerebral involvement. Clin. Exp. Immunol. 30, 333.

Brey, R.L., Holliday, S.L., Saklad, A.R., Navarrete, M.G., Hermosillo-Romo, D., Stallworth, C.L., Valdez, C.R., Escalante, A., Del, R. I, Gronseth, G., Rhine, C.B., Padilla, P., McGlasson, D. 2002. Neuropsychiatric syndromes in lupus: prevalence using standardized definitions. Neurology 58, 1214.

Browndyke, J.N., Albert, A.L., Malone, W., Schatz, P., Paul, R.H., Cohen, R.A., Tucker, K.A., Gouvier, W.D. 2002. Computer-related anxiety: examining the impact of technology-specific affect on the performance of a computerized neuropsychological assessment measure. Appl. Neuropsychol. 9, 210.

Burgess, P.W., Alderman, N., Evans, J., Emslie, H., Wilson, B.A. 1998. The ecological validity of tests of executive function. J. Int. Neuropsychol. Soc. 4, 547.

Burt, D.B., Zembar, M.J., Niederehe, G. 1995. Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. Psychol. Bull. 117, 285.

Caine, E.D. 1986. The neuropsychology of depression: the pseudodementia syndrome. In: I. Grant, K.M. Adams (Eds.), Neuropsychological Assessment of Neuropsychiatric Disorders. Oxford University Press, New York, p. 221.

Carbotte, R.M., Denburg, S.D., Denburg, J.A. 1986. Prevalence of cognitive impairment in systemic lupus erythematosus. J. Nerv. Ment. Dis. 174, 357.
This was the first comprehensive study of cognitive function in unselected SLE patients. It used a broad-based neuropsychological test battery with well-articulated criteria for impairment, and examined the impact of confounding factors on prevalence estimates.

Carbotte, R.M., Denburg, S.D., Denburg, J.A., Nahmias, C., Garnett, E.S. 1992. Fluctuating cognitive abnormalities and cerebral glucose metabolism in neuropsychiatric systemic lupus erythematosus. J. Neurol. Neurosurg. Psychiatry 55, 1054.

Carbotte, R.M., Denburg, S.D., Denburg, J.A. 1995. Cognitive dysfunction in systemic lupus erythematosus is independent of active disease. J. Rheumatol. 22, 863.

Carlomagno, S., Migliaresi, S., Ambrosone, L., Sannino, M., Sanges, G., Di Iorio, G. 2000. Cognitive impairment in systemic lupus erythematosus: a follow-up study. J. Neurol. 247, 273.

Casciola-Rosen, L.A., Anhalt, G., Rosen, A. 1994. Autoantigens targeted in systemic lupus erythematosus are clustered in two populations of surface structures on apoptotic keratinocytes. J. Exp. Med. 179, 1317.

Casciola-Rosen, L.A., Anhalt, G.J., Rosen, A. 1995. DNA-dependent protein kinase is one of a subset of autoantigens specifically cleaved early during apoptosis. J. Exp. Med. 182, 1625.

Cassens, G., Wolfe, L., Zola, M. bcd>/bcd>. The neuropsychology of depressions. J. Neuropsychiatry Clin. Neurosci. 2, 202.

Chinn, R.J.S., Wilkinson, I.D., Hall-Craggs, M.A., Paley, M.N.J., Shortall, E., Carter, S., Kendall, B.E., Isenberg, D.A., Newman, S.P., Harrison, M.J.G. 1997. Magnetic resonance imaging of the brain and cerebral proton spectroscopy in patients with systemic lupus erythematosus. Arthritis Rheum. 40, 36.

Cull, A., Hay, C., Love, S.B., Mackie, M., Smets, E., Stewart, M. 1996. What do cancer patients mean when they complain of concentration and memory problems? Br. J. Cancer 74, 1674.

Da Costa, D., Dobkin, P.L., Pinard, L., Fortin, P.R., Danoff, D.S., Esdaile, J.M., Clarke, A.E. 1999. The role of stress in functional disability among women with systemic lupus erythematosus: a prospective study. Arthritis Care Res. 12, 112.

De Leon, M.J., George, A.E., Ferris, S.H. 1986. Computed tomography and positron emission tomography correlates of cognitive decline in aging and senile dementia. In: L.W. Poon (Ed.), Handbook for Clinical Memory Assessment of Older Adults. American Psychological Association, Washington, p. 367.

Denburg, J.A. 1990. Clinical and subclinical involvement of the central nervous system in systemic lupus erythematosus. In: B.H. Waksman (Ed.), Immunologic Mechanisms in Neurologic and Psychiatric Disease. Raven Press, New York, p. 171.

Denburg, J.A., Carbotte, R.M., Denburg, S.D. 1987a. Neuronal antibodies and cognitive function in systemic lupus erythematosus. Neurology 37, 464.

Denburg, S.D., Carbotte, R.M., Denburg, J.A. 1987b. Cognitive impairment in systemic lupus erythematosus: a neuropsychological study of individual and group deficits. J. Clin. Exp. Neuropsychol. 9, 323.

Denburg, S.D., Carbotte, R.M., Denburg, J.A. 1987c. The effects of corticosteroids on neurocognitive functioning: a trend toward improvement [abstract]. Can. J. Psychol. 28, 132.

Denburg, S.D., Carbotte, R.M., Long, A.A., Denburg, J.A. 1988. Neuropsychological correlates of serum lymphocytotoxic antibodies in systemic lupus erythematosus. Brain Behav. Immun. 2, 222.

Denburg, J.A., Carbotte, R., Denburg, S. 1993a. Central nervous system lupus. Rheumatol. Rev. 2, 123.

Denburg, S.D., Denburg, J.A., Carbotte, R.M., Fisk, J.D., Hanly, J.G. 1993b. Cognitive deficits in systemic lupus erythematosus. Rheum. Dis. Clin. North Am. 19, 815.

Denburg, S.D., Behmann, S.A., Carbotte, R.M., Denburg, J.A. 1994a. Lymphocyte antigens in neuropsychiatric systemic lupus erythematosus: relationship of lymphocyte antibody specificities to clinical disease. Arthritis Rheum. 37, 369.

Denburg, S.D., Carbotte, R.M., Denburg, J.A. 1994b. Corticosteroids and neuropsychological functioning in patients with systemic lupus erythematosus. Arthritis Rheum. 37, 1311.
In this paper we report a series of *N* of 1 clinical trials examining the efficacy of corticosteroid medication in relation to cognition and mood in mild SLE. In the absence of predictors of steroid responsiveness and in the context of continued subjective complaints, this methodology allowed for objective documentation of steroid efficacy in select patients and demonstrated the utility of cognitive status as an end point in intervention studies.

Denburg, J.A., Denburg, S.D., Carbotte, R.M., Sakic, B., Szechtman, H. 1995. Nervous system lupus: pathogenesis and rationale for therapy. Scand. J. Rheumatol. 24, 263.

Denburg, S.D., Carbotte, R.M., Denburg, J.A. 1997a. Cognition and mood in SLE: evaluation and pathogenesis. Ann. N. Y. Acad. Sci. 823, 44.

Denburg, S.D., Carbotte, R.M., Denburg, J.A. 1997b. Psychological aspects of SLE: cognitive function, mood and self-report. J. Rheumatol. 24, 998.

Denburg, S.D., Carbotte, R.M., Ginsberg, J.S., Denburg, J.A. 1997c. The relationship of antiphospholipid antibodies to cognitive function in patients with systemic lupus erythematosus. J. Int. Neuropsychol. Soc. 3, 377.
This study of 118 SLE patients was the first to report a significant association between antiphospholipid positivity and cognitive impairment, even in patients with no evidence of neuropsychiatric involvement. A pattern of cognitive impairment, compatible with subcortical brain involvement, emerged.

Denburg, S.D., Stewart, K.E., Hart, L.E., Denburg, J.A. 2003. How 'soft' are soft neurological signs? The relationship of subjective neuropsychiatric complaints to cognitive function in systemic lupus erythematosus. J. Rheumatol. 30, 1006.

DeVellis, B.M. 1993. Depression in rheumatological diseases. Baillieres Clin. Rheumatol. 7, 241.

Dunn, A.L., Crnic, L.S. 1993. Repeated injections of interferon-α A/D in Balb/c mice: behavioral effects. Brain Behav. Immun. 7, 104.

Emmi, L., Bramati, M., De Cristofaro, M.T.R., Mascalchi, M., Dal Pozzo, G., Marconi, G.P., Massai, G., Passaleva, A. 1993. MRI and SPECT investigations of the CNS in SLE patients. Clin. Exp. Rheumatol. 11, 13.

Farrell, M., Sakic, B., Szechtman, H., Denburg, J.A. 1997. Effect of cyclophosphamide on leukocytic infiltration in the brain of MRL/lpr mice. Lupus 6, 268.

Feldstein, S.N., Keller, F.R., Portman, R.E., Durham, R.L., Klebe, K.J., Davis, H.P. 1999. A comparison of computerized and standard versions of the Wisconsin Card Sorting Test. Clin. Neuropsychol. 13, 303.

Ferstl, R., Niemann, T., Biehl, G., Hinrichsen, H., Kirch, W. 1992. Neuropsychological impairment in auto-immune disease. Eur. J. Clin. Invest. 22, 16.

Fisk, J.D., Eastwood, B., Sherwood, G., Hanly, J.G. 1993. Patterns of cognitive impairment in patients with systemic lupus erythematosus. Br. J. Rheumatol. 32, 458.

Forster, M.J., Retz, K.C., Lal, H. 1988. Learning and memory deficits associated with autoimmunity: significance in aging and Alzheimer's disease. Drug Dev. Res. 15, 253.

Gass, C.S., Apple, C. 1997. Cognitive complaints in closed-head injury: relationship to memory test performance and emotional disturbance. J. Clin. Exp. Neuropsychol. 19, 290.

Gerli, R., Caponi, L., Tincani, A., Scorza, R., Sabbadini, M.G., Danieli, M.G., De Angelis, V., Cesarotti, M., Piccirilli, M., Quartesan, R., Moretti, P., Cantoni, C., Franceschini, F., Cavazzana, I., Origgi, L., Vanoli, M., Bozzolo, E., Ferrario, L., Padovani, A., Gambini, O., Vanzulli, L., Croce, D., Bombardieri, S. 2002. Clinical and serological associations of ribosomal P autoantibodies in systemic lupus erythematosus: prospective evaluation in a large cohort of Italian patients. Rheumatology 41, 1357.

Ginsburg, K.S., Wright, E.A., Larson, M.G., Fossel, A.H., Albert, M., Schur, P.H., Liang, M.H. 1992. A controlled study of the prevalence of cognitive dysfunction in randomly selected patients with systemic lupus erythematosus. Arthritis Rheum. 35, 776.

Gladman, D.D., Urowitz, M.B., Slonim, D., Glanz, B., Carlen, P., Noldy, N., Gough, J., Pauzner, R., Heslegrave, R., Darby, P., MacKinnon, A. 2000. Evaluation of predictive factors for neurocognitive dysfunction in patients with inactive systemic lupus erythematosus. J. Rheumatol. 27, 2367.

Glanz, B.I., Slonim, D., Urowitz, M.B., Gladman, D.D., Gough, J., MacKinnon, A. 1997. Pattern of neuropsychologic dysfunction in inactive systemic lupus erythematosus. Neuropsychiatry Neuropsychol. Behav. Neurol. 10, 232.

Goldberg, E., Podell, K. 2000. Adaptive decision making, ecological validity, and the frontal lobes. J. Clin. Exp. Neuropsychol. 22, 56.

Goodman, C.R., Zarit, S.H. 1995. Ecological measures of cognitive functioning: a validation study. Int. Psychogeriatr. 7, 39.

Grafman, J., Rao, S.M., Litvan, I. 1990. Cognitive dysfunction in multiple sclerosis: disorders of memory. In: S.M. Rao (Ed.), Neurobehavioral Aspects of Multiple Sclerosis. Oxford University Press, New York, p. 102.

Grant, I., Adams, K.M. (Eds.), 1986. Neuropsychological Assessment of Neuropsychiatric Disorders. Oxford University Press, New York.

Grant, I., Olshen, R.A., Atkinson, J.H., Heaton, R.K., Nelson, J., McCutchan, J.A., Weinrich, J.D. 1993. Depressed mood does not explain neuropsychological deficits in HIV-infected persons. Neuropsychology 7, 53.

Gur, R.C., Ragland, J.D., Moberg, P.J., Bilker, W.B., Kohler, C., Siegel, S.J., Gur, R.E. 2001a. Computerized neurocognitive

scanning: II. The profile of schizophrenia. Neuropsychopharmacology 25, 777.

Gur, R.C., Ragland, J.D., Moberg, P.J., Turner, T.H., Bilker, W.B., Kohler, C., Siegel, S.J., Gur, R.E. 2001b. Computerized neurocognitive scanning: I. Methodology and validation in healthy people. Neuropsychopharmacology 25, 766.

Hanly, J.G., Rajaraman, S., Behmann, S., Denburg, J.A. 1988. A novel neuronal antigen identified by sera from patients with systemic lupus erythematosus. Arthritis Rheum. 31, 1492.

Hanly, J.G., Behmann, S., Denburg, S.D., Carbotte, R.M., Denburg, J.A. 1989. The association between sequential changes in serum antineuronal antibodies and neuropsychiatric systemic lupus erythematosus. Postgrad. Med. J. 65, 622.

Hanly, J.G., Fisk, J.D., Sherwood, G., Jones, E., Jones, J.V., Eastwood, B. 1992. Cognitive impairment in patients with systemic lupus erythematosus. J. Rheumatol. 19, 562.

Hanly, J.G., Walsh, N.M., Fisk, J.D., Eastwood, B., Hong, C., Sherwood, G., Jones, J.V., Jones, E., Elkon, K. 1993. Cognitive impairment and autoantibodies in systemic lupus erythematosus. Br. J. Rheumatol. 32, 291.

Hanly, J.G., Fisk, J.D., Sherwood, G., Eastwood, B. 1994. Clinical course of cognitive dysfunction in systemic lupus erythematosus. J. Rheumatol. 21, 1825.

Hanly, J.G., Cassell, K., Fisk, J.D. 1997. Cognitive function in systemic lupus erythematosus: results of a 5-year prospective study. Arthritis Rheum. 40, 1542.

Hanly, J.G., Hong, C., Smith, S., Fisk, J.D. 1999. A prospective analysis of cognitive function and anticardiolipin antibodies in systemic lupus erythematosus. Arthritis Rheum. 42, 728.

Hanson, V.G., Horowitz, M., Rosenbluth, D., Spiera, H., Puszkin, S. 1992. Systemic lupus erythematosus patients with central nervous system involvement show autoantibodies to a 50-kD neuronal membrane protein. J. Exp. Med. 176, 565.

Hay, E.M., Black, D., Huddy, A., Creed, F., Tomenson, B., Bernstein, R.M., Holt, P.J.L. 1992. Psychiatric disorder and cognitive impairment in systemic lupus erythematosus. Arthritis Rheum. 35, 411.

Hay, E.M., Huddy, A., Black, D., Mbaya, P., Tomenson, B., Bernstein, R.M., Holt, P.J.L., Creed, F. 1994. A prospective study of psychiatric disorder and cognitive function in systemic lupus erythematosus. Ann. Rheum. Dis. 53, 298.

The HNRC Group, Heaton, R.K., Velin, R.A., McCutchan, J.A., Gulevich, S.J., Atkinson, J.H., Wallace, M.R., Godfrey, H.P., Kirson, D.A., Grant, I. 1994. Neuropsychological impairment in human immunodeficiency virus-infection: implications for employment. Psychosom. Med. 56, 8.

Hebben, N., Milberg, W. 2002. Essentials of Neuropsychological Assessment. Wiley Press, New York.

Heinrichs, R.W. 1990. Current and emergent applications of neuropsychological assessment: problems of validity and utility. Prof. Psychol.: Res. Pract. 21, 171.

Hermosillo-Romo, D., Brey, R.L. 2002. Neuropsychiatric involvement in systemic lupus erythematosus. Curr. Rheumatol. Rep. 4, 337.

Hiraiwa, M., Nonaka, C., Abe, T., Iio, M. 1983. Positron emission tomography in systemic lupus erythematosus: relation of cerebral vasculitis to PET findings. Am. J. Neuroradiol. 4, 541.

Hoffman, S.A., Narendran, A., Shucard, D.W., Harbeck, R.J. 1988. Autoantibodies, immune complexes, and behavioral disorders: neuropsychiatric involvement in systemic lupus erythematosus. Drug Dev. Res. 15, 237.

Holliday, S., Brey, R., Escalante, G., Ledbetter, M. 1997. Neuropsychological functioning in SLE: computer-assisted testing in a predominantly Hispanic sample [abstract]. J. Int. Neuropsychol. Soc. 3, 17.

How, A., Dent, P.B., Liao, S.-K., Denburg, J.A. 1985. Antineuronal antibodies in neuropsychiatric systemic lupus erythematosus. Arthritis Rheum. 28, 789.

Jennekens, F.G.I., Kater, L. 2002a. The central nervous system in systemic lupus erythematosus. Part 1. Clinical syndromes: a literature investigation. Rheumatology 41, 605.

Jennekens, F.G.I., Kater, L. 2002b. The central nervous system in systemic lupus erythematosus. Part 2. Pathogenetic mechanisms of clinical syndromes: a literature investigation. Rheumatology 41, 619.

Kassan, S.S., Lockshin, M.D. 1979. Central nervous system lupus erythematosus: the need for classification. Arthritis Rheum. 22, 1382.

Katz, P.P., Yelin, E.H. 1993. Prevalence and correlates of depressive symptoms among persons with rheumatoid arthritis. J. Rheumatol. 20, 790.

Kelly, M.C., Denburg, J.A. 1987. Cerebrospinal fluid immunoglobulins and neuronal antibodies in neuropsychiatric systemic lupus erythematosus and related conditions. J. Rheumatol. 14, 740.

Kerr, E.N., Edworthy, S.M., Samuels, M.T., Violato, C. 1994. Attentional capacity in patients with systemic lupus erythematosus (SLE) [abstract]. Arthritis Rheum. 37, S178.

Kesler, S.R., Adams, H.F., Bigler, E.D. 2000. SPECT, MR and quantitative MR imaging: correlates with neuropsychological and psychological outcome in traumatic brain injury. Brain Inj. 14, 851.

Koffler, S. 1987. The role of neuropsychological testing in systemic lupus erythematosus. In: R.G. Lahita (Ed.), Systemic Lupus Erythematosus. Wiley, New York, p. 847.

Kovacs, J.A.J., Urowitz, M.B., Gladman, D.D., Zeman, R. 1995. The use of single photon emission computerized tomography in neuropsychiatric SLE: a pilot study. J. Rheumatol. 22, 1247.

Kozora, E., Thompson, L.L., West, S.G., Kotzin, B.L. 1996. Analysis of cognitive and psychological deficits in systemic lupus erythematosus patients without overt central nervous system disease. Arthritis Rheum. 39, 2035.

Kozora, E., West, S.G., Kotzin, B.L., Julian, L., Porter, S., Bigler, E. 1998. Magnetic resonance imaging abnormalities and cognitive deficits in systemic lupus erythematosus patients without overt central nervous system disease. Arthritis Rheum. 41, 41.

This study is the first attempt to relate cognitive deficits and abnormalities in cerebral magnetic resonance imaging. Although a significant relationship was not found between these two indices of brain integrity, the documented structural abnormalities in non-CNS SLE patients are noteworthy.

Kozora, E., Laudenslager, M., Lemieux, A., West, S.G. 2001. Inflammatory and hormonal measures predict neuropsychological functioning in systemic lupus erythematosus and rheumatoid arthritis patients. J. Int. Neuropsychol. Soc. 7, 745.

Kremer, J.M., Rynes, R.I., Bartholomew, L.E., Rodichok, L.D., Pelton, E.W., Block, E.A., Tassinari, R.B., Silver, R.J. 1981. Non-organic non-psychotic psychopathology (NONPP) in patients with systemic lupus erythematosus. Semin. Arthritis Rheum. 11, 182.

Krupp, L.B., LaRocca, N.C., Muir-Nash, J., Steinberg, A.D. 1989. The fatigue severity scale. Applications to patients with multiple sclerosis and systemic lupus erythematosus. Arch. Neurol. 46, 1121.

Kushner, M.J., Chawluk, M.D., Fazekas, F., Burke, A., Jagg, J., Rosen, M., Reivich, M. 1987. Cerebral blood flow in systemic lupus erythematosus with or without cerebral complications. Neurology 37, 1596.

Kutner, K.C., Busch, H.M., Mahmood, T., Racis, S.P., Krey, P.R. 1988. Neuropsychological functioning in systemic lupus erythematosus. Neuropsychology 2, 119.

Leritz, E., Brandt, J., Minor, M., Reis-Jensen, F., Petri, M. 2000. 'Subcortical' cognitive impairment in patients with systemic lupus erythematosus. J. Int. Neuropsychol. Soc. 6, 821.

Leritz, E., Brandt, J., Minor, M., Reis-Jensen, F., Petri, M. 2002. Neuropsychological functioning and its relationship to antiphospholipid antibodies in patients with systemic lupus erythematosus. J. Clin. Exp. Neuropsychol. 24, 527.

Levin, H.S., Eisenberg, H.M., Benton, A.L. (Eds.), 1989. Mild Head Injury. Oxford University Press, New York.

Levin, H.S., Williams, D.H., Eisenberg, H.M., High, W.M., Guinto, F.C. 1992. Serial MRI and neurobehavioural findings after mild to moderate closed head injury. J. Neurol. Neurosurg. Psychiatry 55, 255.

Lezak, M.D. 1988. Brain damage is a family affair. J. Clin. Exp. Neuropsychol. 10, 111.

Lezak, M.D. 1995. Neuropsychological Assessment. Oxford University Press, New York.

Liang, M.H., Rogers, M., Larson, M., Eaton, H.M., Murawski, B.J., Taylor, J.E., Swafford, J., Schur, P. 1984. The psychosocial impact of systemic lupus erythematosus and rheumatoid arthritis. Arthritis Rheum. 27, 13.

Ling, M.H.M., Perry, P.H., Tsuang, M.T. 1981. Psychiatric side effects of corticosteroid therapy. Arch. Gen. Psychiatry 38, 471.

Long, A.A., Denburg, S.D., Carbotte, R.M., Singal, D.P., Denburg, J.A. 1990. Serum lymphocytotoxic antibodies and neurocognitive function in systemic lupus erythematosus. Ann. Rheum. Dis. 49, 249.

Loukkola, J., Laine, M., Ainiala, H., Peltola, J., Metsanoja, R., Auvinen, A., Hietaharju, A. 2003. Cognitive impairment in systemic lupus erythematosus and neuropsychiatric systemic lupus erythematosus: a population-based neuropsychological study. J. Clin. Exp. Neuropsychol. 25, 145.

Lupien, S.J., McEwen, B.S. 1997. The acute effects of corticosteroids on cognition: integration of animal and human model studies. Brain Res. Brain Res. Rev. 24, 1.

Maric, D., Millward, J.M., Ballok, D., Szechtman, H., Denburg, J.A., Barker, J., Sakic, B. 2001. Neurotoxic properties of cerebrospinal fluid from behaviorally impaired autoimmune mice. Brain Res. 920, 183.

McCune, W.J., Golbus, J. 1988. Neuropsychiatric lupus. Rheum. Dis. Clin. North Am. 14, 149.

McCune, W.J., MacGuire, A., Aisen, A., Gebarski, S. 1988. Identification of brain lesions in neuropsychiatric systemic lupus erythematosus by magnetic resonance scanning. Arthritis Rheum. 31, 159.

Menon, S., Jameson-Shortall, E., Newman, S.P., Hall-Craggs, M.R., Chinn, R., Isenberg, D.A. 1999. A longitudinal study of anticardiolipin antibody levels and cognitive functioning in systemic lupus erythematosus. Arthritis Rheum. 42, 735.

Minden, S.L., Moes, E.J., Orav, J., Kaplan, E., Reich, P. 1990. Memory impairment in multiple sclerosis. J. Clin. Exp. Neuropsychol. 12, 566.

Monastero, R., Bettini, P., Del Zotto, E., Cottini, E., Tincani, A., Balestrieri, G., Cattaneo, R., Camarda, R., Vignolo, L.A., Padovani, A. 2001. Prevalence and pattern of cognitive impairment in systemic lupus erythematosus patients with and without overt neuropsychiatric manifestations. J. Neurol. Sci. 184, 33.

Moore, P.M., Vo, T., Carlock, L.R. 1998. Identification and cloning of a brain autoantigen in neuro-behavioral SLE. J. Neuroimmunol. 82, 116.

Neuwelt, C.M., Lacks, S., Kaye, B.R., Ellman, J.B., Borenstein, D.G. 1995. Role of intravenous cyclophosphamide in the treatment of severe neuropsychiatric systemic lupus erythematosus. Am. J. Med. 98, 32.

Nossent, J.C., Hovestadt, A., Schonfeld, D.H., Swaak, A.J. 1991. Single-photon-emission computed tomography of the brain in the evaluation of cerebral lupus. Arthritis Rheum. 34, 1397.

Otte, A., Weiner, S.M., Hoegerle, S., Wolf, R., Juengling, F.D., Peter, H.H., Nitzsche, E.U. 1998. Neuropsychiatric systemic lupus erythematusos before and after immunosuppressive treatment: a FDG PET study. Lupus 7, 57.

Papero, P.H., Bluestein, H.G., White, P., Lipnick, R.N. 1990. Neuropsychologic deficits and antineuronal antibodies in pediatric systemic lupus erythematosus. Clin. Exp. Rheumatol. 8, 417.

Perry, P.J., Tsuang, M.T., Hwang, M.H. 1984. Prednisolone psychosis: clinical observation. Drug Intell. Clin. Pharm. 18, 603.

Petri, M., 2002. Incidence and predictors of cognitive dysfunction in SLE. 'Neuropsychiatric systemic lupus erythematosus' program. National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), grant # R01 AR49125-01.

Pinching, A.J., Travers, R.L., Hughes, G.R.V., Jones, T., Moss, S. 1978. Oxygen-15 brain scanning for detection of cerebral involvement in systemic lupus erythematosus. Lancet 1, 898.

Posner, J.B., Furneaux, H.M. 1990. Paraneoplastic syndromes. In: B.H. Waksman (Ed.), Immunologic Mechanisms in Neurologic and Psychiatric Disease. Raven Press, New York, p. 187.

Rao, S.M. (Ed.), 1990. Neurobehavioral Aspects of Multiple Sclerosis. Oxford University Press, New York.

Rao, S.M., Leo, G.J., Bernardin, L., Unverzagt, F. 1991a. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. Neurology 41, 685.

Rao, S.M., Leo, G.J., Ellington, L., Nauertz, T., Bernardin, L., Unverzagt, F. 1991b. Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. Neurology 41, 692.

Ready, R.E., Stierman, L., Paulsen, J.S. 2001. Ecological validity of neuropsychological and personality measures of executive functions. Clin. Neuropsychol. 15, 314.

Reif, A.E., Allen, J.M.B. 1964. The AKR thymic antigen and its distribution in leukemias and nervous tissues. J. Exp. Med. 120, 413.

Ritchlin, C.T., Chabot, R.J., Alper, K., Buyon, J., Belmont, H.M., Roubey, R., Abramson, S.B. 1992. Quantitative electroencephalography: a new approach to the diagnosis of cerebral dysfunction in systemic lupus erythematosus. Arthritis Rheum. 35, 1330.

Rummelt, J.K., Sobota, W.L., Brickman, C.M., Doyle, T.H. 1991. Memory and motor scores discriminate systemic lupus (SLE) patients from matched controls [abstract]. J. Clin. Exp. Neuropsychol. 13, 59.

Ryan, C.M., Morrow, L.A., Bromet, E.J., Parkinson, D.K. 1987. The assessment of neuropsychological dysfunction in the workplace: normative data from the Pittsburgh Occupational Exposures Test Battery. J. Clin. Exp. Neuropsychol. 9, 665.

Sabbadini, M.G., Manfredi, A.A., Bozzolo, E., Ferrario, L., Rugarli, C., Scorza, R., Origgi, L., Vanoli, M., Gambini, O., Vanzulli, L., Croce, D., Campana, A., Messa, C., Fazio, F., Tincani, A., Anzola, G., Cattaneo, R., Padovani, A., Gasparotti, R., Gerli, R., Quartesan, R., Piccirilli, M., Farsi, A., Emmi, E., Passaleva, A. 1999. Central nervous system involvement in systemic lupus erythematosus patients without overt neuropsychiatric manifestations. Lupus 8, 11.

Sailer, M., Burchert, W., Ehrenheim, C., Smid, H.G., Haas, J., Wildhagen, K., Wurster, U., Deicher, H. 1997. Positron emission tomography and magnetic resonance imaging for cerebral involvement in patients with systemic lupus erythematosus. J. Neurol. 244, 186.

Sakic, B., Szechtman, H., Keffer, M., Talangbayan, H., Stead, R., Denburg, J.A. 1992. A behavioral profile of autoimmune lupus-prone MRL mice. Brain Behav. Immun. 6, 265.
This is a seminal paper documenting, for the first time, behavioural abnormalities which precede, and accompany, the development of autoimmune disease in MRL mice. The mouse model is presented as representing and validating at least some features of human NPSLE.

Sakic, B., Szechtman, H., Talangbayan, H., Denburg, S., Carbotte, R., Denburg, J.A. 1994a. Behavior and immune status of MRL mice in the postweaning period. Brain Behav. Immun. 8, 1.

Sakic, B., Szechtman, H., Talangbayan, H., Denburg, S.D., Carbotte, R.M., Denburg, J.A. 1994b. Disturbed emotionality in autoimmune MRL-lpr mice. Physiol. Behav. 56, 609.

Sakic, B., Szechtman, H., Denburg, S.D., Denburg, J.A. 1995. Immunosuppressive treatment prevents behavioral deficit in autoimmune MRL-lpr mice. Physiol. Behav. 58, 797.

Sakic, B., Denburg, J.A., Denburg, S.D., Szechtman, H. 1996a. Blunted sensitivity to sucrose in autoimmune MRL-lpr mice: a curve-shift study. Brain Res. Bull. 41, 305.

Sakic, B., Szechtman, H., Stead, R., Denburg, J.A. 1996b. Joint pathology and behavioral performance in autoimmune MRL-lpr mice. Physiol. Behav. 60, 901.

Sakic, B., Szechtman, H., Braciak, T., Richards, C., Gauldie, J., Denburg, J.A. 1997a. Reduced preference for sucrose in autoimmune mice: a possible role of interleukin-6. Brain Res. Bull. 44, 155.

Sakic, B., Szechtman, H., Denburg, J.A. 1997b. Neurobehavioral alterations in autoimmune mice. Neurosci. Biobehav. Rev. 21, 327.

Sakic, B., Szechtman, H., Denburg, J.A., Gorny, G., Kolb, B., Whishaw, I.Q. 1998. Progressive atrophy of pyramidal neuron dendrites in autoimmune MRL-lpr mice. J. Neuroimmunol. 87, 162.
This study demonstrates reductions in specific cortical neuronal cell masses, accompanied by shrinkage of dendritic arborization, in the brains of MRL mice, and restoration of these abnormalities toward normal after cyclophosphamide therapy. The data provide a neurobiological basis for the existence of behavioural and cognitive deficits in SLE.

Sakic, B., Maric, I., Koeberle, P.D., Millward, J.M., Szechtman, H., Maric, D., Denburg, J.A. 2000. Increased TUNEL staining in brains of autoimmune Fas deficient mice. J. Neuroimmunol. 104, 147.

Sakic, B., Lacosta, S., Denburg, J.A., Szechtman, H. 2002. Altered neurotransmission in brains of autoimmune mice: pharmacological and neurochemical evidence. J. Neuroimmunol. 129, 84.

Sapolsky, R.M., Krey, L.C., McEwen, B.S. 1984. Stress down-regulates corticosterone receptors in a site-specific manner in the brain. Endocrinology 114, 287.

Schneebaum, A.B., Singleton, J.D., West, S.G., Blodgett, J.K., Allen, L.G., Cheronis, J.C., Kotzin, B.L. 1991. Association of psychiatric manifestations with antibodies to ribosomal P proteins in systemic lupus erythematosus. Am. J. Med. 90, 54.

Schnider, A., Bassetti, C., Gutbrod, K., Ozdoba, C. 1995. Very severe amnesia with acute onset after isolated hippocampal damage due to systemic lupus erythematosus [letter]. J. Neurol. Neurosurg. Psychiatry 59, 644.

Schrott, L.M., Crnic, L.S. 1998. Attenuation of behavioral abnormalities in autoimmune mice by chronic soluble interferon-γ receptor treatment. Brain Behav. Immun. 12, 90.

Schrott, L.M., Denenberg, V.H., Sherman, G.F., Waters, N.S., Rosen, G.D., Galaburda, A.M. 1992. Environmental enrichment, neocortical ectopias, and behavior in the autoimmune NZB mouse. Brain Res. Dev. Brain Res. 67, 85.

Schrott, L.M., Waters, N.S., Boehm, G.W., Sherman, G.F., Morrison, L., Rosen, G.D., Behan, P.O., Galaburda, A.M., Denenberg, V.H. 1993. Behavior, cortical ectopias, and autoimmunity in BXSB-Yaa and BXSB-Yaa + mice. Brain Behav. Immun. 7, 205.

Schwegler, H., Lipp, H.-P., Crusio, W.E. 1988. NZB mouse: hippocampal mossy fiber patterns and behavioral profiles of young and older animals. Drug Dev. Res. 15, 297.

Shortall, E., Isenberg, D., Newman, S.P. 1995. Factors associated with mood and mood disorders in SLE. Lupus 4, 272.

Sibbitt, W.L., Sibbitt, R.R., Griffey, R.H., Eckel, C., Bankhurst, A.D. 1989. Magnetic resonance imaging in the evaluation of acute neuropsychiatric disease in systemic lupus erythematosus. Ann. Rheum. Dis. 48, 1014.

Sibbitt, W.L., Brooks, W.M., Haseler, L.J., Griffey, R.H., Frank, L.M., Hart, B.L., Sibbitt, R.R. 1995. Spin–spin relaxation of brain tissues in systemic lupus erythematosus. Arthritis Rheum. 38, 810.

Sibbitt, W.L. Jr., Sibbitt, R.R., Brooks, W.M. 1999. Neuroimaging in neuropsychiatric systemic lupus erythematosus. Arthritis Rheum. 42, 2026.

Sibbitt, W.L. Jr., Brandt, J.R., Johnson, C.R., Maldonado, M.E., Patel, S.R., Ford, C.C., Bankhurst, A.D., Brooks, W.M. 2002. The incidence and prevalence of neuropsychiatric syndromes in pediatric onset systemic lupus erythematosus. J. Rheumatol. 29, 1536.

Silver, C.H. 2000. Ecological validity of neuropsychological assessment in childhood traumatic brain injury. J. Head Trauma Rehabil. 15, 973.

Singer, J., Denburg, J.A., the Ad Hoc Neuropsychiatric Lupus Workshop Group 1990. Diagnostic criteria for neuropsychiatric systemic lupus erythematosus: the results of a consensus meeting. J. Rheumatol. 17, 1397.

Skeel, R.L., Johnstone, B. 2000. Neuropsychological deficit profiles in systemic lupus erythematosus. Appl. Neuropsychol. 7, 96.

Sohlberg, M.M., Mateer, C.A. 1989. Introduction to Cognitive Rehabilitation: Theory and Practice. The Guilford Press, New York.

Sonies, B.C., Klippel, J.H., Gerber, R.B., Gerber, L.H. 1982. Cognitive performance in systemic lupus erythematosus [abstract]. Arthritis Rheum. 25, S80.

Spreen, O., Strauss, E. 1998. A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. Oxford University Press, New York.
This book provides a comprehensive compilation of neuropsychiatric tests, describing their psychometric properties. Normative information, including pediatric and geriatric populations where available, is also included.

Stoppe, G., Wildhagen, K., Seidel, J.W., Meyer, G.J., Schober, O., Heintz, P., Kunkel, H., Deicher, H., Hundeshagen, H. 1990. Positron emission tomography in neuropsychiatric lupus erythematosus. Neurology 40, 304.

Szechtman, H., Sakic, B., Denburg, J.A. 1997. Behaviour of MRL mice: an animal model of disturbed behaviour in systemic autoimmune disease. Lupus 6, 223.

Tarter, R.E., Edwards, K.L., Van Thiel, D.H. 1988. Perspective and rationale for neuropsychological assessment of medical disease. In: R.E. Tarter, D.H. Van Thiel, K.L. Edwards (Eds.), Medical Neuropsychology: The Impact of Disease on Behavior. Plenum Press, New York, p. 1.

Temesvari, P., Denburg, J., Denburg, S., Carbotte, R., Bensen, W., Singal, D. 1983. Serum lymphocytotoxic antibodies in neuropsychiatric lupus: a serial study. Clin. Immunol. Immunopathol. 28, 243.

Valesini, G., Priori, R., Francia, A., Balestrieri, G., Tincani, A., Airo, P., Cattaneo, R., Zambruni, A., Troianello, B., Chofflon, M., Miescher, P.A., 1994. Central nervous system involvement in systemic lupus erythematosus: a new therapeutic approach with intrathecal dexamethasone and methotrexate. Springer Semin. Immunopathol. 16, 313.

Vanderploeg, R.D. (Ed.), 2000. Clinician's Guide to Neuropsychological Assessment. Lawrence Erlbaum Associates, Mahwah, NJ.

Varney, N.R., Alexander, B., MacIndoe, J.H. 1984. Reversible steroid dementia in patients without steroid psychosis. Am. J. Psychiatry 141, 369.

Volkow, N.D., Warner, N., McIntyre, R., Valentine, A. 1988. Cerebral involvement in systemic lupus erythematosus. Am. J. Physiol. Imaging 3, 91.

Wang, Y., Schrieber, L., Cohen, M.G., Furphy, L., Webb, J., Chivers, T., Pollard, K.M. 1990. Antiphospholipid antibodies in systemic lupus erythematosus: clinical and laboratory associations in 111 patients. Rheumatol. Int. 10, 75.

Waterloo, K., Omdal, R., Mellgren, S.I., Husby, G. 1997. Neuropsychological functions in systemic lupus erythematosus: a comparison with chronic whiplash patients. Eur. J. Neurol. 4, 171.

Waterloo, K., Omdal, R., Jacobsen, E.A., Klow, N.E., Husby, G., Torbergsen, T., Mellgren, S.I. 1999. Cerebral computed tomography and electroencephalography compared with neuropsychological findings in systemic lupus erythematosus. J. Neurol. 246, 706.

Waterloo, K., Omdal, R., Husby, G., Mellgren, S.I. 2002. Neuropsychological function in systemic lupus erythematosus: a five-year longitudinal study. Rheumatology (Oxford) 41, 411.

Weber, B., Fritze, J., Schneider, B., Kühner, T., Maurer, K. 2002. Bias in computerized neuropsychological assessment of depressive disorders caused by computer attitude. Acta Psychiatr. Scand. 105, 126.

Wekking, E.M., Nossent, J.C., van Dam, A.P., Swaak, A.J.J.G. 1991. Cognitive and emotional disturbances in systemic lupus erythematosus. Psychother. Psychosom. 55, 126.

Wernet, P., Kunkel, H.G. 1973. Antibodies to a specific surface antigen of T cells in human sera inhibiting mixed leukocyte culture reactions. J. Exp. Med. 138, 1021.

West, S.G. 1996. Lupus and the central nervous system. Curr. Opin. Rheumatol. 8, 408.

West, S.G., Emlen, W., Wener, M.H., Kotzin, B.L. 1995. Neuropsychiatric lupus erythematosus: a 10-year prospective study on the value of diagnostic tests. Am. J. Med. 99, 153.

Whitelaw, D.A., Spangenberg, J.J., Rickman, R., Hugo, F.H., Roberts, M. 1999. The association between the antiphospholipid antibody syndrome and neuropsychological impairment in SLE. Lupus 8, 444.

Wilken, J.A., Kane, R., Sullivan, C.L., Wallin, M., Usiskin, J.B., Quig, M.E., Simsarian, J., Saunders, C., Crayton, H., Mandler, R., Kerr, D., Reeves, D., Fuchs, K., Manning, C., Keller, M. 2003. The utility of computerized neuropsychological

assessment of cognitive dysfunction in patients with relapsing-remitting multiple sclerosis. Mult. Scler. 9, 119.

Winfield, J.B. 1985. Anti-lymphocyte antibodies in systemic lupus erythematosis. Clin. Rheum. Dis. 11, 523.

Wolkowitz, O.M., Reus, V.I., Canick, J., Levin, B., Lupien, S. 1997. Glucocorticoid medication, memory and steroid psychosis in medical illness. Ann. N. Y. Acad. Sci. 823, 96.

Woolley, C.S., Gould, E., McEwen, B.S. 1990. Exposure to excess glucocorticoids alters dendritic morphology of adult hippocampal pyramidal neurons. Brain Res. 531, 225.

Yancey, C.L., Doughty, R.A., Athreya, B.H. 1981. Central nervous system involvement in childhood systemic lupus erythematosus. Arthritis Rheum. 24, 1389.

Zelinski, E.M., Gilewski, M.J., Anthony-Bergstone, C.R. 1990. Memory functioning questionnaire: concurrent validity with memory performance and self-reported memory failures. Psychol. Aging 5, 388.

Zonana-Nacach, A., Barr, S.G., Magder, L.S., Petri, M. 2000. Damage in systemic lupus erythematosus and its association with corticosteroids. Arthritis Rheum. 43, 1801.

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CHAPTER 3

Systemic Lupus Erythematosus: Anatomic and Functional Imaging Studies

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1. Introduction

Neuropsychiatric systemic lupus erythematosus (NPSLE), a term that subsumes all of the neurologic and psychiatric complications of SLE, is one of the most common complications of SLE (Adelman et al., 1986; McCune et al., 1988; Jonsen et al., 2002). NPSLE markedly and independently increases the risk of death in SLE, is the most common form of long-term organ damage in SLE, and may continue unabated even in the face of quiescent systemic disease. Despite the development of reasonably effective therapy for glomerulonephritis and renal failure in SLE (chemotherapy, dialysis, renal transplant), the therapy for NPSLE remains uncertain, unproven, and strictly empirical with little basis in proven pathogenesis (Gibson and Myers, 1976; Ginzler and Schorn, 1988; van Dam, 1991; Carbotte et al., 1986; Hanly et al., 1992; Ward et al., 1996).

2. Prevalence

NPSLE occurs in up to 95% of SLE patients (Adelman et al., 1986; Bluestein, 1987; McCune, 1988; Jonsen et al., 2002). Severe or life-threatening NPSLE occurs in 52–72% of patients, and is more common than renal disease (Feinglass et al., 1976; West, 1994).

3. Epidemiology

General SLE epidemiology can be found in previous Chapters.

4. Etiology/pathogenesis relevant to neuroimaging in NPSLE

Neuroimaging must be viewed in the context of the brain pathology of NPSLE. However, there have

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been few paired imaging-autopsy studies (James et al., 1987; Ellis and Verity, 1977; Bluestein, 1992; West, 1994; Carbotte et al., 1992). Careful examination of pathologic tissues at autopsy provides the gold standard for defining cellular and vascular injury. The histopathology of NPSLE is characterized by vasculopathy and the sequelae of vasculopathy, including vascular edema, microinfarcts, cerebral infarct, hemorrhage, neuronal/axonal injury, focal and generalized loss of brain parenchyma, and reactive gliosis (Funata, 1979; Ellison et al., 1993; Shiozawa et al., 1992; Johnson and Richardson, 1968; Ellis and Verity, 1977; Hanly et al., 1992; Devinsky et al., 1988). The histology in NPSLE regularly demonstrates foci of subtle, but widespread vasculopathy-characterized by fibrin thrombi, vascular hyalinization, vessel tortuosity, endothelial proliferation, vascular webs, and perivascular gliosis-findings similar to that of the primary antiphospholipid syndrome (APS) (Hughson et al., 1993). Microthrombi, composed of platelets, platelet fragments, fibrin, or leukocytes, are also common and are associated with microinfarcts (Hammad et al., 1992; Shiozawa et al., 1992; Belmont et al., 1996; Falk et al., 1985; Pohlman et al., 1986; Hopkins et al., 1988; Hanly et al., 1992; van Dam, 1991; Ellison et al., 1993). A recent autopsy study demonstrated two pervasive patterns of cerebrovasculopathy in NPSLE: (1) an antiphospholipid antibody (aPL)-associated non-inflammatory cerebrovasculopathy characterized by bland thromboses, thrombotic microangiopathy (TMA) and arterial intimal fibrous hyperplasia; and (2) a non-aPL associated cerebrovasculopathy associated with increased SLE disease activity and glomerulonephritis (Figs. 1 and 2).

Immune deposits and classic vasculitis (inflammatory or necrotic involvement of the vessel wall) are rare in the cerebral vessels in NPSLE (3–5%) (Devinsky et al., 1988). On the other hand, perivascular leukocyte cuffing and endothelial swelling are common (Devinsky et al., 1988; Sakaki et al., 1990). Complement-derived anaphylatoxins been implicated in the activation of platelets and neutrophils, which then adhere to activated endothelial cells, resulting in vascular occlusion and microinfarcts (Pohlman et al., 1986; Falk et al., 1985; Hopkins et al., 1988). Thus, histopathology shows clear evidence of a complex

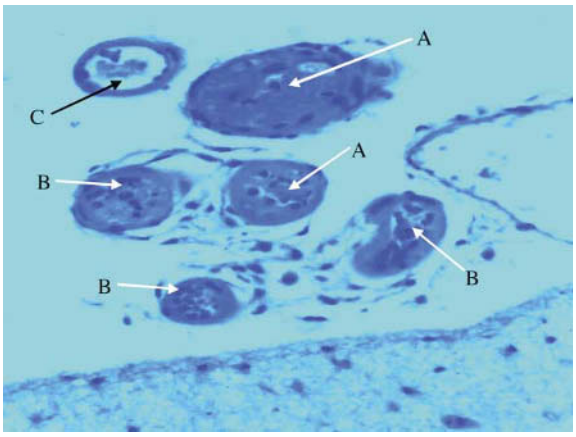

Figure 1. Thrombotic Vasculopathy in NPSLE. These cerebral vessels demonstrate occlusion by fibrin thrombi (A), intimal hypertrophy and vessel wall thickening, platelet thrombi (B), and an occasional patent blood vessel (C).

cerebrovasculopathy and secondary cellular and parenchymal injury in NPSLE. Although histopathology is critical for understanding the causation of NPSLE, brain biopsy is difficult to justify in living SLE subjects. Thus, to characterize the vascular and cellular components of brain injury in NPSLE in living subjects we must rely on neuroimaging, which is now critical in the evaluation of a patient with NPSLE.

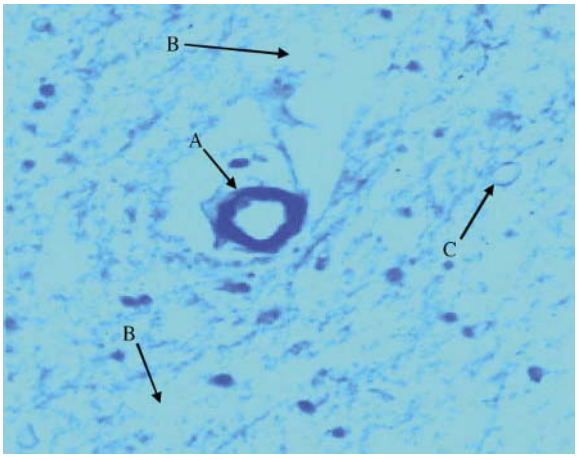

Figure 2. Non-Thrombotic Vasculopathy in NPSLE. The cerebral arteriole (A) is patent, despite extensive surrounding edema, necrosis, neuronal/axoal death (B), and decreased neuronal density and ghost cells (C).

5. Clinical manifestations

NPSLE displays a bewildering array of neurologic abnormalities, including acute confusional state, psychiatric disturbances, amnesic syndromes, dementia, mood disorders, anxiety syndromes, cranial neuropathies, cerebrovascular disease, transverse myelitis, movement disorders, seizures, headaches, aseptic meningitis, pseudotumor cerebri, and demyelinating syndromes (Johnson and Richardson, 1968; Ellis and Verity, 1977; Bluestein, 1992; West, 1994; Carbotte et al., 1986; Carbotte et al., 1992; Hanly et al., 1992; Denburg et al., 1993) (discussed in the previous two chapters). The sheer heterogeneity of NPSLE syndromes has made logical classification and systematic study difficult (West, 1994).

Despite the high incidence of this complication, NPSLE is extremely difficult to diagnose definitively because of the wide variety of different neurologic manifestations and confounding disorders. To help sort through the diagnostic possibilities, brain imaging has become important in the evaluation of a SLE patient with neurologic complaints (Kovacs et al., 1993; West, 1994; Sibbitt and Brooks, 1997; Sibbitt et al., 1997; Weiner et al., 2003). This chapter examines the scientific basis for the use of neuroimaging modalities in SLE and, recognizing current limitations in knowledge, makes preliminary recommendations regarding the clinical application of these methods to the SLE patient with neuropsychiatric complaints.

6. Diagnostic investigations

6.1. Computerized tomography

Computerized tomography (CT) is based on the quantitative absorption or scatter of X-rays through tissues of different radiodensity (electron density), measured indirectly by the X-rays actually transmitted through the tissues to a detector opposite the X-ray source (Marshal, 1982). Thus, CT is sensitive to changes in tissue mass (as in a tumor) or lesions containing metal ions that readily absorb or scatter X-rays (as in hemorrhage), but is insensitive to the state of bound water, perfusion, cellular metabolites, or metabolism.

Computerized tomography may be abnormal in 29–84% of patients with NPSLE (Reiff et al., 1997; Raymond et al., 1996; Walecki, 2002). The most common finding is cerebral atrophy 25–60% which may be seen in as many as 50% of patients, but infarcts, cerebral calcification, hemorrhage, abscess, or meningitis may be visualized (Gonzalez-Scarano et al., 1979; Bilaniuk et al., 1977; Gaylis et al., 1982; Carette et al., 1982; Vermess, 1983; Brant-Zsawadzki et al., 1983; Futran et al., 1987; Shah et al., 1988; Garcia-Raya et al., 1994; Szer et al., 1993, 53 Shapeero and Norman, 1992; Kovacs et al., 1995; Miguel et al., 1994; Bentson et al., 1978; Adelman et al., 1986; Waterloo et al., 1999). In SLE, cerebral atrophy by CT does not appear to be related to corticosteroid dose, but is associated with the presence of seizures (Zanardi, 2001). Computerized tomography may also show extensive but reversible white-matter abnormalities suggestive of cerebral edema (Hinchey et al., 1996; Shintani et al., 1993; Ogura et al., 1992; Vermess, 1983; Brant-Zsawadzki et al., 1983). Computerized tomography is sensitive to overt stroke and cerebral atrophy in NPSLE, but again is not as good as MRI (Sibbitt et al., 1989; Walecki, 2002).

Computerized tomography is usually insensitive to the non-focal presentations of NPSLE even in the presence of seizures, confusional states, major depression, cognitive disorder, or other serious neuropsychiatric manifestations (Gonzalez-Scarano et al., 1979; Grigor et al., 1978; Feinglass et al., 1976; Vermess, 1983; Szer et al., 1993; Shahar et al., 1998; Horoshovski et al., 1995; Nampoory, 1997; Waterloo et al., 1999). Computerized tomography is also insensitive to chronic white matter disease, small infarcts, punctate lesions, focal cerebral edema, transverse myelitis, diffuse brain injury, and leukoencephalopathy obvious by MRI or magnetic resonance spectroscopy (MRS) (Kovacs et al., 1995; Miguel et al., 1994; Aisen et al., 1985; Sibbitt et al., 1989; Kirk et al., 1991). Thus, in the setting of active NPSLE, CT appears most useful for determining the presence of large infarct, intracerebral hemorrhage, massive brain edema, and cerebral atrophy and for excluding confounding disorders including brain abscess, meningitis, mycotic aneurysm, or mass lesion (Shapeero and Norman, 1992; Waterloo et al., 1999). Computerized tomography is clearly an inferior method of anatomic

imaging in NPSLE and should be used as a primary approach only when MRI is unavailable, not tolerated, or contraindicated (Huizinga et al., 2001; Walecki, 2002).

6.2. Angiography

Angiography exists in conventional, digital, subtracted, computed tomographic, or MR angiographic contrasted and non-contrasted formats (Bradley and Bydder, 1997). Angiography is limited to defining macroscopic vascular lesions (segmental narrowing, stenosis, beading, aneurysm) or other vascular lesions including thrombus, stenosis, occlusion, dissection, atheroma, or dysplasia of large or medium-sized arteries and veins (Bradley and Bydder, 1997; Trevor et al., 1972; Sakaki et al., 1990; Levine, 1990; Mitsias and Levine, 1994). However, even in the setting of cerebral infarction, angiography is often completely normal, indicating limited sensitivity (Bradley and Bydder, 1997; Trevor et al., 1972; Sakaki et al., 1990; Levine, 1990; Mitsias and Levine, 1994). Moreover, angiography is usually normal in patients with transient neurologic dysfunction which is the largest group of NPSLE patients (Levine, 1990). With the low sensitivity for NPSLE, invasive angiography should only be considered in those cases where other imaging modalities fail. Practically, magnetic resonance angiography is usually adequate for medium to large vessel involvement and Doppler techniques are useful for investigating the carotids and other large vessels, so invasive radiocontrast angiography is rarely necessary or useful in NPSLE.

6.3. Magnetic resonance techniques

Magnetic resonance imaging (MRI), spectroscopy (MRS), relaxometry (MRR), magnetization transfer imaging (MTI), diffusion weighted imaging (DWI), and other MR techniques are possible because of the physical phenomenon that nuclei with unpaired spins behave as small magnets and align parallel or anti-parallel with the direction of an applied magnetic field (Wood and Wehrli, 1999). Magnetic resonance signals arise primarily from the hydrogen (or proton) signals of water and fat from biological tissue, and spatial information about protons in these tissues is encoded by manipulations of magnetic field gradients. The signal in MRI is comprised mainly of the absolute proton density and the spin–lattice (T_1) and spin–spin (T_2) relaxation processes. Each of these reflects the physical environment of the water or fat, which may be altered in the pathological state, providing image contrast. On the neuroimaging developmental side, integration of above MR-based techniques permits simultaneous measures of brain anatomy, metabolic status, degree of injury, edema, and NPSLE activity which together promise much more effective diagnosis of NPSLE (Huizinga et al., 2001; Steens et al., 2003).

6.3.1. Conventional MRI

Magnetic resonance imaging (MRI) is currently the anatomic imaging modality of choice in NPSLE because MRI is more sensitive than CT for brain lesions associated with NPSLE (Vermess, 1983; Aisen et al., 1985; McCune et al., 1988; Sibbitt et al., 1989; Stimmler et al., 1993; Walecki, 2002; Huizinga et al., 2001). MRI is exceptionally sensitive for cerebral infarcts, central nervous system (CNS) hemorrhage, and transverse myelitis (Boumpas et al., 1990; Baca, 1996; Szer et al., 1993), and certain confounding disorders including infectious meningitis, brain abscess, and mycotic aneurysms (McCune et al., 1988; Robbins et al., 1988; Shapeero and Norman, 1992). In SLE patients without active NPSLE chronic lesions may be observed by MRI in 25–50% of patients, and the numbers of these lesions increase with disease severity, age, and a history of NPSLE (Jarek et al., 1994; Brooks et al., 1997; Rozell et al., 1998; Friedman et al., 1998; Hachulla, 1998).

Small punctate focal lesions in white matter are most common (15–60%), followed in prevalence by cortical atrophy, periventricular white matter changes, ventricular dilation, diffuse white matter changes, and gross infarct (Ishikawa et al., 1994; Rozell et al., 1998; Sabet, 1998; Friedman et al., 1998) (Fig. 3). Small focal lesions are concentrated

in subcortical white matter, especially in the frontoparietal regions, but may be seen elsewhere (Jacobs, 1988; McCune et al., 1988; Sibbitt et al., 1989; Jarek et al., 1994; Ishikawa et al., 1994; Friedman et al., 1998; Chinn et al., 1997). Recent evidence suggests that all focal lesions in NPSLE represent neuronal injury (Brooks et al., 1997; Friedman et al., 1998). In fact, the degree of generalized neuronal injury in NPSLE correlates more closely with these small subcortical focal lesions than other imaging abnormalities (Friedman et al., 1998). Histopathology suggests that the small focal lesions in SLE are a vascular phenomenon representing small infarcts in white matter (Johnson and Richardson, 1968; Moody et al., 1990), although the relevance of these lesions to function or to a specific NPSLE episode is unclear (Sibbitt et al., 1994; Jarek et al., 1994; Falcini, 1998; Chinn et al., 1997; Friedman et al., 1998; Kozora et al., 1998).

MRI abnormalities—including infarcts, small white matter lesions, periventricular white matter hyperintensity, diffuse white matter abnormalities, and cortical atrophy—are present in up to 75% SLE patients with APS, and the prevalence and severity of these changes are greater than SLE alone (Ishikawa et al., 1994; Provenzale et al., 1996; Sabet, 1998). Lesions most closely associated with aPL include cerebral infarct, small focal lesions (Ishikawa et al., 1994; Hachulla, 1998; Sabet, 1998), or lesions similar to those seen in multiple sclerosis (April and Vansonnenberg, 1976; Mizutani et al., 1977; Kinney et al., 1979).

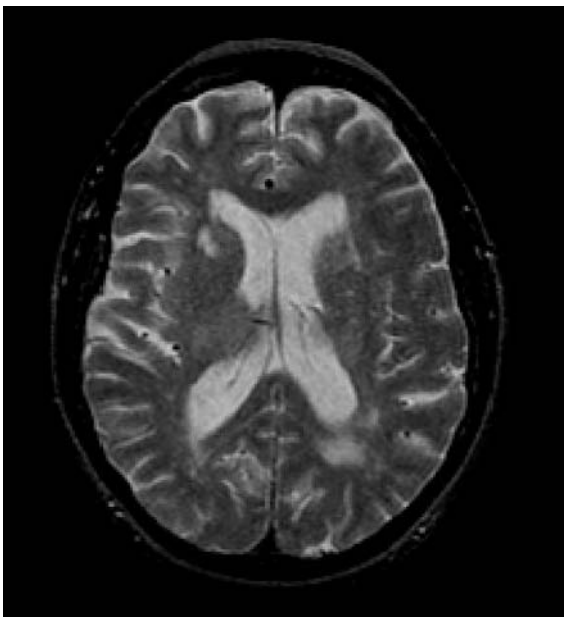

Figure 3. MRI in NPSLE. This T2-weighted MRI demonstrates cortical atrophy, ventricular dilation, small focal white matter lesions, and deep white matter lesions, typical of NPSLE.

Lesions are also commonly observed in active NPSLE, occurring in 15–78% of patients, although in most cases do not represent acute or active disease but rather old injury (McCune et al., 1988; Davie et al., 1995; Colamussi et al., 1995; McLean et al., 1995; Sibbitt et al., 1995; Otte et al., 1997; Reiff et al., 1997; Lin et al., 1997; Weiner et al., 2003; Oku et al., 2003). Acute lesions on T_2-weighted images suggesting active NPSLE include new infarct, discrete gray matter lesions, diffuse gray matter hyperintensities, and cerebral edema (McCune et al., 1988; Sibbitt et al., 1989; Sibbitt et al., 1995; Rozell et al., 1998; Friedman et al., 1998; Mitsias and Levine, 1994). MRI studies may show extensive bilateral white-matter abnormalities suggestive of edema in the cerebral hemispheres, the brain stem, or the cerebellum, which may be associated with hypertension, benign intracranial hypertension (pseudotumor cerebri), immunosuppression, or other signs of active NPSLE (McCune et al., 1988; Sibbitt et al., 1989; Ogura et al., 1992; Hinchey et al., 1996). New lesions are more likely to correspond anatomically with newly acquired but specific neurologic dysfunction (Sibbitt et al., 1989; McAbee and Barasch, 1990), and may reverse with corticosteroid therapy (McCune et al., 1988; Sibbitt et al., 1989, 1995; Shintani et al., 1993). Generalized seizures in particular may be accompanied by reversible focal and punctate high intensity lesions in both white and gray matter, which generally resolve rapidly and must be studied rapidly to be documented (Sibbitt et al., 1989, 1995).

Brain lesions by MRI represent both current NPSLE activity and prior damage caused by NPSLE (Sanna et al., 2000; Sibbitt et al., 2003). Thus, it is difficult to differentiate lesions which indicate active NPSLE from chronic lesions which

represent past NPSLE or changes unrelated to NPSLE (McCune et al., 1988; Jarek et al., 1994), and careful inspection of the structure of lesions on MRI by both the attending physician and radiologist is warranted. The lack of discrete borders, intermediate intensity on T_2-weighted images, intermediate size, a lacey, filamentous pattern, and a peculiar location often following the gray-white matter junction along the sulci and gyri and assuming a semilunate structure, or the presence of overlying or adjacent gray matter hyperintensity all suggest acute, reversible lesions indicating active NPSLE (McCune et al., 1988; Sibbitt et al., 1989, 1995). New lesions or lesions that resolve on repeat studies suggest active disease (McCune et al., 1988; Sibbitt et al., 1989). Lesion enhancement following gadolinium may also indicate active disease (Miller et al., 1992) (Fig. 4). The addition of SPECT or PET does not appear to differentiate old from new MRI-visible lesions (Colamussi et al., 1995, 99; Colamussi et al., 1997). MRI is abnormal in active NPSLE in 71% of subjects compared to 17% in SLE patients without active NPSLE (odds ratio 11.9), which indicates that MRI is of some value in differentiating active from inactive NPSLE (Oku et al., 2003).

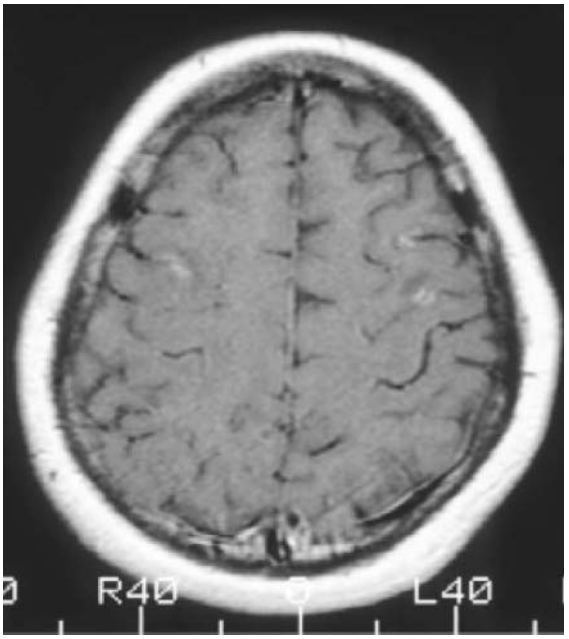

Figure 4. Contrasted MRI in NPSLE. This T1-weighted gadolinium contrasted MRI demonstrates multiple areas of enhancement indicating focal blood–brain barrier breakdown consistent with active NPSLE.

Patients with obvious NPSLE and normal MRI remain a problem (Szer et al., 1993; Shahar et al., 1998), and a combination of imaging, serum, and CSF studies may be most appropriate (Bell et al., 1991; West et al., 1995; Sibbitt et al., 1997). One approach would be complementary functional studies such as radionuclide studies (Hanly et al., 1993l), MRS (Sibbitt and Sibbitt, 1993; Brooks et al., 1997), or MRR (Sibbitt et al., 1995; Petropoulos et al., 1999). MRI may also be more effective when used in combination with other, non-imaging tests including a combination of serum antiribosomal-P antibodies, CSF IgG index/oligoclonal bands, CSF antineuronal antibodies, aPL, and CSF pressure analysis (West et al., 1995a,b; Horoshovski et al., 1995; Nampoory, 1997).

The above evidence suggests that MRI is the technique of choice to define anatomy in NPSLE and is preferable to CT. MRI has limited sensitivity in active NPSLE, but has excellent sensitivity to detect large infarcts, chronic multifocal disease, intracerebral hemorrhage, transverse myelitis, and focal cerebral edema and to exclude confounding disease including brain abscess and mass lesions (Shapeero and Norman, 1992). MRI is more likely to be abnormal with focal neurologic defects, seizures, chronic cognitive dysfunction, and APS, and less likely to be abnormal with affective disorders, confusional states, and headache (West et al., 1995a,b; Sibbitt et al., 1995; Rozell et al., 1998; Sabet, 1998). MRI cannot reliably differentiate NPSLE from confounding disorders common to SLE including infectious meningitis, progressive multifocal leukoencephalopathy, non-inflammatory brain edema, or infarct, hemorrhage, or vasculopathy not-related to SLE (Kinoshita et al., 1998). A cranial MR study should be obtained within 24 h of the initial neurological event since the typical reversible, high intensity lesions associated with diffuse presentations resolve rapidly with corticosteroid therapy (McCune et al., 1988; Sibbitt et al., 1989). Radiologists, rheumatologists, and neurologists should become more sophisticated in distinguishing acute from chronic lesions using

morphologic and intensity criteria, and this should certainly be an ongoing research effort. The small punctate lesions present on MRI are common and often confusing, but should not be interpreted as active disease (Jarek et al., 1994; Friedman et al., 1998).

Thus, MRI remains the most effective anatomic imaging technique and is usually indicated in NPSLE, but it should be combined with other appropriate modalities for improved sensitivity and specificity depending on the clinical presentation.

6.3.2. Fluid attenuated inversion recovery imaging (FLAIR)

Despite the obvious advantages of MRI, certain brain lesions found in NPSLE-especially foci of new-onset ischemia, lesions close to CSF interfaces, and lesions with limited contrast from adjoining normal tissue – are challenging to discern on commonly used MRI sequences such as T_1-weighted (T_1), proton density (PD), and T_2-weighted sequences (T_2) (Hajnal et al., 1992). Fluid attenuated inversion recovery (FLAIR) imaging produces a T_2-weighted image, but with suppressed CSF signal that may be more sensitive for white matter lesions (De Coene et al., 1992). In terms of overall diagnostic sensitivity (normal versus abnormal), FLAIR and PD/T_2 are very similar (Tourbah et al., 1996; Appenzeller et al., 2000; Rovaris et al., 2000). However, FLAIR is definitely superior in terms of conspicuity of lesions in the cortex, subcortical white matter, and periventicular areas (Sibbitt et al., 2003) (Fig. 5). FLAIR also demonstrates an increased number of small focal lesions (approximately 21% more lesions) versus conventional MRI (Sibbitt et al., 2003). This suggests

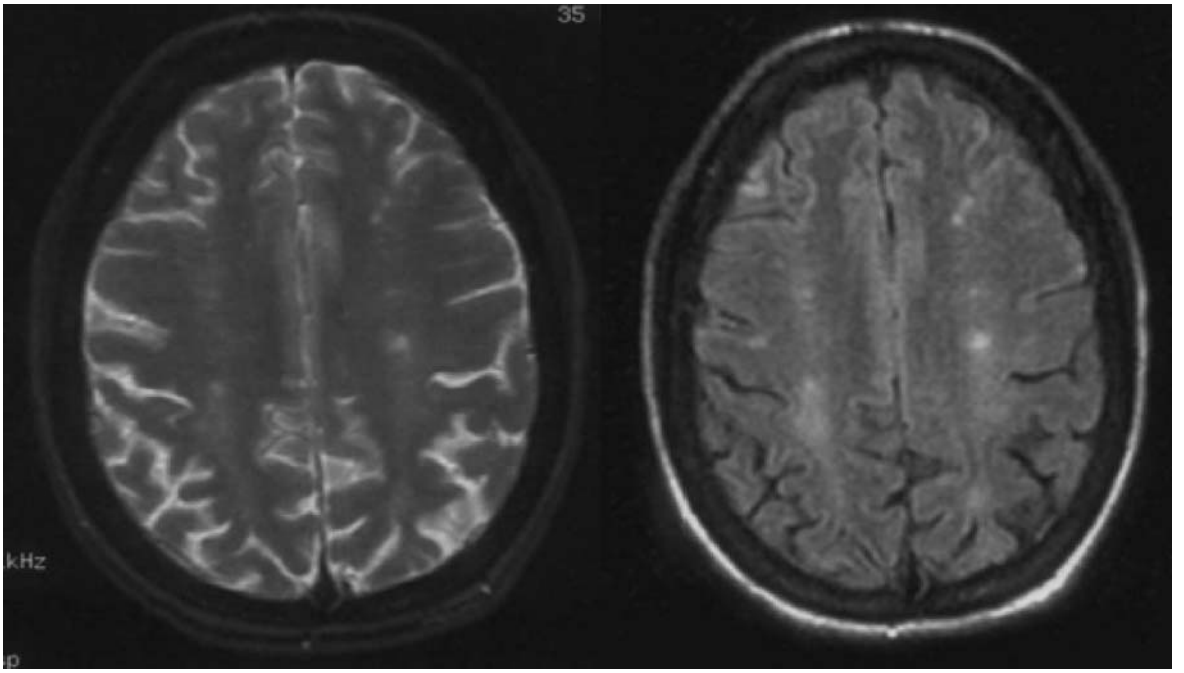

Figure 5. FLAIR and T2 in Neuropsychiatric SLE. The figure on the left is an axial slice demonstrating CSF and cortical, subcortical, and deep white matter lesions by conventional T2 (TE = 100 ms; TR = 3000 ms). The figure on the right demonstrates the same slice by FLAIR (TR = 10,000 ms, TE = 145 ms, TI = 2200 ms). As can be seen by comparison, the signal from CSF is markedly attenuated (darker) with FLAIR, and the lesions (areas of increased signal) have greater conspicuity on FLAIR relative to the corresponding T2 image. The focal and diffuse, ill-defined lesions are best seen on FLAIR compared to T2. Although the larger focal white matter lesion is seen well in the T2 image, the conspicuity is far better on the FLAIR image. Similarly, the ill-defined white matter lesions are barely seen on the T2 weighted image, are much more obvious on the FLAIR image. Finally, the cortical/subcortical lesion (which is a reversible lesion typical of lupus acute leukoencephalopathy) in the frontal lobe is not apparent at all by T2 (left), but is obvious by FLAIR (right).

a superiority of FLAIR in those anatomic regions in close association with CSF, although addition of FLAIR results in only a small improvement of 5% in overall diagnostic sensitivity. However, lesions on FLAIR are more obvious and less likely to be confused with non-lesional structures, and thus, FLAIR images have obvious advantages and are increasingly employed for the evaluation of NPSLE (Walecki, 2002; Sibbitt et al., 2003).

6.3.3. Diffusion weighted imaging (DWI)

DWI is a technique that exploits the differences in diffusivity between normal and abnormal tissues, with diffusivity increased in tissues with vasogenic edema or increased free water, and diffusivity decreased in cytotoxic edema where water movement within the cell is restricted, usually by ischemic injury associated with stroke (Rowley et al., 1999; Beauchamp et al., 1998; Ebisu, 1993). DWI can be a quantitative technique in NPSLE, and apparent diffusion coefficients (ADC) or vectors can be calculated (Bosma et al., 2003). Thus, in the setting of NPSLE, DWI is most useful for confirming whether a lesion present on conventional MRI represents a stroke or not (Walecki, 2002). In active NPSLE DWI demonstrates acute or subacute lesions in 45% (Mortilla et al., 2003). Of these acute and subacute lesions, 50% demonstrate decreased ADC, which indicates acute or subacute infarcts (Fig. 6). In the other 50%, these lesions demonstrate an increased ADC, indicating vasogenic edema (blood–brain barrier breakdown). However, 50% of the lesions with increased ADC demonstrate a small nidus within them of decreased ADC, indicating a small infarct surrounded by vasogenic edema (Moritani et al., 2001). Mean ADC measures across the brain are also abnormal in subjects with prior NPSLE, even when lesions are excluded (Bosma et al., 2003). These whole brain ADC values are higher in subjects with prior NPSLE, probably indicating increased free water in tissues in areas of injury (Bosma et al., 2003). This is probably due to expansion of the Virchow-Robin spaces filled with CSF that surrounds the entering vessels of the brain parenchyma, which would rise in diffusivity of non-lesional brain parenchyma. Thus, in active NPSLE diffusion-weighted imaging shows primarily two patterns parenchymal lesions in patients with SLE: acute or subacute infarction and vasogenic edema with or without microinfarcts, while in prior NPSLE, the images are generally normal appearing, but the actual ADC values are higher, suggesting a passive increase in brain water associated with chronic injury.

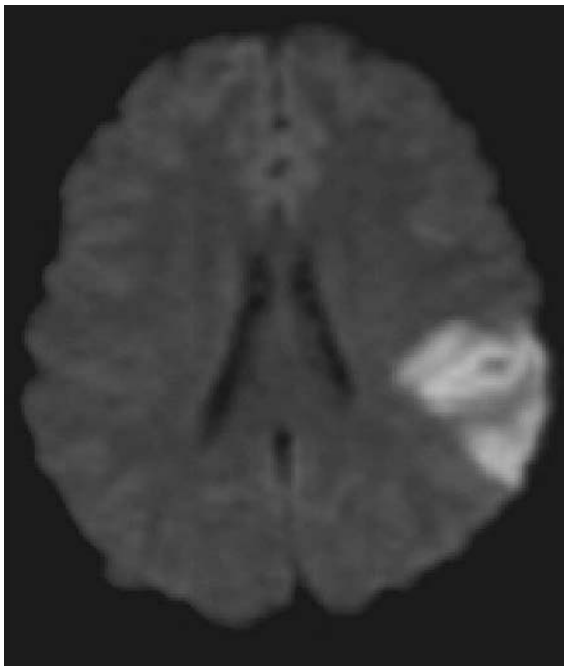

Figure 6. Diffusion Weighted Imaging in Neuropsychiatric SLE. This DWI demonstrates area of reduced diffusion (bright area), consistent with acute cerebral infarct in NPSLE.

6.3.4. Magnetization transfer imaging (MTI)

MTI has become a useful tool in the detection and quantification of diffuse brain disorders including NPSLE (Huizinga et al., 2001). MTI measures are lower in subjects who have had NPSLE, compared to those that have not (Bosma et al., 2000b). These reduced MTI measures indicate significant chronic injury to the myelin sheath in NPSLE. These findings closely resemble those found in multiple sclerosis, again suggesting chronic injury to the myelin sheath (Bosma et al., 2000b). MTI measures also correlate to cognitive dysfunction as measured by formal neurocognitive testing, indicating brain injury (Bosma et al., 2002). In active NPSLE, magnetization transfer ratios (MTR) histograms demonstrate the opposite pattern,

that is, higher values than controls or subjects with previously active NPSLE (Bosma et al., 2000a; Dehmeshki et al., 2002). These data indicate the MTI can measure brain injury in NPSLE, and differentiate chronic injury from acute injury caused by active NPSLE. Because of this MTI and related technologies have great promise for the diagnosis NPSLE.

6.3.5. Magnetic resonance relaxometry (MRR)

Magnetization resonance imaging can provide quantitative data regarding the relaxation properties of water in different chemical environments induced by inflammatory diseases of the brain (Sibbitt et al., 1995). The spin–lattice relaxation time (T1) and spin–spin relaxation time (T2) provide information regarding the total water in brain, the compartmentalization of brain water, and the degree of association between this water and macromolecules such as myelin and protein. The total quantity of water (proton density), T1, and T2 are responsible for the image intensity in both normal and abnormal tissues. Pathological processes—including edema, infarction, and inflammation—usually increase both T2 and proton density. T2 values have been reported to be elevated in normal-appearing white matter of SLE patients and other patients with inflammatory brain disease (Miller et al., 1989). Quantitative MRR has demonstrated increases in the T2 of both white and gray matter in NPSLE (Sadzot et al., 1995). The increase in T2 of white matter appears to be most closely associated with chronic injury, while the increase in T2 of gray matter is most closely associated with NPSLE disease activity. To measure T2 of specifically gray matter, white matter, and lesions, segmentation methods have been developed to measure these values in each pure tissue, since a contamination by CSF would falsely elevate the values (Fig. 7) (Petropoulos et al., 1999). MRR combined with conventional MRI may have a future role in the diagnosis of NPSLE.

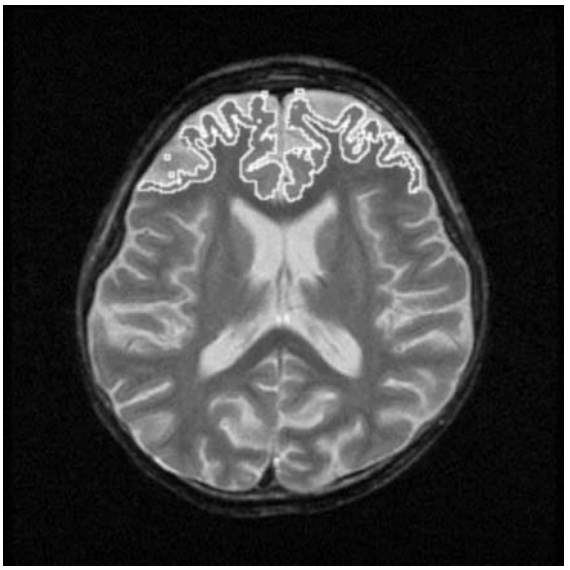

Figure 7. Magnetic Resonance Relaxometry in NPSLE. This GM segmentation of frontal lobe overlaid onto the T2-weighted image. Voxels classified as partial volume CSF are excluded. T2 values are calculated pixel-by-pixel for pure gray and white matter.

6.3.6. Magnetic resonance spectroscopy

MRS uses the same technology as MRI to determine the biochemical composition of tissue non-invasively and can be applied as an extra series to a clinical MRI (Chan, 1985; Iles, 1982; Shulman, 1979). MRS data are usually displayed as spectra with peaks reflecting the chemical structure and concentration of individual metabolites. MRS is sensitive for compounds, which are in fairly high concentrations (>1 mM) and in free solution. Most human studies have employed ^{1}H and ^{31}P (Matson and Weiner, 1999).

6.3.7. Proton magnetic resonance spectroscopy (MRS)

Proton MRS is particularly powerful because hydrogen (^{1}H) is the most abundant nucleus in living tissue and provides high signal strength (Hanstock et al., 1988; van Zijl et al., 1989; Luyten and den Hollander, 1986; Becker and Fisk, 1987; James et al., 1987; Frahm et al., 1989; Chance et al., 1987). Volume-localized, water-suppressed ^{1}H-MRS is the most common form of MRS performed on humans. ^{1}H-MRS of human brain reveals signals from N-acetylaspartate (NAA), creatine (Cre), choline (Cho), inositol (Ins), lactate (Lac), glutamate and glutamine (Glu/Gln), and lipid/macromolecules. Data may be expressed in ratio format (e.g. NAA/Cre) or, preferably, because of greater diagnostic power, as

absolute concentrations (Hennig et al., 1992; Barker et al., 1993; Alger et al., 1993; Brooks et al., 1999a). Fig. 8 is a T_2-weighted image from a 15 mm thick tissue slice in a patient with NPSLE. The grid represents the individual voxels, each of which provides a separate MR spectrum. Representative spectra from the subregions (i.e. A, B, C, or D) are also shown. ^{1}H-MRS is especially attractive because it provides metabolic data from a discrete piece of tissue and, because it can be combined with MRI, excellent anatomical detail.

N-acetylaspartate is located almost entirely in neurons and is the strongest peak in the ^{1}H-MR spectrum in adult brain (Hanstock et al., 1988; van Zijl et al., 1989; Luyten and den Hollander, 1986; Koller et al., 1984; Michaelis et al., 1991). Although the precise function of NAA in neuronal metabolism remains to be determined, reduced NAA has been noted in many diseases and suggests neuronal injury or death (Sibbitt and Sibbitt, 1993; 1994; Davie, 1994; Olson et al., 1992; Sappey-Marinier et al., 1992; Meyerhoff et al., 1994; Ford et al., 1992; Narayana et al., 1992; Haseler, 1998a,b). Reduced NAA is associated with neurocognitive dysfunction (Brooks et al., 1999b; Friedman et al., 1998; Friedman, 1999). In SLE, NAA is reduced in normal-appearing white matter, gray matter, and lesions compared with controls (Sibbitt and Sibbitt, 1993; Sibbitt et al., 1994, 1997; Davie et al., 1995; Brooks et al., 1997; Chinn et al., 1997; Colamussi et al., 1997; Friedman et al., 1998). Although not specific to SLE, these changes are widespread and more dramatic in focal lesions, indicating that focal lesions in SLE usually represent dead or injured tissue (Davie et al., 1995; Chinn et al., 1997; Brooks et al., 1997).

Reduced NAA in normal-appearing tissues in NPSLE correlates with small focal lesions elsewhere in the brain, suggesting that the decline in NAA may be largely due to extensive microlesions, most likely microinfarcts, too small to see by MRI (Friedman et al., 1998). This is supported by the close association between reduced NAA and IgG aPL in NPSLE, suggesting the presence of thrombotic microinfarct (Sabet, 1998). However, decreased NAA is also noted in patients with generalized seizures, psychosis, or confusional states which are not usually associated with thrombosis (Sibbitt and Sibbitt, 1993; Sibbitt et al., 1997), indicating that other causes of injury, including cytotoxic effects of antineuronal antibodies, cytokines, or small molecule neurocytotoxins might

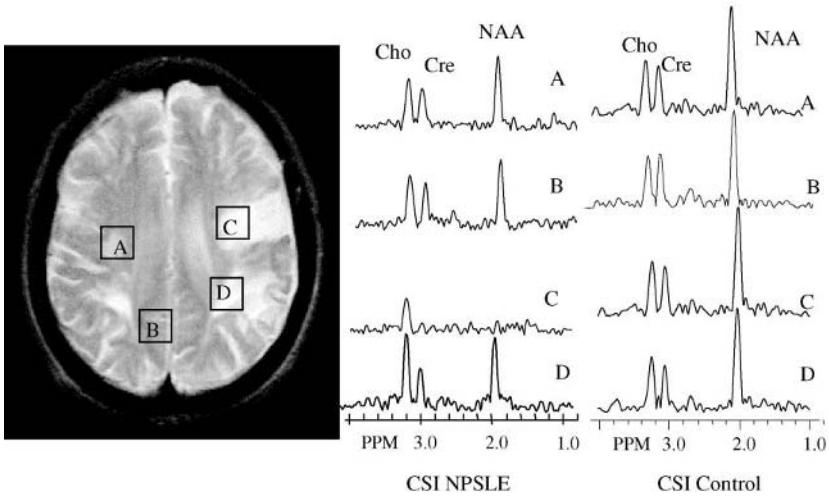

Figure 8. Magnetic Resonance Spectroscopy in NPSLE. Left: T2-weighted image of a NPSLE patient with multiple lesions showing the locations of spectroscopic voxels. (A) normal-appearing white, (B) normal-appearing gray, (C) and (D) hyperintense lesions. Middle: Spectra from voxels A, B, C, and D, demonstrating decreased NAA and increased Cho. These abnormalities are accentuated in the lesions (C and D) which demonstrate different spectroscopic patterns relative to NAA, Cre, and Cho, indicating considerable metabolic heterogeneity within the population of focal lesions. Right: The same areas in a normal control demonstrating greater NAA and less Cho.

be involved. Thus, NAA can be considered a sensitive and accurate measure of brain injury of various causes in NPSLE correlating closely with both neurocognitive dysfunction and MRI findings (Brooks et al., 1999b; Friedman et al., 1998).

Although NAA is generally decreased in NPSLE (Sibbitt and Sibbitt, 1993; Sibbitt et al., 1994), the dynamics and reversibility of NAA decline have not been determined. However, early results suggest that NAA declines with progressive disease (Mortilla et al., 2003). In other diseases, loss of NAA may be permanent, representing neuronal death (Koller et al., 1984; Sappey-Marinier et al., 1992), or may be partially reversible, presumably representing less serious injury (Davie, 1994). However, NAA is substantially reduced in both active NPSLE and SLE patients with a prior history of NPSLE, suggesting that the active events of NPSLE induce an initial irreversible injury, which results in chronically reduced NAA (Sibbitt et al., 1997). Thus, reduced NAA may most properly be a measure of NPSLE severity and outcome, rather than a measure of NPSLE activity per se (Sibbitt et al., 1997; Mortilla et al., 1997; Friedman et al., 1998; Rozell et al., 1998; Sabet, 1998).

Other neuronal metabolites seen by ^{1}H-MRS may have important roles in NPSLE. The Cho peak reflecting the sum of all MRS visible choline moieties ($-N^{+}(CH_3)_3$)—primarily phosphocholine, glycerophosphocholine, and choline—is often elevated in NPSLE, and appears to be related to disease activity, stroke, inflammation, or chronic white matter disease (Sibbitt and Sibbitt, 1993; Sibbitt et al., 1997; Brooks et al., 1997; Chinn et al., 1997; Friedman et al., 1998). Increased Cho is observed in NPSLE without obvious stroke, suggesting considerable neurologic disease invisible to conventional imaging (Sibbitt et al., 1997; Brooks et al., 1997; Friedman et al., 1998) (Fig. 7). There is evidence that increased Cho may be a measure of disease activity or reactive brain inflammation, and should be interpreted as an ominous sign (Sibbitt and Sibbitt, 1993; Sibbitt et al., 1997; Brooks et al., 1997; Brooks et al., 1999a,b). This is further supported by the finding that NAA/Cho is reduced in those NPSLE patients with cognitive impairment indicating that the functional impact is dependent on elevated Cho as well as reduced NAA (Brooks et al., 1999a,b).

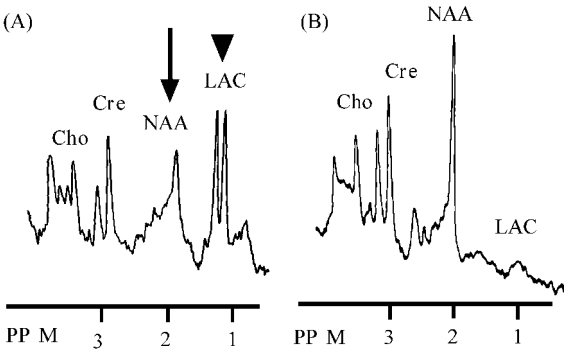

Figure 9. Neurometabolites of Active NPSLE. (A) A typical acute irreversible lesion of NPSLE demonstrating decreased N-acetylaspartic acid (NAA) (arrow), reduced choline (Cho), reduced creatine (Cre), and markedly elevated lactate (LAC) (arrowhead) which produces a doublet, (B) a typical spectrum of a reversible lesion in NPSLE demonstrating essentially normal N-acetylaspartic acid (NAA), choline (Cho), creatine (Cre), and no lactate (LAC).

The presence of upfield peaks at 0.9–1.6 ppm, arising from lipids, other macromolecules, and possibly lactate, is associated with elevated NPSLE activity and may represent injury (Sibbitt and Sibbitt, 1993; Sibbitt et al., 1997; Davie, 1994). Lactate is not frequently observed by MRS in NPSLE, but when present indicates an acute or resolving cerebral infarction (Sibbitt and Sibbitt, 1993; Sibbitt et al., 1994; Sibbitt et al., 1997; Brooks et al., 1997; Colamussi et al., 1997) (Fig. 9).

In summary, ^{1}H-MRS provides important brain metabolite data in NPSLE. N-acetylaspartate measures can be used in NPSLE to: (1) detect and measure brain injury unseen by other neuroimaging methods; (2) determine whether observed cognitive decline has an organic basis; and (3) determine if a lesion on MRI represents serious or non-serious brain injury. The significance of elevated Cho and lactate measure of inflammation, injury, infarct, or NPSLE activity (Friedman et al., 1998; Sibbitt and Brooks, 1997). Thus, ^{1}H-MRS cannot diagnose NPSLE, but can detect the presence of significant organic brain injury, anaerobic metabolism, and possibly, the activity of NPSLE.

6.3.8. Phosphorus MRS

^{31}P MRS assesses the pH, tissue energetics, and phosphorus-containing compounds in the brain,

including those involved in membrane synthesis and breakdown (Oberhaensli, 1987). Adenosine triphosphate (ATP), phosphocreatine (PCr), and inorganic phosphate (Pi) are the principal measures of energy status in living tissues and can be observed by ^{31}P-MRS (Shulman, 1979). Phosphodiesters (PDE) and phosphomonoesters (PME) are also prominent ^{31}P-MRS peaks (Radda, 1987; Glonek et al., 1982; Pettegrew et al., 1988; Miatto et al., 1986).

In active NPSLE, ^{31}P-MRS has demonstrated decreased ATP and PCr in deep white matter (Griffey et al., 1990). These changes were reversible with high dose corticosteroid therapy, and are consistent with cerebral ischemia, increased metabolic requirements, mitochondrial failure, paralysis of enzyme or transport systems, cell injury, or neuronal death (Pettegrew et al., 1988; James et al., 1987; Chance et al., 1987). Although ^{31}P-MRS provides a wealth of metabolic data, it should be considered a research technique because of its limited availability and the preliminary nature of studies in NPSLE.

6.4. Electrophysiologic testing

Electroencephalography (EEG) has only crude spatial resolution, but measures regional (usually cortical) brain electrical activity and is often abnormal in SLE, with figures from 20 to 73% (Feinglass et al., 1976; Gibson and Myers, 1976; Grigor et al., 1978; Kovacs et al., 1995; Khedr et al., 2001; Glanz et al., 2001). EEG may demonstrate diffuse cortical abnormalities with slowing, decreased amplitude, focal abnormalities, or seizure activity, and appears sensitive to seizure disorders, large lobar infarcts, CNS hemorrhage, and movement disorders (Szer et al., 1993; Shahar et al., 1998). Quantitative electroencephalography (QEEG) is more sensitive and specific than conventional EEG (Ritchlin et al., 1992) and is abnormal in 87% percent of patients with definite NPSLE, 74% of patients with probable NPSLE, and 28% of SLE patients without neuropsychiatric symptoms, consistent with the clinical course in many cases (Nobili et al., 1996). The most common EEG abnormalities are found in the left temporal region, which occur in 70% of subjects (Glanz et al., 2001). QEEG demonstrates theta and delta slow activity predominantly affecting the left hemisphere in 75% of patients with SLE (Glanz et al., 2001).

However, EEG and QEEG are hampered by a high false positive rate, non-specificity for NPSLE versus other forms of encephalopathy, and the inability to determine active from inactive (new versus old) disease. Indeed, EEG may demonstrate frequent abnormalities (19–67%) in patients with active NPSLE, but these abnormalities may not be statistically different from those SLE patients without active disease (Colamussi et al., 1995; Miguel et al., 1994; Lin et al., 1997; Reiff et al., 1997; Waterloo et al., 1999). Importantly, both EEG and QEEG cannot distinguish abnormalities associated with active NPSLE from unrelated confounding disorders common to SLE patients, including idiopathic epilepsy, cognitive disorders, drug effects, primary affective disorders, or metabolic encephalopathy (Abou-Khalil, 1995; Rodriguez et al., 1996; Rodriguez et al., 1998). Moreover, EEG and QEEG are not interpretable without a prior anatomic imaging modality for comparison.

Other electrophysiologic modalites including visual evoked response (VER) and brain-stem auditory evoked response (BAER) have been used to study NPSLE (Mongey et al., 1987; Khedr et al., 2001). Sixty-three percent of subjects with active NPSLE have abnormal VER and/or BAER, while 50% of those without active NPSLE demonstrated these abnormalties (Mongey et al., 1987). Other studies find lower prevalences (7–28%) of VER and BAER abnormalities in SLE (McNicholl et al., 1994; Omdal et al., 1989). These findings suggest that VER and BAER are measures of brain damage caused by NPSLE rather than a measure of active NPSLE. This is further suggested by the relationship of cognitive dysfunction, which is strongly affected by brain damage, to abnormal electrophysiologic tests (Khedr et al., 2001).

Thus, in the setting of NPSLE, EEG and QEEG are most useful as problem solving tools to: (1) confirm the presence of a seizure disorder; (2) to determine a brain abnormality when other methods fail; and (3) to confirm brain death, but do not specifically confirm the presence of NPSLE even when abnormal in a SLE patient (Waterloo et al., 1999). Thus, at the current state of development and knowledge, EEG or QEEG cannot be used to define NPSLE and should be ordered in only selected patients.

6.5. Conventional radionuclide brain scans

Although conventional radionuclide scanning was initially considered to be useful for NPSLE (Bennahum et al., 1974; Tan, 1978), this technique actually has little clinical utility because of poor sensitivity and specificity (Bluestein, 1987; Grigor et al., 1978; Feinglass et al., 1976; Gibson and Myers, 1976). However, the derivative radionuclide techniques of PET and SPECT have considerably more promise in NPSLE as discussed below.

6.5.1. Positron emission tomography

Positron emission tomography (PET) is a radionuclide technique which employs unstable isotopes of biologically relevant elements which decay rapidly, releasing a large burst of positrons (Pawlik and Heiss, 1989). The half-life of PET isotopes is relatively short, usually less than 2 h. The advantage of PET scanning over conventional nuclear medicine techniques is greater resolution and the ability to estimate compartmental kinetics and transform these data into images which represent metabolic activity. The main disadvantages of PET scanning are the large dose of radiation associated with each study, the necessity for a cyclotron to produce relevant isotopes, and the necessity for rapid, wet chemistry to produce biologically relevant isotopically labeled molecules. Since PET scanning is such an expensive undertaking requiring considerable infrastructure in order to perform routine scans, it is not widely available as a clinical tool, but remains largely a research technique confined to a few research institutions.

Glucose uptake and utilization can be quantified with PET, most commonly using 2-(^{18}F)-fluoro-2-deoxyglucose (FDG) (Reivich et al., 1979). Brain oxygen consumption can also be estimated using PET using inhaled ^{15}O-labeled molecular oxygen (Frackowiak et al., 1980). Cerebral blood flow can be determined employing the principle of diffusible tracer exchange, using ^{15}O-labeled water, ^{15}O-labeled carbon dioxide, or methyl fluoride labeled with ^{18}F or ^{11}C (Frackowiak et al., 1980; Herscovitch, 1983; Koeppe et al., 1985; Koseda-Dragan et al., 2001).

PET is often abnormal in active NPSLE demonstrating multiple focal defects in oxygen uptake, glucose uptake, and cerebral flow that may not be evident by CT or MRI (Holman, 1993; Pinching et al., 1978; Stoppe et al., 1990; Meyer et al., 1989; Carbotte et al., 1992; Kao, 1999a). The abnormalities characterized by hypometabolism may be matched with perfusion abnormalities or lesions by MRI or may occur in an isolated manner (Kao, 1999a; Weiner et al., 2003). Parieto-occipital hypometabolism by PET is often the most conspicuous finding in NPSLE occuring in up to 96%, followed by parietal regions at 32% (Otte et al., 1997; Weiner et al., 2003). The focal changes may be present in the presumed area of neurologic impairment and may improve after corticosteroid therapy or clinical resolution (Stoppe et al., 1990; Meyer et al., 1989; Carbotte, 1992, Guttman et al., 1987; Hiraiwa et al., 1983; Otte et al., 1998). ^{18}FDG-PET scans are abnormal 86–100% in active major NPSLE even in the setting of normal MRI (Otte et al., 1997; Kao, 1999a; Weiner et al., 2003). Perfusion defects are thought to be more sensitive for NPSLE than ^{18}FDG uptake abnormalities (Kao, 1999b). Thus, PET detects abnormalities in CBF and metabolite uptake suggesting hypometabolism or ischemia in active NPSLE.

Nonetheless, metabolism and perfusion abnormalities should be interpreted cautiously and should not be equated with active NPSLE. It should be recognized that generalized neuronal cell loss, decreased neuronal density, and focal lesions, which are all common in SLE but may not be obvious by CT or MRI, will result in hypometabolism and decreased perfusion. Indeed, the chronic brain injury measured by MRS and reflected in decreased NAA and/or increased Cho may be result in decreased perfusion by PET and still not reflect active disease. Thus, it should be expected that a large number of SLE patients without active NPSLE will demonstrate PET abnormalities (Herscovitch et al., 1983; Sibbitt and Sibbitt, 1993; Sibbitt et al., 1994; Sibbitt et al., 1997; Brooks et al., 1997; Friedman et al., 1998; Rozell et al., 1998; Sabet, 1998). In addition, focal or multifocal perfusion or metabolic abnormalities distant from an obvious focal lesion by MRI may not represent active disease, but rather diaschisis, that is, a decrease in local neuronal activity in a brain structure distant from a lesion due to the loss of afferent projection from the region of damage (Feeney and Baron, 1986).

Volume averaging is also a limitation of PET studies. Averaging of areas of decreased perfusion or

metabolism with adjacent normal tissue will create the artifactual perception that a PET lesion is much larger than it actually is (Powers, 1988). Volume averaging of perfused cortex with the increased volume of CSF in patients with cerebral atrophy will also create apparent, but artifactual PET abnormalities. Thus, PET studies should be corrected for the presence of cerebral atrophy, although this is rarely done (Herscovitch et al., 1986). Other drawbacks include the sensitivity to confounding disorders common to SLE, but not representing NPSLE. Indeed, decreased cerebral blood flow and metabolism are seen by PET in primary headache (Bednarczyk et al., 1998; Diener, 1997; Sadzot et al., 1995; Olesen et al., 1993), primary affective disorders (George et al., 1993; Dolan et al., 1994), non-SLE cognitive disorders (Heiss et al., 1991), and primary seizures (Ferrie et al., 1996; Pawlik, 1990). Finally, to be interpretable, PET requires an anatomic image, MRI or CT, to identify whether abnormalities are associated with an obvious focal lesion representing stroke or injury. Recent evidence suggests that PET may not add anything diagnostically beyond MRI alone (Sailer et al., 1997).

Thus, although PET may be sensitive to NPSLE, its usefulness is considerably degraded by non-specificity, cost, limited availability, radiation dose, inability to differentiate old from new lesions, sensitivity to confounding disorders common in SLE, and the need for parallel anatomic imaging. Due to these considerations, at the current state of development PET should be considered an important research technique, rather than a routine clinical examination.

6.5.1.1. Single photon emission computerized tomography (SPECT). SPECT uses computerized tomographic reconstruction to image single photons emitted by radiolabeled tracers. Inhaled ^{133}Xe gas, ^{123}I-iodoamphetamine (^{123}I-IMP), ^{99}Tc-HMPAO, and other labeled tracers are used for CBF determinations (Sharp et al., 1986). SPECT is often abnormal in both SLE and NPSLE demonstrating regional CBF abnormalities (Obrist et al., 1975; Kushner et al., 1987; Awada et al., 1987; Rogers et al., 1992; Koseda-Dragan et al., 2001). Preliminary evidence suggests acetazolamide-enhanced SPECT may be more sensitive than conventional SPECT or PET for NPSLE (Grunwald et al., 1995).

The most common abnormal SPECT scan pattern in patients with NPSLE is one of widespread small areas of decreased uptake at multiple sites, suggesting patchy hypoperfusion (Russo et al., 1998; Kovacs et al., 1995). Diffuse patchy areas of hypoperfusion are more typical of patients with acute diffuse NPSLE while focal areas of hypoperfusion typify focal NPSLE (Russo et al., 1998). Perfusion abnormalities in NPSLE by SPECT are most common in the distribution of the middle cerebral artery affecting the parietal (95–80%) and frontal lobes (57–65%), as well as the temporal lobes (46–57%), and basal ganglia (12–30%) (Colamussi et al., 1995; Lin et al., 1997). The cerebellum is usually the least common brain area to demonstrate abnormalities (Huang et al., 1997). Hypoperfusion tends to be pronounced in patients with more severe or complicated NPSLE manifestations (Colamussi et al., 1995, Huang et al., 1997), but is seen in a significant percentage of asymptomatic patients, usually around 20% (Emmi et al., 1993; Huang et al., 1997; Chen et al., 2002; Oku et al., 2003).

^{99}Tc-HMPAO SPECT is abnormal in 86–100% of patients with major NPSLE (stroke, seizures, psychosis), 33–85% of patients with minor NPSLE (headache, dizziness, recent memory impairment), and 0–50% of SLE patients without NPSLE (Rogers et al., 1992; Lin et al., 1997; Kovacs et al., 1995; Colamussi et al., 1995; Falcini, 1998; Kodama et al., 1995; Rubbert et al., 1993; Reiff et al., 1997; Kao, 1999a; Kikukawa et al., 2000). Longitudinal studies of SPECT are inconsistent, showing reversible abnormalities in certain studies and persistent abnormalities in others (Falcini, 1998; Huang et al., 1997; Nobili et al., 1996; Shahar et al., 1998; Russo et al., 1998; Szer et al., 1993; Reiff et al., 1997).

SPECT appears to be a sensitive technique for detecting the major manifestations of NPSLE, but is hampered by lack of specificity, and, paradoxically, by both insensitivity and oversensitivity in certain clinical situations (Nobili et al., 1996; Russo et al., 1998; Kovacs et al., 1995). Specificity for active NPSLE may be poor in certain situations (Holman, 1993; Hanly, 1998; Nossent et al., 1991; Emmi et al., 1993), and focal lesions by SPECT may or may not correlate to specific focal neurologic abnormalities (Kovacs et al., 1995; Falcini, 1998). SPECT cannot easily differentiate major from minor NPSLE (33–85% false

positive rate), but may be somewhat better for SLE without NPSLE, although many asymptomatic patients demonstrate lesions (Lin et al., 1997; Kovacs et al., 1995; Emmi et al., 1993). SPECT cannot easily differentiate: (1) irreversible stroke from reversible neurologic abnormalities (Lin et al., 1997; Kovacs et al., 1995); (2) new brain lesions from old (Kovacs et al., 1995); or (3) active NPSLE from confounding disorders such as chronic cognitive dysfunction (Rodriguez et al., 1998), primary headache (Afra et al., 1995; Basoglu et al., 1996; Obrist et al., 1975; Woods et al., 1994), primary seizures (Duncan, 1992), primary depression (George et al., 1993), or established cerebrovascular disease (194 Rodriguez, 1993) that frequently occur in SLE with or without NPSLE.

SPECT also has the disadvantage of not being useful as a stand-alone modality, and usually must be coupled with MRI to be interpretable (Colamussi et al., 1995). More perfusion defects by SPECT can be anticipated in SLE patients with fixed focal lesions, decreasing the utility of this technique in patients with complicated images by MRI (Colamussi et al., 1995). A recent report demonstrated that 100% of SLE subjects with abnormal MRI demonstrated abnormal rCBF by SPECT (Chen et al., 2002). However, only 60% of MRI-visible lesions are hypoperfused by SPECT, making interpretation difficult (Nomura et al., 1999). Thus, SPECT may not correlate with lesions evident by MRI (Emmi et al., 1993), can be quite abnormal with a normal MRI (Colamussi et al., 1997), or be normal with an abnormal MRI (Falcini, 1998; Chen et al., 2002). Increased SPECT findings are present with increased duration of disease, indicating that chronic changes as well as acute changes may be detected (Rubbert et al., 1993). However, SPECT integrated with MRI may be more effective. Patients with CNS manifestations have been demonstrated to have a markedly increased frequency of abnormal MRI and SPECT compared with those without CNS manifestations (80 versus. 7%; OR 56, CI 4.4–719, $P = 0.0003$) with a positive predictive value of abnormality in both techniques at 89% (Oku et al., 2003). Considering all of the above, and abnormal regional CBF by SPECT is more significant when the MRI is normal, and is a better technique when combined with MRI (Chen et al., 2002; Oku et al., 2003). On the other hand, in the evaluation of cognitive abnormalities in NPSLE, MRI is very useful, while regional CBF by SPECT provides no greater predicitive value than MRI alone (Waterloo et al., 2001).

SPECT certainly has an important research role, and further clinical trials may better define its clinical diagnostic role. Like PET, SPECT is limited as a stand-alone modality, and MRI is necessary to interpret results, thus, extra cost will be incurred if a SPECT scan is ordered. However, since SPECT uses commercially available tracers, it is much less expensive than PET and is a much more available technology.

7. Conclusion

Neuroimaging has greatly advanced the understanding of NPSLE, which appears to be caused by vascular and cellular injury, occurring through a number of mechanisms, which are still being defined. All of the neuroimaging methods provide different and in many ways, complementary information. However, angiography has only limited uses in NPSLE, particularly in certain cases where large to medium vessel disease is suspected and other methods are not applicable. MR angiography (MRA) should be used preferentially to radiocontrast angiography in the setting of stroke or other ischemic process where possible because of greater safety and lesser expense. MRI is the anatomic imaging modality of choice for NPSLE, and where available, should be used instead of CT. MRI is more sensitive for NPSLE than CT, and is particularly useful for demonstrating small focal lesions, chronic white matter disease, reversible abnormalities, brain stem lesions, and cord lesions. Magnetic resonance contrast studies, MRR, MTI, and DWI, but have not been extensively studied, but have specific uses where available. Although MRS cannot specifically diagnose NPSLE, MRS is sensitive and specific for brain injury in NPSLE, and may be useful to confirm an organic basis for neurocognitive decline, determine if a lesion on MRI represents serious or non-serious brain injury, determine the presence of anaerobic metabolism, and possibly, to confirm brain death. EEG and QEEG should be used as problem solving tools, most specifically when a seizure disorder is suspected among other applications. SPECT and PET may be more sensitive for NPSLE in general than MRI, CT, EEG, and QEEG, but have poor specificity

for differentiating between NPSLE versus SLE without NPSLE, reversible versus irreversible lesions, old versus new lesions, and differentiating NPSLE from confounding disorders common to SLE. PET and SPECT also detect considerable background abnormalities of uncertain significance, and must be combined with MRI to be interpretable in the context of NPSLE. Thus, PET and SPECT may be useful in subsets of NPSLE, but clearly are not a definitive for NPSLE and may be used judiciously in selected patients after MRI and other routine tests. It is to be recommended that all neuroimaging studies in NPSLE not be overinterpreted, and that the limitations of each method be understood and accepted. Further controlled trials will help determine the best combination of methods to diagnose NPSLE (West, 1994). However, the above neuroimaging methods will have an increasing role in the diagnosis of NPSLE.

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Key points

- Neuropsychiatric systemic lupus erythematosus (NPSLE) is one of the most common complications of SLE, occurring in up to 95% of SLE subjects.
- NPSLE is extremely difficult to diagnose, and neuroimaging is often essential to confirm the diagnosis and exclude confounding disease.
- Computed tomography is generally insensitive to NPSLE except for large cerebral infarctions or intracerebral hemorrhage.
- Magnetic resonance (MR) imaging is the gold standard and method of choice for anatomic imaging in NPSLE.
- FLAIR imaging is the MR technique of choice to determine brain lesions in NPSLE.
- MR spectroscopy is sensitive to neuronal injury or death, and to demyelination.
- MR DWI is sensitive to certain forms of NPSLE characterized by brain edema or injury.
- MR MTI is sensitive to chronic and active NPSLE.
- SPECT and PET are sensitive to NPSLE, but must have concomitant MR anatomic imaging in order to be interpretable, and do not exclude confounding syndromes.

References

Abou-Khalil, B., Fakhoury, T., Jennings, M., Moots, P., Warner, J., Kessler, R.M. 1995. Inhibitory motor seizures: correlation with centroparietal structural and functional abnormalities. Acta. Neurol. Scand. 91, 103–108.

ACR, 1999. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum. 41, 599–608.
This reference established the modern nosology for NPSLE which is to be used in research and clinical studies.

Adelman, D.C., Saltiel, E., Klinenberg, J.R. 1986. The neuropsychiatric manifestations of systemic lupus erythematosus: an overview. Sem. Arthritis Rheum. 15, 185–199.

Afra, J., Ertsey, C., Jelencsik, H., Dabasi, G., Panczel, G. 1995. SPECT and TCD studies in cluster headache patients. Funct. Neurol. 10, 259–264.

Aisen, A.M., Gabrielsen, T.O., McCune, W.J. 1985. MR imaging of systemic lupus erythematosus involving the brain. Am. J. Radiol. 144, 1027–1031.

Alger, J.R., Symko, S.C., Bizzi, A., Posse, S., DesPres, D.J., Armstrong, M.R.E. 1993. Absolute quantitation of short TE brain 1H-MR spectra and spectroscopic imaging data. J. Comput. Assist. Tomogr. 17, 191–199.

Appenzeller, S., Kobayashi, E., Costallat, L.T., Zanardi, V.D., RibeirNet, J.M., Damascen, B.P., Cendes, F. 2000. Magnetic resonance imaging in the evaluation of patients with aseptic meningoencephalitis and connective tissue disorders. Arq. Neuropsiquiatr. 58, 45–51.

April, R.S., Vansonnenberg, E. 1976. A case of neuromyelitis optica (Devic's syndrome) in systemic lupus erythematosus. Neurology 26, 1066–1070.

Awada, H.H., Mamo, H.L., Luft, A.G., Ponsin, J.C., Kahn, M.F. 1987. Cerebral blood-flow in systemic lupus-erythematosus with and without central nervous-system involvement. J. Neurol. Neurosurg. Psychiatry 50, 1597–1601.

Baca, V., Sanchez-Vaca, G., Martinez-Muniz, I., Ramirez-Lacayo, M., Lavalle, C. 1996. Successful treatment of transverse myelitis in a child with systemic lupus-erythematosus. Neuropediatrics 27, 42–44.

Barker, P.B., Soher, B.J., Blackband, S.J., Chatham, J.C., Mathews, V.P., Bryan, R.N. 1993. Quantitation of proton NMR spectra of the human brain using tissue water as an internal concentration standard. NMR Biomed. 6, 89–94.

Basoglu, T., Ozbenli, T., Bernay, I., Sahin, M., Onur, A., Demircali, A.E. 1996. Demonstration of frontal hypoperfusion in benign exertional headache by technetium-99m-HMPAO SPECT. J. Nucl. Med. 37, 1172–1174.

Beauchamp, N.J., Ulug, A.M., Passe, T.J. 1998. MR diffusion imaging in stroke: review and controversies. RadioGraphics 18, 1269–1283.

Becker, E.D., Fisk, C.L. 1987. NMR: Physical principles and current status as a biomedical technique. Ann. NY Acad. Sci. 508, 1–9.

Bednarczyk, E.M., Remler, B., Weikart, C., Nelson, A., Reed, R.C. 1998. Global cerebral blood flow, blood volume, and oxygen metabolism in patients with migraine headache. Neurology 50, 1736–1740.

Bell, C.L., Partington, C., Robbins, M., Graziano, F., Turski, P., Kornguth, S. 1991. Magnetic-resonance-imaging of central-nervous-system lesions in patients with lupus-erythematosus: correlation with clinical remission and antineurofilament and anticardiolipin antibody-titers. Arth. Rheum. 34, 432–441.

Belmont, H.M., Abramson, S.B., Lie, J.T. 1996. Pathology and pathogenesis of vascular injury in systemic lupus erythematosus: Interactions of inflammatory cells and activated endothelium. Arth. Rheum. 39, 9–22.

Bennahum, D.A., Messner, R.P., Shoop, J.D. 1974. Brain scan findings in central nervous system involvement by lupus erythematosus. Ann. Intern. Med. 81, 763–765.

Bentson, J., Rezon, M., Winters, J., Wilson, G. 1978. Steroids and apparent cerebral atrophy on computed tomography scans. J. Comp. Assist. Tomogr. 2, 16–23.

Bilaniuk, L.T., Patell, S., Zimmerman, R.A. 1977. Central nervous system disease in systemic lupus erythematosus. Radiology 124, 119–121.

Bluestein, H.G. 1987. Neuropsychiatric manifestations of systemic lupus erythematosus. N. Eng. J. Med. 317, 309–311.

Bluestein, H.G. 1992. The central nervous system in systemic lupus erythematosus. In: R.G. Lahita (Ed.), Systemic Lupus Erythematosus, 2nd ed., Churchill Livingstone pp. 639–655.

Bosma, G.P., Rood, M.J., Huizinga, T.W., de Jong, B.A., Bollen, E.L., van Buchem, M.A. 2000a. Detection of cerebral involvement in patients with active neuropsychiatric systemic lupus erythematosus by the use of volumetric magnetization transfer imaging. Arthritis Rheum. 43, 2428–2436.

This reference applies the modern technique of MTR to NPSLE, and finds significant and perhaps diagnostic differences between active and inactive NPSLE.

Bosma, G.P., Rood, M.J., Zwinderman, A.H., Huizinga, T.W., van Buchem, M.A. 2000b. Evidence of central nervous system damage in patients with neuropsychiatric systemic lupus erythematosus, demonstrated by magnetization transfer imaging. Arthritis Rheum. 43, 48–54.

Bosma, G.P., Middelkoop, H.A., Rood, M.J., Bollen, E.L., Huizinga, T.W., van Buchem, M.A. 2002. Association of global brain damage and clinical functioning in neuropsychiatric systemic lupus erythematosus. Arthritis Rheum. 46, 2665–2672.

Bosma, G.P., Huizinga, T.W., Mooijaart, S.P., Van Buchem, M.A. 2003. Abnormal brain diffusivity in patients with neuropsychiatric systemic lupus erythematosus. AJNR Am. J. Neuroradiol. 24, 850–854.

This is one of the most important studies of diffusion abnormalities present in the brain of NPSLE subjects.

Boumpas, D.T., Patronas, A.J., Dalakas, M.C., Hakim, C.A., Klippel, J.H., Balow, J.E. 1990. Acute transverse myelitis in systemic lupus erythematosus: magnetic resonance imaging and review of the literature. J. Rheumatol. 17, 89–92.

Bradley, W.G., Bydder, G.M. 1997. Advanced MR Imaging Techniques. Mosby Inc, St Louis.

Brant-Zawadzki, M.N., Atkinson, D., Detrick, M. 1996. Fluid attenuated inversion recovery (FLAIR) for assessment of cerebral infarction: initial clinical experience in 50 cases. Stroke 27, 187.

Brant-Zsawadzki, M., Mills, C.M., Norma, D. 1983. Central nervous system. In: A.R. Margulis, C.B. Higgins, L. Kaufman (Eds.), Clinical Magnetic Resonance Imaging. Radiology Research and Education Foundation, San Francisco, p. 91.

Brooks, W.M., Sabet, A., Sibbitt, W.L. Jr., Barker, P.B., van Zijl, P.C.M., Duyn, J.H. 1997. Neurochemistry of brain lesions determined by spectroscopic imaging in systemic lupus erythematosus. J. Rheumatol. 24, 2323–2329.

This study demonstrates that lesions present by MRI in NPSLE have markedly abnormal neurometabolites.

Brooks, W.M., Friedman, S.D., Stidley, C.A. 1999a. Reproducibility of ^{1}H-MRS *in vivo*. Magn. Reson. Med. 41, 193–197.

Brooks, W.M., Jung, R.E., Ford, C.C., Greinel, E.J., Sibbitt, W.L. Jr. 1999b. Relationship between neurometabolite derangement and neurocognitive dysfunction in systemic lupus erythematosus. J. Rheum. 26, 81–85.

Bruyn, G.A. 1995. Controversies in lupus: nervous system involvement. Ann. Rheum. Dis. 54, 159–167.

Carbotte, R.M., Denburg, S.D., Denburg, J.A. 1986. Prevalence of cognitive impairment in systemic lupus erythematosus. J. Nervous Mental. Dis. 174, 357–364.

Carbotte, R.M., Denburg, S.D., Denburg, J.A., Nahmias, C., Garnett, E.S. 1992. Fluctuating cognitive abnormalities and cerebral glucuse metabolism in neuropsychiatric systemic lupus erythematosus. J. Neurol. Neurosurg. Psychiatry 55, 1054–1059.

Carette, S., Urowitz, M.B., Grossman, H., St. Louis, E.L. 1982. Cranial computerized tomography in systemic lupus erythematosus. J. Rheumatol. 9, 855–859.

Chan, L. 1985. The current status of magnetic resonance spectroscopy; basic and clinical aspects. West J. Med. 143, 773.

Chance, B., Leigh, J.S. Jr., Nioka, S., Sinwell, T., Younkin, D., Smith, D.S. 1987. An approach to the problem of metabolic heterogeneity in the brain: ischemia and reflow after ischemia. Ann. NY Acad. Sci. 508, 309–320.

Chen, J.J., Yen, R.F., Kao, A., Lin, C.C., Lee, C.C. 2002. Abnormal regional cerebral blood flow found by technetium-99m ethyl cysteinate dimer brain single

photon emission computed tomography in systemic lupus erythematosus patients with normal brain MRI findings. Clin. Rheumatol. 21, 516–519.
This study further demonstrates that even apparently normal brain is affected by disordered cerebral perfusion in NPSLE.

Chinn, R.J.S., Wilkinson, I.D., Hall-Craggs, M.A., Paley, M.N.J., Shorthall, E., Carter, S. 1997. Magnetic resonance imaging of ther brain and cerebral proton spectroscopy in patients with systemic lupus erythematosus. Arth. Rheum. 40, 36–46.

Colamussi, P., Giganti, M., Cittanti, C., Dovigo, L., Trotta, F., Tola, M.R. 1995. Brain single-photon emission tomography with 99mTc-HMPAO in neuropsychiatric systemic lupus erythematosus: relations with EEG and MRI findings and clinical manifestations. Eur. J. Nucl. Med. 22, 17–24.

Colamussi, P., Trotta, F., Ricci, R., Cittanti, C., Govoni, M., Barbarella, G. 1997. Brain perfusion SPET and proton magnetic resonance spectroscopy in the evaluation of two systemic lupus erythematosus patients with mild neuropsychiatric manifestations. Nucl. Med. Commun. 18, 269–273.

Davie, C.A., Hawkins, C.P., Barker, G.J., Brennan, A., Tofts, P.S., Miller, D.H. 1994. Serial proton magnetic resonance spectroscopy in acute multiple sclerosis lesions. Brain 117, 49–58.

Davie, C.A., Feinstein, A., Kartsounis, L.D., Barker, G.J., McHugh, N.J., Walport, M.J. 1995. Proton magnetic resonance spectroscopy of systemic lupus erythematosus involving the central nervous system. J. Neurol. 242, 522–528.

De Coene, B., Hajnal, J.V., Gatehouse, P., Longmore, D.B., White, S.J., Oatridge, A., Pennock, J.M., Young, I.R., Bydder, G.M. 1992. MR of the brain using fluid-attenuated inversion recovery (FLAIR) pulse sequences. AJNR Am. J. Neuroradiol. 13, 1555–1564.

Dehmeshki, J., Van Buchem, M.A., Bosma, G.P., Huizinga, T.W., Tofts, P.S. 2002. Systemic lupus erythematosus: diagnostic application of magnetization transfer ratio histograms in patients with neuropsychiatric symptoms—initial results. Radiology 222, 722–728.

Denburg, S.D., Denburg, J.A., Carbotte, R.M., Fisk, J.D., Hanly, J.G. 1993. Cognitive deficits in system lupus erythematosus. Rheum. Dis.Clinics N. Am. 19, 815–831.

Devinsky, O., Petito, C.K., Alonso, D.R. 1988. Clinical and neuropathological findings in systemic lupus erythematosus: The role of vasculitis, heart emboli, and thrombotic thrombocytopenic purpura. Ann. Neurol. 23, 380–384.
This is one of classic articles on the neuropathology of NPSLE.

Diener, H.C. 1997. Positron emission tomography studies in headache. Headache 37, 622–625.

Dolan, R.J., Bench, C.J., Brown, R.G., Scott, L.C., Frackowiak, R.S. 1994. Neuropsychological dysfunction in depression: the relationship to regional cerebral blood flow. Psychol. Med. 24, 849–857.

Duncan, R. 1992. Epilepsy, cerebral blood flow, and cerebral metabolic rate. Cerebrovasc. Brain Metab. Rev. 4, 105–121.

Ebisu, T., Naruse, S., Horikawa, Y. 1993. Discrimination between different types of white matter edema with diffusion-weighted MR imaging. J. Magn. Reson. Imaging 3, 863–868.

Ellis, S.G., Verity, M.A. 1977. Central nervous systemic involvement in systemic lupus erythematosus: a review of neuropathological findings in 57 cases, 1955–1977. Semin. Arthritis Rheum. 8, 212–221.
This is the most important pathologic studies of NPSLE.

Ellison, D., Gatter, K., Heryet, A., Esiri, M. 1993. Intramural platelet deposition in cerebral vasculopathy of systemic lupus erythematosus. J. Clin. Pathol. 46, 37–40.

Emmi, L., Bramati, M., Cristofaro, M.T.R., Mascalchi, M., Dalpozzo, G., Marconi, G.P. 1993. MRI and SPECT investigations of the CNS in SLE patients. Clin. Exp. Rheumatol. 11, 13–20.

Falcini, F., De Cristofaro, M.T., Ermini, M., Guarnieri, M., Massai, G., Olmastroni, M. 1998. Regional cerebral blood flow in juvenile systemic lupus erythematosus: a prospective SPECT study. Single photon emission computed tomography. J. Rheumatol. 25, 583–588.

Falk, R.J., Dalmasso, A.P., Kim, Y., Lam, S., Michael, A. 1985. Radioimmunoassay of the attack complex of complement in serum from patients with systemic lupus erythematosus. N. Engl. J. Med. 312, 1594–1599.

Feeney, D.M., Baron, J. 1986. Diaschisis. Stroke 17, 817–830.

Feinglass, E.J., Arnett, F.C., Dorsch, C.A., Zizic, M., Stevens, M.B. 1976. Neuropsychiatric manifestations of systemic lupus erythematosus: diagnosis, clinical spectrum, and relationship to other features of the disease. Medicine (Baltimore) 55, 323–339.

Ferrie, C.D., Maisey, M., Cox, T., Polkey, C., Barrington, S.F., Panayiotopoulos, C.P. 1996. Focal abnormalities detected by 18FDG PET in epileptic encephalopathies. Arch. Dis. Child. 75, 102–107.

Ford, C.C., Griffey, R.H., Matwiyoff, N.A., Rosenberg, G.A. 1992. Multivoxel MRS of stroke. Neurology 42, 1408–1412.

Frackowiak, R.S.J., Lenzi, G.-L., Jones, T., Heather, J.D. 1980. Quantitative measurement of regional cerebral blood flow and oxygen metabolism in man using 15O and positron emission tomography: Theory, procedure, and normal values. J. Comp. Assist. Tomogr. 4, 727–736.

Frahm, J., Bruhn, H., Gyngell, M.L., Merboldt, K.D., Haenicke, W., Sauter, R. 1989. Localized proton NMR spectroscopy in different regions of the human brain in vivo. Relaxation times and concentrations of cerebral metabolites. Mag. Res. Med. 11, 47–63.

Friedman, S.D., Stidley, C., Brooks, W.M., Hart, B.L., Sibbitt, W.L. Jr. 1998. Brain injury and neurometabolic abnormalities in systemic lupus erythematosus. Radiology 209, 79–84.

Friedman, S.D., Brooks, W.M., Jung, R., Hart, B.L., Yeo, R.A. 1998. Proton MR spectroscopic findings correspond to diffuse neuropsychological function in traumatic brain injury. AJNR: Am. J. Neuroradiol. 19, 1879–1895.

Funata, N. 1979. Cerebral vascular changes in systemic lupus erythematosus. Bull. Tokyo Med. Dent. Univ. 26, 91–112.

Futran, J., Shore, A., Urowitz, M.B., Grossman, H. 1987. Subdural hematoma in systemic lupus erythematosus: report and review of the literature. J. Rheumatol. 14, 378–383.

Garcia-Raya, P.G., Gil-Aguado, A., Simon-Merlo, M.J., Lavilla-Uriol, P., Vega-Astudillo, A., Garcia-Puig, J. 1994. Massive cerebral calcification in systemic lupus erythematosus: report of an unusual case. Lupus 3, 133–135.

Gaylis, N.B., Altman, R.D., Ostrov, S., Quencer, R. 1982. The selective value of computed tomography of the brain in cerebritis due to systemic lupus erythematosus. J. Rheumatol. 9, 850–854.

George, M.S., Ketter, T.A., Post, R.M. 1993. SPECT and PET imaging in mood disorders. J. Clin. Psychiatry 54, 6–13.

Gibson, T., Myers, A.R. 1976. Nervous system involvement in systemic lupus erythematosus. Ann. Rheum. Dis. 35d, 398–406.

Ginzler, E.M. 1991. Clinical manifestations of disease activity, its measurement, and associated morbidity in systemic lupus erythematosus. Curr. Opin. Rheumatol. 3, 780–788.

Ginzler, E.M., Schorn, K. 1988. Outcome and prognosis in systemic lupus erythematosus. Rheum. Dis. Clin. North Am. 14, 67–78.

Glanz, B.I., Laoprasert, P., Schur, P.H., Robertson-Thompson, A., Khoshbin, S. 2001. Lateralized EEG findings in patients with neuropsychiatric manifestations of systemic lupus erythematosus. Clin. Electroencephalogr. 32, 14–19.

Glonek, T., Kopp, S.J., Kot, E., Pettegrew, J.W., Harrison, W.H., Cohen, M.M. 1982. P-31 nuclear magnetic resonance analysis of brain: The perchloric acid extract spectrum. J. Neurochem. 39, 1210.

Gonzalez-Scarano, F., Lisak, R.P., Bilaniuk, L.T., Zimmerman, R.A., Atkins, P.C., Zweiman, B. 1979. Cranial computed tomography in the diagnosis of systemic lupus erythematosus. Ann. Neurol. 5, 158–165.

Griffey, R.H., Brown, M.S., Bankhurst, A.D., Sibbitt, R.R., Sibbitt, W.L. Jr. 1990. Depletion of high-energy phosphates in the central nervous system of patients with systemic lupus erythematosus, as determined by phosphorus-31 nuclear magnetic resonance spectroscopy. Arth. Rheum. 33, 827–833.

This study demonstrates abnormalities in high energy phosphates in NPSLE.

Grigor, R., Edmonds, J., Lekonia, R., Bresnihan, B., Hughes, G.R. 1978. Systemic lupus erythematosus. A prospective analysis. Ann. Rheum. Dis. 37, 121–128.

Grunwald, F., Schomburg, A., Badali, A., Ruhlmann, J., Pavics, L., Biersack, H.J. 1995. 18FDG PET and acetazolamide-enhanced 99mTc-HMPAO SPET in systemic lupus erythematosus. Eur. J. Nucl. Med. 22, 1073–1077.

Guttman, M., Lang, A.E., Garnett, E.S., Nahmias, C., Firnau, G., Tyndel, F.J. 1987. Regional cerebral glucose metabolism in SLE chorea: further evidence that striatal hypometabolism is not a correlate of chorea. Mov. Disord. 2, 201–210.

Hachulla, E., Michonpasturel, U., Leys, D., Pruvo, J.P., Queyrel, V., Masy, E. 1998. Cerebral magnetic resonance-imaging in patients with or without antiphospholipid antibodies. Lupus 7, 124–131.

Hajnal, J.V., Bryant, D.J., Kasuboski, L. 1992. Use of fluid attenuated inversion recovery (FLAIR) pulse sequences in MRI of the brain. J. Comput. Assist. Tomogr. 16, 841–847.

Hammad, A., Tsukada, Y., Torre, N. 1992. Cerebral occlusive vasculopathy in systemic lupus erythematosus and speculation on the part played by complement. Ann. Rheum. Dis. 51, 550–552.

Hanly, J.G. 1998. Single photon emission computed tomography scanning in neuropsychiatric systemic lupus erythematosus. J. Rheumatol. 25, 401–403.

Hanly, J.G., Walsh, N.M.G., Sangalang, V. 1992. Brain pathology in systemic lupus erythematosus. J. Rheumatol. 19, 732–741.

Hanly, J.G., Walsh, N.M., Fisk, J.D., Eastwood, B., Hong, C., Sherwood, G. 1993. Cognitive impairment and autoantibodies in systemic lupus erythematosus. Brit. J. Rheumatol. 32, 291–296.

Hanstock, C.C., Rothman, D.L., Pritchard, J.W., Jue, T., Shulman, R.G. 1988. Spatially localized 1H NMR spectra of metabolites in the human brain. Proc. Natl. Acad. Sci. USA 85, 1821–1825.

Haseler, L.J., Sibbitt, W.L. Jr., Mojtahedzadeh, H.N., Reddy, S., Agarwal, V.P., McCarthy, D.M., Proton, M.R. 1998a. spectroscopic measurement of neurometabolites in hepatic encephalopathy during oral lactulose therapy. AJNR: Am. J. Neurorad. 19, 1681–1686.

Haseler, L.J., Sibbitt, W.L. Jr., Sibbitt, R.R., Hart, B.L. 1998b. Neurologic, MR imaging, and MR spectroscopic findings in eosinophilia myalgia syndrome. AJNR: Am. J. Neurorad. 19, 1687–1694.

Heiss, W.D., Kessler, J., Szelies, B., Grond, M., Fink, G., Herholz, K. 1991. Positron emission tomography in the differential diagnosis of organic dementias. J. Neural Transm. Suppl. 33, 13–19.

Hennig, J., Pfister, H., Ernst, T., Ott, D. 1992. Direct absolute quantification of metabolites in the human brain with in vivo localized proton spectroscopy. NMR BioMed. 5, 193–199.

Herscovitch, P., Markham, J., Raichle, M.E. 1983. Brain blood flow measured with intravenous $H_2^{15}O$. I. Theory and error analysis. J. Nucl. Med. 24, 782–789.

Herscovitch, P., Auchus, A.P., Gado, M., Chi, D., Raichle, M.E. 1986. Correction of positron emission tomography data for cerebral atrophy. J. Cereb. Blood Flow Metab. 6, 120–124.

Hinchey, J., Chaves, C., Appignani, B., Breen, J., Pao, L., Wang, A. 1996. A reversible posterior leukoencephalopathy syndrome. N. Engl. J. Med. 334, 494–500.

Hiraiwa, M., Nonaka, C., Abe, T., Iio, M. 1983. Positron emission tomography in systemic lupus erythematosus: relation of cerebral vasculitis to PET findings. AJNR: Am. J. Neuroradiol. 4, 541–543.

Holman, B.L. 1993. Functional imaging in systemic lupus erythematosus: an accurate indicator of central nervous sytem involvement? Arthritis Rheum. 36, 1193–1195.

Hopkins, P., Belmont, H.M., Buyon, J., Philips, M., Weissman, G., Abramson, S.B. 1988. Increased levels of plasma anaphylatoxins in systemic lupus erythematosus predict flares of the disease and may elicit vascular injury in lupus cerebritis. Arthritis Rheum. 31d, 632–641.

Horoshovski, D., Amital, H., Katz, M., Shoenfeld, Y. 1995. Pseudotumour cerebri in SLE. Clin. Rheumatol. 14, 708–710.

Huang, J.L., Yeh, K.W., You, D.L., Hsieh, K.H. 1997. Serial single photon emission computed tomography imaging in patients; with cerebral lupus during acute exacerbation and after treatment. Pediatr. Neurol. 17, 44–48.

Hughson, M.D., McCarty, G.A., Sholer, C.M., Brumback, R.A. 1993. Thrombotic cerebral arteriopathy in patients with the antiphospholipid syndrome. Mod. Pathol. 6, 644–653.

Huizinga, T.W., Steens, S.C., van Buchem, M.A. 2001. Imaging modalities in central nervous system systemic lupus erythematosus. Curr. Opin. Rheumatol. 13, 383–388.

Iles, R.A., Stevens, A.N., Griffiths, J.R. 1982. NMR studies of metabolites in living tissue. Prog. NMR Spectrosc. 15, 49.

Ishikawa, O., Ohnishi, K., Miyachi, Y., Ishizaka, H. 1994. Cerebral lesions in systemic lupus erythematosus detected by magnetic resonance imaging. Relationship to anticardiolipin antibody. J. Rheumatol. 21, 87–90.

Jacobs, L., Kinkel, P.R., Costello, P.B., Alukal, M.K., Kinkel, W.R., Green, F.A. 1988. Central nervous systemic lupus erythematosus: the value of magnetic resonance imaging. J. Rheumatol. 15, 601–606.

James, T.L., Chang, L.-H., Chew, W., Gonzales-Mendez, R., Litt, L., Mills, P. 1987. In situ brain metabolism. Ann. NY Acad. Sci. 508, 64–80.

Jarek, M., West, S.G., Baker, M.R., Rak, K.M. 1994. Magnetic resonance imaging in systemic lupus erythematotus patients without a history of neuropsychiatric lupus erythematosus. Arth. Rheum. 37, 1609–1613.

Johnson, R.T., Richardson, E.P. 1968. The neurological manifestations of systemic lupus erythematosus. A clinical-pathological study of 24 cases and review of the literature. Medicine 47, 337–369.

Jonsen, A., Bengtsson, A.A., Nived, O., Ryberg, B., Sturfelt, G. 2002. Outcome of neuropsychiatric systemic lupus erythematosus within a defined Swedish population: increased morbidity but low mortality. Rheumatology (Oxford) 41, 1308–1312.

Kao, C.H., Ho, Y.J., Lan, J.L., Changlai, S.P., Liao, K.K., Chieng, P.U. 1999a. Discrepancy between regional cerebral blood flow and glucose metabolism of the brain in systemic lupus erythematosus patients with normal brain magnetic resonance imaging findings. Arthritis Rheum. 42, 61–68.

Kao, C.H., Lan, J.L., ChangLai, S.P., Liao, K.K., Yen, R.F., Chieng, P.U. 1999b. The role of FDG-PET, HMPAO-SPET and MRI in the detection of brain involvement in patients with systemic lupus erythematosus. Eur. J. Nucl. Med. 26, 129–134.

This study demonstrates the heterogenous brain-perfusion abnormalities in NPSLE.

Khedr, E.M., Khedr, T., Farweez, H.M., Abdella, G., El Beih, E.A. 2001. Multimodal electroneurophysiological studies of systemic lupus erythematosus. Neuropsychobiology 43, 204–212.

Kikukawa, K., Toyama, H., Katayama, M., Nishimura, T., Ejiri, K., Minami, K., Matsumura, K., Miyama, H., Emoto, Y., Maeda, H., Senda, K., Takeuchi, A., Oshima, H., Yoshida, S., Torikai, K., Koga, S. 2000. Early and delayed Tc-99m ECD brain SPECT in SLE patients with CNS involvement. Ann. Nucl. Med. 14, 25–32.

Kinney, E.L., Berdoff, R.L., Rao, N.S., Fox, L.M. 1979. Devic's syndrome and systemic lupus erythematosus: a case report with necropsy. Arch. Neurol. 36, 643–644.

Kinoshita, M., Iwana, K., Shinoura, H., Aotsuka, S., Sumiya, M. 1998. Progressive multifocal leukoencephalopathy resembling central-nervous system sytemic lupus erythematosus. Clin. Exp. Rheumatol. 16, 313–315.

Kirk, A., Kertesz, A., Polk, M.J. 1991. Dementia with leukoencephalopathy in systemic lupus erythematosus. Can. J. Neurol. Sci. 18, 344–348.

Kodama, K., Okada, S., Hino, T., Takabayashi, K., Nawata, Y., Uchida, Y. 1995. Single photon emission computed tomography in systemic lupus erythematosus with psychiatric symptoms. J. Neurol. Neurosurg. Psychiatry 58, 307–311.

Koeppe, R.A., Holden, J.E., Polcyn, R.E., Nickles, R.J., Hutchins, G.D., Weese, J.L. 1985. Quantitation of local cerebral flow and partition coefficient without arterial sampling: theory and validation. J. Cereb. Blood Flow Metab. 5, 214–223.

Koller, K.J., Zaczek, R., Coyle, J.T. 1984. N-aceytl-aspartylglutamate: region levels in rat brain and the effects of brain lesions as determined by a new HPLC method. J. Neurochem. 43, 1136–1142.

Koseda-Dragan, M., Lass, P., Hebanowski, M. 2001. Cerebral blood flow in systemic lupus erythematosus. Lupus 10, 519–520.

Kovacs, J.A., Urowitz, M.B., Gladman, D.D. 1993. Dilemmas in neuropsychiatric lupus. Rheum. Dis. Clinic N. Am. 19, 795–814.

Kovacs, J.A., Urowitz, M.B., Gladman, D.D., Zeman, R. 1995. The use of single photon emission computerized tomography in neuropsychiatric SLE: a pilot study. J. Rheumatol. 22, 1247–1253.

Kozora, E., West, S.G., Kotzin, B.L., Julian, l., Porter, S., Bigler, E. 1998. Magnetic resonance imaging abnormalities and cognitive defects in systemic lupus erythematosus patients without overt central nervous system disease. Arth. Rheum. 41, 41–47.

Kushner, M.J., Chawluk, J., Fazekas, F., Mandell, B., Burke, A., Jaggi, J. 1987. Cerebral blood flow in systemic lupus erythematosus with or without cerebral complications. Neurology 37, 1596–1598.

Levine, S.R., Deegan, M.J., Futrell, N., Welch, K.M. 1990. Cerebrovascular and neurologic disease associated with antiphospholipid antibodies: 48 cases. Neurology 40, 1181–1189.

Lin, W.Y., Wang, S.J., Yen, T.C., Lan, J.L. 1997. Technetium-99m-HMPAO brain SPECT in systemic lupus erythematosus with CNS involvement. J. Nucl. Med. 38, 1112–1115.

Luyten, P.R., den Hollander, J.A. 1986. Observation of metabolites in the human brain by MR spectroscopy. Radiology 161, 795–798.

Marshal, C.M. 1982. The Physical Basis of Computed Tomography. Warren H Green Inc, St. Louis.

Matson, M.W., Weiner, M.W. 1999. Spectroscopy. In: D.D. Stark, WG Bradley (Eds.), Magnetic Resonance Imaging, 3rd ed., Mosby Inc, St. Louis, pp. 181–214.

McAbee, G.N., Barasch, E.S. 1990. Resolving MRI lesions in lupus erythematosus selectively involving the brainstem. Pediatr. Neurol. 6, 186–189.

McCune, W.J., MacGuire, A., Aisen, A., Gebarski, S. 1988. Identification of brain lesions in neuropsychiatric systemic lupus erythematosus by magnetic resonance scanning. Arthr. Rheum. 31, 159–166.

McLean, B.N., Miller, D., Thompson, E.J. 1995. Oligoclonal banding of IgG in CSF, blood–brain barrier function, and MRI

findings in patients with sarcoidosis, systemic lupus erythematosus, and Behcet's disease involving the nervous system. J. Neurol. Neurosurg. Psychiatry 58, 548–554.

McNicholl, J.M., Glynn, D., Mongey, A.B., Hutchinson, M., Bresnihan, B. 1994. A prospective study of neurophysiologic, neurologic and immunologic abnormalities in systemic lupus erythematosus. J. Rheumatol. 21, 1061–1066.

Meyer, G.J., Schober, O., Stoppe, G., Wildhagen, K., Seidel, J.W., Hundeshagen, H. 1989. Cerebral involvement in systemic lupus erythematosus (SLE): comparison of positron emission tomography (PET) with other imaging methods. Psychiatry Res. 29, 367–368.

Meyerhoff, D.J., MacKay, S., Poole, N., Dillon, W.P., Weiner, M.W., Fein, G. 1994. N-acetylaspartate reductions measured by 1H MRS in cognitively impaired HIV-seropositive individuals. Magn. Reson. Imag. 12, 653–659.

Miatto, O., Gonzalez, G., Buonanno, F. 1986. In vitro 31P NMR spectroscopy detects altered phospholipid metabolism in Alzheimer's disease. Can. J. Neurol. Sci. 13, 535.

Michaelis, T., Merboldt, K.-D., Haenicke, W., Gyngell, M.L., Bruhn, H., Frahm, J. 1991. On the identification of cerebral metabolites in localized 1-H NMR spectra of human brain in vivo. NMR BioMed. 4, 90–98.

Miguel, E.C., Pereira, R.M., Pereira, C.A., Baer, L., Gomes, R.E., de Sa, L.C. 1994. Psychiatric manifestations of systemic lupus erythematosus: clinical features, symptoms, and signs of central nervous system activity in 43 patients. Medicine 73, 224–232.

Miller, D.H., Johnson, G., Tofts, P.S., MacManus, D., McDonald, W.I. 1989. Precise relaxation time measurements of normal-appearing white matter in inflammatory central nervous system disease. Magn. Reson. Med. 11, 331–336.

Miller, D.H., Buchanan, N., Barker, G., Morrisey, S.P., Kendall, B.E., Rudge, P. 1992. Gadolinium-enhanced magnetic resonance imaging of the central nervous system in systemic lupus erythematosus. J. Neurol. 239, 460–464.

Mitsias, P., Levine, S.R. 1994. Large cerebral vessel occlusive disease in systemic lupus erythematosus. Neurology 44, 385–393.

Mizutani, T., Oda, M., Tsuganezawa, M., Abe, H., Ohshio, C., Suzuki, K. 1977. A case of demyelinating encephalomyelitis with some resemblance to collagen disease. J. Neurol. 217, 43–52.

Mongey, A.B., Glynn, D., Hutchinson, M., Bresnihan, B. 1987. Clinical neurophysiology in the assessment of neurological symptoms in systemic lupus erythematosus. Rheumatol. Int. 7, 49–52.

Moody, D.M., Bell, M.A., Challa, V.R. 1990. Features of the cerebral vascular pattern that predict vulnerability to perfusion or oxygenation deficiency: An anatomic study. AJNR: Am. J. Neuroradiol. 11, 431–439.

Moritani, T., Shrier, D.A., Numaguchi, Y., Takahashi, C., Yano, T., Nakai, K., Zhong, J., Wang, H.Z., Shibata, D.K., Naselli, S.M. 2001. Diffusion-weighted echo-planar MR imaging of CNS involvement in systemic lupus erythematosus. Acad. Radiol. 8, 741–753.

Mortilla, M., Ermini, M., Nistri, M., Dalpozzo, G., Falcini, F. 1997. MRI and proton spectrosopy of the brain in pediatric onset SLE. Rivista di neuroradiologia 10, 28–30.

Mortilla, M., Ermini, M., Nistri, M., Dal Pozzo, G., Falcini, F. 2003. Brain study using magnetic resonance imaging and proton MR spectroscopy in pediatric onset systemic lupus erythematosus. Clin. Exp. Rheumatol. 21, 129–135.

Nampoory, M.R., Johny, K.V., Gupta, R.K., Constandi, J.N., Nair, M.P., al-Muzeiri, I. 1997. Treatable intracranial hypertension in patients with lupus nephritis. Lupus 6, 597–602.

Narayana, P.A., Wolinsky, J.S., Jackson, E.F., McCarthy, M. 1992. Proton MR spectroscopy of gadolinium-enhanced multiple sclerosis plaques. J. Magn. Reson. Imaging 2, 263–270.

Nobili, F., Rodriguez, G., Arrigo, A., Stubinski, B.M., Rossi, E., Cerri, R. 1996. Accuracy of 133-xenon regional cerebral blood flow and quantitative electroencephalography in systemic lupus erythematosus. Lupus 5, 93–102.

Nomura, K., Yamano, S., Ikeda, Y., Yamada, H., Fujimoto, T., Minami, S., Fukui, R., Takaoka, M., Yamamoto, Y., Dohi, K. 1999. Asymptomatic cerebrovascular lesions detected by magnetic resonance imaging in patients with systemic lupus erythematosus lacking a history of neuropsychiatric events. Intern. Med. 38, 785–795.

Nossent, J.C., Hovestadt, A., Shoenfeld, D.H.W., Swaak, A.J.G. 1991. Single-photon-emission computed tomography of the brain in the evaluation of cerebral lupus. Arth. Rheum. 34, 1397–1403.

Oberhaensli, R.D., Galloway, G.J., Hilton-Jones, D., Bore, P.J., Styles, P., Rajagopalan, B. 1987. The study of human organs by P-31 topical magnetic-resonance spectroscopy. Brit. J. Radiol. 60, 367–373.

Obrist, W.D., Thompson, H.K., Wang, H.S., Wilkinson, W.F. 1975. Regional cerebral blood flow estimated by 133-xenon inhalation. Stroke 6, 245–256.

Ogura, N., Atsumi, T., Sagawa, A., Jodo, S., Amasaki, Y., Nakabayashi, T. 1992. Systemic lupus erythematosus associated with benign intracranial hypertension: a case report. Ryumachi 32, 66–72.

Oku, K., Atsumi, T., Furukawa, S., Horita, T., Sakai, Y., Jodo, S., Amasaki, Y., Ichikawa, K., Amengual, O., Koike, T. 2003. Cerebral imaging by magnetic resonance imaging and single photon emission computed tomography in systemic lupus erythematosus with central nervous system involvement. Rheumatology (Oxford) 42 (6), 773–777.

Olson, J.E., Katz-Stein, A., Reo, N.V., Jolesz, F.A. 1992. Evaluation of acute brain edema using quantitative magnetic resonance imaging: effects of pretreatment with dexamethasone. Mag. Reson. Med. 24, 64–74.

Olesen, J., Friberg, L., Skyhoj-Olsen, T., Andersen, A.R., Lassen, N.A., Hansen, P.E. 1993. Ischaemia-induced (symptomatic) migraine attacks may be more frequent than migraine-induced ischemic insults. Brain 116, 187–202.

Omdal, R., Selseth, B., Klow, N.E., Husby, G., Mellgren, S.I. 1989. Clinical neurological, electrophysiological, and cerebral CT scan findings in systemic lupus erythematosus. Scand. J. Rheumatol. 18, 283–289.

Ostergaard, L., Sorensen, A.G., Kwong, K.K., Weisskoff, R.M., Gyldensted, C., Rosen, B.R. 1996. High resolution measurement of cerebral blood flow using intravascular tracer bolus passages. Part II: Experimental comparison and preliminary results. Magn. Reson. Med. 36, 726–736.

Otte, A., Weiner, S.M., Peter, H.H., Mueller-Brand, J., Goetze, M., Moser, E. 1997. Brain glucose utilization in systemic lupus erythematosus with neuropsychiatric symptoms: a controlled positron emission tomography study. Eur. J. Nucl. Med. 24, 787–791.

Otte, A., Weiner, S.M., Hoegerle, S., Wolf, R., Juengling, F.D., Peter, H.H. 1998. Neuropsychiatric systemic lupus erythematosus before and after immunosuppressive treatment: a FDG PET study. Lupus 7, 57–59.

Pawlik, G., Heiss, W.D. 1989. Positron emission tomography and neuropsychological function. Neuropsychological Function and Brain Imaging, Plenum Press, New York, p. 65–138.

Pawlik, G., Holthoff, V.A., Kessler, J., Rudolf, J., Hebold, I.R., Lottgen, J. 1990. Positron emission tomography findings relevant to neurosurgery for epilepsy. Acta Neurochir. Suppl. 50, 84–87.

Petropoulos, H., Brooks, W.M., Sibbitt, W.L. Jr. 1999. Automated T_2 quantitation in neuropsychiatric lupus erythematosus: A marker of active disease. J. Magn. Reson. Imaging 9, 39–43.

Pettegrew, J.W., Moossy, J., Withers, G., McKeag, D., Panchalingam, K. 1988. ^{31}P nuclear magnetic resonance study of the brain in Alzheimer's disease. J. Neuropathol. Exp. Neurol. 47, 235–243.

Pinching, A.J., Travers, R.L., Hughes, G.R., Jones, T., Moss, S. 1978. Oxygen-15 brain scanning for detection of cerebral involvement in systemic lupus erythematosus. Lancet 1 (8070), 898–900.

Pohlman, T.H., Stanness, K.A., Beatty, P.G., Ochs, H.D., Harlan, J.M. 1986. An endothelial cell's surface factor(s) induced in vitro by lipopolysaccharide, interleukin 1, and tumor necrosis factor-alpha increase neutrophil adherence by a CDw18-dependent mechanism. J. Immunol. 136, S4548–S4553.

Powers, W.J. 1988. Positron emission tomography in the evaluation of cerebrovascular disease. Clinical applications. In: W.H. Theodore (Ed.), Clinical Neuroimaging. Alan R Liss, New York, p. 49.

Provenzale, J.M., Barboriak, D.P., Allen, N.B., Ortel, T.L. 1996. Patients with antiphospholipid antibodies: CT and MR findings of the brain. AJR Am. J. Roentgenol. 167, 1573–1578.

Radda, G.K., Oberhaensli, R.D., Taylor, D.J. 1987. The biochemistry of human diseases as studied by 31P NMR in man and animal models. Ann. NY Acad. Sci. 508, 300–308.

Raymond, A.A., Zariah, A.A., Samad, S.A., Chin, C.N., Kong, N.C.T. 1996. Brain calcification in patients with cerebral lupus. Lupus 5, 123–128.

Reiff, A., Miller, J., Shaham, B., Bernstein, B., Szer, I.S. 1997. Childhood central nervous system lupus; longitudinal assessment using single photon emission computed tomography. J. Rheumatol. 24, 2461–2465.

Reivich, M., Kuhl, D., Wolf, A., Greenberg, J., Phelps, M.E., Ido, T. 1979. The (18F) fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man. Circ. Res. 44, 127–137.

Ritchlin, C.T., Chabot, R.J., Alper, K., Buyon, J., Belmost, H.M., Roubey, R. 1992. Quantitative electroencephalography. A new approach to the diagnosis of cerebral dysfunction in systemic lupus erythematosus. Arth. Rheum. 35, 1330–1342.

Robbins, M.L., Kornguth, S.E., Bell, C.L., Kalinke, T., England, D., Turski, P. 1988. Antineurofilament antibody evaluation in neuropsychiatric systemic lupus erythematosus: combination with anticardiolipin antibody assay and magnetic resonance imaging. Arth. Rheum. 31, 623–641.

Rodriguez, G., Nobili, F., De Carli, F., Francione, S., Marenco, S., Celestino, M.A. 1993. Regional cerebral blood flow in chronic stroke patients. Stroke 24, 94–99.

Rodriguez, G., Nobili, F., Arrigo, A., Priano, F., De Carli, F., Francione, S. 1996. Prognostic significance of quantitative electroencephalography in Alzheimer patients: preliminary observations. Electroencephalogr. Clin. Neurophysiol. 99, 123–128.

Rodriguez, G., Nobili, F., Rocca, G., De Carli, F., Gianelli, M.V., Rosadini, G. 1998. Quantitative electroencephalography and regional cerebral blood flow: discriminant analysis between Alzheimer's patients and healthy controls. Dement. Geriatr. Cogn. Disord. 9, 274–283.

Rogers, M.P., Waterhouse, E., Nagel, J.S., Roberts, N.W., Stern, S.S., Fraser, P. 1992. I-123 iofetamine SPECT scan in systemic lupus with cognitive and other minor neuropyschiatric symptoms: a pilot study. Lupus 1, 215–219.

Rozell, C.L., Sibbitt, W.L. Jr., Brooks, W.M. 1998. Structural and neurochemical markers of brain injury in the migraine diathesis of systemic lupus-erythematous. Cephalalgia 18, 209–215.

Rovaris, M., Inglese, M., Viti, B., Cibodd, G., Gerevini, S., Capra, R., Filippi, M. 2000. The contribution of fast-FLAIR MRI for lesion detection in the brain of patients with systemic autoimmune diseases. J. Neurol. 247, 29–33.

Rowley, H.A., Grant, P.E., Roberts, T.P.L. 1999. Diffusion MR imaging: theory and applications. Neuroimaging Clin. N. Am. 9, 343–361.

Rubbert, A., Marienhagen, J., Pirner, K., Manger, B., Grebmeier, J., Engelhardt, A. 1993. Single-photon-emission computed tomography analysis of cerebral blood flow in the evaluation of central nervous system involvement in patients with systemic lupus erythematosus. Arth. Rheum. 36, 1253–1262.

Runge, V.M., Kirsch, J.E., Wells, J.W., Dunworth, J.N., Hilaire, L., Woolfolk, C.E. 1994. Repeat cerebral blood volume assessment with first-pass MR imaging. J. Magn. Reson. Imaging 4, 457–461.

Russo, R., Gilday, D., Laxer, R.M., Eddy, A., Silverman, E.D. 1998. Single-photon emission computed-tomography scanning in childhood systemic lupus-erythematosus. J. Rheumatol. 25, 576–582.

Sabet, A., Sibbitt, W.L. Jr., Stidley, C., Danska, J., Brooks, W.M. 1998. Neurometabolite markers of cerebral injury in the antiphospholipid antibody syndrome of Systemic Lupus Erythematosus. Stroke 29, 2254–2260.

Sadzot, B., Maquet, P., Franck, G. 1995. Is positron emission tomography a useful tool for studying migraine? Cephalalgia 15, 316–322.

Sailer, M., Burchert, W., Ehrenheim, C., Smid, H.T.O.M., Haas, J., Wildhagen, K., Wurster, U., Deicher, H. 1997. Positron emission tomography and magnetic resonance imaging for cerebral involvement in patients with systemic lupus erythematosus. J. Neurol. 244, 186–193.

Sakaki, T., Morimoto, T., Utsumi, S. 1990. Cerebral transmural angiitis and ruptured cerebral aneurysms in patients with systemic lupus erythematosus. Neurochirurgia (Stuttg) 33, 132–135.

Sanna, G., Piga, M., Terryberry, J.W., Peltz, M.T., Giagheddu, S., Satta, L., Ahmed, A., Cauli, A., Montaldo, C., Passiu, G., Peter, J.B., Shoenfeld, Y., Mathieu, A. 2000. Central nervous system involvement in systemic lupus erythematosus: cerebral imaging and serological profile in patients with and without overt neuropsychiatric manifestations. Lupus 9, 573–583.

Sappey-Marinier, D., Calabrese, G., Hetherington, H.P., Fisher, S.N.G., Deicken, R., Van Dyke, C. 1992. Proton magnetic resonance spectroscopy of human brain: application to normal white matter, chronic infarction, and MRI white matter signal hyperintensities. Magn. Reson. Med. 26, 313–327.

Shah, Z.R., Bellon, E.M., Toor, A.H., Shields, R. 1988. CT demonstration of brain infarcts due to deep venous thrombosis in systemic lupus erythematousus. Comput. Med. Imaging Graph. 12, 241–247.

Shapeero, L.G., Norman, A. 1992. Imaging of systemic lupus erythematosus. In: Robert G. Lahita (Ed.), Systemic Lupus Erythematosus, 2nd ed., Churchill Livingstone, New York.

Shahar, E., Goshen, E., Tauber, Z., Lahat, E. 1998. Parkinsonian syndrome complicating systemic lupus erythematosus. Pediatr. Neurol. 18, 456–458.

Sharp, P.F., Smith, F.W., Glemmell, H.G. 1986. Technetium HM-PAO stereoisomeres as potential agents for imaging regional cerebral blood flow imaging. J. Nucl. Med. 27, 171–177.

Shintaku, M., Matsumoto, R. 1998. Disseminated perivenous necrotizing encephalomyelitis in systemic lupus erythematosus: report of an autopsy case. Acta Neuropathol. (Berl) 95, 313–317.

Shintani, S., Ono, K., Hinoshita, H., Shiigai, T., Tsuruoka, S. 1993. Unusual neuroradiological findings in systemic lupus erythematosus. Eur. Neurol. 33, 13–16.

Shiozawa, S., Kuroki, Y., Kim, M., Hirohata, S., Ogino, T. 1992. Interferon-alpha in lupus psychosis. Arth. Rheum. 35, 417–422.

Shulman, R.G. (Ed.), 1979. Biological Applications of Magnetic Resonance. Academic Press, New York.

Sibbitt, W.L. Jr., Brooks, W.M. 1997. When neuropsychiatric symptoms complicate SLE. J. Musculoskeletal Med. 14, 31–41.

Sibbitt, W.L. Jr., Sibbitt, R.R. 1993. Magnetic resonance spectroscopy and positron emission tomography scanning in neuropsychiatric systemic lupus erythematosus. Rheum. Dis. Clinics N. Am. 19, 851–868.

Sibbitt, W.L. Jr., Sibbitt, R.R., Griffey, R.H., Eckel, C.G., Bankhurst, A.D. 1989. Magnetic resonance and CT imaging in the evaluation of acute neuropsychiatric disease in systemic lupus erythematosus. Ann. Rheum. Dis. 48, 1014–1022.

Sibbitt, W.L. Jr., Haseler, L.H., Griffey, R.H., Hart, B.L., Sibbitt, R.R., Matwiyoff, N.A. 1994. Analysis of cerebral structural changes in systemic lupus erythematosus by proton magnetic resonance spectroscopy. AJNR: Am. J. Neuroradiol. 15, 923–928.

Sibbitt, W.L. Jr., Brooks, W.M., Haseler, L.J., Griffey, R.H., Frank, L.M., Hart, B.L. 1995. Spin–spin relaxation of brain tissues in systemic lupus erythematosus. Arth. Rheum. 38, 810–818.

Sibbitt, W.L. Jr., Haseler, L.J., Griffey, R.R., Friedman, S.D., Brooks, W.M. 1997. Neurometabolism of active neuropsychiatric lupus determined by proton MR spectroscopy. AJNR: Am. J. Neuroradiol. 18, 1271–1277.
This article demonstrates profound changes in neurometabolites with active NPSLE.

Sibbitt, W.L. Jr., Schmidt, P.J., Hart, B.L., Brooks, W.M. 2003. Fluid attenuated inversion recovery (FLAIR) imaging in neuropsychiatric systemic lupus erythematosus. J. Rheumatol. 30, 1983–1989.

Sibley, J.T., Olszynski, W.P., Decoteau, W.E., Sundaram, M.B. 1992. The incidence and prognosis of central nervous system disease in systemic lupus erythematosus. J. Rheumatol. 19, 47–52.

Singer, J., Denburg, J.A. 1990. Diagnostic criteria for neuropsychiatric systemic lupus erythematosus: The results of a consensus meeting. J. Rheumatol. 17, 1397–1402.

Steens, S.C., Bosma, G.P., ten Cate, R., Doornbos, J., Kros, J.M., Laan, L.A., Steup-Beekman, G.M., van Buchem, M.A., Huizinga, T.W. 2003. A neuroimaging follow up study of a patient with juvenile central nervous system systemic lupus erythematosus. Ann. Rheum. Dis. 62, 583–586.

Stimmler, M.M., Coletti, P.M., Quismorio, F.P. Jr. 1993. Magnetic resonance imaging of the brain in neuropsychiatric systemic lupus erythematosus. Sem. Arth. Rheum. 22, 345–349.

Stoppe, G., Wildhagen, K., Seidel, J.W., Meyer, G.J., Schober, O., Heintz, P. 1990. Positron emission tomography in neuropsychiatric lupus erythematosus. Neurology 40, 304–308.

Szer, I.S., Miller, J.H., Rawlings, D., Shaham, B., Bernstein, B. 1993. Cerebral perfusion abnormalities in children with central nervous system manifestations of lupus detected by single photon emission computed tomography. J. Rheumatol. 20, 2143–2148.

Tan, R.F., Gladman, D.D., Urowitz, M.B., Milne, N. 1978. Brain scan diagnosis of central nervous system involvement in systemic lupus erythematosus. Ann. Rheum. Dis. 37, 357–362.

Tourbah, A., Deschamps, R., Stievenart, J.L., Lopez, A., Iba-Zizen, M.T., Lyon-Caen, O., Cabanis, E.A. 1996. Magnetic resonance imaging using FLAIR pulse sequence in white matter diseases. J. Neuroradiol. 23, 217–222.

Trevor, R.P., Sondheimer, F.K., Fessel, W.J. 1972. Angiographic demonstration of major cerebral vessel occlusion in systemic lupus erythematosus. Neuroradiology 4, 202–207.

van Dam, A.P. 1991. Diagnosis and pathogenesis of CNS lupus. Rheumatol. Int. 11, 1–11.

van Zijl, P., Moonen, C.T., Alger, J.R., Cohen, J., Chesnick, S.A. 1989. High field localized proton spectroscopy in small volumes: greatly improved localization and shimming using shielded strong gradients. Magn. Res. Med. 10, 256–265.

Vermess, M., Bernstein, R.M., Bydder, G.M., Steiner, R.E., Young, I.R., Hughes, G.R.V. 1983. Nucl.ear magnetic resonance (NMR) imaging in systemic lupus erythematosus. J. Comp. Assist. Tomogr. 7, 461–467.

Walecki, J., Sierakowski, S., Lewszuk, A., Sulik, A., Tarasow, E., Lebkowska, U. 2002. MR in neurological syndromes of connective tissue diseases. Med. Sci. Monit. 8, 105–111.

Ward, M.M., Pyun, E., Studenski, S. 1996. Mortality risks associated with specific clinical manifestations of systemic lupus erythematosus. Arch. Intern. Med. 156, 1337–1344.

Waterloo, K., Omdal, R., Jacobsen, E.A., Klow, N.E., Husby, G., Torbergsen, T., Mellgren, S.I. 1999. Cerebral computed tomography and electroencephalography compared with neuropsychological findings in systemic lupus erythematosus. J. Neurol. 246, 706–711.

Waterloo, K., Omdal, R., Sjoholm, H., Koldingsnes, W., Jacobsen, E.A., Sundsfjord, J.A., Husby, G., Mellgren, S.I. 2001. Neuropsychological dysfunction in systemic lupus erythematosus is not associated with changes in cerebral blood flow. J. Neurol. 248, 595–602.

Weiner, S.M., Otte, A., Uhl, M., Brink, I., Schumacher, M., Peter, H.H. 2003. Neuropsychiatric involvement in systemic lupus erythematosus, Part 2: diagnostic and therapy. Med. Klin. 98 (2), 79–90. Feb, 15.

West, S.G. 1994. Neuropsychiatric lupus. Rheum. Dis. Clinics N. Am. 20, 129–158.

This is one of the best general references on NPSLE.

West, S.G., Emlen, W., Wener, M.H., Kotzin, B.L. 1995. Neuropsychiatric lupus erythematosus: a 10-year prospective study on the value of diagnostic tests. Am. J. Med. 99, 153–163.

Wood, M.L., Wehrli, F.W. 1999. Principles of magnetic resonance imaging. In: D.D. Stark, W.G. Bradley, Jr. (Eds.), Magnetic Resonance Imaging, 3rd ed., Mosby Inc, St. Louis, pp. 1–14.

Woods, R.P., Iacoboni, M., Mazziotta, J.C. 1994. Bilateral spreading cerebral hypoperfusion during spontaneous migraine headache. New Eng. J. Med. 331, 1689–1692.

Zanardi, V.A., Magna, L.A., Costallat, L.T. 2001. Cerebral atrophy related to corticotherapy in systemic lupus erythematosus (SLE). Clin. Rheumatol. 20, 245–250.

PART II

Antiphospholipid Syndrome

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CHAPTER 4

Antiphospholipid Syndrome

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1. Introduction

The antiphospholipid syndrome (APS) (Hughes, 1983; Hughes et al., 1986) is characterized by thrombosis (arterial or venous) and/or pregnancy loss in the presence of persistent (at least two occasions) circulating antiphospholipid antibodies (aPL), most commonly anticardiolipin antibodies (aCL) and/or a positive lupus anticoagulants (LA) (Bowie et al., 1963) (Wilson et al., 1999) (Table 1). The prevalence of aPL is estimated to be 2–5% in the general population and increases with age. Several large-scale studies report the prevalence of LA and aCL in systemic lupus erythematosus (SLE) patients between 15 and 34% and 12 and 30%, respectively (Petri, 2000). In the absence of an underlying connective tissue disorder (CTD), this syndrome is 'primary' APS, whereas 'secondary' APS occurs in patients with other CTDs, most often SLE.

The presence of aPL in the absence of symptoms does not indicate APS; asymptomatic aPL-positive patients exist. These asymptomatic patients are generally identified as part of an autoimmune disease serologic evaluation, most commonly SLE, or during evaluation for an elevated activated partial thromboplastin time (aPTT), e.g. during pre-surgical or pre-procedural screening. A subgroup of APS patients is diagnosed solely after pregnancy loss without systemic or cerebral vascular events.

APS-related vascular events can range from deep venous thrombosis (DVT) to life-threatening multiple organ system thromboses (Wahl et al., 1998) developing over a short period (catastrophic APS). Thus, aPL-associated clinical manifestations represent a spectrum; patients should not be evaluated and managed as a single disease entity (Table 2).

APS can result in both venous and arterial non-inflammatory thromboses anywhere within the vascular tree. DVT of the lower extremities is the most common site for venous thromboses and the cerebral vasculature is the most common site for arterial thromboses. Thus, APS patients may present with a wide spectrum of neurologic manifestations including arterial and venous stroke, transient ischemic attack (TIA), amaurosis fugax, occular occlusive vascular disease, or acute/subacute ischemic encephalopathy. Non-thrombotic manifestations such as cognitive dysfunction, psychiatric problems, migraine, seizure, chorea, multiple sclerosis-like syndrome, and transverse myelitis can occur in aPL-positive patients (in the absence of SLE or other autoimmune disorder) although these associations are still under debate, are based essentially of case reports or small series (Table 3), and are not accepted as a clinical diagnostic criterion for the APS.

A recent consensus meeting of APS experts (Brey et al., 2003) determined that ischemic stroke is the only neurological manifestation accepted as a

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Table 1
Summary of the Sapporo classification criteria for the antiphospholipid syndrome (Wilson et al., 1999)

Clinical criteria
Vascular thrombosis
Arterial, venous, or small vessel thrombosis, in any organ or tissue
Pregnancy morbidity
One or more unexplained deaths of morphologically normal fetus at or beyond the 10th week of gestation or
One or more premature births of a morphologically normal neonate at or before the 34th week of gestation because of severe preeclampsia or eclampsia, or severe placental insufficiency or
Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation
Laboratory criteria
Anticardiolipin antibody of IgG and/or IgM isotype in blood, present in medium or high titer, on two or more occasions, at least 6 weeks apart and/or
Lupus anticoagulant present in the plasma on two or more occasions at least 6 weeks apart

Definite APS is considered to be present if at least one of the clinical and one of the laboratory criteria are met.

clinical diagnostic criterion for the APS. This association is reasonably well established in patients who are first diagnosed with APS. However, this association is less clear in randomly selected stroke patients who test positive for aPL on one occasion and who have no other clinical or laboratory features of APS.

Table 2
The spectrum of antiphospholipid antibodies (aPL) and antiphospholipid syndrome (APS)

Asymptomatic aPL-positive patients
Medium-to-high titer IgG/M aCL and/or positive LA test
Low titer aCL or isolated IgA aCL
APS patients with only pregnancy morbidity
Patients who fulfill the Sapporo criteria
Patients who do not fulfill the Sapporo criteria (i.e. single early pregnancy loss with positive aPL)
APS patients with vascular thrombosis with or without pregnancy morbidity
Patients with venous events
Patients with arterial events
Patients with catastrophic APS

It is important to note that the presence or absence of other vascular risk factors should also be taken into consideration while determining the aPL/APS spectrum. aPL: antiphospholipid antibodies; aCL: anticardiolipin antibodies; LA: lupus anticoagulant.

Table 3
Neurologic manifestations of the antiphospholipid syndrome

Focal cerebral ischemia
Stroke (cerebral and ocular)
Transient ischemic attacks (cerebral and ocular)
Cortical venous sinus thrombosis
Cognitive dysfunction (vascular dementia)
? Psychiatric problems and mood disorders
? Migrainous-like events
? Seizures
? Chorea
? Transverse myelopathy

?: debatable manifestations of aPL.

For non-stroke neurological syndromes associated with aPL (reviewed in Chapman et al., 2003), it should be recognized up front that none of the syndromes discussed in this chapter have been definitively linked with either aPL or APS. There are suggestive anecdotes and generally small case series for most of these syndromes and there are epidemiological data that fail to link migraine and migrainous neurological events with aPL.

2. Prevalence—epidemiology

2.1. Focal cerebral ischemia

Case-control studies of stroke in young patients have been uniformly positive for an association of aPL (predominantly aCL) and ischemic stroke (Brey et al., 1990; Nencini et al., 1992; Angelini et al., 1994; Nagaraja et al., 1997). However, some (Kushner, 1990; Chakravarty et al., 1991; Hess et al., 1991; APASS, 1993), but not all (Muir et al., 1994; Metz et al., 1998) studies among older adults have found this association. The odds ratios found in positive studies of unselected stroke patients have ranged from 2.3 (APASS, 1993) to 6.7 (Camerlingo et al., 1995) or higher (Chakravarty et al., 1991). Case-control studies have been criticized because of the difficulty of establishing the temporal relationship. However, studies which obtained blood within 7 days of the event (APASS, 1993), or even within 6 h of onset (Camerlingo et al., 1995) have had positive findings. While these time periods may be too short to allow the development of measurable immunoglobulin (Ig) G levels due to a primary or

anamnestic immune response (Barret, 1983), they do not preclude the possibility of antibodies induced by a recent prior febrile illness. Indeed, infection-associated cerebral infarction is not only quite common, but is also associated with higher levels of IgG aCL (Ameriso et al., 1991).

Until recently, all published prospective studies of aPL and stroke were negative (Ginsburg et al., 1992; Sletnes et al., 1992). However, these studies were limited in statistical power and suffered from technical limitations. The most recent, a prospective case-control study of men enrolled in the Honolulu Heart Program (Brey et al., 1999) found an independent association between aPL and stroke and myocardial infarction. The overall risk factor-adjusted odds ratio of aCL IgG for stroke was 2.2 ($p < 0.001$).

Although TIAs frequently can be seen in association with aPL, the largest study to date did not show a definitive association of these types of spells specifically with elevated aCL levels (testing for LA was not systematically performed for this cohort). Tietjen et al.'s (1998) data also suggests that aCL is not a risk factor for transient focal neurologic defects or migraine. In the largest case-control study specifically addressing transient focal neurological symptoms, they compared 645 patients with transient focal neurologic events, 518 patients with migraine (with aura), 497 patients with migraine (without aura), and 366 controls and found no difference in aPL status.

Recurrent stroke and thromboembolic events in patients with thrombosis and aPL can occur both early (within the first year of an index episode of cerebral ischemia) and late (5–10 years) (Levine et al., 1997). High titers of IgG aCL have been associated with recurrent events in patients with primary and secondary APS in relatively small studies (Harris et al., 1986; Levine et al., 1995).

2.2. Cognitive dysfunction

Denburg et al. (1997) reported a significant association between aPL (measured by LA test) and cognitive impairment in patients with SLE. They found LA-positive patients to score significantly lower than LA-negative patients on measures of verbal memory, cognitive flexibility and psychomotor speed. The impairment was found to be quite significant; LA-positive patients were rated as 2–3 times more impaired than the LA-negative patients. Hermosillo-Romo and Brey (2002) have also found a similar relationship between aPL and cognitive dysfunction in patients with SLE.

Furthermore, Schmidt et al. (1995) found subtle neuropsychological dysfunction in otherwise normal elderly people with increased levels of IgG aCL. This correlation with aCL IgG titers was significant despite the lack of evidence of any anatomic abnormalities on magnetic resonance imaging (MRI). de Moerloose et al. (1997) evaluated the prevalence of aCL in 192 elderly patients. The overall prevalence of aCL was 10.9% and decreased by decade in patients 70–99 years of age from 18 to 10 to 7%, whereas the prevalence of antinuclear antibody (ANA) positivity increased by decade from 22 to 32 to 42%. There was no association between the presence of aCL and decreased survival. In contrast, and in keeping with previous findings, Cesbron et al. (1997) found a trend towards an increased prevalence of aCL by decade in 1042 elderly subjects between the ages of 60 and 99 years. In addition, high aCL levels were associated with increased physical disability in this population independent of age, gender, visual or hearing abnormalities, Mini-Mental Status Exam score, or history of cerebro- or cardiovascular disease.

2.3. Psychiatric problems and mood alterations

The wide diversity of potential etiologies, combined with numerous clinical manifestations, makes any psychiatric diagnosis secondary to APS very difficult. In addition, behavioral complications such as psychosis and mood disorders may manifest independently of cognitive loss, although in many cases these two occur concurrently.

Although depression and psychosis have been associated with aPL, it remains unclear to what extent this finding is simply related to the development of medication-induced aPL (Schwartz et al., 1998). Schwartz et al. (1998) demonstrated an association between aCL and LA and psychosis in 34 unmedicated patients without known autoimmune disorder admitted to the hospital with a first acute episode of psychosis. Thirty-four percent of patients had aCL

IgG and 9% had LA, neither of which was present in 20 normal control subjects. Patients were treated with a variety of neuroleptics and reassessed for the presence of these antibodies 3–9 months later. Although one patient developed aCL IgM and four developed aCL IgG after treatment, three patients who were aCL IgG positive prior to treatment were negative for these antibodies post-treatment. There was no relationship between the presence of aCL or LA and thrombotic manifestations, response to antipsychotic therapy or type of neuroleptic used. The authors speculated that aPL may be causally related to the development of psychosis in some patients on an autoimmune basis and concluded that their presence cannot be assumed to simply be the result of antipsychotic treatment.

2.4. Migraine

The prevalence of aPL in patients with migraine does not appear to be increased, even in an SLE population in whom the prevalence of both migraine and aPL are increased over the general population. In addition, the largest case-control study to date has failed to demonstrate an association of aCL immunoreactivity in patients under 60 years of age with either migraine with aura, migraine without aura, or transient focal neurologic events compared to controls (Tietjen et al., 1998).

Although migrainous stroke is rare, Silvestrini et al. (1993) found aPL immunoreactivity in 6/16 patients with migrainous cerebral infarction. None of these patients had SLE, but all had other risk factors for stroke. These data highlight the importance of considering the presence of aPL and other risk factors in migrainous stroke. However, taken together with the case-control study by Tietjen et al. (1998) described above, there is insufficient evidence to support a need to evaluate all migraine patients for aPL.

2.5. Seizures

aPL have been reported with increased frequency in SLE patients with epilepsy by some (Inzelberg and Korczyn, 1989; Peltola et al., 2000; Herranz et al., 1994) but not all (Formiga et al., 1997) investigators. Brey and colleagues did not find either aCL immunoreactivity or LA in a small group of young epileptic patients without SLE who served as controls in a study of aPL and cerebral ischemia (Brey et al., 1990). However, the prevalence of aPL has not been studied in either the general epilepsy population or in late-onset epilepsy patients, many of whom also have seizures related to cerebral infarction. Verrot et al. (1997) conducted a study with the general epilepsy population to find a relationship between aPL and epilepsy. Similar to studies with SLE patients, the authors found a high correlation between aCL antibodies and epilepsy.

2.6. Chorea

Cervera and colleagues reviewed chorea in adults and children with APS (Cervera et al., 1997), which can occur in both primary and secondary APS (Asherson and Hughes, 1988; Hatron et al., 1987) and is often the presenting clinical feature (Cervera et al., 1997). Of the 50 patients described and reviewed by Cervera and colleagues, six developed chorea with estrogen-containing oral contraceptive use, and four in association with pregnancy or the post-partum period, highlighting the potential role of estrogen in this disorder. The chorea was bilateral in 55% of patients and, fortunately, reversible in most patients with treatment with haldoperidol, corticosteroids or the discontinuation of oral contraceptives. In patients with persistent chorea, aPL-associated striatal ischemia has been postulated. However, in patients with reversible chorea, dysfunction related to striatal binding of aPL is quite plausible. This hypothesis, first suggested by Asherson and Hughes (1988), is supported by several recent case reports describing patients with aPL-associated chorea studied serially using positron emission tomography (PET). Transient hypermetabolism in the contralateral basal ganglia was seen in all patients (Furie et al., 1994; Sunden-Cullberg et al., 1998) suggesting an underlying excitatory rather than an ischemic pathophysiologic mechanism.

2.7. Transverse myelopathy

Harris et al. (1985) described a woman with transverse myelitis, aPL immunoreactivity and a ‘lupus-like’

disease. Lavalle et al. (1990) described 12 SLE patients with transverse myelitis and found all of them to have aPL immunoreactivity. Six also had other APS clinical manifestations (thrombocytopenia, thrombosis, livedo reticularis and leg ulcers). Transverse myelitis only occurs in 1% of patients with SLE (Harris et al., 1985), therefore, the number of patients described in this report is remarkable. Ruiz-Arguelles et al. (1998) recently described a patient with refractory hiccups as the heralding symptom of transverse myelitis in association with aCL. This patient was successfully treated with corticosteroids and cross-linked fibrin derivatives (an indicator of ongoing thrombosis) were negative during the time of maximal neurologic deficit.

3. Etiology—pathogenesis

When discussing potential mechanisms and models for the thrombotic and neurologic complications associated with aPL, several points must be made. First, no conclusive and direct human evidence yet exists that aPL per se are pathogenic or are direct mediators in the development of thrombotic or neurologic complications (Ziporen and Shoenfeld, 1998). They may be epiphenomena (Piette and Cacoub, 1998) and may simply be markers of a more primary and fundamental disturbance. Second, although both obstetric and thrombotic complications are frequently associated with the presence of aPL, they may arise from different and independent mechanisms. For example, the idea is plausible that aPL are directly responsible for fetal loss, as evidence from some animal models (Pierangeli and Harris, 1994) would suggest, but they may not be directly responsible for thrombotic complications. Furthermore, the high frequency of 'thrombotic' neurologic complications suggests a selective vulnerability of the CNS or, more specifically, a selective vulnerability of the cerebral vasculature to aPL. Finally, evidence exists that thrombotic events in patients with aPL segregate into venous or arterial events (usually stroke or TIAs). A general pattern has been observed whereby patients who present with a venous event such as a DVT tend to have recurrent DVT, whereas patients with stroke tend to have recurrent stroke (Rosove and Brewer, 1992). This implies that 'thrombotic' mechanisms may be heterogeneous or that differences exist in host susceptibilities (Ginsberg et al., 1993; Bokarewa et al., 1995; Meroni et al., 1998).

The underlying pathology of most of the neurologic complications is a thrombotic occlusion of cerebral vessels with fibrin-platelet thrombus, without evidence of vasculitis (Briley et al., 1989; Levine et al., 1990; Perez et al., 1992; Greisman et al., 1991; Ford et al., 1994). However, other alleged neurologic associations such as migraine, chorea, and transverse myelopathy are more difficult to attribute solely to a hypercoagulable state.

3.1. Cerebral ischemia

The average age of onset of APS with cerebral ischemia is several decades younger than the typical cerebral ischemia population (Levine et al., 1995). Regardless of age, patients with cerebral ischemia often have other risk factors for cerebrovascular disease (Levine et al., 1990, 1995; Brey et al., 1990; APASS, 1993). A higher than expected frequency of coronary artery (Klemp et al., 1988) and peripheral arterial (Ciocca et al., 1995) graft occlusion has also been noted in patients with aPL. These clinical observations coupled with recent findings of endothelial cell activation by aPL (Del Papa et al., 1997a, b) support the hypothesis that aPL may act in concert with other vascular risk factors which damage endothelial cells.

A variety of cardiac valvular lesions have also been associated with aPL making cardiac emboli a possible stroke mechanism in some patients. Echocardiography, when abnormal, typically demonstrates nonspecific left-sided valvular (predominantly mitral) lesions, characterized by valve thickening—a potential cardiac source of stroke. In a large consecutive autopsy series, a higher incidence of cardiac valvular abnormalities and 'bland' (non-vasculitic) thromboembolic lesions were found in patients with aPL than in patients without aPL (Ford et al., 1994).

Smoking is an additional risk factor for stroke and the most common stroke risk factor seen in association with high positive IgG aCL (more than 100 GPL units) in the authors' experience (Verro et al., 1998).

The mechanism of TIA or transient visual disturbances is most likely to be ischemic but this has not been well characterized. Giorgi et al. (1998) reviewed

literature in transient visual symptoms in SLE and APS patients and concluded that thromboembolism, which is likely induced by cardiac valve abnormalities, is the most probable cause of transient visual symptoms. Others have suggested vasospasm as a mechanism of the visual loss.

In summary, mechanisms of thrombosis associated with aPL are heterogeneous (e.g. cardiac valvular disease, cerebral microemboli, endothelial hyperplasia, adhesion molecule expression) (Brey et al., 2003).

3.2. Cognitive dysfunction

Although the specific role of these antibodies remains unclear, it is believed that a majority of cognitive disorders associated with aPL are a result of thrombotic events. Nevertheless, there are many reported cases of neurocognitive deficits secondary to APS that are not related to cerebrovascular disease, as described below.

3.3. Psychiatric problems and mood alterations

Whether or not aPL are responsible for the pathogenesis of psychiatric symptoms and disorders and/or mood alterations remains speculative. Kent et al. (1997, 2000) described aPL-reactive sites in the central nervous system (CNS). They had previously shown that two monoclonal phosphatidylserine-reactive antibodies (aPS) binded to ependyma and myelin of fixed cat brain. Both monoclonal antibodies reacted strongly with myelin, and both also reacted with an antigen that appears associated with the axoneme in cilia of ependymal and choroid plexus epithelium. One monoclonal aPS also showed some reactivity with brain vascular endothelium and reacted slightly with mitochondria, while the other aPS did not react with these structures. These data suggest possible target sites within the CNS with which aPL can react.

3.4. Migraine

The etiology and pathogenesis of migraine is not known. Recent, prospective data fails to link aPL with migraine or migrainous neurological events. Therefore, it is difficult to offer a tenable basis for the role of aPL in migraine pathogenesis.

3.5. Seizures

The etiology of seizures in SLE patients may be aPL-associated cerebral infarction (Inzelberg and Korczyn, 1989; Formiga et al., 1997). There are some animal data that support the possibility of a primary immunologic basis for seizures associated with aPL (Liou et al., 1994; Kent et al., 1997). aPL have been demonstrated to bind directly to cat brain (Kent et al., 1997) and have been shown to reduce a GABA receptor-mediated chloride current in snail neurons (Liou et al., 1994). This inhibitory effect suggests a direct and reversible mechanism through which aPL might lower seizure threshold.

3.6. Chorea

In aPL-positive patients with chorea, neuroimaging studies seldom reveal infarctions in the brain (Khamashta et al., 1988). In a patient with alternating chorea and APS (Karussis et al., 1998), F-fluorodeoxyglucose PET scanning demonstrated contralateral striatal hypermetabolism during episodes of chorea (Furie et al., 1994). These findings tend to argue against microvascular occlusion as the cause of chorea.

3.7. Transverse myelitis

The pathophysiology of spinal cord damage in aPL-associated myelopathy is uncertain, however, both ischemia and an antibody-mediated interaction have been suggested. In the case presented by Ruiz-Arguelles et al. (1998), the response to corticosteroids and the lack of evidence acutely for ongoing thrombosis suggest that either inflammation or an antibody-mediated interaction with spinal cord phospholipids may be more likely.

4. Clinical manifestations

4.1. Cerebral ischemia

The most common neurologic manifestation of aPL is focal cerebral ischemia resulting in stroke or TIAs. Other cerebral arterial manifestations include

ischemic encephalopathy (either acute or subacute), and vascular dementia.

The onset of cerebral venous thrombosis (CVT) in patients with aPL (Descheins et al., 1996) may occur at a younger age and have more extensive superficial and deep cerebral venous system involvement than CVT without aPL (Carhuapoma et al., 1997). In addition, a higher rate of post-CVT migraine and more infarctions on brain imaging studies are seen in patients with aPL than in those without them (Carhuapoma et al., 1997).

In a cohort of 89 patients with severe, non-specific cardiac valve disease from the Mayo Clinic followed prospectively for a mean of 59 months, those with aPL were more likely to have subsequent thromboembolic events that the aPL-negative group (7/19 (37%) vs. 9/70 (11%), $p = 0.01$). However, in multivariate Cox analysis, presence of aPLs was not an independent risk factor for thromboembolic events (Bulckaen et al., 2003).

4.2. Cognitive dysfunction

Cognitive dysfunction associated to primary or secondary APS can vary from mild deficits to vascular dementia (Coull et al., 1987) and is reviewed in depth in other chapters.

4.3. Psychiatric problems and mood alterations

Other than possibly psychosis, no specific clinical psychiatric problems and mood alterations have been clearly associated with aPL.

4.4. Migraine

There is no clear clinical migrainous manifestations associated with aPL different from idiopathic migraine.

4.5. Seizures

There are no clear features of seizures associated with aPL that are different from seizures not associated with aPL.

4.6. Chorea

Both hemichorea and alternating hemichorea have been described with aPL—either in primary APS or secondary APS.

4.7. Transverse myelitis

The clinical features of transverse myelitis associated with aPL are not known to be specific or different in any significant way than lupus myelopathy in the absence of aPL.

4.8. Other possible neurologic manifestations of aPL

Several studies suggest an anecdotal association between aPL and Guillain–Barre syndrome (Jackson et al., 1992; Harris et al., 1983a,b). One study suggests that a failure of plasma exchange to normalize the aPL levels may be predictive of eventual relapse (Jackson et al., 1992).

Toubi et al. (1997) studied the association between aCL and sudden or progressive sensorineural hearing loss in 30 patients and matched normal controls. None of the control group had aCL, whereas 27% of the patient group had aCL in low-moderate titers. Of the patients with aCL, five of eight had sudden deafness. In addition, two of five patients with sudden deafness and aCL relapsed as compared with none of six patients without them. Naarendorp and Spiera (1998) reported six patients with SLE or a lupus-like syndrome with sudden sensorineural hearing loss, all of which had aCL or positive LA test. The authors suggest that sudden sensorineural hearing loss may be a previously unrecognized manifestation of APS, that the mechanism is likely to be vascular and speculate that the appropriate treatment for these patients may be anticoagulant therapy.

Transient global amnesia (TGA), a syndrome of sudden, unexplained memory loss has been anecdotally associated with aPL (Montalban et al., 1989). The etiology of TGA in patients without aPL is controversial and thought to be related to ischemia or epileptiform activity in bilateral hippocampal areas. As both cerebral ischemia and epilepsy have been

associated with aPL, either could play a role in aPL-associated TGA.

Many reports of stroke and TIA associated with aPL include some patients with ocular ischemia as well (Rafuse and Canny, 1992; Labutta, 1996). The ophthalmologic ischemic manifestations associated (generally uncontrolled studies) with aPL include anterior ischemic optic neuropathy, branch and central retinal artery occlusions, cilioretinal artery occlusions, combined artery and vein occlusions and amaurosis fugax (Labutta, 1996). These manifestations can be seen in patients with either primary or secondary APS.

5. Diagnostic investigations

aPL comprise a heterogeneous family of autoantibodies that are detected as immunoreactivity to negatively charged phospholipids (commonly cardiolipin [aCL] or beta-2-glycoprotein 1 (anti-β_2GP1) (Cabides et al., 1995) or by their ability to prolong phospholipid dependent coagulation tests (LA test) (McNeil et al., 1991). The term aPL is typically used to refer generically to the entire family of autoantibodies. Thus, what we refer to as 'aPL' probably make up a group of antibodies whose unique common feature is reactivity to phospholipid/phospholipid binding plasma protein complexes (Roubey et al., 1995), but with different specificities (Galli et al., 1990) and different genetic associations and, therefore, likely, different immune-mediated phenotypes and risk strata (Horbach et al., 1996), although unproven. Newer antibodies to phospholipids, such as antiphosphatidylserine, phosphatidylethanolamine, phosphatidylcholine, and phosphatidic acid have been less frequently studied and their significance is still emerging (Rote et al., 1990; Rauch and Aminoff, 1996; Lopez-Soto et al., 1997; Tuhrim et al., 1999). Likewise, commercial tests are available to detect antibodies to the aPL 'co-factor', β_2GP1. In some studies the presence of these antibodies rivals the presence of LAC in identifying patients with the highest risk for thrombosis, however, this question is still being debated.

According to the Sapporo APS classification criteria, the only diagnostic neurologic manifestation of aPL is a cerebral thrombotic event. Although aPL are likely to be risk factors for TIA, aPL-positive patients presenting solely with TIA do not fulfill the Sapporo classification criteria for APS (Wilson et al., 1999). The presence of an embolic source such as carotid plaque or cardiac valve disease should be excluded in all patients. In general, all clinical manifestations of associated with aPL should be given the full differential diagnostic consideration and evaluation as in the absence of aPL and multiple potential risk factors and risk markers could be involved.

Toubi et al. (1995) found aPL immunoreactivity in 53/96 (55%) SLE patients with CNS manifestations as compared to 20/100 (20%) of SLE patients without them. In this study, 53 patients with CNS manifestations underwent MRI imaging and 33 showed high-intensity lesions that were interpreted as 'suggestive of vasculopathy'. MRI abnormalities were seen more frequently in patients with as compared to those without aPL immunoreactivity. Some of these patients with MRI abnormalities had seizures or psychiatric disturbances and not stroke. This allows for the speculation that in some cases, aPL-associated neurologic manifestations may be due to an aPL–brain phospholipid interaction whereas in other the underlying pathogenic feature may be thrombotic.

Although useful in demonstrating structural lesions such as infarcts and bleeds in brains of patients with focal lesions, imaging techniques are poorly correlated with diffuse or global dysfunction. For example, the status of aCL titers in a group of 233 normal elderly participants were found to have no influence in the MRI results (de Moerloose et al., 1997). Sailer et al. (1997) studied 35 SLE patients with inactive SLE patients using brain MRI and PET imaging, neuropsychological testing, a neurological examination, and serum testing for aPL antibodies and anti-neuronal antibodies. Twenty patients had neurological deficits, three had psychiatric symptoms and 10 had cognitive impairment. No differences in global glucose utilization by PET imaging were seen between SLE patients with as compared to those without neurological or cognitive abnormalities. On MRI imaging, the number and size of the white matter lesions correlated with the presence of neurological deficit, but were unrelated to the severity of cognitive impairment cognitive. Large lesions (8 mm or greater) were associated with high aCL IgG levels.

Tietjen et al. (1993) also found an association between brain neuroimaging lesions and aCL levels in young patients with migraine-associated transient focal neurologic events. In a study evaluating the association between neuropsychological abnormalities and aPL in an elderly population, no association between aCL and MRI lesions was found, supporting Sailer et al.'s (1997) findings in the group with cognitive impairment only.

Hachulla et al. (1998) performed brain MRI in patients with primary and secondary APS. Both cerebral atrophy and white matter lesions were more common in both groups in comparison with control subjects. The number and volume of white matter lesions were increased in patients with primary and secondary APS who also had neurological symptoms. Only a weak correlation was found between the presence of a LA and cerebral atrophy.

6. Differential diagnosis

The differential diagnosis of primary APS often depends on what vascular bed (arterial, venous, placental) is first involved in the thrombotic process. For example, the combination of ischemic cerebrovascular disease and livedo reticularis (ischemic dermatopathy) has been termed *Sneddon's syndrome* for the British dermatologist who first reported six similar cases in 1965. In the literature, approximately 40–50% of these cases are positive for aPL.

Diagnostic evaluation of Sneddon's syndrome may reveal a non-vasculitic cerebral arteriopathy, normal cerebral vessels, general lack of a definitive cardiac source of embolism, and a variety of anecdotal coagulopathies with or without aPL positivity (Kalashnikova et al., 1990). It is a syndrome with many potential causes (a differential diagnosis of livedo that can include atherosclerosis, vasculitis, coagulopathy, cryoglobulinemia, etc. and that has overlap with those conditions that cause stroke). Sneddon's syndrome can also be seen as part of the secondary APS associated with SLE.

This syndrome is also frequently accompanied by dementia, most likely on the basis of multiple infarctions. Sneddon's original patients all had focal neurological deficits, which he considered to be 'limited and benign,' leaving little residual disability (Sneddon, 1965). Subsequent descriptions of the syndrome have revealed a spectrum of clinical neurological manifestations. Zelzer et al. (1993) described three stages of neurological involvement: (1) 'prodromal' symptoms such as dizziness or headaches preceding focal neurological deficits by years; (2) recurrent focal neurological deficits due to recurrent cerebral ischemia, also lasting years; and (3) progressive cognitive impairment leading to severe dementia.

Tourbah et al. (1997) correlated the MRI abnormalities found in 26 patients with Sneddon's syndrome with disability, presence of cardiovascular risk factors, cardiac valvular abnormalities on echocardiography and titer of aPL. Disability (defined by memory disturbance or ability to perform activities of daily living) was found in 50% of the patients. Severe disability, which was consistent with dementia, was present in over half of the patients with disability. Systemic hypertension was present in 65%, cardiac valvular abnormalities in 61%, and aPL in 42% of patients with no correlation found between any of these and MRI abnormalities. The presence of disability was correlated with increasing severity of MRI lesions. An aPL-associated dementia without the other features of Sneddon's syndrome has also been described. In many patients this appears to be due to multiple cerebral infarctions (Zelzer et al., 1993). In addition, the catastrophic APS can present with an acute organic brain syndrome characterized by fulminant encephalopathy (Chinnery et al., 1997).

In patients with primary APS, the main differential diagnosis for cerebral arterial involvement includes demyelinating disease (multiple sclerosis), vasculitides (discussed further in other chapters), coagulopathies apart from aPL, cardiac sources of embolism apart from Libman Sacks endocarditis (e.g. atrial myxoma), and atherosclerosis and arteropathy due to conventional risk factors (cigarette smoking, hypertension, diabetes, hyperlipidemia).

For the clinician to ascribe a stroke to aPL, certain criteria should be met (Brey et al., 2003). There should be an exclusion of other clear mechanisms (e.g. dissection, atrial fibrillation, cocaine) and the stroke should be confirmed clinically and radiologically. It would be helpful to have other features of the APS (recurrent abortions, thrombocytopenia, cardiac valvulopathy, other thrombotic events), or the presence of other autoimmune disease (Matsurra et al., 1990).

7. Treatment

The mechanism by which aPL may lead to thrombosis is probably heterogeneous and it is likely, though still speculative and unproven, that the most appropriate therapeutic choice for a given patient may depend on which of these mechanisms the patient's thromboembolic episode was due to. A variety of prothrombotic effects on platelets, coagulation proteins, prostaglandins, and endothelial cells have been associated with aPL (reviewed in McNeil et al., 1990). For platelet or prostaglandin abnormalities aspirin or ticlopidine might be expected to be beneficial whereas for thrombomodulin, protein C, protein S or cardiac valvular abnormalities anticoagulation may be reasonable. This may provide a partial explanation for the discrepant findings in the aPL treatment literature on thromboembolic manifestations. In support of this are the findings that there is no apparent difference between warfarin and aspirin in preventing recurrent thrombo-occlusive APS manifestations after an initial stroke (APASS Investigators, 2004).

The Antiphospholipid Antibody in Stroke Study Group (APASS) recently completed the first prospective randomized study of the role of aPL in recurrent ischemic stroke in collaboration with the WARSS group (WARSS, APASS, PICSS and HAS Study Groups, 1997). This controlled and blinded study was initiated in 1993 and compared the risk of recurrent stroke and other thromboembolic disease over a 2 year follow-up period in patients with ischemic stroke who were randomized to either aspirin therapy (325 mg per day) or warfarin therapy at a dose to maintain the INR between 1.4 and 2.8. The suggested target INR was 2.2. Exclusion criteria for WARSS included indication for warfarin therapy (e.g. atrial fibrillation), contraindication for warfarin therapy, and high-grade carotid stenosis suggesting the need for carotid endarterectomy. There were 882 patients randomized to warfarin and 890 patients randomized to aspirin. The average age of APASS subjects was 62.5 years. In the warfarin arm, 35.9% (64/882) of patients who were positive for both aCL and LA had a recurrent event as compared to 21.1% (128/882) who were LA + /aCL −, 26.6% (169/882) who were LA − /aCL + and 26.1% (521/882) who were LA − /aCL −. In the aspirin arm, 26.8% (56/890) of patients who were positive for both aCL and LA had a recurrent event as compared to 18.2% (110/890) who were LA + /aCL −, 23.3% (193/890) who were LA − /aCL + and 21.7% (531/890) who were LA − /aCL −. None of these differences were statistically significant. There was no difference in major bleeding complications between treatment groups (unpublished data). This study suggested that in patients with aPL and ischemic stroke, in the typical stroke age group, who do not have either atrial fibrillation or high-grade carotid stenosis aspirin and warfarin therapy at an INR of approximately 2 are equivalent in both efficacy and major bleeding complications. The INR selected for this study was based on current treatment recommendations for secondary prevention of ischemic stroke in patients without aPL. Higher INR-producing dose of warfarin that has been suggested as necessary for successful secondary prevention of aPL-associated thrombotic events (Khamashta et al., 1995) has not been shown to be of benefit compared to the INR range of 2–3 (Crowther et al., 2003). It is not yet clear whether the APASS data can be extrapolated accurately to younger patients with the typical APS.

Derksen et al. (2003) described the course and outcome of eight patients with ischemic stroke as the first thrombotic manifestation of APS who received low-dose aspirin as prophylactic treatment. During 8.9 years of follow-up, two patients had a recurrent stroke. Recurrent stroke rate per 100 patient-years on aspirin was 3.5 (95% CI 0.4–12.5).

Event rate calculated from Crowther et al. (2003) study was 4 per 100 patient-years (95% CI 1–7).

After a first ischemic event, aggressive modification of all other stroke risk factors (with screening on a yearly basis) should be performed. In young people who clearly have the diagnosis of APS, warfarin has been given empirically. In the absence of prospective data that demonstrates the superiority of warfarin over any other antithrombotic regimen and in the presence of a recent randomized controlled trial data showing no benefit of high-intensity warfarin treatment (INR 3–4) over low-intensity (INR 2–3) (of note, only one-fifth of studied patients had arterial events) (Crowther et al., 2003), we do not know if warfarin treatment is better than aspirin for every aPL-positive stroke patient. Thus, after a first cerebral ischemic event that occurs in the presence of aPL, the discussion

of aspirin therapy with the patient is reasonable, provided there is no other identified high-risk cause found (i.e., cardiac source of embolism, extracranial internal carotid artery high-grade stenosis) on diagnostic investigation. Further cerebrovascular episodes on aspirin warrant consideration of anticoagulation therapy, although again unproven.

There are no prospective data to support treating a TIA associated with aPL any different than treating an ischemic stroke associated with aPL. Generally these patients are treated with low-dose aspirin. Anticoagulation can be considered in patients with recurrent TIAs despite aspirin treatment (Erkan et al., 2002).

Management of these patients' spells often is difficult, and the spells tend to recur (although not in all patients) on antithrombotic regimens. Some patients respond to migraine prophylaxis therapies, such as beta-blockers or calcium-channel antagonists (Winterkorn et al., 1993), and some, but not all, respond to warfarin therapy. However, the risks of warfarin therapy need to be weighed carefully in patients experiencing only transient events.

Treatment of non-thrombotic neurologic manifestations such as seizures, chorea, dementia unassociated with multiple cerebral infarctions or transverse myelitis has usually been limited to immunotherapy in combination with other symptomatic treatment.

Key points

- Ischemic stroke is the only neurological manifestation accepted as a clinical diagnostic criterion for the APS.
- None of the non-stroke neurological syndromes associated with aPL have been definitively linked with either aPL or APS.
- Optimum therapy for stroke and aPL or cerebrovascular manifestations of APS is uncertain. In stroke patients with aPL, there is no superiority of warfarin (INR 1.4–2.8) over aspirin (325 mg/day) for the prevention of recurrent thrombo-occlusive events over a 2 year period.

References

Ameriso, S.F., Wong, V.L., Quismorio, F.P. Jr., Fisher, M. 1991. Immunohematologic characteristics of infection-associated cerebral infarction. Stroke 22, 1004.

Angelini, L., Ravelli, A., Caporali, R., Rumi, V., Nardocci, N., Martini, A. 1994. High prevalence of antiphospholipid antibodies in children with idiopathic cerebral ischemia. Pediatrics 94, 500.

Antiphospholipid antibodies in stroke study group (APASS), 1993. Anticardiolipin antibodies are an independent risk factor for first ischemic stroke. Neurology 43, 2069.
A large case-control study demonstrating the association of aCL with first ischemic stoke, and particularly the IgG isotype.

APASS Investigators. 2004. Antiphospholipid antibodies and subsequent thrombo-occlusive events in patients with ischemic stroke. The Antiphospholipid Antibodies and Stroke Study (APASS). JAMA 291, 576.
The largest study to date on the role of aPL in stroke (1770 subjects tested and over 30% positive). APL, either aCL or LA, tested at baseline did not predicted an increased risk of future thrombo-occlusive events over 2 years; aspirin or warfarin did not have a differential effect on aPL positive and aPL negative subjects. There was a suggestion that subjects positive for both aCL and LA had a greater risk of further events, regardless of treatment arm.

Asherson, R.A., Hughes, G.R.V. 1988. Antiphospholipid antibodies and chorea. J. Rheumatol. 15, 377.

Asherson, R.A., Khamashta, M.A., Ordi-ros, J., Derksen, R.H., Machin, S.J., Barquinero, J., Outt, H.H., Harris, E.N., Vilardell-Torres, M., Hughes, G.R. 1989. The 'primary'antiphospholipid syndrome: major clinical and serological features. Medicine (Baltimore) 68, 366.
A comprehensive review of the primary APS.

Barret, J.T. 1983. Natural resistance and acquired immunity. In: S.E. Harshberger (Ed.), Textbook of Immunology. Mosby, St Louis, p. 203.

Bokarewa, M.I., Bremme, K., Falk, G., Sten-Linder, M., Egberg, N., Blomback, M. 1995. Studies on antiphospholipid antibodies, APC-resistance and associated mutation in the coagulation factor V gene. Thromb. Res. 78, 193.

Bowie, W.E.J., Thompson, J.H., Pasacuzzi, C.A., Owen, C.A. 1963. Thrombosis in systemic lupus erythematosus despite circulating anticoagulants. J. Clin. Invest. 62, 416.
A seminal paper reporting that within the SLE cohort from the Mayo Clinic, aPL-positive SLE patients had more thrombotic events than those SLE patients without aPL.

Brey, R.L., Hart, R.G., Sherman, D.G., Tegeler, C.T. 1990. Antiphospholipid antibodies and cerebral ischemia in young people. Neurology 40, 1190.

Brey, R.L., Abbott, R.D., Sharp, D.S., Ross, G.W., Curb, J.D., Kittner, S.J. 1999. Beta-2-glycoprotein 1-dependent (B2GP1-dep) anticardiolipin antibodies are an independent risk factor for Ischemic stroke in the Honolulu Heart Cohort. Stroke 39, 252.
The first prospective data to implicate cofactor-dependent aCL as an independent risk factor for first ischemic stroke in a stroke-free cohort.

Brey, R.L., Chapman, J., Levine, S.R., Ruiz-Irastorza, G., Derksen, R.H.W.M., Khamashta, M., Shoenfeld, Y. 2003. Stroke and the antiphospholipid syndrome: consensus meeting Taormina 2002. Lupus 12, 508.

A critical review of the evidence for aPL and stroke.

Briley, D.P., Coull, B.M., Goodnight, S.H. 1989. Neurologic disease associated with antiphospholipid antibodies. Ann. Neurol. 25, 221.

Bulckaen, H.G., Puisieux, F.L., Bulckaen, E.d., DiPompeo, C., Bouillanne, O.M., Watel, A.A., Fauchacs, A.L., De Groote, P., Millaire, A. 2003. Antiphospholipid antibodies and the risk of thromboembolic events in valvular heart disease. Mayo Clin. Proc. 78, 294.

Cabides, J., Cabral, A., Alarcon-Segovia, D. 1995. Clinical manifestations of antiphospholipid antibody syndrome in systemic lupus erythematosus associated more strongly with anti-β2 glycoprotein. J. Rheumatol. 22, 1899.

Camerlingo, M., Casto, L., Censori, B., Drago, G., Frigeni, A., Ferraro, B., Servalli, M.C., Radice, E., Mamoli, A. 1995. Anticardiolipin antibodies in acute non-hemorrhagic stroke seen within six hours after onset. Acta Neurol. Scand. 92, 69.

Carhuapoma, J.R., Mitsias, P., Levine, S.R. 1997. Cerebral venous thrombosis and anticardiolipin antibodies. Neurology 28, 2363.

Cervera, R., Asherson, R.A., Font, J., Tikly, M., Pallares, L., Chamorro, A., Ingelmo, M. 1997. Chorea in the antiphospholipid syndrome: clinical, radiologic, and immunologic characteristics of 50 patients from our clinics and recent literature. Medicine 76, 203.

Cesbron, J.Y., Amouyel, P., Masy, E. 1997. Anticardiolipin antibodies and physical disability in the elderly. Ann. Intern. Med. 126, 1003.

Chakravarty, K.K., Byron, M.A., Webley, M., Durkin, C.J., Al-Hillawi, A.H., Bodley, R., Wozniak, J. 1991. Antibodies to cardiolipin in stroke: association with mortality and functional recovery in patients without systemic lupus erythematosus. Q. J. Med. 79, 397.

Chapman, J., Rand, J.H., Brey, R.L., Levine, S.R., Blatt, I., Khamashta, M.A., Shoenfeld, Y. 2003. Non-stroke neurological syndromes associated with antiphospholipid antibodies: evaluation of clinical and experimental studies. Lupus 12, 514.

A critical review of the evidence associated non-stroke neurological syndromes with aPL. None of them can be said to be supportive by solid scientific evidence.

Chinnery, P.F., Shaw, P.I., Ince, P.G., Jackson, G.H., Bishop, R.I. 1997. Fulminant encephalopathy due to the catastrophic primary antiphospholipid syndrome. J. Neurol. Neurosurg. Psychiatry 62, 300.

Ciocca, R.G., Choi, J., Graham, A.M. 1995. Antiphospholipid antibodies lead to increased risk in cardiovascular surgery. Am. J. Surg. 170, 198.

Coull, B.M., Bourdette, D.N., Goodnight, S.H., Briley, D.P., Hart, R. 1987. Multiple cerebral infarctions and dementia associated with anticardiolipin antibodies. Stroke 18, 1107.

Crowther, M.A., Ginsberg, J.S., Julian, J., Denburg, J., Hirsh, J., Douketis, J., Laskin, C., Fortin, P., Anderson, D., Kearon, C., Clarke, A., Geerts, W., Forgie, M., Green, D., Constantini, L., Yacura, W., Wilson, S., Gent, M., Kovacs, M.J. 2003. A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. N. Engl. J. Med. 349, 1133.

An important, randomized clinical trial that failed to show that using warfarin at an INR of 3–4 was superior to maintaining an INR of 2–3 in the prevention of recurrent thrombotic events in patients with aPL and a first event.

Del Papa, N., Raschi, E.R., Catelli, L., Khamashta, M.A., Ichikawa, K., Tincani, A., Balestrieri, G., Meroni, P.L. 1997a. Endothelial cells as a target for antiphospholipid antibodies: role of anti-beta-2-glycoprotein 1 antibodies. AJRI 38, 212.

Del Papa, N., Guidali, L., Sala, A., Buccellati, C., Khamashta, M.A., Ichikawa, K., Koike, T., Balestrieri, G., Tincani, A., Hughes, G.R.V., Meroni, P.L. 1997b. Rndothelial cells as target for antiphospholipid antibodies. Arthritis Rheumatol. 40, 551.

de Moerloose, P., Boehlen, F., Reber, G., Dechevrens, O., Herrmann, F., Michel, J.P. 1997. Prevalence of anticardiolipin and antinuclear antibodies in an elderly hospitalized population and mortality after a 6-year follow-up. Age Ageing 26, 319.

Denburg, S.D., Carbotte, R.M., Ginsberg, J.S., Denburg, J.A. 1997. The relationship of antiphospholipid antibodies to cognitive function in patients with systemic lupus erythematosus. J. Int. Neuropsychol. Soc. 3, 377.

Derksen, R.H., De Groot, P.G., Kappelle, L.J. 2003. Low dose aspirin after ischemic stroke associated with antiphospholipid syndrome. Neurology 61, 111.

Descheins, M.-A., Conard, J., Horellou, M.H., Ameri, A., Preter, M., Chendru, F., Samana, M.M., Bousser, M.-G. 1996. Coagulations studies, factor V Leiden, and anticardiolipin antibodies in 40 cases of cerebral venous sinus thrombosis. Stroke, 1724.

Erkan, D., Efthimious, P., Sammaritano, L., Lockshin, M.D. 2002. Antiphospholipid antibody-related transient ischemic attacks: what is the optimal management? Arthritis Rheum. 24, S47(abstract).

Ford, S.E., Kennedy, L., Ford, P.M. 1994. Clinicopathologic correlations of antiphospholipid antibodies. An autopsy study. Arch. Pathol. Lab. Med. 118, 491.

Formiga, F., Mitjavila, F., Pac, M., Moga, I. 1997. Epilepsy and antiphospholipid antibodies in systemic lupus erythematosus patients. Lupus 6, 486.

Furie, R., Ishikawa, T., Dhawan, V., Eidelberg, D. 1994. Alternating hemichorea in primary antiphospholipid syndrome: evidence for contralateral striatal hypermetabolism. Neurology 44, 2197.

Galli, M., Comfurius, P., Maassen, C., Hemker, H.C., de Baets, M.H., van Breda-Vriesman, P.J., Barbui, T., Zwaal, R.F., Bevers, E.M. 1990. Anticardiolipin antibodies are directed not against cardiolipin but to a plasma cofactor. Lancet 335, 1544.

Ginsberg, J.S., Demers, C., Brill-Edwards, P., Johnston, M., Bona, R., Burrows, R.F., Weitz, J., Denburg, J.A. 1993. Increased thrombin generation and activity in patients with systemic lupus erythematosus and aCL: evidence for a prothrombotic state. Blood 81, 2958.

Ginsburg, K.S., Liang, M.H., Newcomer, L., Goldbaber, S.Z., Schur, P.H., Henekens, C.H., Stampfer, M.J. 1992. Anticardiolipin antibodies and the risk for ischemic stroke and venous thrombosis. Ann. Intern. Med. 117, 997.

Giorgi, D., Gabrieli, C.B., Bonomo, L. 1998. The clinico-ophthalmological spectrum of antiphospholipid syndrome. Ocul. Immunol. Inflamm. 6, 269.

Greisman, S.G., Thayaparan, R.S., Godwin, T.A., Lockshin, M.D. 1991. Occlusive vasculopathy in systemic lupus erythematosus: association with anticardiolipin antibody. Arch. Intern. Med. 151, 389.

Hachulla, E., Michon-Pasturel, U., Leys, D., Pruvo, J.-P., Queyrel, V., Masy, E., Arvieux, J., Caron, C., Brevet-Coupe, F., Hatron, P.-Y., Devulder, B. 1998. Cerebral magnetic imaging in patients with or without antiphospholipid antibodies. Lupus 7, 124.

Harris, E.N., Gharavi, A.E., Boey, M.L., Patel, B.M., Mackworth-Young, C.G., Loizou, S., Hughes, G.R. 1983a. Anticardiolipin antibodies: detection by radioimmunoassay and association with thrombosis in systemic lupus erythematosus. Lancet 2, 1211.

Harris, E.N., Englert, H., Derue, G., Hughes, G.R., Gharavi, A., 1983b. Antiphospholipid antibodies in acute Guillain–Barre syndrome. Lancet 2, 1361.

Harris, E.N., Gharavi, A.E., Mackworth-Young, C.G., Patel, B.M., Derue, G., Hughes, G.R. 1985. Lupoid sclerosis: a possible pathogenic role for antiphospholipid antibodies. Ann. Rheum. Dis. 44, 281.

Harris, E.N., Chan, J.K.H., Asherson, R.A., Aber, V.R., Gharavi, A.E., Hughes, G.R. 1986. Thrombosis, recurrent fetal loss, and thrombocytopenia. Predictive value of the anticardiolipin antibody test. Arch. Intern. Med. 146, 2153.

Hatron, P.Y., Bouchez, B., Wattel, A., Arnott, G., Devalder, B. 1987. Chorea, systemic lupus erythematosus, circulating lupus anticoagulants. J. Rheumatol. 4, 991.

Hermosillo-Romo, D., Brey, R.L. 2002. Neuropsychiatric involvement in systemic lupus erythematosus. Curr. Rheumatol. Rep. 4, 337.

Herranz, M.T., Rivier, G., Khamashta, M.A., Blaser, K.U., Highes, G.R. 1994. Arthritis Rheum. 37, 568.

Hess, D.C., Krauss, J., Adams, R.J., Nichols, F.T., Zhang, D., Rountree, H.A. 1991. Anticardiolipin antibodies: a study of frequency in TIA and stroke. Neurology 41, 525.

Horbach, D.A., Oort, E.V., Donders, R.C.J.M., Derksen, R.H., de Groot, P.G. 1996. Lupus anticoagulant is the strongest risk factor for both venous and arterial thrombosis in patients with systemic lupus erythematosus. Comparison between different assays for the detection of antiphospholipid antibodies. Thromb. Haemost. 76, 916.

Hughes, G.R.V. 1983. Thrombosis, abortion, cerebral disease and lupus anticoagulant. BMJ 287, 1088.

Hughes, G.R.V., Harris, E.N., Gharavi, A.E. 1986. The anticardiolipin syndrome. J. Rheumatol. 13, 486.

Inzelberg, R., Korczyn, A.D. 1989. Lupus anticoagulant and late onset seizures. Acta Neurol. Scand. 79, 114.

Jackson, C., Brey, R.L., Barohn, R., 1992. Anticardiolipin antibodies in Guillain–Barre syndrome. Clin. Exp. Rheumatol. 10, 657.

Kalashnikova, L.A., Nasonov, E.L., Kushekbaeva, A.E., Gracheva, L.A. 1990. Anticardiolipin antibodies in Sneddon's syndrome. Neurology 40, 464.

Karussis, D., Leker, R.R., Ashkenazi, A., Abramsky, O. 1998. A subgroup of multiple sclerosis patients with aCL and unusual clinical manifestations: do they represent a new nosological entity? Ann. Neurol. 44, 629.

Kent, M., Vogt, E., Rote, N.S. 1997. Monoclonal antiphosatidylserine antibodies react directly with feline and murine central nervous system. J. Rheumatol. 24, 1725.

Kent, M.N., Alvarez, F.J., Ng, A.K., Rote, N.S. 2000. Ultrastructural localization of monoclonal antiphospholipid antibody binding to rat brain. Exp. Neurol. 163, 173.

Khamashta, M.A., Gil, A., Anciones, B., Lavilla, P., Valencia, M.E., Pintado, V., Vazquez, J.J. 1988. Chorea in systemic lupus erythematosus: association with antiphospholipid antibodies. Ann. Rheum. Dis. 47, 681.

Khamashta, M.A., Cuadrado, M.J., Mujic, F., Taub, N.A., Hunt, B.J., Hughes, G.R. 1995. The management of thrombosis in the antiphospholipid antibody syndrome. N. Engl. J. Med. 332, 993.

Klemp, P., Cooper, R.C., Strauss, F.J., Jordaan, E.R., Przybojewski, J.Z., Nel, N. 1988. Anticardiolipin antibodies in ischemic heart disease. Clin. Exp. Immunol. 89, 411.

Kushner, M.J. 1990. Prospective study of anticardiolipin antibodies in stroke. Stroke 21, 295.

Labutta, R.J. 1996. Ophthalmic manifestations in the antiphospholipid syndrome. In: R.A. Asherson, R. Cervera, J.C. Piette, Y. Shoenfeld (Eds.), The Antiphospholipid Syndrome. CRC Press, Boca Raton, FL, p. 213.

Lavalle, C., Pizarro, S., Drenkard, C., Sanchez-Guerrero, J., Alarcon-Segovia, D. 1990. Transverse myelitis: a manifestation of systemic lupus erythematosus associated with antiphospholipid antibodies. J. Rheumatol. 17, 34.

Levine, S.R., Brey, R.L., Sawaya, K.L., Salowich-Palm, L., Kokkinos, J., Kostrzema, B., Perry, M., Havstad, S., Carey, J. 1995. Recurrent stroke and thrombo-occlusive events in the antiphospholipid syndrome. Ann. Neurol. 38, 119.

Levine, S.R., Salowich-Palm, L., Sawaya, K.L., Perry, M., Spencer, H.J., Winkler, H.J., Alam, Z., Carey, J.L. 1997. IgG anticardiolipin antibody titer >40 GPL and the risk of subsequent thrombo-occlusive events and death. Stroke 28, 1660.

Levine, S.R., Deegan, M.J., Futrell, N., Welch, K.M.A. 1990. Cerebrovascular and neurologic disease associated with antiphospholipid antibodies: 48 cases. Neurology 40, 1181.

Liou, H.H., Wang, C.R., Chou, H.C., Arvanov, V.L., Chen, R.C., Chang, Y.C., Chuang, C.Y., Chen, C.Y., Tsai, M.C. 1994. Anticardiolipin antisera from lupus patients with seizures reduce a gaba receptor-medicated chloride current in snail neurons. Life Sci. 54, 1119.

Lopez-Soto, A., Cervera, R., Font, J., Bove, A., Reverta, J.C., Munoz, F.J., Miret, C., Espinosa, G., Ordinas, A., Igelmo, M. 1997. Isotype distribution and clinical significance of antibodies to cardiolipin, phosphatidic acid, phosphatidylinnositol, and phosphatidylserine in systemic lupus erythematosus: prospective analysis of 92 patients. Clin. Exp. Rheumatol. 15, 143.

Matsurra, E., Igarashi, Y., Fujimoto, M., Ichikawa, K., Koike, T. 1990. Anticardiolipin cofactors and the differential diagnosis of autoimmune disease. Lancet 336, 177.

McNeil, H.P., Chesterman, C.N., Krilis, S.A. 1991. Immunology and clinical importance of antiphospholipid antibodies. Adv. Immunol. 49, 193.

McNeil, H.P., Simpson, R.J., Chesterman, C.N., Krilis, S.A. 1990. Antiphospholipid antibodies are directed against a complex antigen that includes a lipid-binding inhibitor of coagulation β2 glycoprotein 1 (apolipoprotein H). Proc. Natl Acad. Sci. USA 87, 4120.

Meroni, P.L., Del Papa, N., Raschi, E., Panzeri, P., Borghi, M.O., Tincani, A., Balestrieri, G., Khamashta, M.A., Hughes, G.R., Koike, T., Krilis, S.A. 1998. β2 glycoprotein 1 as a co-factor for antiphospholipid reactivity with endothelial cells. Lupus 5, S44.

Metz, L.M., Edworthy, S., Mydlarski, R., Fritzler, M.J. 1998. The frequency of phospholipid antibodies in an unselected stroke population. Can. J. Neurol. Sci. 25, 64.

Montalban, J., Arboix, A., Staub, H., Barquinero, J., Marti-Vilalta, J., Codina, A., Hughes, G.R. 1989. Transient global amnesia and antiphospholipid antibodies. Clin. Exp. Rheumatol. 7, 85.

Muir, K.W., Squire, I.B., Alwan, W., Lees, K.R. 1994. Anticardiolipin antibodies in an unselected stroke population. Lancet 344, 452.

Naarendorp, M., Spiera, H. 1998. Sudden sensorineural hearing loss in patients with systemic lupus erythematosus or lupus-like syndromes and antiphospholipid antibodies. J. Rheumatol. 25, 589.

Nagarja, D., Christopher, R., Manjari, T. 1997. Anticardiolipin antibodies in ischemic stroke in the young: Indian experience. J. Neurol. Sci. 150, 137.

Nencini, P., Baruffi, M.C., Abbate, R., Massai, G., Amaducci, L., Inzitari, D. 1992. Lupus anticoagulant and anticardiolipin antibodies in young adults with cerebral ischemia. Stroke 23, 189.

Peltola, J.T., Haapala, A., Isojarvi, J.I. 2000. Antiphospholipid and antinuclear antibodies in patients with epilepsy or new-onset seizure disorders. Am. J. Med. 109, 712.

Perez, R.E., McClendon, J.R., Lie, J.T. 1992. Primary antiphospholipid syndrome with multiorgan arterial and venous thromboses. J. Rheumatol. 19, 1289.

Petri, M. 2000. Epidemiology of the antiphospholipid antibody syndrome. J. Autoimmun. 15, 145.

Pierangeli, S.S., Harris, E.N. 1994. Antiphospholipid antibodies in an in vivo thrombosis model in mice. Lupus 3, 247.

Piette, J.C., Cacoub, P. 1998. Antiphospholipid syndrome in the elderly: caution. Circulation 9, 2195.

Rafuse, P.E., Canny, C.L. 1992. Initial identification of antinuclear-antibody-negative systemic lupus erythematosus on ophthalmic examination: a case report, with a discussion of the ocular significance of anticardiolipin. Can. J. Ophthalmol. 27, 189.

Rauch, J., Aminoff, A.S. 1996. Antiphospholipid antibodies against phospholipids other than cardiolipin: potential roles for both phospholipid and protein. Lupus 5, 498.

Rosove, M.H., Brewer, P.M.C. 1992. Antiphospholipid thrombosis: clinical course after the first thrombotic event in 70 patients. Ann. Intern. Med. 117, 303.

Rote, N.S., Dostal-Johnson, D., Branch, D.W. 1990. Antiphospholipid antibodies and recurrent pregnancy loss: correlation between the activated partial thromboplastin time and antibodies against phosphatidylserine and cardiolipin. Am. J. Obstet. Gynecol. 163, 575.

Roubey, R.A.S., Eisenberg, R.A., Harper, M.F., Winfield, J.B. 1995. 'Anticardiolipin' autoantibodies recognize β2 glycoprotein 1 in the absence of phospholipids: importance of antigen density and bivalent binding. J. Immunol. 154, 954.

Ruiz-Arguelles, G.J., Guzman-Ramos, J., Flores-Flores, J., Garay-Martinez, J. 1998. Refractory hiccough heralding transverse myelitis in the primary antiphospholipid syndrome. Lupus 7, 49.

Sailer, M., Burchert, W., Ehrenheim, C., Smid, H.G.O.M., Haas, J., Wildhagen, K., Wurster, U., Deicher, H. 1997. Positron emission tomography and magnetic resonance imaging for cerebral involvement in patients with systemic lupus erythematosus. J. Neurol. 244, 186.

Schmidt, R., Auer-Grumbach, P., Fazekas, F., Offenbacher, H., Kapeller, P. 1995. Anticardiolipin antibodies in normal subjects. Neuropsychological correlates and MRI findings. Stroke 26, 749.

Schwartz, M., Rochas, M., Weller, B., Sheinkman, A., Tal, I., Golan, D., Toubi, N., Eldar, I., Sharf, B., Attias, D. 1998. High association of anticardiolipin antibodies with psychosis. J. Clin. Psychiatry 59, 20.

Silvestrini, M., Cupini, L.M., Matteis, M., De Simone, R., Bernardi, G. 1993. Migraine in patients with stroke and antiphospholipid antibodies. Headache 33, 421.

Sletnes, K.E., Smith, P., Abdolnoor, M., Arnosen, H., Wisloff, F. 1992. Antiphospholipid antibodies after myocardial infarction and their relation to mortality, reinfarction, and non-haemorrhagic stroke. Lancet 339, 451.

Sneddon, I.B. 1965. Cerebral vascular lesions in livedo reticularis. Br. J. Dermatol. 77, 180.

Sunden-Cullberg, J., Tedroff, J., Aquilonius, S.-M. 1998. Reversible chorea in primary antiphospholipid syndrome. Mov. Dis. 13, 147.

Tietjen, G.E., Levine, S.R., Brown, E., et al. 1993. Factors which predict antiphospholipid immuno-reactivity in young people with focal neurologic deficits. Arch. Neurol. 50, 833.

Tietjen, G.E., Day, M., Norris, L., Aurora, S., Halvorson, A., Schultz, L.R., Levine, S.R. 1998. The role of anticardiolipin antibodies in young persons with migraine and transient focal neurologic deficits: a prospective study. Neurology 50, 1433. A large prospective study that failed to show a link between aCL and migraine or transient focal neurological deficits in young people.

Toubi, E., Khamashta, M.A., Panarra, A., Hughes, G.R.V. 1995. Association of antiphospholipid antibodies with central nervous system disease in systemic lupus erythematosus. Am. J. Med. 99, 397.

Toubi, E., Ben-David, J., Kessel, A., Podoshin, L., Golan, T.D. 1997. Autoimmune aberration in sudden sensorineural hearing loss: association with anti-cardiolipin antibodies. Lupus 6, 540.

Tourbah, A., Peitte, J.C., Iba-Zizen, M.T., Lyon-Caen, O., Godeau, P., Frances, C. 1997. The natural course of cerebral lesions in Sneddon syndrome. Arch. Neurol. 54, 53.

Tuhrim, S., Rand, J.H., Wu, X., Horowitz, D.R., Weinberger, J., Goldman, M.E., Godbold, J.H. 1999. Antiphosphatidyl serine antibodies are independently associated with ischemic stroke. Neurology 53, 1523.

Verro, P., Levine, S.R., Tietjen, G.E. 1998. Cerebrovascular ischemic events with high positive anticardiolipin antibodies. Stroke 29, 2245.

Verrot, D., San-Marco, M., Dravet, C., Genton, P., Disdier, P., Bolla, G., Harle, J.R., Reynaud, L., Weiller, P.J. 1997. Prevalence and signification of antinuclear and anticardiolipin antibodies in patients with epilepsy. Am. J. Med. 103, 33.

Wahl, D.G., Guillemin, F., de Maistre, E., Perret-Guillaume, C., Lecompte, T., Thibaut, G. 1998. Meta-analysis of the risk of venous thrombosis in individuals with antiphospholipid antibodies without underlying autoimmune disease or previous thrombosis. Lupus 7, 15.

WARSS, APASS, PICSS and HAS Study Groups, 1997. The feasibility of a collaborative, double-blind study using anticoagulant: the Warfarin–Aspirin Recurrent Stroke Study (WARSS), the Antiphospholipid Antibody in Stroke Study (APASS), the Patent Foramen Ovale Study (PICSS) and the Hemostatic System Activation Study (HAS). Cerebrovasc. Dis. 7, 100.

Wilson, W.A., Gharavi, A.E., Koike, T., Lockshin, M.D., Branch, D.W., Piette, J.-C., Brey, R.L., Derkson, R., Harris, E.N., Hughes, G.R.V., Triplett, D.A., Khamashta, M.A. 1999. International Consensus Statement on Preliminary Classification Criteria for Definite Antiphospholipid Syndrome: Report of an International Workshop. Arthritis Rheum. 2, 1309.

Winterkorn, J.M.S., Kupersmith, M.J., Wirtschafter, J.D., Forman, S. 1993. Brief report: treatment of vasospastic amaurosis fugax with calcium-channel blockers. N. Engl. J. Med. 329, 396.

Zelzer, B., Sepp, N., Stockhammer, G., Dosch, E., Hilty, E., Offner, D., Aichner, F., Fritsch, P.O. 1993. Sneddon;s syndrome; a long term follow-up of 21 patients. Arch. Dermatol. 129, 437.

Ziporen, L., Shoenfeld, Y. 1998. Antiphospholipid syndrome: from patient's bedside to experimental animal models and back to the patient's bedside. Hematol. Cell Ther. 40, 175.

PART III

Rheumatoid Arthritis

Handbook of Systemic Autoimmune Diseases, Volume 3
Neurologic Involvement in Systemic Autoimmune Diseases
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CHAPTER 5

Rheumatoid Arthritis: Spine Involvement

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1. Introduction

Clinically important spine involvement in rheumatoid arthritis (RA) is focused primarily in the cervical region. The same destructive inflammatory process that affects peripheral joints can also affect the cervical spine, with ensuing disruption of surrounding ligaments, joint space, and cartilage and their attendant symptoms, signs and potential neurologic compromise (Boden, 1994). Cervical spine disease (CSD) in RA usually takes one of three forms: atlantoaxial subluxation (AAS), cranial settling, or subaxial subluxation (Rawlins et al., 1998). A diagnostic and therapeutic challenge, CSD has protean clinical manifestations, from neck pain with minimal radiographic changes to clinically silent basilar invagination that may result in sudden death. While the advent of Magnetic Resonance Imaging (MRI) has aided considerably in the diagnosis of CSD, anywhere from 19 to 88% of these patients have no correlation between radiographic changes and clinical manifestations (Bouchaud-Chabot and Liote, 2002; Reijnierse et al., 1996). Moreover, surgical treatment is difficult, has morbidity and mortality, and may not improve outcome of a subset of patients (Boden et al., 1993). The challenge then lies in determining the optimal ways to diagnose and manage RA patients with CSD:

- Which patients should be screened and which clinical and imaging assessments are the most sensitive?
- Do we ever treat asymptomatic disease?
- What nonsurgical therapeutic options are available to patients? Has our modern and aggressive therapeutic approach to RA had an impact upon the development and progression of CSD?
- Which patients will profit from surgery?
- From which patients should surgery be withheld?

Recent clinical studies have made advances in addressing these challenging questions.

2. Prevalence

Much of the data used to define the prevalence of CSD in RA comes from studies carried out between 1970 and 1990 and not from the modern era of RA treatment. That said, studies in the natural history of RA indicate that CSD *of any kind* occurs in 43–86% of RA patients (Bouchaud-Chabot and Liote, 2002) and clinically significant disease occurs in up to 78% of patients (Gurley and Bell, 1997). Seven to 13% of RA patients with CSD have neurologic deficits (Pellicci et al., 1981), while approximately 50% of patients with radiographic cervical instability are asymptomatic. In the distant past, 10% of RA patients died of unrecognized spinal cord or brain stem compression (Mikulowski et al., 1975).

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3. Epidemiology

CSD in RA occurs in a particular subset of patients characterized by: male gender; severe peripheral polyarthritis with evidence of radiographic destruction; the presence of rheumatoid nodules; the presence of rheumatoid factor (seropositivity); long-term glucocorticoid therapy; and prolonged disease duration (Bouchaud-Chabot and Liote, 2002; Rawlins et al., 1998; Smith et al., 1972; Weissman et al., 1982). This suggests that such patients should have routine radiographs of the cervical spine, even in the absence of cervical symptoms. This is particularly important prior to general anesthesia or neck manipulation.

4. Anatomy/etiology/pathogenesis

The cervical spine consists of the upper cervical spine (C1 and C2, with the atlantoaxial, atlantoodontoid, and atlantooccipital joints), and the lower cervical spine (C3 to C7) (Netter, 1993). The major pathophysiologic manifestations of CSD in RA are atlantoaxial dislocation, cranial settling, and subaxial subluxation; combinations of these abnormalities occur as well and when they do, the patient is at increased risk of developing neurologic deficits.

The upper spine is stabilized by many ligaments including the transverse, alar, and accessory atlantoaxial ligaments (Netter, 1993). Synovitis in the atlantoodontoid joint may result in erosion, laxity, and rupture of the transverse and other adjacent ligaments, resulting in atlantoaxial dislocation (AAD) (Fig. 1). Atlantoaxial dislocation occurs in anterior, lateral or posterior fashion. Anterior AAD, accounting for 75% of cases, occurs when the transverse ligament is disrupted, resulting in C1 slipping anteriorly over C2 (Fig. 2). It is defined as an atlas-dens interval of more than 3 mm. An atlas-dens interval of 9 mm or more is more likely to cause cord compression (Weissman et al., 1982; Bouchaud-Chabot and Liote, 2002). Neurologic deficits may be avoided in this region because of concomitant erosion of the dens leading to a more capacious area in the upper C-spine. Lateral AAD occurs when loss of cartilage on the lateral mass of C1 or articular process of C2 results in a lateral shift of C1 of least 2.5 mm (Bouchaud-Chabot and Liote, 2002). Posterior dislocation, the least common form of AAD, is usually due to destruction of the dens by pannus or fracture, leading to posterior slippage of C1 and thus a greater potential for neurologic impairment (Rawlins et al., 1998).

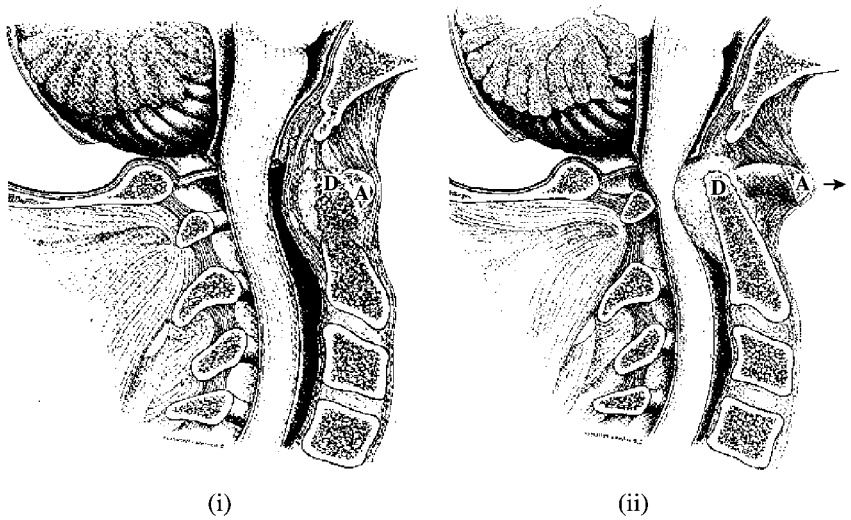

Figure 1. (i) Pannus formation around the dens (D) leads to bony erosion and ligament laxity. In (ii), atlanto-axial subluxation occurs as the dens is displaced posteriorly to the anterior arch (A) of C1. ©1993. The Journal of bone and Joint Surgery. Reprinted from J. Bone Joint Surg. 75(A), p. 1282 with permission.

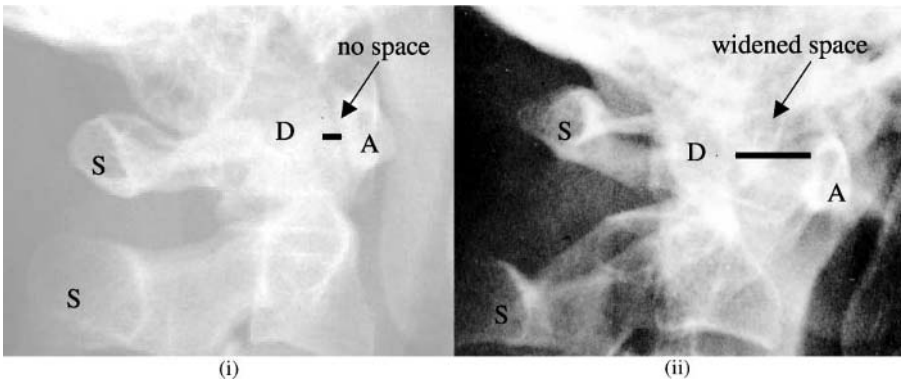

Figure 2. Atlantoaxial dislocation (AAD) in RA: (i) demonstrates a normal C1–C2 joint, with the anterior arch of C1 (A) and the dens (D) in close proximity, and the spinous processes (S) of C1 and C2 well aligned.(ii) demonstrates AAD in RA, with posterior displacement of the dens in relation to the anterior arch of C1, and anterior displacement of the spinous process of C1 with relation to the spinous process of C2. Horizontal lines denote the anterior atlanto-dens interval (A–AD interval), considerably widened in AAD.

Cranial settling, known also as basilar invagination or vertical translocation of the dens, occurs in 4 to 35% of RA patients with severe disease. Erosion of the occipitoatlantal and atlantoaxial joints results in collapse of the lateral masses of C1 and settling of the skull on the upper cervical spine. This process allows the dens to enter the foramen magnum and cause brain stem or spinal cord compression (Bouchaud-Chabot and Liote, 2002; Rawlins et al., 1998) (Fig. 3). In patients with an untreated myelopathic presentation there is a 50% reported death rate within 6 months (Marks et al., 1989).

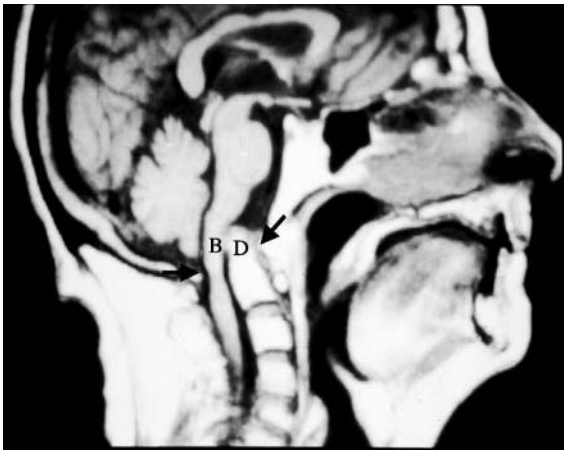

Figure 3. Basilar invagination: MRI demonstrates the dens (D) protruding through the foramen magnum(arrows) and compressing the brain stem (B) in a patient with RA.

Subaxial subluxation, occurring in 7–29% of patients with CSD (Bouchaud-Chabot and Liote, 2002), is caused by destruction of the facet joints, interspinous ligament, or discovertebral junction, resulting in a 'step ladder' type deformity (Rawlins et al., 1998) (Fig. 4). Spinal cord compression may occur via displacement of the

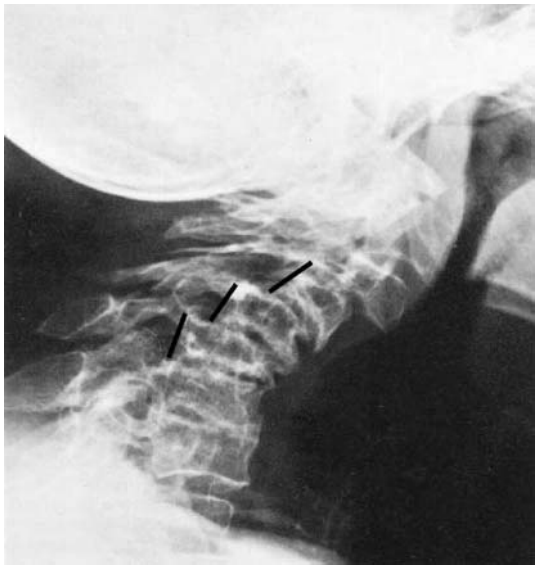

Figure 4. Subaxial subluxation: Step ladder deformities with subluxation at C3–C4, C4–C5, and C5–C6. Note that posterior edges of vertebral bodies (marked in black) should be aligned in a straight line.

vertebral body, direct pannus formation, or rheumatoid discitis (Bouchaud-Chabot and Liote, 2002). Anterior subluxation of 3.5 mm or more has been associated with a high risk of cord compression. Long-term follow-up studies have reported radiographic progression in 16 to 60% and neurologic progression in 2 to 36% of untreated patients (Rawlins et al., 1998). This is because this region of the C-spine is narrower and less forgiving.

5. Clinical manifestations

As a rule, there is considerable variety in the manifestations of symptoms and signs in RA patients with CSD, and there is often no correlation with the severity of damage as defined by imaging (Bouchaud-Chabot and Liote, 2002). Patients may present in a nonspecific, vague and insidious manner, noting the slow development of an impaired gait, generalized weakness and failure to thrive; they may also be asymptomatic. Most commonly the presentation is of pain in the cervical and occipital spine. Other symptoms may include a sensation of the head falling forward, a 'clunking feeling' on movement of the neck, distal extremity weakness, paresthesias and clumsiness of the hands, heaviness in the legs, and gait disturbances (Rawlins et al., 1998). Depending on the severity and level of the lesion one may see a wide range of neurologic manifestations, from nerve root and spinal cord compression (motor/sensory loss, urinary incontinence) to cranial nerve impairment (suggesting brainstem compression due to cranial settling), to vertebrobasilar insufficiency (suggesting basilar invagination-symptoms include tinnitus, vertigo, visual disturbances, dysarthria, or loss of balance).

Examination of RA patients for signs of CSD often presents a diagnostic challenge, because abnormalities related to neurological compromise may be difficult to differentiate from those related to joint and muscle involvement; for example, subtle loss of strength from spinal cord compromise is difficult to distinguish from weakness or disuse atrophy arising from the longstanding peripheral joint arthritis that is so common in this group of patients (Dreyer et al., 1999). Manifestations on exam reflect the level of cervical involvement and the degree of spinal cord compression. If there is cervical root compression, signs may include dysesthesia, weakness, and hyporeflexia in the affected root dermatome. In the case of myelopathy or cord compression, one may see L'Hermitte's phenomenon (electric shock sensation with forward flexion of the head), extremity weakness, hyperreflexia (may progress to ankle clonus), diminished proprioception, a positive Babinski test, or impaired gait (Gurley and Bell, 1997).

6. Diagnostic investigations

Radiographic studies, taken in flexion and extension of the neck, are used to screen patients for evidence of dislocation. Radiological criteria are used for each condition to evaluate the severity of dislocations. As mentioned above, AAD is defined by an increase in the anterior atlanto-dens interval (A–AD interval) to more than 2.5 mm; maximum displacement is 12 mm when all three ligaments are disrupted. Boden et al. (1993) found that the distance between the posterior margin of the dens and the anterior rim of the posterior arch of C1 (the posterior atlas-dens or P–AD interval) showed a greater correlation with the risk of neurologic compromise than the A–AD interval. A P–AD interval of less than 14 mm was associated with neurological abnormalities (Boden et al., 1993).

For cranial settling, the position of the dens in relation to the base of the skull is assessed on a lateral radiograph. Various lines have been used to assess the position of the dens: the two most widely used are *McGregor's line* (Fig. 5i—the line drawn from the hard palate to the caudal surface of the occiput; basilar invagination is considered present in men when the tip of the odontoid is 8 mm above the line and in women when it is 9.7 mm above), and *Ranawat's index* (Fig. 5ii—the perpendicular distance from the center of the pedicle of the axis (base of the odontoid) to a line connecting the anterior and posterior arches of C1; a distance of less than 15 mm for men and 13 mm for women is considered significant for basilar invagination) (Rawlins et al., 1998).

Subaxial dislocation of the lower cervical spine can be visualized on X-ray by observing a step-off in the line running along the posterior wall of the vertebral bodies (Fig. 4).

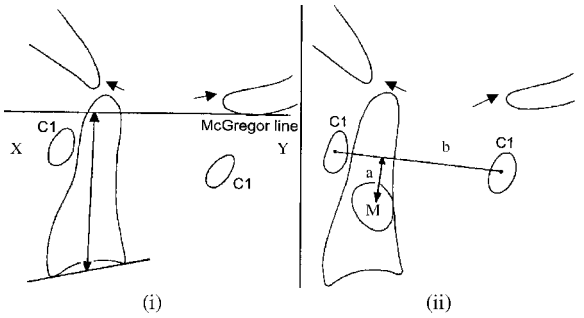

Figure 5. (i) The McGregor Line. Drawn from the posterior aspect of the hard palate (X) to the most inferior aspect of the occiput(Y). Atlanto-axial impaction is defined if the tip of the odontoid is >4.5 mm above this line. (ii) The Ranawat Index. Line (a) is drawn from the lateral mass of C2(M) perpendicularly to a line (b) connecting the anterior arch of C1 with the spinous process of C1. If a < 15 mm in men or < 13 mm in women, this signifies significant basilar invagination. Red arrows denote borders of the foramen magnum. (1997 American Academy of Orthopaedic Surgeons. Reprinted from J. Am. Acad. Orthop. Surg. 5(5), pp 240–248 with permission.)

Radiographs of the spine are used primarily for screening of patients to rule out dislocation. Once this is established, or in the case where radiographic visualization is poor, computed tomography (CT) and MRI may be obtained for more detailed imaging. CT is particularly useful for the evaluation of bone lesions, axial and sagittal anatomy, and dislocations (Halla et al., 1990). CT with myelography, while used less commonly, is a reliable way to evaluate patients for cord compression. MRI reveals detailed imaging of the spinal cord and its relations to the vertebrae, with information on the presence, size and position of pannus as well; it is particularly useful for the evaluation of cranial settling (Bouchaud-Chabot and Liote, 2002). Dynamic MRI allows one to evaluate the extent of dislocation and spinal cord compression with changing positions of the neck.

As a further diagnostic aid, somatosensory evoked potentials (SEPs) provide a reproducible and objective evaluation of sensory conduction. A study on 50 RA patients suggested that SEP monitoring was 90% specific (and 56% sensitive) for AAD (Reijnierse et al., 2000). SEPs suggest information about the level of the lesion and are useful for intraoperative monitoring of patients as well, with one study revealing a decrease in mortality and intraoperative neurological adverse event rate in surgical patients whose SEPs were monitored (Epstein et al., 1993).

According to a review by Gurley and Bell (1997), routine anteroposterior, lateral, open-mouth, and flexion-extension cervical spine radiographs should be performed for high risk RA patients who had never had a cervical spine evaluation, for patients of the same category who had not had cervical spine imaging within the past two or three years, for RA patients undergoing surgery requiring endotracheal intubation, and for patients in whom there is a high index of suspicion of atlantoaxial instability. Additional imaging is necessary for patients with a neurologic deficit suggesting myelopathy or basilar invagination. In these cases MRI is considered the modality of choice. A dynamic flexion-extension study is valuable because it can reveal subtle instability patterns. For those patients in whom MRI imaging is not an option, cervical myelography with CT is recommended (Gurley and Bell, 1997).

7. Treatment

Although many patients with CSD may not be responsive to disease modifying agents in RA, there is evidence that combination therapy with sulfasalazine, methotrexate, and hydroxychloroquine during the first two years of RA onset may reduce the degree of cervical spine involvement; this is consistent with the current paradigm of early aggressive RA treatment (Neva et al., 2000). The effectiveness of anti-tumor necrosis factor (TNF) medications on CSD has yet to be defined. However, since these biological agents seem to stop the development of erosions, they are likely to prevent or limit the evolution of C-spine disease.

Spine immobilization with a cervical collar often decreases instability and alleviates pain (Kauppi et al., 1995). Analgesics provide pain relief in most patients. Finally, there may be a role for local injection under radiographic guidance: a recent retrospective study of 26 patients receiving steroid injections at C1–C2 revealed significant pain relief for a mean duration of 16.9 months (Glemarec et al., 2000).

The need for surgery is generally evaluated on a case-by-case basis. The consensus, however, is that surgery is needed in patients with spinal cord

compression (especially those with cranial settling and AAD), evidence of vertebral artery compromise, severe intractable pain, or major radiological dislocation (anterior A–AD of 9 mm or more, or P–AD of 14 mm or less, with canal diameter less than 13 mm). Even these conditions have caveats: one study suggested that surgery is only needed in patients with *progressive* neurological compromise (Pellicci et al., 1981); severe pain unresponsive to standard analgesics may respond to localized injection, as mentioned above; and some studies have shown that even patients with major displacements and instability may be free of neurological symptoms and undergo spontaneous fusion of the affected vertebrae (King, 1985). Ultimately, a judgment needs to be made in each circumstance regarding the risk of neurological complications—with the aforementioned situations considered high risk.

Patients with upper cervical spine lesions, particularly AAD, usually undergo C1–C2 fusion, in which metal wires or hooks are used to stabilize the posterior arches of C1 and C2. For patients with cranial settling in which MRI gives evidence of cord compression, cord decompression is indicated, followed by occipitocervical fusion, in which fixation with metal plates combined with bone grafts ensures the stability of the cervical spine. This procedure often results in considerable loss of motion. Without bone grafting a high rate of disassembly may occur (McAfee et al., 1986). Dislocation of the lower cervical spine is treated with cord decompression, internal fixation, and bone grafting (Fig. 6).

Although the posterior approach tends to be used more often for surgery, occasionally the anterior approach is utilized, especially when there is dislocation with cord compression at several layers, or a vertebral body needs to be removed anteriorly. The trans-oral approach has been recommended for cases of anterior decompression via odontoid resection (Rawlins et al., 1998). Decompression is satisfactory in most patients, although there is a higher risk of infection and instability via the anterior approach (Bouchaud-Chabot and Liote, 2002). In all patients, rigid postoperative immobilization is required (Rawlins et al., 1998).

There have been at least 12 surgical case series on CSD in RA published over the past 20 years. Since patient numbers are small (the largest had 134 patients) and the range of indications, lesions, and surgical techniques varied between studies, results of the studies differ and are difficult to compare. As mentioned before, Boden et al. (1993) identified preoperative P–AD as a significant factor in patient outcome, both short and long-term. In this study, patients with a P–AD of less than 10 mm and neurological deficits had very poor postoperative recovery. The suggestion is that greatly advanced disease, as manifested by severe canal narrowing, may be a contraindication to surgery. In many patients, however, surgery improves the pain and neurological manifestations: In four different case series, the improvement rate ranged from 50 to 66% (Rawlins et al., 1998). The cumulative data suggest that surgery may be most beneficial when done early, in patients not yet bedridden but with intractable pain and/or instability with neurological manifestations (Santavirta et al., 1988).

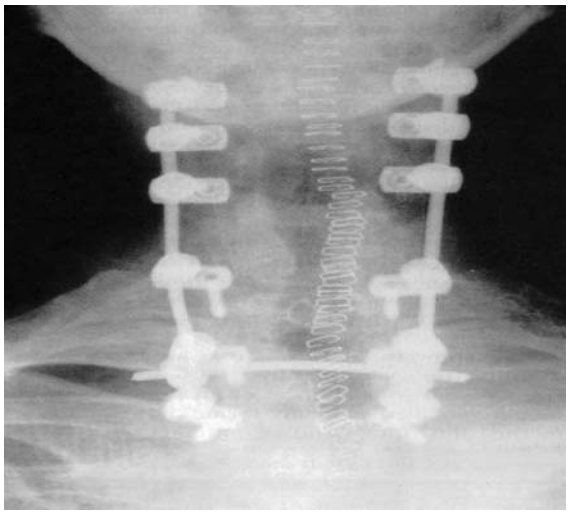

Figure 6. Multiple laminectomies, posterior fusion rods and lateral mass screws in a patient with subaxial subluxation.

Depending on the series, complication rates have ranged from 2–31%. The most common postoperative complication is nonunion of the fusion (Bouchaud-Chabot and Liote, 2002). Other complications include infection, early disassembly, and worsening neurological loss. Repeat surgery is needed in about 10% of patients (Santavirta et al., 1991), with higher re-operation rates found for patients with more advanced disease (Peppelman et al., 1993). Long-term

mortality is high, up to 50% in the earlier studies. Functional prognosis is poorer in bedridden patients (Casey et al., 1996). These results may reflect the fact that CSD is associated with more severe RA that, therefore, confers a poorer prognosis in general.

8. Conclusions

CSD is common in RA. Based on the findings of five recent reviews, it is reasonable to consider surgical referral for patients with severe cervical pain, myelopathy, or neurologic deficits associated with any of the three cervical instability patterns. Asymptomatic patients should be screened with lateral cervical spine radiographs. If the anterior atlanto-dens interval rises above 9 mm, the posterior atlanto-dens interval falls below 14 mm, or if basilar invagination is suspected, an MRI should be performed to evaluate cord anatomy. The presence of cord diameter less than 6 mm, canal diameter less than 13 mm, or cord compression on MRI are strong indications for surgical referral. In general, active, young patients with asymptomatic AAD should be considered for surgery before the disease progresses significantly.

There is a point of disease beyond which outcome may be poor, even with surgery. High grade neurologic deficits with severe canal narrowing (less than 10 mm), for example, or basilar invagination together with atlantoaxial instability may portend a poor recovery and prognosis. Additional larger and long term studies are needed to determine which patients with CSD will benefit from intervention, and when the optimal time for intervention is. Above all, it is important to realize that the clinical presentation of CSD in RA is a continuum, with no two patients presenting exactly the same way; aggressive treatment of RA, close, regular follow-up, and constant communication with the patient and consulting surgeon are paramount to optimizing the patient's outcome and prognosis.

Acknowledgements

We thank Dr. Matthew Cunningham and Dr. Barry Ghelman for their assistance with radiographic images. We also thank Bobby Kakar and Eugene Calma for their assistance with the figures.

Key points

- Cervical Spine Disease (CSD) in RA is common, has a variety of manifestations, and is often under-diagnosed.
- The three primary forms of CSD in RA are AAS, basilar invagination, and subaxial subluxation.
- A flexion/extension C-spine radiograph is the screening modality of choice; MRI offers the greatest anatomic detail.
- Consider surgery in patients with intractable pain, neurologic findings, or radiographic instability.
- Aggressive management of RA is the key to preventing progression of CSD.

References

Boden, S.D. 1994. Rheumatoid arthritis of the cervical spine: Surgical decision making based on predictors of paralysis and recovery. Spine 19, 2275.

Boden, S.D., Dodge, L.D., Bohlman, H.H., et al. 1993. Rheumatoid arthritis of the cervical spine. J. Bone Joint Surg. Am. 75A, 1282.

Bouchaud-Chabot, A., Liote, F. 2002. Cervical spine disease in rheumatoid arthritis. A review. Joint Bone Spine 69, 141.
A thorough and up-to-date review on the medical and surgical approach to cervical spine disease in rheumatoid arthritis.

Casey, A., Crockard, H.A., Bland, J.M., Stevens, S. 1996. Surgery on the rheumatoid cervical spine for the non ambulant myelopathic patients—too much, too late? Lancet 347, 1004–1007.

Dreyer, S.J., Boden, S.D. 1999. Natural history of rheumatoid arthritis of the cervical spine. Clin. Orthop. Relat. Res. 366, 98.
Review of natural history of cervical spine disease in rheumatoid arthritis and effectiveness of different surgical approaches based upon numerous long-term studies.

Epstein, N., Danto, J., Nardi, D. 1993. Evaluation of intraoperative somatosensory evoked potential monitoring during 100 cervical operations. Spine 18, 737.

Glemarec, J., Guillot, P., Laborie, Y., Berthelot, J.M., Prost, A., Maugars, Y. 2000. Intraarticular glucocorticosteroid injection into the lateral atlantoaxial joint under fluoroscopic control. Joint Bone Spine 67, 54.

Gurley, J.P., Bell, G.R. 1997. The surgical management of patients with rheumatoid cervical spine disease. Rheum. Dis. Clin. N. Am. 23 (2), 317.
Review of the surgical approach to rheumatoid cervical spine disease with an emphasis on indications for surgery.

Halla, J., Hardin, J. 1990. The spectrum of atlantoaxial facet joint involvement of rheumatoid arthritis. Arthritis Rheum. 33, 325.

Kauppi, M., Antilla, P.A. 1995. A stiff collar can restrict atlantoaxial instability in rheumatoid cervical spine in selected cases. Ann. Rheum. Dis. 54, 305.

King, T.T. 1985. Editorial rheumatoid subluxations of the cervical spine. Ann. Rheum. Dis. 44, 807.

Marks, J.S., Sharp, J. 1989. Rheumatoid cervical myelopathy. QJM 50, 307.

McAfee, P., Bohlman, H., Ducker, T., Eismont, F. 1986. Failure of stabilization of the spine with methylmethacrylate. J. Bone Joint Surg. 68, 1145.

Mikulowski, P., Wollheim, F.A., Rotmil, P., Olsen, I. 1975. Sudden death in rheumatoid arthritiswith atlantoaxial dislocation. Acta Med. Scan. 198, 445.

Neva, M., Kauppi, M., Kautiainen, H., Luukainen, R., Hannonen, P., Leirisalo-Repo, M. 2000. Combination drug therapy retards the development of rheumatoid atlantoaxial subluxations. Arthritis Rheum. 43, 2397.

Netter, F.H. 1993. The CIBA Collection of Medical Illustrations: Volume 8 Musculoskeletal System. Part I. CIBA-GEIGY Corporation, Summit, NJ, plates 9, 12, 24, 25.

Pellicci, P.M., Ranawat, C.S., Tsairis, P., Bryan, W.J. 1981. A prospective study of the progression of rheumatoid arthritis of the cervical spine. J. Bone Joint Surg. 63A, 342.

Peppelman, W., Kraus, D., Donaldson, W., Agarwal, A. 1993. Cervical spine surgery in rheumatoid arthritis: improvement of neurological deficit after cervical spine fusion. Spine 18, 2375.

Rawlins, B.A., Girardi, F.P., Boachie-Adjei, O. 1998. Trends in orthopedic surgery for rheumatoid arthritis. Rheum. Dis. Clin. N. Am. 24, 55.
A comprehensive review of surgical management of cervical spine disease in rheumatoid arhtritis.

Reijnierse, M., Bloem, J., Dijkmans, B., Kroon, H., Holscher, H., Hansen, B., et al. 1996. The cervical spine in rheumatoid arthritis: relationship between neurologic signs and morphology on MR imaging and radiographs. Skeletal Radiol. 25, 113.

Reijnierse, M., Breedveld, F., Kroon, H., Hansen, B., Pope, T., Bloem, J. 2000. Are magnetic resonance flexion views useful in evaluating the cervical spine of patients with rheumatoid arthritis? Skeletal Radiol. 29, 85.

Santavirta, S., Slatis, P., Kankaanpaa, V., et al. 1988. Treatment of the cervical spine in rheumatoid arthritis. J. Bone Joint Surg. Am. 70, 658.

Santavirta, S., Konttinen, Y., Laasonen, E., Honkanen, V., Anttipoika, I., Kauppi, M. 1991. Ten years results of operations for rheumatoid cervical spine disorders. J. Bone Joint Surg. 73B, 116.

Smith, P.H., Benn, R.T., Sharp, J. 1972. Natural history of rheumatoid cervical luxations. Ann. Rheum. Dis. 31, 431.

Weissman, B.N., Aliabadi, P., Weinfeld, M.S., Thomas, W.H., Sosman, J.L. 1982. Prognostic features of atlantoaxial subluxation in rheumatoid arthritis patients. Radiology 144, 745–751.

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CHAPTER 6

Rheumatoid Arthritis: Peripheral and Central Nervous System Involvement

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1. Introduction

Rheumatoid arthritis (RA) is an inflammatory disease affecting primarily joints. Some of the common neurological complications of RA are directly connected to inflammation and deformation of joints. The involvement of the spinal cord and cranio-cervical junction is a central feature of RA and this aspect is dealt with in a separate chapter in this book. Peripheral nerve entrapments are commonly caused directly by joint disease. Other processes that may affect peripheral nerves include ischemic lesions causing mononeuropathies and more diffuse processes associated with polyneuropathies. Many of these pathological factors are associated with pain which is, of course, also a central feature of the joint pathology in RA. The issue of pain in RA involves a complex interaction between joint and peripheral nerve, spinal cord and pain centers in the brain stem and cerebral hemispheres. This interaction is a major factor in the central effects of RA of which the most common are depression, fatigue and insomnia.

2. Prevalence

In the United States, the prevalence of RA is approximately 1% of the population (range 0.3–2.1%), which is similar to the reported prevalence across the world. This prevalence is similar in all races. Pain is a significant universal problem for patients with RA. The central nervous system (CNS) effects of pain which include depression and sleep disturbances are very common, affecting almost all patients with the disease. Forty-five percent of patients experience compression neuropathies, predominantly as a result of entrapment of nerves by bulging synovial sacks and periarticular rheumatoid pannus. Carpal tunnel syndrome and peroneal neuropathy are the most common neuropathies.

3. Epidemiology

RA affects women approximately three times more often than men. Sex differences diminish in older age groups. Although RA can occur at any age, the incidence increases with advancing age. The peak incidence of RA occurs in individuals aged 40–60 years. The occurrence of neurological complications is similar in men and women and peripheral nerve involvement increases with duration of the disease but not with age. Depression is a common feature associated with RA. Interestingly, one study found that young patients with RA are more prone to depression (Wright et al., 1998).

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4. Etiology/Pathogenesis

The pathologic mechanisms affecting the nervous system include entrapment neuropathies, rheumatoid vasculitis associated with neuritis, myositis and occasionally encephalitis, steroid myopathy, and plaque-like forms of rheumatoid nodules involving the dura or eyes.

RA is primarily an inflammatory disease involving joints and surrounding tissue and the most common neurological complications are connected to the local effects of this process. Peripheral neuropathies can be produced by proliferating synovium causing compression of nerves. Areas most liable to such damage are those in which the nerve is adjacent to the inflammation and in a restricted passage such as the carpal tunnel. As the peripheral nerve passes through a compartment involved by synovitis or tenosynovitis, there is potential for nerve compression.

More systemic effects of RA include rheumatoid vasculitis causing a mononeuritis multiplex condition with patchy sensory loss in one or more extremities, often in association with wristdrop or footdrop. The CNS is usually spared, although cerebral vasculitis and rheumatoid nodules in the meninges have been described (Beck and Corbett, 1983). An interesting phenomenon exists of the protective effects of hemiplegia on the progression of RA, which is probably due to immobilization (Yaghmai et al., 1977).

There are indications that increased sensitivity to pain involves both peripheral and central mechanisms (Morris et al., 1997). Many studies indicate the value of cognitive and behavioral control of arthritis pain (Keefe et al., 1997; Keefe et al., 1989; Keefe and Caldwell, 1997; Keefe et al., 2000). CNS in RA may undergo changes in response to the chronic stimulation with pain. This is reflected by a study, which showed differences between RA patients and controls when patients were stimulated by painful stimulus at short intervals. RA patients had larger cortical responses to the first stimuli of a series of painful stimuli indicating that in RA central nervous changes of nociceptive processing are present. Another study utilizing positron emission tomography described CNS changes in opiate binding in RA patients (Jones et al., 1991).

The CNS substrate of chronic pain in RA is the subject of ongoing experiments utilizing advanced functional brain imaging techniques. Jones (1999) reviewed the contribution of functional imaging techniques to our understanding of rheumatic pain. The main cerebral components of the human pain matrix have been defined using functional imaging techniques. The experience of pain is likely to be elaborated as a result of parallel processing within this matrix. The precise function of the different components of the matrix is just beginning to be defined. There appear to be important adaptive responses in the forebrain components of the matrix during arthritic pain. Endogenous opioid peptides are strong candidates for the modulation of some of these responses.

The complexity of the interaction between pain and RA is also manifested in the neuroendocrine-immune network mediator levels between RA patients and healthy subjects. In a study of these factors in RA patients (Mukai et al., 2000), the hypothalamic-pituitary-adrenal (HPA) axis is altered and this condition is correlated to deterioration in symptoms.

A major cause of neurological disorders in RA is treatment side effects including muscle diseases (Magyar et al., 1979; Magyar et al., 1977; Miro et al., 1996). Chronic steroid use is associated with impaired protein production and muscle atrophy in RA patients (Gibson et al., 1991). Surgical procedures may also have neurological complications such as peroneal-nerve palsy following total knee arthroplasty (Rose et al., 1982).

5. Clinical manifestations

5.1. Neuropathy

The common localized neuropathies associated with RA include median nerve compression at the carpal tunnel, ulnar nerve compression at the Guyon canal, posterior interosseous nerve compression at the antecubital fossa, compression of the femoral nerve anterior to the hip joint, compression of the peroneal nerve adjacent to the fibular head, and compression of the interdigital nerve at the metatarsophalengeal (MTP) joint.

Carpal tunnel syndrome (median neuropathy) (Ishikawa et al., 1987) is common, and a similar

entrapment of the anterior tibial nerve (tarsal tunnel syndrome) can result in paresthesias with foot drop. Peripheral nerve involvement includes posterior interosseous nerve palsy as described in patients with rheumatoid synovitis of the elbow (Westkaemper et al., 1999; White et al., 1988). One illustrative study describes a 54-year-old woman with RA who developed loss of finger extension in the left hand. History, physical examination, and electromyography led to the diagnosis of posterior interosseous nerve palsy secondary to synovitis of the elbow. Anterior decompression and synovectomy resulted in a complete recovery. Involvement of the carpal tunnel is well documented (Yii and Elliot, 1994).

A mild distal sensory neuropathy occurs in at least one third of patients. It is often asymptomatic but may cause numbness, paresthesias, or burning sensations, most marked in the feet. The etiology is not clear but in some patients may be vasculitic.

The syndrome of mononeuritis multiplex is marked by an abrupt onset of a persistent peripheral neuropathy that is unaltered by either a change in joint position or a reduction in synovial inflammation. Vasculitic neuropathy, predominantly manifesting as mononeuritis multiplex, usually occurs in patients with severe RA, a high sedimentation rate, and diminished serum complement levels. Approximately 60% of affected patients have other organ system involvement, usually the skin, muscle, or viscera.

Involvement of the autonomic nervous system in RA is well documented. One study (Geenen et al., 1996) describes that diminished autonomic nervous system response is observed in RA of recent onset, most clearly in patients with more severe pain. Autonomic dysfunction manifests itself in many patients with RA: cold, clammy, cyanotic extremities, peripheral vasospasm, tachycardia, trophic changes in skin, hair, and nails, and rarely, orthostatic hypotension. Areas of absent sweating, defective cardiac responses to deep breathing, standing and Valsalva's maneuver, and altered or absent sympathetic skin responses occur in the majority of patients with disabling RA.

5.2. Myopathy

Rheumatoid myopathy is multifactorial (Miro et al., 1996). First, affected patients are often immobilized to a great degree by joint disease, in which case disuse atrophy may occur. Patients with particularly acute and painful courses often demonstrate rapid muscle wasting. The predominantly type II fiber atrophy seen on biopsy specimens may be abetted by corticosteroid treatment. Second, a focal myositis often occurs in muscles immediately adjacent to involved joints. Third, disseminated nodular myositis is observed in many patients. Fourthly, 4–6% of patients have superimposed polymyositis or dermatomyositis, which can be distinguished from the more common nodular myositis by its more malignant course, marked muscle enzyme elevation, and diffuse inflammatory infiltrates on muscle biopsy. Finally, vasculitic myopathy may contribute to weakness in some patients.

Muscle involvement in RA has been characterized systematically in one study of 21 symptomatic cases (Miro et al., 1996). Weakness and muscle atrophy were the most common symptoms. Serum creatine kinase was increased in eight cases (38%). In a majority of the cases, a treatable disease was diagnosed including dermatomyositis, D-penicillamine-related dermatomyositis, polymyositis, muscular mononuclear cell infiltration, polyarteritis nodosa, glucocorticoid myopathy, and toxic chloroquine myopathy. Another study examined muscle changes in biopsy material obtained from 100 patients suffering from classical RA. The abnormalities consisted of denervation atrophy of type II muscle fibers, degenerative changes in the sarcoplasm including presence of nemaline rods, and changes within the interstitium (perivascular nodular myositis, lymphocytic accumulations, different stages of vasculitis and abnormalities within the intramuscular nerves and muscle spindles). The muscles examined were always severely affected and it was concluded that the simultaneous presence of these abnormalities is suggestive of RA (Magyar et al., 1979; Magyar et al., 1977).

5.3. Ocular manifestations

Ocular involvement in RA includes the superior oblique tendon sheath syndrome (Brown syndrome) (Akar et al., 2001; Beck and Hickling, 1980; Cooper et al., 1990; Hickling and Beck, 1991; Kaufman et al., 1987; Killian et al., 1977; Knopf, 1989; Lawson et al.,

2001; Roifman et al., 1985; Tien et al., 1990; Wang et al., 1984). This syndrome is characterized by diplopia on downward gaze, which utilizes the superior oblique muscle, due to trapping of the tendon in diseased trochlea. This may present first in patients as they reverse a car and are trying to look through the rear window.

5.4. Central nervous system manifestations

The CNS manifestations of RA may be categorized into those caused by direct inflammatory involvement and those, which are probably indirect consequences of the disease.

Direct CNS manifestations include dural and leptomeningeal plaques and nodules which are often asymptomatic. Rarely, massive rheumatoid pannus may involve the chiasmal region, optic nerves, and tentorium. Cerebral rheumatoid pachymeningitis may cause seizures, encephalopathy, ischemic stroke, and intracerebral hemorrhage as a consequence of associated encephalitis and localized vasculitis (Gururaj et al., 1988). Rheumatoid disease of the CNS had been described with meningeal vasculitis presenting with a seizure (Neamtu et al., 2001). Cerebral rheumatoid vasculitis may also occur in the absence of observable pachymeningeal plaque, most often in the context of aggressive systemic rheumatoid vasculitis but sometimes also in isolation. Cerebral manifestations of RA are rare, and cerebral events in RA patients are most likely to reflect diseases that are prevalent in the general population, such as stroke caused by atheromatous disease or cardiogenic embolism or the development of infection in the context of immunosuppression (Riskind, 1995).

Indirect CNS manifestations include the many patients with RA suffering from chronic fatigue, sleep disturbances, cognitive dysfunction, and depression (Frank et al., 1988a; Hawley and Wolfe, 1988). The link between this syndrome and the chronic pain typical of RA has been hypothesized and examined in a number of studies. Recently, Brown et al. (2002) examined the relationship of pain and depression to cognitive function in RA patients. Individuals who performed poorly on cognitive tasks reported more pain and depression and were older than those individuals who performed well on cognitive tasks. Moreover, high levels of pain are associated with depression (Blumer and Heilbronn, 1982). Further analyses revealed that depression mediated the relationship between pain and cognition. That is, when depression was entered into the analyses, the previously significant effects of pain on cognition were no longer found. Interestingly, depression still mediated the pain-cognition relationship even after controlling for age. These findings suggest the importance of both pain and depression for understanding cognitive function in RA and may have important implications for treating this disease.

Dickens et al. (2002) have addressed this issue by meta-analysis of studies on depression in RA. Twelve independent studies comparing depression in patients with RA with depression in healthy control subjects were included in the meta-analysis. Depression was found to be more common in patients with RA than in healthy individuals. This difference was not due to sociodemographic differences between groups, but it may be attributable, in part, to the levels of pain experienced.

The experience of pain in arthritis conditions has important affective (Huyser and Parker, 1999; Huyser et al., 1998) dimensions. One article reviewed (Huyser and Parker, 1999) the evidence for a relatively strong association between negative affect (i.e., depression, anxiety, and anger) and RA-related pain. Possible physiologic and psychologic mechanisms of the relationship between negative affect and pain were examined, and issues relevant to future research, particularly the need for biopsychosocial theoretical models were discussed. Depression and the long-term risk of pain, fatigue, and disability in patients with RA have been examined in a number of studies by the same group (Fifield et al., 2001; Fifield et al., 1998; McQuillan et al., 2003). These studies confirm the significant and probably causal link between these complaints (Brown, 1990; Magni et al., 1994; McBeth et al., 2002).

The interaction of RA with sleep disturbances through pain has been addressed in many studies (Drewes, 1999; Drewes et al., 2000). Sleep complaints are frequent in patients with RA and sleep disturbances may contribute to pain and other daytime complaints. The aims of one such study (Drewes et al., 1998) were to compare ambulatory sleep recordings

from consecutively selected RA patients to those obtained in healthy controls, and to study the relationships between sleep structure and clinical symptoms. Sleep recordings were obtained from 41 out-patients with RA and 19 matched controls. The patients had many sleep-related complaints. An increase in the number of periodic movements of the legs during sleep was seen in RA patients in comparison with controls, but otherwise only minor differences were observed in classical sleep stages. The statistical model demonstrated a complex but independent correlation between morning stiffness, pain and joint tenderness on the one hand, and awakenings, stage NREM2, slow-wave sleep and stage REM on the other, probably reflecting a relationship between sleep patterns and pain in RA. Twenty-five percent of 178 consecutive patients with RA had symptoms of restless legs syndrome, compared with 4% of 48 patients with osteoarthritis or seronegative arthropathy. Sleep disorders other than those associated with depression and pain have also been described (Lavie et al., 1991; 1992) and include periodic leg movements, sleep apnea and sleep fragmentation (Mahowald et al., 1989). Patients with restless legs syndrome have more severe rheumatic disease, and 64% had evidence of polyneuropathy versus 11% of patients without restless legs syndrome.

Some studies have assessed the hypothesis that intellectual functioning affects the mental health of individuals with RA. Intellectual functioning was directly related to mental health and, also, indirectly related to mental health through self-efficacy and pain. Older individuals who performed poorly on cognitive tasks reported less self-efficacy, more pain, and poorer mental health than those individuals who performed well on cognitive tasks (Shifren et al., 1999).

5.5. Juvenile RA (JRA)

JRA comprises a number of syndromes which differ to varying extents from adult RA. Neurological manifestations of JRA are rare and limited mainly to the cervical spine. Mild to moderate generalized weakness is often noted in patients with JRA, particularly in muscles adjacent to affected joints, but the underlying pathology is unknown. Torticollis had been described as the sole initial presenting sign of systemic onset JRA (Uziel et al., 1998). Brain infarction as a complication of JRA has also been described (Gururaj et al., 1988). Brown's syndrome is well established in JRA (Akar et al., 2001; Kaufman et al., 1987; Killian et al., 1977; Roifman et al., 1985; Tien et al., 1990; Wang et al., 1984).

5.6. Side effects of treatment

Side effects of gold treatment have been described (Hill et al., 1995), highlighting the fact that nitritoid reactions can be severe and may be heralded by milder symptoms. Gold-induced neuroencephalopathy responding to dimercaprol has also been described. (Dubowitz et al., 1991). A more extensive report of gold induced neurological disease (Fam et al., 1984) includes peripheral neuropathy, a Guillain-Barre-type syndrome, cranial nerve palsies, and encephalopathy.

Exposure of RA patients to long term immunosuppression and cytotoxic drugs may be associated with CNS infection such as Progressive Multifocal Leukoencephalopathy (Riskind, 1995). Salicilate ototoxicity is a common complication (Halla et al., 1991; Halla and Hardin, 1988). It is important to note that other causes of hearing loss are found in RA patients (Elwany et al., 1986).

6. Diagnostic investigations

6.1. General

The diagnosis of RA depends on joint symptoms and signs as well as serological markers. Because elevated titers of rheumatoid factor (RF) may be seen with almost any disease characterized by a chronic antigenic challenge, the latex fixation test for IgM RF serves only as an adjunct to diagnosis.

6.2. History

In evaluating complaints that may be attributable to neurological complications special attention should be paid to weakness, sensory loss and pain not attributable to joints. CNS manifestations must be evaluated for the relative contribution of chronic pain, depression, sleep disturbances and cognitive function.

6.3. Physical examination

It is important to differentiate upper motor neuron disease from lower motor neuron involvement and myopathy in the characterization of weakness. Atrophy, absent tendon reflexes and distal weakness and sensory loss are typical of a neuropathy. Distal weakness, increased tone with brisk tendon and extensor plantar reflexes indicate brain or spinal cord disease. Myopathy may be characterized by proximal weakness with localized muscle pain. Another key point is the distribution of the weakness, which should enable the differentiation between polyneuropathy and the more patchy mononeuritis.

6.4. Electrophysiology

An evaluation of suspected peripheral nerve disease should always include detailed nerve conduction studies and electromyography. Complete studies, which include a history and physical examination by an expert physician in peripheral neurology, often provide an exact diagnosis of the underlying problem. Quantitative sensory assessment may offer the possibility for diagnosing small fiber neuropathy. Electroencephalography indicates epileptic brain activity and focal or generalized slowing which help characterize CNS disease.

6.5. Pathology

Sural or superficial peroneal nerve (and neighboring muscle) biopsy offers the means for definitively diagnosing vasculitis. Advanced methods now also include skin biopsy for the assessment of small fiber neuropathy. For CNS involvement, examination of the cerebrospinal fluid through lumbar puncture may be informative with lymphocytic pleocytosis indicating active inflammatory disease. This examination may also provide cytological, DNA and antibody data crucial for the diagnosis of infectious disease.

6.6. Imaging

Computerized tomography and magnetic resonance imaging provide the most efficient ancillary exams for characterizing CNS disease. Tissue damage may be delineated and active inflammation indicated by contrast enhancement. Functional imaging studies are for now restricted to research purposes.

7. Differential diagnosis

Since the neurological complications of RA occur in more advanced disease the neurological assessment is often difficult because of the presence of severe joint disease, debilitation, and pain. As in many neurological diseases, the history assumes particular importance in determining the nature and course of disease. In many such patients, the question is not so much whether cervical articular disease, myositis, vasculitis, depression or sleep disturbances are present, but whether the progress of disability is sufficiently great or the neurologic prognosis sufficiently grave to motivate more aggressive treatment, and hence, further diagnostic evaluation. The most important disorders requiring aggressive diagnosis and treatment include progressive neurologic manifestations and rapid progression in disability related to rheumatoid vasculitis and associated mononeuritis multiplex.

8. Treatment

Treatment of the non-neurological features of RA includes mainly anti-inflammatory drugs and joint care. Treatment of the neurological complications of RA must begin with treatment of the underlying disease. More specific therapies depend on the pathology underlying the neurological deficit.

Nerve entrapment due to localized inflammatory processes may be treated by increasing the dosage of immune mediated drugs such as brief courses of corticosteroids. Local decompression should also be carefully considered. Myositis may also be addressed by relatively low doses of steroids. More generalized severe problems such as rheumatoid vasculitis may be treated effective with pulse intravenous cyclophosphamide. Severe and relatively rare cases of direct involvement of the CNS probably indicate similar cyclophosphamide treatment in most cases.

As described above, the most common CNS related problems in RA patients relate to pain and the spectrum of pain-related disorders, which include

sleep disturbances, anxiety and depression. All these are amenable primarily to treatment with antidepressants. From clinical experience tricyclic antidepressants such as amitriptyline are very useful for treating chronic pain (Fishbain, 2000; Frank et al., 1988b). The immediate relief for the sleep associated disturbances and pain offered by tricylic antidepressants make them especially useful for this purpose. Selective serotonin reuptake inhibitors have the advantage of having generally less side effects but lack an immediate effect on sleep. Mirtazapine and other relatively new compounds may offer the advantages of immediate relief for sleep disorders with a better side effect profile than tricyclic antidepressants. A fundamental advantage of antidepressant medication is the minimal tendency to develop tolerance and dependence. This is especially relevant when these medications are compared to opiate analgesics and benzodiazepines, which are commonly used in RA and to which patients commonly develop tolerance and dependence.

Given the limitations of medical treatment and the ongoing problems with symptom management, it is not at all surprising that many individuals with RA turn to 'complementary' and 'alternative' medicine (CAM) therapies. The spectrum of CNS modulated pain associated disorders has also been the target of many CAM methods. None of these has been established to be efficient by evidence based scientific methodology. This may be due to the fact that these methods work to a great degree by suggestion (such as placebo effect) and it is difficult to separate out any objective effects on such a strong background since the endpoints measured in RA, such as pain, depression, fatigue and insomnia, are inherently subjective. Taibi and Bourguignon offer an excellent recent review on available CAM in RA (Taibi and Bourguignon, 2003).

Key points

- RA is predominantly a disease of joints
- RA affects 1% of the population and about half of patients suffer from peripheral nerve entrapments due to local joint inflammation or vasculitis. The median nerve in the carpal tunnel and the peroneal nerve are the most commonly involved.
- Investigation of peripheral nerve involvement should include detailed nerve conduction studies and electromyography. Nerve biopsy may reveal vasculitis and myositis may be a factor in some patients. Treatment is aimed at alleviating joint inflammation or vasculitis.
- Pain is a central feature of RA and chronic pain syndromes including depression, fatigue and insomnia affect most patients. All these are amenable primarily to treatment with antidepressants.
- CNS is usually spared, although cerebral vasculitis and rheumatoid nodules in the meninges have been described.
- Superior oblique tenosynovitis (Brown's syndrome) is an unusual but distinctive syndrome in RA.

References

Akar, S., Soylev, M., Onen, F., Ada, E., Birlik, M., Akkoc, N. 2001. Acquired Brown's syndrome with juvenile idiopathic arthritis: resolution with early steroid treatment. Clin. Exp. Rheumatol. 19, 354.

Beck, D.O., Corbett, J.J. 1983. Seizures due to central nervous system rheumatoid meningovasculitis. Neurology 33, 1058–1061.

Beck, M., Hickling, P. 1980. Treatment of bilateral superior oblique tendon sheath syndrome complicating rheumatoid arthritis. Br. J. Ophthalmol. 64, 358–361.

Blumer, D., Heilbronn, M. 1982. Chronic pain as a variant of depressive disease: the pain-prone disorder. J. Nerv. Ment. Dis. 170, 381–406.

Brown, G.K. 1990. A causal analysis of chronic pain and depression. J. Abnorm. Psychol. 99, 127–137.

Brown, S.C., Glass, J.M., Park, D.C. 2002. The relationship of pain and depression to cognitive function in rheumatoid arthritis patients. Pain 96, 279–284.

Cooper, C., Kirwan, J.R., McGill, N.W., Dieppe, P.A. 1990. Brown's syndrome: an unusual ocular complication of rheumatoid arthritis. Ann. Rheum. Dis. 49, 188–189.

Dickens, C., McGowan, L., Clark-Carter, D., Creed, F. 2002. Depression in rheumatoid arthritis: a systematic review of the literature with meta-analysis. Psychosom. Med. 64, 52–60.

Drewes, A.M. 1999. Pain and sleep disturbances with special reference to fibromyalgia and rheumatoid arthritis. Rheumatology (Oxford) 38, 1035–1038.

Drewes, A.M., Svendsen, L., Taagholt, S.J., Bjerregard, K., Nielsen, K.D., Hansen, B. 1998. Sleep in rheumatoid arthritis: a comparison with healthy subjects and studies of sleep/wake interactions. Br. J. Rheumatol. 37, 71–81.

Drewes, A.M., Nielsen, K.D., Hansen, B., Taagholt, S.J., Bjerregard, K., Svendsen, L. 2000. A longitudinal study of clinical symptoms and sleep parameters in rheumatoid arthritis. Rheumatology (Oxford) 39, 1287–1289.

Dubowitz, M.N., Hughes, P.J., Lane, R.J., Wade, J.P. 1991. Gold-induced neuroencephalopathy responding to dimercaprol. Lancet 337, 850–851.

Elwany, S., el Garf, A., Kamel, T. 1986. Hearing and middle ear function in rheumatoid arthritis. J. Rheumatol. 13, 878–881.

Fam, A.G., Gordon, D.A., Sarkozi, J., Blair, G.R., Cooper, P.W., Harth, M., Lewis, A.J. 1984. Neurologic complications associated with gold therapy for rheumatoid arthritis. J. Rheumatol. 11, 700–706.

Fifield, J., Tennen, H., Reisine, S., McQuillan, J. 1998. Depression and the long-term risk of pain, fatigue, and disability in patients with rheumatoid arthritis. Arthritis Rheum. 41, 1851–1857.

Fifield, J., McQuillan, J., Tennen, H., Sheehan, T.J., Reisine, S., Hesselbrock, V., Rothfield, N. 2001. History of affective disorder and the temporal trajectory of fatigue in rheumatoid arthritis. Ann. Behav. Med. 23, 34–41.

Fishbain, D. 2000. Evidence-based data on pain relief with antidepressants. Ann. Med. 32, 305–316.

Frank, R.G., Beck, N.C., Parker, J.C., Kashani, J.H., Elliott, T.R., Haut, A.E., Smith, E., Atwood, C., Brownlee-Duffeck, M., Kay, D.R. 1988a. Depression in rheumatoid arthritis. J. Rheumatol. 15, 920–925.

Frank, R.G., Kashani, J.H., Parker, J.C., Beck, N.C., Brownlee-Duffeck, M., Elliott, T.R., Haut, A.E., Atwood, C., Smith, E., Kay, D.R. 1988b. Antidepressant analgesia in rheumatoid arthritis. J. Rheumatol. 15, 1632–1638.

Geenen, R., Godaert, G.L., Jacobs, J.W., Peters, M.L., Bijlsma, J.W. 1996. Diminished autonomic nervous system responsiveness in rheumatoid arthritis of recent onset. J. Rheumatol. 23, 258–264.

Gibson, J.N., Poyser, N.L., Morrison, W.L., Scrimgeour, C.M., Rennie, M.J. 1991. Muscle protein synthesis in patients with rheumatoid arthritis: effect of chronic corticosteroid therapy on prostaglandin F2 alpha availability. Eur. J. Clin. Invest. 21, 406–412.

Gururaj, A.K., Chand, R.P., Chuah, S.P. 1988. Cerebral infarction in juvenile rheumatoid arthritis. Clin. Neurol. Neurosurg. 90, 261–263.

Halla, J.T., Hardin, J.G. 1988. Salicylate ototoxicity in patients with rheumatoid arthritis: a controlled study. Ann. Rheum. Dis. 47, 134–137.

Halla, J.T., Atchison, S.L., Hardin, J.G. 1991. Symptomatic salicylate ototoxicity: a useful indicator of serum salicylate concentration? Ann. Rheum. Dis. 50, 682–684.

Hawley, D.J., Wolfe, F. 1988. Anxiety and depression in patients with rheumatoid arthritis: a prospective study of 400 patients. J. Rheumatol. 15, 932–941.

Hickling, P., Beck, M. 1991. Brown's syndrome: an unusual ocular complication of rheumatoid arthritis. Ann. Rheum. Dis. 50, 66.

Hill, C., Pile, K., Henderson, D., Kirkham, B. 1995. Neurological side effects in two patients receiving gold injections for rheumatoid arthritis. Br. J. Rheumatol. 34, 989–990.

Huyser, B.A., Parker, J.C. 1999. Negative affect and pain in arthritis. Rheum. Dis. Clin. N. Am. 25 (vi), 105–121.

Huyser, B.A., Parker, J.C., Thoreson, R., Smarr, K.L., Johnson, J.C., Hoffman, R. 1998. Predictors of subjective fatigue among individuals with rheumatoid arthritis. Arthritis Rheum. 41, 2230–2237.

Ishikawa, K., Kondo, M., Vainio, K., Patiala, H., Lehtimaki, M., Raunio, P. 1987. Atrophy of the thumb web space in rheumatoid arthritis: clinical and electrodiagnostic studies. Arch. Orthop. Trauma Surg. 106, 309–313.

Jones, A.K. 1999. The contribution of functional imaging techniques to our understanding of rheumatic pain. Rheum. Dis. Clin. N. Am. 25, 123–152.
An interesting new approach to very common central nervous system effects of chronic pain in RA.

Jones, A.K., Liyi, Q., Cunningham, V.V., Brown, D.W., Ha-Kawa, S., Fujiwara, T., Friston, K.F., Silva, S., Luthra, S.K., Jones, T. 1991. Endogenous opiate response to pain in rheumatoid arthritis and cortical and subcortical response to pain in normal volunteers using positron emission tomography. Int. J. Clin. Pharmacol. Res. 11, 261–266.

Kaufman, L.D., Sibony, P.A., Anand, A.K., Gruber, B.L. 1987. Superior oblique tenosynovitis (Brown's syndrome) as a manifestation of adult Still's disease. J. Rheumatol. 14, 625–627.

Keefe, F.J., Caldwell, D.S. 1997. Cognitive behavioral control of arthritis pain. Med. Clin. N. Am. 81, 277–290.

Keefe, F.J., Brown, G.K., Wallston, K.A., Caldwell, D.S. 1989. Coping with rheumatoid arthritis pain: catastrophizing as a maladaptive strategy. Pain 37, 51–56.

Keefe, F.J., Affleck, G., Lefebvre, J.C., Starr, K., Caldwell, D.S., Tennen, H. 1997. Pain coping strategies and coping efficacy in rheumatoid arthritis: a daily process analysis. Pain 69, 35–42.

Keefe, F.J., Lefebvre, J.C., Kerns, R.D., Rosenberg, R., Beaupre, P., Prochaska, J., Prochaska, J.O., Caldwell, D.S. 2000. Understanding the adoption of arthritis self-management: stages of change profiles among arthritis patients. Pain 87, 303–313.

Killian, P.J., McClain, B., Lawless, O.J. 1977. Brown's syndrome. An unusual manifestation of rheumatoid arthritis. Arthritis Rheum. 20, 1080–1084.

Knopf, H.L. 1989. An unusual case of painful ophthalmoplegia in a patient with rheumatoid arthritis. Ann. Ophthalmol. 21, 412–413.

Lavie, P., Nahir, M., Lorber, M., Scharf, Y. 1991. Nonsteroidal antiinflammatory drug therapy in rheumatoid arthritis patients. Lack of association between clinical improvement and effects on sleep. Arthritis Rheum. 34, 655–659.

Lavie, P., Epstein, R., Tzischinsky, O., Gilad, D., Nahir, M., Lorber, M., Scharf, Y. 1992. Actigraphic measurements of sleep in rheumatoid arthritis: comparison of patients with low back pain and healthy controls. J. Rheumatol. 19, 362–365.

Lawson, T.M., Siebert, S., Williams, B.D. 2001. Clinical images: Brown's syndrome: an unusual cause of diplopia in rheumatoid arthritis. Arthritis Rheum. 44, 2460.

Magni, G., Moreschi, C., Rigatti-Luchini, S., Merskey, H. 1994. Prospective study on the relationship between depressive symptoms and chronic musculoskeletal pain. Pain 56, 289–297.

Magyar, E., Talerman, A., Mohacsy, J., Wouters, H.W., de Bruijn, W.C. 1977. Muscle changes in rheumatoid arthritis. A review of the literature with a study of 100 cases. Virchows Arch. A Pathol. Anat. Histol. 373, 267–278.

Magyar, E., Talerman, A., de Bruijn, W.C., Mohacsy, J., Wouters, H.W. 1979. Muscle spindles in rheumatoid arthritis. An ultrastructural study. Virchows Arch. A Pathol. Anat. Histol. 382, 191–200.

Mahowald, M.W., Mahowald, M.L., Bundlie, S.R., Ytterberg, S.R. 1989. Sleep fragmentation in rheumatoid arthritis. Arthritis Rheum. 32, 974–983.

McBeth, J., Macfarlane, G.J., Silman, A.J. 2002. Does chronic pain predict future psychological distress? Pain 96, 239–245.

McQuillan, J., Fifield, J., Sheehan, T.J., Reisine, S., Tennen, H., Hesselbrock, V., Rothfield, N. 2003. A comparison of self-reports of distress and affective disorder diagnoses in rheumatoid arthritis: a receiver operator characteristic analysis. Arthritis Rheum. 49, 368–376.

Miro, O., Pedrol, E., Casademont, J., Garcia-Carrasco, M., Sanmarti, R., Cebrian, M., Grau, J.M. 1996. Muscle involvement in rheumatoid arthritis: clinicopathological study of 21 symptomatic cases. Semin. Arthritis Rheum. 25, 421–428.

Morris, V.H., Cruwys, S.C., Kidd, B.L. 1997. Characterisation of capsaicin-induced mechanical hyperalgesia as a marker for altered nociceptive processing in patients with rheumatoid arthritis. Pain 71, 179–186.

Mukai, E., Nagashima, M., Hirano, D., Yoshino, S. 2000. Comparative study of symptoms and neuroendocrine-immune network mediator levels between rheumatoid arthritis patients and healthy subjects. Clin. Exp. Rheumatol. 18, 585–590.

Neamtu, L., Belmont, M., Miller, D.C., Leroux, P., Weinberg, H., Zagzag, D. 2001. Rheumatoid disease of the CNS with meningeal vasculitis presenting with a seizure. Neurology 56, 814–815.

Riskind, P.N. 1995. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 20-1995. A 66-year-old man with a history of rheumatoid arthritis treated with adrenocorticosteroids, with the development of aphasia and right-sided weakness. N. Engl. J. Med. 332, 1773–1780.

Roifman, C.M., Lavi, S., Moore, A.T., Morin, D.J., Stein, L.D., Gelfand, E.W. 1985. Tenosynovitis of the superior oblique muscle (Brown syndrome) associated with juvenile rheumatoid arthritis. J. Pediatr. 106, 617–619.

Rose, H.A., Hood, R.W., Otis, J.C., Ranawat, C.S., Insall, J.N. 1982. Peroneal-nerve palsy following total knee arthroplasty. A review of The Hospital for Special Surgery experience. J. Bone Joint. Surg. Am. 64, 347–351.

Shifren, K., Park, D.C., Bennett, J.M., Morrell, R.W. 1999. Do cognitive processes predict mental health in individuals with rheumatoid arthritis? J. Behav. Med. 22, 529–547.

Taibi, D.M., Bourguignon, C. 2003. The role of complementary and alternative therapies in managing rheumatoid arthritis. Fam. Community Health 26, 41–52.
An excellent review of the very common use of surogate/complimentary/alternative medicent in RA.

Tien, R.D., Duberg, A., Chu, P.K., Bessette, J., Hesselink, J.R., Hazelhurst, J.A. 1990. Superior oblique tendon sheath syndrome (Brown syndrome): MR findings. AJNR Am. J. Neuroradiol. 11, 1210.

Uziel, Y., Rathaus, V., Pomeranz, A., Solan, H., Wolach, B. 1998. Torticollis as the sole initial presenting sign of systemic onset juvenile rheumatoid arthritis. J. Rheumatol. 25, 166–168.

Wang, F.M., Wertenbaker, C., Behrens, M.M., Jacobs, J.C. 1984. Acquired Brown's syndrome in children with juvenile rheumatoid arthritis. Ophthalmology 91, 23–26.

Westkaemper, J.G., Varitimidis, S.E., Sotereanos, D.G. 1999. Posterior interosseous nerve palsy in a patient with rheumatoid synovitis of the elbow: a case report and review of the literature. J. Hand Surg. [Am.] 24, 727–731.

White, S.H., Goodfellow, J.W., Mowat, A. 1988. Posterior interosseous nerve palsy in rheumatoid arthritis. J. Bone Joint Surg. Br. 70, 468–471.

Wright, G.E., Parker, J.C., Smarr, K.L., Johnson, J.C., Hewett, J.E., Walker, S.E. 1998. Age, depressive symptoms, and rheumatoid arthritis. Arthritis Rheum. 41, 298–305.

Yaghmai, I., Rooholamini, S.M., Faunce, H.F. 1977. Unilateral rheumatoid arthritis: protective effect of neurologic deficits. AJR Am. J. Roentgenol. 128, 299–301.

Yii, N.W., Elliot, D. 1994. A study of the dynamic relationship of the lumbrical muscles and the carpal tunnel. J. Hand Surg. [Br.] 19, 439–443.

PART IV

Inflammatory Muscle Diseases

Handbook of Systemic Autoimmune Diseases, Volume 3
Neurologic Involvement in Systemic Autoimmune Diseases
D. Erkan and S.R. Levine, editors

CHAPTER 7

Inflammatory Muscle Diseases: Pathogenesis and Clinical Features

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1. Introduction

Dermatomyositis (DM), polymyositis (PM) and inclusion body myositis (IBM) are the three major categories of idiopathic inflammatory myopathy (IIM) (Table 1). These categories exclude supporative, infective and parasitic varieties of myositis.

In 1863, Erlich Wagner first described a patient with an 'acute progressive generalised muscle affection' associated with a pronounced skin rash who died within 6 days of the start of his symptoms. Unvernicht first used the term dermatomyositis in 1887. The generally accepted diagnostic criteria of Bohan and Peter were not published until 1975 (Bohan and Peter, 1975), but have since increased the recognition of the disease. The classification does not recognise IBM or other distinctive forms of myositis. More recent attempts have been made to make use of recent developments of differing histological patterns (Dalakas, 1991) or specific autoantibodies (Love et al., 1991).

The presence of a characteristic vasculitic rash, especially around the eyes and the dorsum of the hands and forearms clinically distinguishes dermatomyositis from PM. The brunt of the disease often falls upon the skeletal muscles but there is usually a variable degree of systemic involvement.

Polymyositis and DM are autoimmune diseases associated with disease specific autoantibodies, sharing an MHC haplotype (B8, DR3) often found in patients with systemic lupus erythematosus (SLE) or Sjögren's syndrome and often responding to corticosteroids. In contrast, IBM appears as a related condition in which vacuoles are present in the muscles containing diverse proteins such as amyloid and prions; this entity almost certainly has a very different, non-immunological basis.

Although muscle symptoms may be profound, there does not appear to be a good correlation between the degree of muscle weakness and fatigue and the degree of inflammatory cell infiltrate in the muscle biopsy. It appears that different mechanisms cause muscle weakness in different phases of the disease and that different mechanisms exist in PM, DM and IBM.

2. Prevalence

The reported incidence is 1–10 cases per million and the prevalence ranging from 8 to 50 per 100,000. In most published series of adult onset disease, PM is more common than DM (Arnett et al., 1996; Bohan et al., 1977; Hill et al., 2001). However, most of these reports describe retrospective hospital-based studies in which the true incidence of IIM may have been underestimated. Also different diagnostic

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Table 1
Classification of idiopathic inflammatory myopathies (Targoff, 2000)

1. Primary idiopathic polymyositis
2. Primary idiopathic dermatomyositis
3. Polymyositis or Dermatomyositis with malignancy
4. Juvenile dermatomyositis (or polymyositis)
5. Overlap syndrome of polymyositis or dermatomyositis with another connective tissue disease
6. Inclusion body myositis
7. Rare forms of idiopathic myositis
(a) Granulomatous myositis
(b) Eosinophilic myositis
(c) Focal myositis
(d) Orbital myositis

criteria were employed and so it is difficult to compare results.

The female to male ratio is in the order of 2–3:1 and the female preponderance is increased when there is an associated autoimmune rheumatic condition. Overlap syndromes with other autoimmune rheumatic diseases occur in 15–20% (Love et al., 1991).

3. Epidemiology

There does not appear to be a correlation of adult onset diseases with the time of year. However, certain autoantibody subgroups show seasonal differences: anti-Jo-1 associated myositis begins more often in the spring and anti-SRP myositis more often in the autumn (Targoff, 2000). Polymyositis and DM occur in all parts of the world. The incidence of DM may be higher relative to PM in lower latitudes and certain myositis specific autoantibodies, and several myositis associated autoantibodies may differ in prevalence in different regions, making an environmental trigger important in the pathogenesis (Brouwer et al., 2001).

Polymyositis and DM are four times more common in African-American patients than in Caucasian patients. There are two peaks of onset, childhood onset and then adult onset usually from 40 to 60 yrs. A family history of muscle disease should lead one to reassess the diagnosis, but a history of other autoimmune diseases in relatives is not unusual (Ginn et al., 1998). Autoimmune diseases were significantly increased in frequency in relatives of patients with IIM (21.9 vs 4.9% in the controls).

4. Etiology and pathogenesis

The pathological process is clearly autoimmune. However, just like other autoimmune conditions, the principal etiological factors are likely to include an inciting agent in a genetically susceptible individual. Potential etiological factors include:

4.1. Infection

Various infections can induce a syndrome that closely resembles myositis in humans and animals through persistent infection, molecular mimicry, and presentation of muscle antigens and immune dysregulation (Targoff, 1998). A variety of viruses such as influenza, picornaviruses, parvovirus B19, small RNA viruses that include enteroviruses (coxsackie, echo) have been suspected as possible triggers. However, efforts to culture viruses from muscle have been unsuccessful. A syndrome of chronic myositis following Coxsackie virus infection has been noted in susceptible strains of neonatal mice (Leff et al., 1992). The animals develop proximal muscle weakness about 7 days after the viral challenge, and the symptoms persist for a few months without a further challenge. The virus itself is not detectable after 2 weeks following the initial injection but electromyographic and histological abnormalities are evident throughout this time and the pathological picture may persist for up to 6 months. Some studies have found autoantibodies to coxsackie virus to be more frequent in myositis, but the virus has not been demonstrated in muscle (Leff et al., 1992).

The D-type simian retrovirus SRV-1 may induce a myositis-like picture in macaque monkeys, and so may human immunodeficiency virus (HIV) in patients with the acquired immunodeficiency syndrome (AIDS) as may HTLV-1. However, most studies using PCR have been negative for the enteroviruses and other viruses (Leff et al., 1992). Infection with Toxoplasma gondii can cause a clinical picture resembling PM (Ytterberg, 1994). Immunoglobulin (Ig) M antibodies were more frequently found in

PM patients than in controls, suggesting recent infection. However, no toxoplasma DNA was found by PCR in the three patients with PM who had elevated IgM titres.

4.2. Other Environmental factors

A variety of drugs, including D-penicillamine and cimetidine, can induce a myopathy. There is no clear relationship to the dose or duration of treatment. It usually disappears once the offending drugs are discontinued but steroids are often needed (Targoff, 1998).

Various environmental toxins such as natural fish toxin ciguatera, silica exposure, bovine collagen dermal implants, silicone breast implants, and vaccinations have all been implicated (Love and Miller, 1993).

4.3. Genetic factors

Immunogenetically, human leukocyte antigen DR3 (HLA-DR3) has been shown to be significantly increased among Caucasian patients (DR3 45% in PM/DM vs 23% in controls) and HLA-DR6 amongst African-American patients with myositis (Love et al., 1991). Genes on extended haplotypes such as DRB3, DQA1 and DQB1 have also been linked to myositis. The predominant subtype of DR3-DRB1*0301 is in linkage disequilibrium with the DQA1 and DQB1 genes. DQA1*0501 has been strongly associated with PM in caucasians (Arnett et al., 1996). The MHC association with DQA1*0501 and *0401 was stronger in patients with anti-synthetases. The association of autoimmune diseases in relatives of PM and DM patients suggest that these disorders share genes that may act as polygenic risk factors for autoimmunity (Ginn et al., 1998).

5. Pathogenic mechanisms

5.1. Cellular immunity

Until recently it was customary to group PM and DM together, but it is now known that these conditions differ in several aspects. Polymyositis is due to T cell mediated cytotoxicity. Although the precise targets of the T cells remain uncertain, it is hard to avoid the conclusion that they are located on the surface of muscle fibres. Lymphocytes in inflammatory infiltrates in muscle have been characterised using monoclonal antibodies to cell surface markers. These studies reveal that a cellular immune attack on muscle fibres is a prominent pathogenic process in PM but not in DM (Messner, 2000). In contrast, DM appears to be a consequence of muscle blood vessel injury by circulating immune complexes and the autoimmune process is humoral rather than cell mediated. Histologically vasculitis is common and so is perifascicular atrophy of muscle fibres. In patients with PM, inflammatory infiltrates around the blood vessels consist predominately of CD4 + cells, but the cells that actually invade the muscle fibres tend to be CD8 + cells. CD8 + T cells are therefore abundant in the endomysial areas. Many non-necrotic muscle fibres are surrounded and invaded by mononuclear cells and necrotic fibres become infiltrated predominately by macrophages.

Studies of the T-cell receptor (TCR) of the infiltrating lymphocyte suggests an antigen directed T-cell attack in PM, with TCR rearrangements and marked restriction in V-gene usage ($V \propto 1$, $V \propto 5$, $V\beta 1$ and $V\beta 15$ in one study and $V\beta 6$ in another) (Hohlfeld et al., 1997; O'Hanlon et al., 1995). These findings suggest local clonal expansion, in response to an antigen, presumably on the muscle surface that remains unidentified (Targoff, 1998).

The role of specific pro- and anti-apoptotic molecules has been reviewed due to the absence of characteristic apoptotic changes in myositis biopsies (Nagaraju, 2000b).

5.1.1. Role of major histocompatibility complex class on skeletal muscle cells

Skeletal muscle fibres do not constituitively express MHC molecules. However, muscle fibres in patients with myositis show high levels of MHC class I (HLA-DR) expression (Rowe et al., 1983). This occurs on both surrounding and invaded fibres. It has been suggested that in patients with early disease with clinical symptoms of muscle weakness but in whom no inflammatory infiltrate is detectable in the muscle there is an increased expression

of MHC class I antigen on muscle fibres (Englund et al., 2001). It has also been suggested that clinical symptoms persist even in the absence of inflammatory infiltrates in muscle biopsies of patients implying that the delay in recovery of strength may be caused by the increased expression of IL-1 alpha in the capillaries and the MHC class I expression in the muscle fibres of patients with DM and PM (Nyberg et al., 2000; Lundberg et al., 2000). These findings suggest that MHC class I might have a role in causing a decreased muscle strength as well as fatigue in myositis patients. The role of MHC class I has been shown recently in a transgenic mouse model in which expression of MHC-1 in muscles leads to myositis (Nagaraju, 2000a). The mice were weak despite the absence of infiltrates with T cells in muscle tissue. The overexpression of MHC class I was associated with clinical, biochemical, and histological features of human myositis. The muscle fibre damage occurred in the absence of heavy lymphocyte accumulation. The upregulation of MHC class I caused decrease muscle strength at a stage even before any histological changes could be demonstrated. However, studies of expression of MHC class II molecules on muscle fibres in myositis are conflicting (Hohlfeld et al., 1997) but they can be induced in-vitro, and could further promote muscle antigen presentation. What is not clear is if these MHC expressing muscle cells process and present antigens to naïve T cells to initiate an autoimmune response against muscle antigens.

5.1.2. Role of cytokines and chemokines

The sequence of events that leads to the inflammatory process in IIM is not well understood. However, following a trigger—perhaps following viral exposure cytokines are likely to play a role in the enhancement and/or perpetuation of the autoimmune response. Several cytokines; both pro- and anti-inflammatory (IL-1 alpha, IL-1 beta, TNF alpha, TGF beta, interferon alpha, IL-2, IL-4, IL-6, IL-10, IL-13) and chemokines (MIP-alpha, MIP-1beta, and RANTES) have all been described in inflammatory myopathies (Rowe et al., 1983; Lundberg and Nberg, 1998). These probably amplify the lymphocyte migration and thereby maintain the immune attack on muscle.

Interferon alpha can enhance MHC class I and induce expression of MHC class II on cultured muscle fibres, and enhance T cell adhesion to muscle by increasing intracellular adhesion molecule-1 (ICAM-1) expression. Interferon alpha can inhibit proliferation and differentiation, an effect enhanced by tumor necrosis factor alpha (Kalovidouris et al., 1993). Interestingly PM has occurred after IFN therapy (Lee et al., 2002). There does appear to be an increased expression of proinflammatory cytokines such as IL-1 and tumor necrosis factor (TNF) alpha. Interleukin-1 may be toxic to human muscle cells and it has been noted in damaged muscle fibres from patients with myositis (Authier et al., 1997; Tews and Goebel, 1996). It has also been suggested that IL-1 plays a role in muscle fibre regeneration, in which it can suppress myoblast proliferation as well as myoblast fusion, leading to poor muscle cell regeneration (Ji et al., 1998). Tumor necrosis factor alpha contributes to both preventing the formation of new fibres and damaging existing muscle fibres leading to loss of muscle mass (Guttridge et al., 2000). Increased expression of these molecules was particularly evident in capillaries and small vessels in biopsy specimens from symptomatic muscles, both in the presence and absence of an inflammatory infiltrate (Lundberg et al., 1997). This observation also suggests that, not only the cell infiltrate in the muscle, but also molecular changes in the muscle tissue and in the blood vessels of the muscle are of both functional and diagnostic importance in patients with myositis (Lundberg and Nberg, 1998). Trafficking of both lymphocytes and monocytes is a multistep event involving expression of adhesion molecules, cytokines, and chemokines. Monocyte chemoattractant protein-1 (MCP-1) is produced in response to TNF alpha stimulation and its expression during monocyte–endothelial cell interaction is mediated by ICAM-1. The selective MCP-1 expression on perimysial and perifascicular blood vessels indicates its role in the complement-mediated immune response in DM (De Bleecker et al., 2002). Interleukin-8 was not detected but this may not be surprising, as this is mainly a chemoattractant for neutrophils. Neutrophil infiltration is not a feature of IBM (Engel and Arahata, 1986).

5.1.3. Role of adhesion molecules

A role for blood vessels in the pathogenesis of myositis has been suggested in patients with DM. The recirculation and homing of lymphocytes is accomplished via interaction with endothelial cells. There appears to be a reduction in the number of capillaries in the muscle tissue even early in the disease and in muscle biopsies with no or minimal histological changes (Emslie-Smith and Engel, 1990). Expression of IL-1 alpha, as well as adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule (VCAM), can be induced during inflammation on muscle and on endothelial cells by cytokines. The complementary marker LFA-1 is expressed on infiltrating T-cells. This expression may contribute to the immune response against muscle. It also appears that serum levels of ICAM-1 and VCAM-1 are elevated and correlate with disease activity.

Strength can return with treatment sooner than would otherwise be expected if regeneration were required. Inflammation, atrophy and damage do not always correlate with weakness. The weakness may relate to muscle cell dysfunction. Expression of IL-1 alpha, TNF alpha and expression of MHC class I may persist and contribute to muscle dysfunction (Nyberg et al., 2000).

5.2. Humoral immunity

5.2.1. Microvascular damage

DM biopsies show a higher proportion of B-cells and a lower proportion of CD8 + T-cells. T-cell mediated attack on muscle fibres does not appear to be a significant process in DM. There is intense B-cell and CD4 + T-cell infiltrate in the perivascular area, suggesting a local humoral response. There is little endomysial infiltrate (Targoff, 1998). Vasculopathy, with loss of capillaries leading to ischaemic damage and perifascicular atrophy, is an important mechanism of muscle injury in DM (Emslie-Smith and Engel, 1990). It is generally not found in typical PM. Approximately 10% with evidence of this process do not have a DM rash, but many still consider these patients to have DM. Involvement of the microvasculature is also suggested by the presence of features such as nailfold capillary infarcts. Microvasculature damage in muscle appears to be mediated by complement. The membrane attack complex (MAC) of complement is deposited in muscle capillaries in DM but not PM or IBM, indicating local activation of complement. Muscle biopsies from DM patients that show little or no structural change by routine examination often still show vascular abnormalities, including endothelial cell injury, microtubular inclusions and MAC deposition (Emslie-Smith and Engel, 1990). This early involvement suggests that the microvasculature is the primary target in DM. What causes complement activation is not known. The C5b-9 MAC deposition is also found in vessels of the skin lesion of most DM patients, although this was also seen in 21% of patients with lupus (Magro et al., 1997).

5.2.2. Autoantibodies

As part of the abnormal immune response, autoantibodies can be found in the sera of most patients with IBM. These autoantibodies to nuclear and cytoplasmic antigens are found in up to 89% of patients (Targoff, 2000). Many of these autoantibodies are not specific for IBM and are also encountered in patients with other autoimmune diseases without myositis i.e. myositis-associated antibodies (MAA). Myositis – specific autoantibodies (MSA) are found in approximately half of the patients with IBM. Most MSAs are associated with specific clinical syndromes within the spectrum of IBM, and an individual most often has only a single MSA and, as a result, new classification systems were proposed based on the presence of specific MSA (Love et al., 1991). Although the MSAs are specific for the muscle disorder myositis, the target antigens are not specific for muscle tissue. Most MSAs are directed against cytoplasmic RNA–protein (ribonucleoprotein) complexes, which are present in all cells and in most cases are involved in the process of protein synthesis. The target antigens include cytoplasmic RNA synthetases, other cytoplasmic proteins, ribonucleoproteins and certain nuclear antigens. Why these antigens are targeted by the immune response in IBM is unknown. It is also not known whether the MSAs are simply an epiphenomenon or have a role to play in the pathophysiology of IBM.

5.2.3. Myositis specific autoantibodies (MSA)

5.2.3.1. Anti-synthetases. About 25% of PM and DM patients have antibodies to an aminoacyl-tRNA synthetase. There are 20 aminoacyl-tRNA synthetases in every cell. These cytoplasmic enzymes catalyze the binding of an amino acid to it to its corresponding tRNAs (to form aminoacyl-tRNA). Five anti-synthetases have been found in myositis sera (Table 2), the most prevalent MSA the anti-histidyl-tRNA synthetase (anti-Jo1 antibody), is available for diagnostic testing. It is present in about 20% of patients. The other autoantibodies within this group are only present in 1–3% of patients with IBM. Anti-synthetases are mainly seen in DM and PM and hardly ever detected in patients with IBM. A continuing mystery in the origins of myositis is whether these antibodies are an integral part of the immunopathology or merely a by-stander phenomenon. Some recent intriguing work by Oppenheim et al. (2002) suggests that the presence of these antibodies correlate with the ability of the synthetase enzyme to have chemotactic effects on immature dendritic cells expressing receptors. The implication being that these antigens induce both the specific antibodies and inflammatory cells into skeletal muscle as part of the immunopathological process.

The clinical association of anti-Jo-1 antibody with interstitial lung disease (ILD) (50–90% of patients) is well known. Patients also classically have Raynaud's phenomenon (62%), inflammatory polyarthritis (usually mild-but a third may have finger deformity, usually non-erosive, occasionally with calcinosis), and mechanic's hands (71%) (Love et al., 1991; Marguerie et al., 1990). It is associated with more relapses and incomplete response to treatment (Love et al., 1991). Thirty to fifty per cent have the DM rash, less with anti-Jo-1 than others. The combination of clinical features associated with the anti-synthetase antibodies has been referred to as the 'anti-synthetase syndrome'. It may appear as an overlap syndrome, but the myositis is usually more prominent and significant ILD is more frequent. Occasionally, ILD (or arthritis) may occur without overt myositis. This clinical feature is more common with anti-PL 12, and possibly anti-OJ and anti-KS, than anti-Jo-1. Mozaffar and Pestronk (2000) found that perifascicular atrophy and perimysial inflammation (a characteristic feature of DM) were seen in all of their anti-Jo-1 positive patients but without capillary loss and most of them did not have the characteristic rash of DM. They also noted fragmentation of perimysial connective tissue, which was not found in most DM patients. Endomysial inflammation was not prominent. Also, of interest is that in the mouse model described by Nagaraju (2000a), the mice developed anti-Jo-1 antibodies.

Table 2
Myositis-specific antibodies in PM/DM (Targoff, 1998)

Antibody	Antigen	%[a]	Myositis subgroup
Anticytoplasmic			
Anti-synthetase	Aminoacyl-tRNA synthetases	25–30	
Anti-Jo-1	Histidyl-tRNA synthetase	18–20	Anti-synthetase syndrome
Anti-PL-7	Threonyl-tRNA synthetase	<3	Anti-synthetase syndrome
Anti-PL-12	Alanyl-tRNA synthetase	<3	Anti-synthetase syndrome
Anti-OJ	Isoleucyl-tRNA synthetase	<2	Anti-synthetase syndrome
Anti-EJ	Glycyl-tRNA synthetase	<2	Anti-synthetase syndrome
Anti-SRP	Signal recognition particle	4	PM
Anti-nuclear			
Anti-Mi-2	Nuclear protein complex	8	DM
Anti-56 kD	56 kD nuclear protein	85–90	All
Anti-PM-Scl	nucleolar protein complex	8	PM/DM-scleroderma overlap

[a] Percentage of all PM/DM.

It has previously been observed that anti-Jo-1 antibodies may occur before the onset of clinically detectable myositis (Miller, 1990).

Sicca symptoms occur more frequently in patients with anti-tRNA synthetase antibodies (59%) (Marguerie et al., 1990). In addition, anti-Jo-1 positive patients with myositis are more likely to have anti-Ro-52 antibodies than anti-Jo-1 negative patients with myositis (Frank et al., 1999).

5.2.3.2. Anti-SRP. The signal recognition particle (SRP) is a cytoplasmic ribonucleoprotein complex consisting of one small RNA and six proteins. It is involved in the co-translational transport of proteins to the endoplasmic reticulum. It is almost exclusively found in PM (Targoff, 2000), with no increase in ILD, Raynauds or arthritis. It has been suggested that there may be an association between anti-SRP and cardiac involvement, a poor response to treatment and a high mortality (Love et al., 1991; Targoff et al., 1990). However, due to the small number of anti-SRP-positive patients in these studies the association is less convincing than with anti-Jo-1 and the antisynthetase syndrome. It is based on two studies with a total of 20 patients with anti-SRP. Only in one patient was a cardiomyopathy diagnosed, 11 patients reported palpitations but not other investigations were conducted. In another study of five anti-SRP-positive patients no cardiac pathology was found (Hengstman et al., 2000).

5.2.3.3. Anti-Mi-2 antibodies. These are directed against a nuclear antigen and is more common than anti-cytoplasmic antibodies, but have been less studied. It is directed against a helicase involved in transcriptional activation (Targoff, 2000) and is strongly associated with DM. No increase in ILD or Raynaud's is seen. It is seen in 7–30% of patients (Brouwer et al., 2001). Most anti-Mi-2 positive patients have a good response to immunosuppressive treatment.

5.2.4. Myositis associated autoantibodies

These are autoantibodies seen in patients with myositis overlap syndromes. Although not myositis-specific, these antibodies can be helpful in evaluating patients with suspected myositis.

5.2.4.1. Anti-snRNP. This is directed to the 70 kd polypeptide of the U1 small nuclear RNP complex. This is often seen as part of overlap syndrome, combining features of SLE, PM and SSc (systemic sclerosis) (Ioannou et al., 1999; Dayal and Isenberg, 2002). Anti-Sm may occur, usually with SLE overlap. When these patients are followed for a period of years, one of the three overlapping conditions tends to dominate the clinical picture (Nimelstein et al., 1980).

5.2.4.2. Anti-PM-Scl. This antibody reacts with a protein complex of polypeptides in the nucleolus and nucleus; involved in RNA processing. These patients often have an overlap syndrome with features of myositis and scleroderma, although some may only have one of the diseases. The clinical features are similar to the other PM overlap syndromes with myositis (which is usually mild), Raynauds phenomenon, arthritis and ILD (usually less severe) and good response to treatment. Cutaneous scleroderma is usually limited when it does occur.

5.2.4.3. Anti-Ro/SSA. Anti-Ro52 antibodies are known to be present frequently in patients with Sjögren's syndrome. A recent study has shown that a high proportion (25%) of sera with anti-PM-Scl antibodies also contain antibodies to the Ro52 protein (Frank et al., 1999). They are much more frequent in patients with anti-synthetases.

Other antibodies have been described in myositis but are either rare or non-specific (Targoff, 2000). Some studies have attempted to shed light on the etiopathogenesis of anti-tRNA synthetase overlap syndrome. Clues pointing to an immunogenetic susceptibility have been suggested (Love et al., 1991). In patients with anti-Jo-1 antibodies, almost all have HLA DR3 (91%) and DR2 (80%), whereas patients with other antisynthetase antibodies have a lower frequency of these HLA loci with a preponderance for DR2 (45%) and DQ1 (70%) (Love et al., 1991). An environmental influence on this background of genetic susceptibility is also suggested. Viral infections have been implicated, specifically Coxsackie virus (Venebles, 1998) and hepatitis C (Weidensaul, 1995) suggesting molecular

mimicry. This suggests that the responses derive from a unique initiating event, not secondary to muscle damage.

Although IBM is seen by some as the third most common cause of an IIM, it appears that the pathological process is probably not autoimmune. Although there are some similarities to PM; partial invasion of non-necrotic muscle fibres and the expression of MHC class I, the distinguishing feature remains the rimmed vacuoles containing various proteins. These have been shown to include amyloid suggesting similarities with Alzheimer's disease. It has been suggested that the overexpression of the beta amyloid is an early event in the pathological process (Askanas and Engel, 2001). Whether these are a secondary phenomenon due to chronic damage or play a primary role in the pathogenesis of this disease remains much debated.

6. Clinical manifestations

Patients with severe disease may present with fever and weight loss. Raynaud's phenomenon may also occur and is common in patients with the anti-synthetase syndrome. These patients may also develop a polyarthritis. A monoarthritis should raise suspicion of infection.

6.1. Muscle

6.1.1. Weakness

This is the most common presenting sign of IBM. The onset is usually insidious with gradual worsening over a period of several months before medical attention is sought. Occasionally there is an acute onset of symptoms, particularly in DM. The distribution of weakness is usually symmetric and proximal. Patients often have impairment in performance of daily activities such as standing from a chair, climbing stairs, or combing hair. Distal muscle weakness may occur, particularly late in the course of the disease (Love et al., 1991). It tends to be very mild and usually does not cause significant functional impairment. If significant, IBM should be considered. Involvement of the face is unusual, and involvement of extraocular muscles is rare and would suggest another diagnosis.

Muscle strength should be assessed as part of initial evaluation and then as part of the monitoring (Miller et al., 2001).

6.1.2. Myalgia and muscle tenderness

This occurs in ~50% of patients (Love et al., 1991) and can be severe when myositis develops acutely. Even in the absence of weakness decreased endurance of the muscles and fatigue is a common feature.

Atrophy may occur with chronic disease and is contributed to by both the disease, chronic steroid use, disuse, or replacement of muscle tissue by fibrotic tissue and fat.

6.2. Rash

Skin involvement is seen in the majority of cases of DM. Several distinct rashes occur in DM and not infrequently precede the weakness by weeks to months. Ninety percent of adult DM patients may have the rash at presentation, while only half have weakness (Bohan et al., 1977). However, the cutaneous manifestations may be transient and may have resolved by the time the patient presents with weakness and may then erroneously be diagnosed as PM. The rash may persist after the myositis resolves.

6.2.1. Heliotrope rash

This is a violaceous eruption on the upper eyelids, often accompanied by periorbital edema. The purplish, lilac-coloured (like the heliotrope flower) eruption is found in 30–60% of patients with DM but may also be seen in allergy, trichinosis and lupus (Drake et al., 1996).

6.2.2. Erythematous shawl/V-sign

It is a diffuse photosensitive erythema in a 'shawl'-like distribution over the back of the neck, upper torso, and shoulders may occur. It may also occur in a V-shaped distribution over the anterior neck and chest; or occur over the forehead, malar region or chin (causing confusion with lupus, but the nasolabial fold may be involved). The distribution suggests photosensitivity and may be aggravated by sun exposure. Atrophy may occur and poikiloderma may develop,

and hyper- and hypopigmentation with atrophy and telangiectasia (Targoff, 1998).

6.2.3. Gottron's lesions

This is the most common rash occurring in 70–80% of patients (Drake et al., 1996). It is a symmetrical, non-scaling, violaceous papules or plaques (Gottron's papules) or erythematous macular eruption (Gottron's sign) over the extensor surfaces of the metacarpophalangeal and interphalangeal joints of the fingers. Similar lesions can occur over the extensor aspects of the elbows and knees, at times mimicking psoriasis. Skin biopsy reveals vascular ectasia with areas of vascular dropout.

6.2.4. Nail fold changes

They are abnormal nailbed capillary loops—changes similar to those seen in scleroderma are seen. The cuticles may be roughened, and irregular.

6.2.5. Mechanic's hands

Hyperkeratosis and often a painful roughening and cracking of the skin of the tips and lateral aspects of the fingers is strongly associated with the antisynthetase syndrome (Love et al., 1991).

6.2.6. Calcinosis

This is more common in children but be widespread in adults and may occur late in the disease. Cutaneous ulceration is rarely seen in adults and appears to be a severe vasculopathy limited to children.

There is increasing recognition of patients with typical cutaneous DM who do not develop myositis. They may have subclinical myositis or the myositis may develop later in the course of the disease, but years may lapse between onset of the rash and the muscle disease (Sontheimer, 1999). 'Amyotrophic DM' or 'DM sine myositis' is applied to those with a rash but no clinical myositis for at least 2 years without treatment (Drake, et al., 1996). The risk of malignancy and systemic complications appears similar to classical DM.

6.3. Pulmonary disease

6.3.1. Interstitial lung disease

This occurs in 10–40% of patients but has a higher frequency in patients with the antisynthetase syndrome and certain overlap syndromes (Love et al., 1991; Targoff et al., 1990). It may occur in amyopathic DM and the severity of ILD is not related to the extent/activity of the myositis. Even early in the disease pulmonary function tests show a restrictive defect with decreased diffusing capacity and hypoxaemia with exercise. Pulmonary hypertension may occur in association with the ILD. There have been case reports of pneumomediastinum usually in association with ILD.

6.3.2. Respiratory muscle weakness

Breathlessness due to muscle weakness occurs in a small number of patients (4–7%) (Targoff, 2000). This will be reflected in reduced vital capacity and elevated residual volume. Respiratory failure may develop, but usually responds to treatment. Patients should be monitored carefully using peak flow meters or ideally vital capacity using a mobile spirometer.

Involvement of the pharyngeal and tongue muscles may cause dysphagia and dysarthria. These patients are at risk of aspiration. A pointer to those at risk is an impaired cough, difficulty turning or sitting up in bed. Pneumonia due to stasis may occur in up to 21% of patients (Marie et al., 1999).

6.3.3. Complications of treatment

Methotrexate hypersensitivity pneumonitis may present with acute onset of fever, cough, shortness of breath and interstitial infiltrates on chest X-ray. It can be difficult to distinguish from disease-related pneumonitis. Opportunistic infections may occur particularly if the lymphocyte count is low, in particular Pneumocystis carinii pneumonia may occur (Kadoya et al., 1996).

6.4. Cardiac disease

Asymptomatic disease occurs frequently in patients including conduction abnormalities on ECG, arrhythmia and pericardial effusion. Complete heart block may occur, requiring a pacemaker. Significant

pericarditis is unusual without SLE overlap. Myocarditis may also occur.

6.5. Gastrointestinal disease

Dysphagia occurs in a third of patients and is more common in older patients (Marie et al., 1999). Weakness of the pharyngeal muscles and oesophagus may result in nasal speech, hoarseness, regurgitation of liquids into the nose on swallowing and correlates with disease activity.

Abnormal oesophageal motility causing dysphagia, heartburn, reflux and stricture, may occur as in scleroderma and does not respond to immunosuppressive treatment (Targoff, 1998).

Cricopharyngeal muscle dysfunction from inflammation or fibrosis may cause dysphagia with a sensation of food sticking in the back of the throat, or coughing with swallowing, and may require surgical myotomy (Oddis, 2000b).

6.6. Malignancy

A wide variety of tumours have been reported in patients with myositis. The risk appears to be greatest with DM in males over 45. Initial evaluation should include stool occult blood testing, mammography and gynecological examination, routine laboratory tests and chest X-ray. Those with disease that is resistant to treatment should be thoroughly investigated. Myositis may present as a paraneoplastic syndrome in about of 20% of DM-cancers, and in these cases the myositis is resistant to treatment until the cancer is resected.

6.7. Overlap syndromes

Overlap with systemic lupus erythematosus, scleroderma or Sjögren's may occur (Love et al., 1991), particularly in those with anti-PM-Scl, anti-U1RNP, or anti-Ku antibodies. Renal disease almost never occurs without overlap. Renal injury is most often occurs from myoglobinuria.

6.8. Pregnancy and idiopathic inflammatory myopathies

There does not appear to be an effect on fertility. Pregnancy outcome is favorable in those with well-controlled disease. Active disease, however, is associated with early pregnancy loss and poor foetal outcome if disease flares occur in the last trimester (Sultan et al., 2002). Prednisolone can be used to treat disease flares.

7. Diagnostic investigations

The most widely used criteria are of Bohan and Peter (1975) (Table 3). Attempts have been made to devise new criteria that take advantage of histological features and autoantibodies (Dalakas, 1991; Tanimoto et al., 1995; Targoff et al., 1997). Other causes of muscle disease must be excluded.

7.1. Muscle enzymes

Creatine kinase (CK) is the most widely used and is elevated in most adult patients. There is a general correlation of CK level and disease activity for most individuals over time, but it may be normal in some adults despite active myositis (more often in DM than PM) (Rider and Miller, 1995). Lesser elevations may occur in chronic disease, especially in the presence of atrophy. Steroids may lower the CK level even if they do not suppress the disease activity. A fall in CK usually indicates improvement, and can precede recovery of strength by 3–4 weeks. CK may be elevated in a wide variety of conditions leading to muscle necrosis. The normal range for CK is higher in men than for women, and higher for African-Americans than for Caucasians. However, up to 10%

Table 3
Criteria for the diagnosis of polymyositis and dermatomyositis (Bohan and Peter, 1975)

1. Proximal muscle weakness: usually symmetrical
2. Elevated serum muscle enzymes: CK, aldolase
3. Electromyographic abnormalities:
   (a) common: myopathic potential: low amplitude, short duration and polyphasic action potentials
   (b) Characteristic triad: (i) myopathic potentials, (ii) fibrillations, positive sharp waves, increased insertional activity, (iii) complex repetitive discharges
4. Muscle biopsy findings typical of PM or DM: Necrosis, phagocytosis, regeneration, inflammation
5. Dermatologic features of DM

of patients may have a normal CK (Bohan et al., 1977).

Serum CK-MB isoenzyme can be elevated in 50% of patients without evidence of cardiac involvement (Targoff, 1998). Regenerating skeletal muscles are the likely source of this. Cardiac troponin-I is not expressed in normal, regenerating, or inflamed skeletal muscle and is, therefore, specific and sensitive marker of cardiac damage. Cardiac troponin-T can be elevated in the absence of cardiac involvement (Kobayashi et al., 1992).

Lactate dehydrogenase (LDH) is also elevated, as are aspartate amino-transferase (AST) and alanine amino-transferase (ALT) and correlate with disease activity, but are less sensitive than CK. Aldolase may be elevated when CK is not, but it is not specific and does not correlate as well with disease activity.

Myoglobin is unique to skeletal and cardiac muscle and is detectable in the serum of most patients with active disease and appears to correlate with disease flares and remission (Kagen, 2000). However, the test is not widely available.

7.2. Autoantibodies

Antinuclear antibodies detected by standard immunofluorescence methods are detected in around 80% of patients. Nuclear speckled patterns are most common. Cytoplasmic patterns suggest antisynthetase or anti-SRP and also an increased risk for ILD (Table 2) as discussed earlier.

7.3. Other tests

The ESR and CRP usually slightly elevated but correlate poorly with disease activity. Rheumatoid factor may be positive particularly in the overlap group. Complement is usually normal unless there is overlap with lupus.

7.4. Electromyography (EMG)

The EMG shows evidence of increased membrane irritability with increased insertional activity and spontaneous fibrillations and sharp waves, abnormal myopathic (low amplitude, short-duration) motor unit action potentials, polyphasic potentials, and bizarre high frequency discharges are seen. With disease of long duration, high amplitude polyphasic potentials may be seen, secondary to reinnervation of regenerating fibres. Patients with myositis have early recruitment and full interference patterns (more fibres required to achieve a given force) in contrast to the decreased recruitment and interference seen in neuropathies (Targoff, 1998). The EMG provides evidence that the process is myopathic and supports the diagnosis, but it is by no means diagnostic. Similar findings may occur in infections, toxic or metabolic myopathies. It is of value in distinguishing myopathic origins of weakness from neuropathic disorders, such as peripheral polyneuropathy and motor neurone disease. As the disease may be patchy, the EMG need to performed at multiple sites, and may only be limited to the paraspinal muscles. A normal EMG may occur in up to 10% of patients and may reflect the limited nature of the disease (Bohan et al., 1977).

7.5. Biopsy

This is the definitive test in establishing the diagnosis and excluding other causes of myopathy. It should be done contralateral to the site of EMG and from a clinically weak muscle. An open biopsy may be preferable as the size of the biopsy is bigger and fibre orientation is preserved. However, needle or conchotome samples leave much smaller scars and through the same incision site several samples may be obtained. Magnetic resonance imaging (MRI) and ultrasound have been used to direct the biopsy to areas of disease activity.

Inflammation is the hallmark of the disease with lymphocytes predominating in the infiltrate, although macrophages and plasma cells may be seen. Although fibre necrosis, degeneration, and regeneration are seen in both DM and PM, each have characteristic features reflecting their distinct pathogenesis. In PM, the cellular infiltrate is predominantly endomysial, around the muscle fibres (and invading individual muscle fibres), without perifascicular atrophy. Abnormal fibres are scattered throughout the fascicle and not limited to one portion. There is internalisation of the nuclei, and prominent nucleoli. There is evidence of cell-mediated immune

response with increased numbers of cytotoxic CD8 + T cells and increased expression of MHC antigens by the muscle fibres. In DM, the infiltrate is perifascicular (around the fascicles) and perivascular (around the small blood vessels), occasionally extending into the endomysial area. Microvascular changes such as perifascicular atrophy (i.e. decreased fibre size at the periphery of the fascicle) are a characteristic feature of DM. There is also evidence of endothelial injury, swelling, hyperplasia, vacuolization, degeneration and regeneration in the small blood vessels. Some patients without a DM rash clinically can have this histological picture. DM is considered to be a humorally mediated disorder in which the primary lesion in the muscle is located in the blood vessel. The inflammatory cell infiltrate is composed of B cells and an increased ratio of CD4 + cells are seen. The abnormalities are usually grouped in one portion of the fascicle suggestive of a microinfarct. Steroids may enhance type II fibre atrophy.

Electron microscopy is performed to exclude IBM or mitochondrial myopathies and enzyme histochemistry may be helpful to exclude metabolic myopathies.

7.6. Imaging

MRI can demonstrate areas of muscle inflammation, edema suggesting active disease and areas of fibrosis and calcification (Reimers et al., 1997). It can be repeated sequentially and can be useful for guiding areas from which to take biopsies. T2-weighted images, which show increased water content as increased intensity, best demonstrate areas of active muscle inflammation. Gadolinium enhancement is not helpful. MRI may show increased intensity in active disease, even when enzymes and other tests are normal (although false negatives do occur).

Magnetic resonance spectroscopy (MRS) provides a view of muscle metabolism comparing the ratio of muscle phosphorus contained in phosphocreatine to the level of inorganic phosphorus. This ratio is decreased in abnormal muscle. MRS is very sensitive (whilst not very specific) and has been used to detect muscle abnormalities in the amyopathic variant of DM (Park et al., 1995). Ultrasound is abnormal in 80% of patients but is less sensitive and specific. It may be useful to direct biopsies (Park and Olsen, 2000).

It is likely that the use of imaging will become a routine part of the evaluation of patients in both diagnosis and follow-up.

7.7. Lung function testing

Early in the disease lung function tests may show a restrictive defect with a decreased diffusing capacity and hypoxaemia with exercise and this can be used to monitor progress.

8. Assessment of disease activity and damage

The assessment of disease activity is central to patient management, and with the prospect of new therapies there is an urgent need to achieve internationally accepted methods of disease assessment. In our experience disease activity is not always reflected by the serum creatinine kinase levels. In order to assess more accurately the advantages and disadvantages of both conventional therapy and newer therapies, a validated and reliable tool is needed, which assess disease activity (i.e. those clinical features which are reversible or may potentially improve with therapy) and damage (implying permanent change). Recently developed tools to assess disease activity and damage have been reported (Isenberg et al., 2004). Myositis disease activity can be measured by two tools known as the MITAX (myositis intention to treat index) and MYOACT (myositis disease activity assessment visual analogue scales). The MITAX index is derived in concept from the BILAG lupus disease activity index and has been developed on the basis of the 'physician's intention to treat'. The myositis damage index (MDI) assesses the extent and severity of damage in several organ systems. These measures have been reviewed by myositis experts participating in the International Myositis Assessment and Clinical Studies (IMACS) Group and have been shown to have good face validity and to be comprehensive. Further studies are underway to assess the validity of these tools in several countries.

9. Differential diagnosis

Other conditions that cause muscle weakness, myalgias, or elevated CK levels need to be distinguished from IBM (Table 4). Patients with risk factors should be tested for retroviral infection. Other conditions mimicking IBM are:

9.1. Drug and Toxin induced Myopathies

Penicillamine, colchicine, HMG-CoA reductase inhibitors, chloroquine and less often hydroxychloroquine can mimic the subacute onset of IBM with proximal muscle weakness and elevated muscle enzymes (Zuckner, 1990). Myopathies associated with alcohol, heroin and cocaine tend to have an acute, fulminant presentation with the features of rhabdomyolysis.

9.2. Infections

Weakness in HIV-infected patients can be a diagnostic challenge. Weakness may be due to chronic disease, but it is also associated with an IIM that is identical to PM (rarely a rash) (Dalakas and Pezeshkpour, 1988). It may be a presenting feature or occur in patients with long-standing disease. The pathogenesis of HIV-myositis has many similarities to idiopathic PM. CD8 + cytotoxic T cells predominate with endomysial infiltration and expression of MHC-1 on muscle fibres (Dalakas, 1993). In addition to the role of HIV infection, treatment with zidovudine can result in a mitochondrial myopathy with elevated muscle enzymes and weakness. Zidovudine inhibits mitochondrial DNA synthesis, and thus results in muscle mitochondrial toxicity. Muscle biopsy demonstrates ragged red fibres. The weakness improves with discontinuation of the drug.

Table 4
Major causes of myopathy to consider in the differential diagnosis

Inflammatory (idiopathic)	*Other myopathies*
Polymyositis	*Dystrophies*
Dermatomyositis	Limb girdle, fascopscapulohumeral
Inclusion body myositis	*Congenital*
Juvenile dermatomyositis	Mitochondrial
Vascultitis	*Metabolic*
Other ARD—lupus, scleroderma	Myophosphorylase deficiency (McArdles)
Sjogrens, rheumatoid arthritis	Phosphofructokinase deficiency
	Acid maltase deficiency
Infections	Lipid storage diseases
Viral—influenza, coxsackie, HIV,	Carcinomatous myopathy
cytomegalovirus, echovirus, adenovirus, EBV	*Neurological*
	Motor neurone disease
Bacterial—pyomyositis, lyme myositis	Myasthenia gravis or Eaton-Lambert
Fungal	Guillain-Barre syndrome
Parasitic—trichinosis, toxoplasma	
	Rhabdomyoslysis
Endocrine disorders	Crush injuries
Hypo/hyperthyroidism	Seizures
Hypo/hyperparathyroidism	Alcohol abuse
Cushings syndrome (or exogenous steroid)	Exertion
	Malignant hyperthermia
Electrolyte disorders	
Hypokalaemia	*Drugs and toxins*
Hypocalcaemia	Illicit drugs—heroin, cocaine
Hyper/hyponatraemia	Alcohol
	Corticosteroids
	Other—HMG-CoA reductase inhibitors, D-penicillamine, cimetidine, Zidovudine, colchicine, anti-malarials

Pyomyositis, resulting in muscle abscesses, usually from staphylococcus aureus may affect older patients, diabetics, chronically ill and AIDS patients.

9.3. Other Neurological conditions

Muscular Dystrophy (MD) may present with similar clinical features. The muscle biopsy may also show inflammatory infiltrates, very similar to PM. The hypertrophied fibres, which distinguish MD, may not be evident early in the disease. Some MDs, including the more recently recognised dysferlinopathy, do not give a family history.

Motor neurone disease can present with elevated muscle enzymes, proximal muscle weakness (although distal weakness is more common), and dysphagia. There are, however, associated long-track signs, fasciculation and prominent atrophy and the EMG is not myopathic.

Myasthenia gravis may cause a diffuse weakness without prominent fatigability. However, involvement of the extraocular and facial muscles is a distinguishing feature.

Inherited metabolic myopathies due to disorders of carbohydrate and lipid metabolism may be present in adults. They are characterised by episodic acute, usually post-exertional muscle pain and tenderness. Biopsy may show increased glycogen deposition: if suspected, enzyme histochemistry should be performed. The forearm ischaemic exercise test is often used to screen for such disorders. Mitochondrial myopathy may sometimes present in adults with just limb weakness, with 'ragged red fibres' on biopsy.

IBM is the most common IIM to be misdiagnosed as PM. The onset tends to be more insidious, with more prominent distal muscle weakness. The patients tend to be older and appear to have treatment resistant PM. Biopsies may need to be repeated multiple times before the typical inclusion bodies on muscle biopsy is seen, which is diagnostic of this disorder.

9.4. Endocrine and steroid myopathies

Hypothyroidism may present with a PM like picture with elevated CK levels. Thyroid function tests should be checked routinely in all patients complaining of weakness.

Corticosteroid use over time may lead to a proximal muscle weakness with lower extremity predominance and may cause management difficulties and be confused with active disease. It is more likely with high doses for extended periods. The EMG should not show any spontaneous activity and biopsy shows enhanced type II fibre atrophy.

9.5. Unusual myopathies

Macrophagic myofasciitis is a recently described condition in which patients may present with weakness and myalgia. The CK may be elevated and EMG may show myopathic changes. Muscle biopsy reveals a unique pattern of PAS-positive macrophages infiltrating the fascia and underlying muscle. Fibre damage was not prominent, with no necrosis. Treatment with steroids and antibiotics helped.

Granulomatous myositis may occur and is associated with sarcoidosis. Eosinophilic myositis may occur as part of the hypereosinophilic syndrome. Biopsy usually confirms the diagnosis.

10. Treatment

The prognosis of DM and PM was poor before the introduction of corticosteroids. Adverse prognostic factors common to many studies include old age at onset, bulbar involvement, delayed treatment, cardiac and pulmonary involvement. The level of CK and degree of muscle weakness do not correlate with prognosis. As these conditions are uncommon, there have been few randomised controlled trials, those that have been conducted involve small number of patients, and therefore optimum therapy is still debatable.

10.1. Corticosteroids

Although this is now the standard therapy, their efficacy has not been fully tested in randomised, placebo-controlled trials, and it is unlikely they will ever be. Most physicians advocate 0.5–1 mg/kg/day initially, either as a single dose or in divided doses through the day. The latter is more potent but a single morning dose limits the steroid related toxicity

(Oddis, 2000b). The major drawback of long-term corticosteroid treatment are its side effects and in some patients, insufficient efficacy. In long-term studies, disability was associated with corticosteroid side effects, especially osteonecrosis and osteoporotic vertebral fractures (Clark et al., 1995). However, with better recognition and treatment with prophylactic bisphosphonates therapy, there should be an improvement in this aspect of long-term outcome. It has been suggested that a lower dose (0.5 mg/kg/day or less), in combination with an immunosuppressive agent, could be equally effective with fewer side effects (Nzeusseu et al., 1999). This strategy should be considered in patients with mild disease.

In patients with severe disease, ILD or myocarditis, intravenous pulse methylprednisolone may be used to gain more rapid control of the disease. Again, there is no evidence from randomised control trials. 0.5–1 g per day for three consecutive days has been suggested, followed by oral prednisolone.

A high initial dose is usually continued for 1–2 months, until a response is seen with a decline in CK and improvement in muscle strength. The CK usually normalises weeks to months earlier than the muscle strength. The dose is tapered slowly to a maintenance level of 5–10 mg/day over about 6 months. This can be achieved by 25% reduction per month, tapered slowly over 1–2 years.

10.2. Immunosuppressive drugs

Most patients with IBM have at least a partial response to corticosteroid therapy alone, many do require other agents to be added to their treatment regime either as a steroid-sparing agents, for disease relapse after repeated tapering attempts, or for rapidly progressive disease with extramuscular involvement. Recent trends are toward earlier introduction of immunosuppressive agents to reduce the risk of steroid side effects and improve response. The use of most of these agents is based on clinical experience rather than randomised controlled trials.

10.2.1. Azathioprine

It is the most commonly used steroid-sparing agent. The studies looking at efficacy are small or retrospective. Up to 75% of patients show a good response in retrospective review. In a small, randomised, placebo controlled trial of prednisolone and azathioprine (2 mg/kg/day) in 16 patients, there was no significant difference in muscle strength, CK or histological features in the two treatment arms (Bunch, 1980). In contrast, a subsequent open study of the same patients concluded that the corticosteroid and azathioprine treated patients had a better long-term outcome after three years than corticosteroids alone (Bunch, 1981). It is used in doses of 1.5–3 mg/kg/day and a trial requires 3–6 months of therapy.

10.2.2. Methotrexate

A recent randomised trial compared the efficacy and tolerability of Cyclosporin A with methotrexate in 36 patients with active PM and DM (Villalba et al., 1998; Vencovsky et al., 2000). Clinical improvement and decreased CK were seen in both groups. Methotrexate is usually started at 7.5 mg/wk, and is increased to 20–25 mg/wk if clinically indicated.

10.2.3. Cyclosporin A

This is being increasingly reported as being efficacious in the treatment of IBM. Given the cell-mediated contribution to the pathogenesis of PM, one may expect better efficacy of Cyclosporin in this subgroup. The dose used in various studies ranged from 3–10 mg/kg/day with a decrease in CK and increase in muscle strength. However, the side-effect profile in patients treated with >4 mg/kg/day is likely to prove unacceptable.

10.2.4. Cyclophosphamide

The use is generally restricted to those who are refractory to corticosteroids and other immunosuppressants or who have manifestations such as severe ILD.

10.2.5. Chlorambucil

Experience is extremely limited. One study of five patients with disease resistant to azathioprine and methotrexate suggested at a dose of 4 mg/kg had some benefit and four of the five patients achieved disease remission after 13–30 months of therapy (Sinoway et al., 1993). However, as with cyclophosphamide it has a higher risk of bone marrow suppression and malignancy.

10.2.6. Combination therapy

Methotrexate plus Cyclosporin A (Wallace et al., 1985) has been suggested to be efficacious. A recent randomised cross-over trial compared the effect of weekly oral methotrexate and daily azathioprine with that of intravenous methotrexate with leucovorin rescue given fortnightly (Villalba et al., 1998). The combination appeared to be more effective.

10.3. Intravenous immunoglobulin

Although the mechanism of action remains unknown, its efficacy in autoimmune diseases suggests it is immunomodulatory. Dalakas (1998) reported a randomised, double-blind, placebo-controlled trial in 15 patients with refractory dermatomyositis. Nine out of 12 had major improvement vs 0 of 11 with placebo. Muscle biopsies also showed an improvement. There are a number of studies also reporting success in PM. The monthly dose that has been studied is 2 g/kg/day given over 2–5 days. The effectiveness of a single treatment appears to be limited to 4–6 weeks, although prolonged courses may have long-term benefit. A major advantage is the low risk. Testing for IgA deficiency to avoid anaphylaxis, high viscosity due to the significant rise with IVIG, and renal impairment is suggested.

10.4. Plasmapheresis

This is used in treatment of refractory autoimmune diseases to remove circulating autoantibodies and immune complexes. Numerous case reports and open studies have suggested its success. However, the result of a controlled, double-blind trial, was disappointing with no difference seen in strength or functional outcome with leukapheresis or plasmapheresis (12 treatments in 1 month) (Miller et al., 1992). Given the cost, potential complications and evidence for lack of efficacy there appears little justification for plasma exchange.

10.5. Experimental therapies

Preliminary reports suggest benefit from anti-TNF in some patients (Hengstman et al., 2003), although caution should be exercised in those with lupus overlap. It is suggested that rituximab (monoclonal anti-CD20) may be beneficial in those with refractory disease but controlled studies are awaited (Levine, 2002).

It generally accepted that typical IBM responds poorly to steroids and immunosuppressive therapy, and in patients with treatment resistant PM/DM the diagnosis should be reviewed and if necessary, with a repeat biopsy.

11. Treatment of specific manifestations

11.1. Dermatomyositis rash

The rash is usually responsive to the treatment of the underlying myositis. If it persists, hydroxychloroquine 200–400 mg/day may be helpful. Quinacrine 100 mg/day or isotretinoin 0.5–1.0 mg/kg/day may be helpful in those with resistant disease (Oddis, 2000b). Topical steroids are often unsuccessful. The rash may be photosensitive and sunscreens are recommended. Intravenous immunoglobulin has been effective for persistent cutaneous ulceration.

11.2. Calcinosis

This is usually a problem of juvenile DM. Several treatments have been tried, such as diltiazem, probenecid, alendronate, low dose warfarin, but none of these are of proven benefit. An inflammatory component may respond to colchicine. Aggressive treatment of the underlying disease may prevent calcinosis, but does not affect established calcinosis.

11.3. Interstitial lung disease

Treatment is effective when the biopsy shows active inflammation, or there is a ‘ground glass’ appearance on high-resolution computed tomography. Treatment should be considered for clinically significant and progressive disease. Prednisolone is used initially, but immunosuppressive drugs are usually required. A prospective trial of intravenous cyclophosphamide in patients with progressive ILD associated with autoimmune rheumatic diseases, included two patients with PM. All six patients had improvement and

the treatment was well tolerated (Schnabel et al., 1998), Treatment was with 0.5 g/m^2 every 4 weeks for nine cycles. Prednisolone at 50 mg daily was also used and tapered over 3 weeks to 5–7.5 mg/day.

In a retrospective analysis of 111 patients with PM and DM, the effect of cyclosporin on corticosteroid-resistant ILD (Nawata et al., 1999) was assessed. ILD developed in a third of these patients and interestingly corticosteroid-resistant disease occurred in half of these patients and these patients tended to have pneumonitis without CK elevation. Conversely patients with pneumonitis with CK elevation were more likely to respond to corticosteroids. Tacrolimus has also been suggested to be effective in patients with refractory disease with ILD (Oddis et al., 1999). Three patients that responded the most had anti-Jo-1 positive disease. Treatment dose of 0.075 mg/kg/day in two divided doses is suggested.

11.4. Oesophageal involvement

This is a serious complication, and in resistant or very severe cases IVIG may be effective.

12. Rehabilitation

Passive exercises should be started early to prevent joint contractures. Once the acute inflammation subsides, active graded exercise, should be introduced cautiously to help recover strength and can be considered even if some disease activity remains (Alexanderson, et al., 2000).

13. Prognosis

Prognosis for recovery of full strength is worse if treatment is delayed (Joffe et al., 1993), or if the course is chronic and progressive. Anti-synthetase and anti-SRP patients have a higher frequency of incomplete response a relapsing remitting course.

Survival rates are higher now than prior to the corticosteroid era. Five year survival in the period 1947–1968 was 65% (Medsger et al., 1971), 1970–1981 was 80.4% (Hochberg et al., 1986), and now may be as high as 95% in the period 1978–1999, with 10 year survival of 83.8% (Sultan et al., 2002). Most common causes of mortality are from malignancy, infection, cardiac and lung. Factors associated with a worse prognosis are older age at onset, cardiac or ILD.

About one third of patients will do well with treatment (and may be able to dispense with it altogether). Another third will be left with significant weakness (some of whom may die of the disease directly or its complications) and require long-term immunosuppression, the remaining third will be left with some residual weakness and require modest doses of immunosuppression.

Key points

- DM, PM and IBM are the three major categories of IIM.
- Muscle weakness is the most common presenting sign of IIM.
- Other conditions causing muscle weakness, myalgias, or increased creatine kinase levels need to be distinguished from IIM.
- Muscle biopsy is important in establishing the correct diagnosis and to exclude several rare but distinctive forms of myositis. Repeat biopsies may be required to exclude IBM.
- Imaging, in particular MRI, is increasingly used in identifying subclinical disease and may increase diagnostic yield from muscle biopsy.
- A thorough initial evaluation is important to exclude an underlying malignancy and should include rectal examination, breast examination, screening mammography, chest X-ray, pelvic computed tomography in women and PSA in men.
- Detection of specific antibodies may help guide treatment and prognosis e.g. Anti-synthetase antibodies should alert to the increase risk of interstitial lung disease and incomplete response to treatment.
- Most patients with IIM have at least a partial response to corticosteroid therapy alone. Most patients require other agents to be added to their treatment regime as steroid-sparing agents.

References

Alexanderson, H., Stenström, C.H., Jenner, G., Lundberg, I. 2000. The safety of a resistive home exercise program in patients with recent onset active polymyositis or dermatomyositis. Scand. J. Rheum. 29, 295–301.

Arnett, F.C., et al. 1996. Interrelationship of major histocompatability complex class II alleles and autoantibodies in four ethnic groups with various forms of myositis. Arthritis Rheum. 39, 1507–1518.

Askanas, V., Engel, W.K. 2001. Inclusion-body myositis: newest concepts of pathogenesis and relation to aging and Alzheimer disease. J. Neuropathol. Exp. Neurol. 60, 1–14.

Authier, F.J., et al. 1997. Interleukin-1 expression in inflammatory myopathies: evidence of marked immunoreactivity in sarcoid granulomas and muscle fibres showing ischaemic and regenerative changes. Neurolpathol. Appl. Neurobiol. 23, 132–140.

Bohan, A., Peter, J.B. 1975. Polymyositis and dermatomyositis (parts 1 and 2). N. Engl. J. Med. 292, 344–347, 403–407.

Bohan, A., et al. 1977. A computer-assisted analysis of 153 patients with polymyositis and dermatomyositis. Medicine (Baltimore) 56, 255–286.

Brouwer, R., et al. 2001. Autoantibody profiles in the sera of European patients with myositis. Ann. Rheum. Dis. 60, 116–123.

Bunch, T.W. 1981. Prednisone and azathioprine for polymyositis: long-term followup. Arthritis Rheum. 24, 45–48.

Bunch, T.W., et al. 1980. Azathioprine with prednisone for polymyositis. A controlled, clinical trial. Ann. Intern. Med. 92, 365–369.

Clarke, A.E., et al. 1995. A longitudinal study of functional disability in a national cohort of patients with polymyositis/dermatomyositis. Arthritis Rheum. 38, 1218–1224.

Crowson, A.N., Magro, C.M., Dawood, M.R. 2000. A causal role for parvovirus B19 infection in adult dermatomyositis and other autoimmune syndromes. J. Cutan. Pathol. 27, 505–515.

Dalakas, M.C., Pezeshkpour, G.H. 1988. Neuromuscular diseases associated with human immunodeficiency virus infection. Ann. Neurol. 23, S38.

Dalakas, M.C. 1991. Polymyositis, dermatomyositis, and inclusion-body myositis. N. Engl. J. Med. 325, 1487–1498.

Dalakas, M.C. 1993. Retroviruses and inflammatory myopathies in humans and primates. Baillieres Clin. Neurol. 2, 659–691.

Dalakas, M.C. 1998. Controlled studies with high-dose intravenous immunoglobulins in the treatment of dermatomyositis, inclusion body myositis and polymyositis. Neurology. 51, S37–45.

Dayal, N., Isenberg, D.A. 2002. SLE/myositis overlap: are the manifestations of SLE different in overlap disease. Lupus 11, 293–298.

De Bleecker, J.L., et al. 2002. Differential expression of chemokines in inflammatory myopathies. Neurology 58, 1779–1785.

Drake, L.A., et al. 1996. Guidelines of care for dermatomyositis. J. Am. Acad. Dermatol. 34, 824.

Drlacher, P., et al. 2001. Cardiac troponin and beta-type myosin heavy chain concentrations in patients with polymyositis or dermatomyositis. Clin. Chim. Acta 306, 27–33.

Emslie-Smith, A.M., Engel, A.G. 1990. Microvascular changes in early and advanced dermatomyositis: a quantitative study. Ann. Neurol. 27, 343–356.
One of the early studies suggesting histological differences between polymyositis and dermatomyositis and that the capillaries are targeted early in the disease process—even prior to inflammatory cell infiltrate.

Engel, A.G., Arahata, K. 1986. Mononuclear cells in myopathies: quantitation of functionally distinct subsets, recognition of antigen specific cell-mediated cytotoxicity in some diseases, and implications for the pathogenesis of the different inflammatory myopathies. Hum. Pathol. 17, 704–721.

Englund, P., et al. 2001. Skeletal muscle fibers express major histocompatability complex class II antigens independently of inflammatory infiltrates in inflammatory myopathies. Am. J. Pathol. 159, 1263–1273.

Frank, M.B., et al. 1999. The association of anti-Ro-52 autoantibodies with myositis and scleroderma autoantibodies. J. Autoimmun. 12, 137–142.

Ginn, L.R., et al. 1998. Familial autoimmunity in pedigrees of idiopathic inflammatory myopathy patients suggests common genetic risk factors for many autoimmune diseases. Arthritis Rheum. 41, 400–405.

Guttridge, et al. 2000. NF kappa B induced loss of myo-D messenger RNA: possible role in muscle decay and cachexia. Science. 289, 2363–2366.

Hill, C.L., et al. 2001. Frequency of specific cancer types in dermatomyositis and polym yositis: a population-based study. Lancet 357, 96–100.

Hochberg, M.C., Feldman, D., Stevens, M.B. 1986. Adult onset polymyositis/dermatomyositis: an analysis of clinical and laboratory features and survival in 76 patients with a review of the literature. Semin. Arthritis Rheum. 15, 168–178.

Hohlfeld, R., et al. 1997. Cellular immune mechanisms in inflammatory myopathies. Curr. Opin. Rheum. 9, 520–526.

Hengstman, G.J.D., et al. 2000. Clinical and serological characteristics of myositis:myositis specific autoantibodies aid in the differential diagnosis of the idiopathic inflammatory myopathies. Neurology 2000 54 (Suppl. 3), A240.

Hengstman, G.J., et al. 2003. Successful treatment of dermatomyositis and polymyositis with anti-tumor-necrosis-factor-alpha: preliminaary observations. Eur. Neurol. 50, 10–15.

Ioannou, Y., Sultan, S., Isenberg, D.A. 1999. Myositis overlap syndromes. Curr. Opin. Rheum. 11, 468–474.

Isenberg, D.A., et al. 2004. International consensus outcome measures for patients with idiopathic inflammatory myoathies: development and initial validation of myositis activity and damage indices in patients with adult onset disease. Rheumatology 43, 49–54.

Ji, S.Q., et al. 1998. Proinflammatory cytokines regulate myogenic cell proliferation and fusion but have no impact on myotube protein metabolism or stress protein. J. Interferon Cyt. Res. 18, 879–888.

Joffe, M.M., et al. 1993. Drug therapy of the idiopathic inflammatory myopathies: predictors of response to prednisolone, azathioprine and methotrexate and a comparison of their efficacy. Am. J. Med. 94, 379–387.

Kadoya, A., et al. 1996. Risk factors for Pneumocystis carinii pneumonia in patients with polymyositis/dermatomyositis or systemic lupus erythematosus. J. Rheum. 23, 1186–1188.

Kagen, L.J. 2000. History, physical examination, and laboratory tests in the evaluation of myopathy. In: R.L. Wortmann (Ed.), Diseases of Skeletal Muscle. Lippincott, Williams & Wilkins, Philadelphia, pp. 255–266.

Kalovidouris, A.E., Plotkin, Z., Graesser, D. 1993. Interferon-gamma inhibits proliferation differentiation and creatine kinase activity of cultured human muscle cells.II. a possible role in myositis. J. Rheum. 20, 1718–1723.

Kobayashi, S., et al. 1992. Serum cardiac troponin T in polymyositis/dermatomyositis. Lancet 340, 726.

Lee, S.W., et al. 2002. A case of polymyositis with dilated cardiomyopathy associated with interferon alpha treatment for hepatitis B. J. Korean Med. Sci. 17, 141–143.

Leff, R.L., et al. 1992. Viruses in idiopathic inflammatory myopathies: absence of candidate viral genomes in muscle. Lancet 339, 1192–1195.

Levine, T.D. 2002. A pilot study of rituximab therapy for refractory dermatomyositis. Arthritis Rheum. 46, 1299.

Love, L.A., Miller, F.W. 1993. Noninfectious environmental agents associated with myopathies. Curr. Opin. Rheum. 10, 521–529.

Love, L.A., et al. 1991. A new approach to the classification of idiopathic inflammatory myopathy: myositis specific autoantibodies define useful homogeneous patient groups. Medicine (Baltimore) 70, 360–374.

Lundberg, I., Nberg, P. 1998. New developments in the role of cytokines and chemokines in inflammatory myopathies. Curr. Opin. Rheum. 10, 521–529.

Lundberg, I., et al. 1997. Cytokine production in muscle tissue of patients with idiopathic inflammatory myopathies. Arthritis Rheum. 40, 865–874.

Lundberg, I., Kratz, A.D., Alexanderson, H., et al. 2000. Decreased expression of interleukin-1 alpha, interleukin-1beta, and cell adhesion molecules in muscle tissue following corticosteroid treatment in patients with polymyositis and dermatomyositis. Arthritis Rheum. 43, 336–348.

Magro, C.M., Crowson, A.N. 1997. The immunofluorescent profile of dermatomyositis: a comparative study with lupus erythematosus. J. Cutan. Pathol. 24, 543–552.

Marguerie, C., et al. 1990. Polymyositis, pulmonary fibrosis and autoantibodies to aminoacyl-tRNA synthetase enzymes. Quart. J. Med. 77, 1019–1038.

Marie, I., et al. 1999. Influence of age on characteristics of polymyositis and dermatomyositis in adults. Medicine (Baltimore) 78, 139–147.

Medsger, T.A., Robinson, H., Masi, A.T. 1971. Factors affecting survivorship in polymyositis. A life table study of 124 patients. Arthritis Rheum. 14, 249–258.

Messner, R.P. 2000. Pathogenesis of idiopathic inflammatory myopathies. In: R.L. Wortmann (Ed.), Diseases of Skeletal Muscle. Lippincott, Philadelphia, pp. 1117–1127.

Miller, F.W., et al. 1992. Controlled trial of plasma exchange and leukapheresis in polymyositis and dermatomyositis. N. Engl. J. Med. 326, 1380–1384.

Miller, F.W. 2001. Proposed preliminary core set measures for disease outcome assessment in adult and juvenile idiopathic inflammatory myopathies. Rheumatitis 40, 1262–1273.

Miller, F.W., Twitty, S.A., Biswas, T., Plotz, P.H. 1990. Origin and regulation of a disease-specific autoantibody response. Antigenic epitopes, spectrotype stability and isotype restriction of anti-Jo-1 autoantibodies. J. Clin. Invest. 85, 468–475.

Mozaffar, T., Pestronk, A. 2000. Myopathy with anti-Jo-1 antibodies: pathology in perimysium and neighboring muscle fibres. J. Neurol. Neurosurg. and Psych. 68, 472–478.

Nagaraju, K. 2000. Conditional up-regulation of MHC class I in skeletal muscle leads to self-sustaining autoimmune myositis and myositis-specific autoantibodies. Proc. Nat. Acad. Sci. USA 97, 9209–9214.

In this mouse model, transgenic for MHC class I in skeletal muscle, cells spontaneously develop muscle weakness and a chronic muscle inflammation supporting a role of MHC class I expression on muscle fibers in causing muscle weakness.

Nagaraju, K. 2001. Update on immunopathogenesis in inflammatory myopathies (review). Curr. Opin. Rheum. 13, 461–468..

Nawata, Y., Kurasawa, K., Takabayashi, K., et al. 1999. Corticosteroid resistant interstial pneumonitis in dermatomyositis/polymyositis: prediction and treatment with cyclosporin. J. Rheum. 26, 1527–1533.

Nimelstein, S.H., Brody, S., McShane, D., Holman, H.R. 1980. Mixed connective tissue disease: a subsequent evaluation of the original 25 patients. Medicine (Baltimore) 59, 239.

Nyberg, P., et al. 2000. Increased expression of interleukin 1 alpha and MHC class I in muscle tissue of patients with chronic, inactive polymyositis and dermatomyositis. J. Rheum. 27, 940–948.

Nzeusseu, A., Brion, F., Lefebvre, C., Knoops, P., Devogelar, J.P., Houssiau, F.A. 1999. Functional outcome of myositis patients: can a low dose Glucocorticoid regimen achieve good functional results? Clin. Exp. Rheum. 27, 441–446.

Oddis, C.V. 2000a. Idiopathic inflammatory myopathies. In: R.L. Wortman (Ed.), Diseases of Skeletal Muscle. Lippincott, Philadelphia, pp. 45–85.

Oddis, C.V. 2000b. Current approach to the treatment of polymyosiits and dermatomyositis. Curr. Opin. Rheum. 12, 492–497.

Oddis, C.V., Sciurba, F.C., Elmagd, K.A., et al. 1999. Tacrolimus in refractory polymyositis with interstitial lung disease. Lancet 353, 1662–1763.

O'Hanlon, T.P., Messersmith, W.A., Dalakas, M.C. 1995. Gamma delta T-cell receptor gene expression by muscle infiltrating lymphocytes in the idiopathic inflammatory myopathies. Clin. Exp. Immunol. 100, 519–528.

Oppenheim, J.J., Yang, D., Biragyn, A., Howard, O.M.Z., Plotz, P. 2002. Arthritis Res. 4 (Suppl. 3), S183–S188.

Park, J.H., et al. 1994. MRI and P-31 magnetic resonance spectroscopy detect and quantify muscle dysfunction in the amyopathic and myopathic variants of dermatomyositis. Arthritis Rheum. 38, 68.

Park, J.H., et al. 2000. Muscle abnormalities in juvenile dermatomyositis patients; P-31 magnetic resonance spectroscopy studies. Arthritis Rheum. 43, 2359–2367.

Reimers, C.D., Finkenstaedt, M. 1997. Muscle imaging in inflammatory myopathies. Curr. Opin. Rheum. 4, 475.

Rider, L.G., Miller, F.W. 1995. Laboratory evaluation of the inflammatory myopathies. Clin. Diagn. Lab. Immunol. 2, 1–9.

Rowe, D.J., Isenberg, D.A., Beverley, P.C.L. 1983. Monoclonal antibodies to leucocyte antigen in polymyositis and muscular dystrophy. Clin. Exp. Immunol. 54, 327–336.

Schnabel, A., Reuter, M., Gross, W.L. 1998. Intravenous pulse cyclophosphamide in the treatment of interstitial lung disease due to collagen vascular diseases. Arthritis Rheum. 41, 1215–1220.

Sinoway, P.A., Callen, J.P. 1993. Chlorambucil. An effective corticosteroid-sparing agent for patients with recalcitrant dermatomyositis. Arthritis Rheum. 36, 319–324.

Sontheimer, R.D. 1999. Cutaneous features of classic dermatomyositis and amyopathic dermatomyositis. Curr. Opin. Rheum. 11, 475–482.

Sultan, S.M., Ioannou, Y., Moss, K., Isenberg, D.A. 2002. Outcome in patients with idiopathic inflammatory myositis: morbidity and mortality. Rheumatology 41, 22–26.

Silva, C.A., Sultan, S.M., Isenberg, D.A. 2003. Pregnancy outcome in adult-onset idiopathic inflammatory myopathy. Rheumatology 42, 1168–1172.

Tanimoto, K., et al. 1995. Classification criteria for polymyositis and dermatomyositis. J. Rheum. 22, 668–674.

Targoff, I.N., et al. 1997. Classification criteria for the idiopathic inflammatory myopathies. Curr. Opin. Rheum. 9, 527–535.

Targoff, I.N. 1998. Polymyositis and dermatomyositis. Oxford Textbook of Rheumtology, Oxford Medical Publications, Oxford, pp. 1249–1287.

Targoff, I.N. 2000. Autoantibodies and muscle disease. In: R.L. Wortman (Ed.), Diseases of Skeletal Muscle. Lippincott Williams, Philadelphia, pp. 267–291.

Targoff, I.N., Johnson, A.E., Miller, F.W. 1990. Antibody to signal recognition particle in polymyositis. Arthritis Rheum. 33, 1361–1370.

Tews, D.S., Goebel, H.H. 1996. Cytokine expression profile in idiopathic inflammatory myopathies. J. Neuropathol. Exp. Neurol. 55, 342–347.

Vencovsky, J., Jarosova, K., Machacek, S., et al. 2000. Cyclosporin A versus methotrexate in the treatment of polymyositis and dermatomyositis. Scand. J. Rheum. 29, 95–102.

Venebles, P.J.W. 1998. Overlap syndromes. In: J.H. Klippel, P.A. Dieppe (Eds.), Rheumatology. Mosby-Year Book 7, Mosby, London, pp. 31–38.

Villalba, L., Hicks, J.E., Adams, E.M., et al. 1998. Treatment of refractory myositis: a randomized crossover study of two new cytotoxic regimens. Arthritis Rheum. 41, 392–399.

Wallace, D.J., Metzger, A.L., White, K.K. 1995. Combination immunosuppressive treatment of steroid-resistant dermatomyositis/polymyositis. Arthritis Rheum. 28, 590–592.

Weidensaul, K., et al. 1995. Polymyositis, pulmonary fibrosis and hepatitis C. Arthritis Rheum. 38, 437–439.

Ytterberg, S.R. 1994. The relationship of infectious agents to inflammatory myositis. Rheum. Dis. Clin. N. Am. 20, 995–1016.

Zuckner, J. 1990. Drug induced myopathies. Sem. Arth. Rheum. 19, 259.

PART V

Vasculitides

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CHAPTER 8

Antineutrophil Cytoplasmic Autoantibody-Associated Vasculitides and Polyarteritis Nodosa

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1. Introduction

Vasculitides are multiple organ and/or system diseases characterized by inflammation of the blood vessel walls with resulting vascular obstruction, subsequent ischemia and injury of the involved tissues. They are classified according to the type of vessels affected, running the gamut from the aorta to capillaries to veins, and to the different target end-organs.

All these entities may affect the central (CNS) and peripheral (PNS) nervous systems. PNS involvement is frequent and, in patients with arthralgia and/or general symptoms, the presence of peripheral neurologic symptoms, most strikingly mononeuritis multiplex, should alert physicians to the possibility of vasculitis. Conversely, CNS involvement occurs less frequently but has a poorer prognostic value (Guillevin et al., 1996).

After a brief review of the definitions, classification and pathogenic mechanisms of vasculitides, we describe the neurologic manifestations that can occur in polyarteritis nodosa (PAN) and antineutrophil cytoplasmic autoantibodies (ANCA)-associated vasculitides, and their therapies. We have also included isolated peripheral nerve vasculitis and primary angiitis of the CNS (PACNS), which are sufficiently close to these vasculitides to pose 'differential' diagnostic difficulties and therapeutic challenges.

2. Definition and classification of vasculitides

Vasculitides are defined based upon their histologic features. Three main lesions can commonly be observed that are relatively specific for vasculitis: fibrinoid necrosis of vessel walls; vascular inflammatory infiltrates; and fibrin deposits. Perivascular inflammatory infiltrates usually progressing to fibrotic scar replacement and thromboses, resulting in tissue ischemia and damage, can also be observed but these changes are less specific (Fig. 1).

Vasculitic lesions have a segmental distribution pattern, with a predilection for arterial bifurcations. Early inflammatory infiltrates of or around the vessel walls contain lymphocytes, plasmocytes, histiocytes and some neutrophils. Fibrinoid necrosis predominates in the internal layer of the artery media, thereby supporting thrombosis development. Segmental necrosis of medium-sized vessels may also give rise to microaneurysms. As some vasculitides have an activity pattern of successive flares, different histologic stages may be seen in a single specimen. Giant cell arteritis and Takayasu's arteritis have no (or only mild) fibrinoid necrosis, affect large vessels and should be distinguished from necrotizing angiitis. Thus, the presence of fibrinoid necrosis in a temporal

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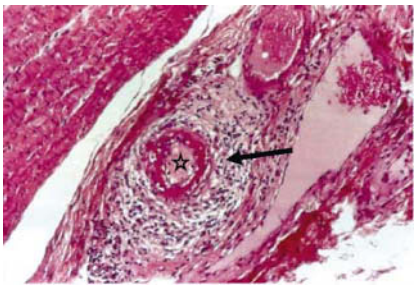

Figure 1. Muscle biopsy from a patient with polyarteritis nodosa. Vasculitis of a medium-sized artery, with perivascular leukocyte infiltration (arrow), arterial wall thickening, and luminal thrombosis (star).

artery should be interpreted as a sign of small or medium-sized vessel arteritis with temporal artery involvement, with exclusion of the diagnosis of giant cell arteritis (Chomette et al., 1983; Généreau, 1999; Saveuse et al., 1988). On the other hand, granulomatous inflammation is one of the characteristic features of Wegener's granulomatosis (WG) and Churg–Strauss syndrome (CSS).

Primary vasculitides can be classified according to the 1990 American College of Rheumatology classification criteria (Arend et al., 1990; Bloch et al., 1990; Calabrese et al., 1990; Fries et al., 1990; Hunder et al., 1990; Leavitt et al., 1990; Lightfoot et al., 1990; Masi et al., 1990; Mills et al., 1990) or to the more accurate and complete Nomenclature of Systemic Vasculitis, established at the Chapel Hill Consensus Conference (Jennette et al., 1994), reproduced in Table 1. This latter classification distinguishes large, medium-sized and small vessel vasculitides, and also recognizes some overlap syndromes, with some, but not predominant, involvement of small vessels in PAN (ANCA Workshop, Birmingham, UK, 1998, unpublished revised version of the Nomenclature).

Diagnosis of vasculitis is established by histology. However, as tissue easily accessible to biopsy may show only non-specific inflammation or may even be normal, diagnosis sometimes requires a combination of clinical findings, and results of biologic, immunologic and radiologic investigations. ANCA and angiography are useful tools to help make the diagnosis of vasculitides. In immunofluorescence assays C-ANCA label the cytoplasm of ethanol-fixed neutrophils and are detected in 60–90% of the patients with systemic WG, and in 50–75% of those with localized forms of WG (Kallenberg et al., 1992). P-ANCA, which give a perinuclear labeling pattern in immunofluorescence assays, are more closely linked to pauci-immune glomerulonephritis (80% of the patients), microscopic polyangiitis (MPA; 50–75%) and CSS (47%) (Ewert et al., 1991; Guillevin et al., 1999a; Hagen et al., 1998). Celiomesenteric and renal angiographic findings, such as multiple 1–5 mm diameter aneurysms or irregular stenoses are present in approximately 80% of PAN patients (D'Izarn et al., 1976; Guillevin et al., 1995a). Although suggestive, these findings are not absolutely specific. ANCA have also been detected in non-vasculitic diseases, such as inflammatory bowel and autoimmune liver diseases, rheumatoid arthritis, tuberculosis (Flores-Suarez et al., 2003), drug reactions (Guillevin et al., 1995a; Halbwachs-Mecarelli et al., 1992; Specks et al., 1993), and in up to two-thirds (mainly P-ANCA with anti-myeloperoxydase (MPO) specificity) of patients with other non-vasculitic neuropathies or CNS diseases (Chalk et al., 1993; Nakashima et al., 1998). In addition, visceral artery aneurysms may also be found in thrombotic thrombocytopenic purpura, mycotic aneurysms, fibromuscular dysplasia, atrial myxoma and in a few patients with small vessel vasculitides (Ha et al., 2000; Jee et al., 2000; Miller, 2000). Indeed, to date, no diagnostic criteria for vasculitides have been established.

Notably, some vasculitides may develop in a setting of infection (e.g. hepatitis B virus (HBV), hepatitis C virus (HCV) or human immunodeficiency virus (HIV)), cancer, malignant hemopathy or drug hypersensitivity (Calabrese et al., 1990; Garcia-Porrua et al., 2001; Gisselbrecht et al., 1997; Lortholary et al., 1999; Rieu et al., 2002). In the late 1980s, HBV was responsible for one-third of the cases of PAN (Guillevin et al., 1993). HBV-related PAN now represents less than 10% of all PAN cases (Guillevin and Lhote, 1997; Guillevin et al., 2001). Conversely, HCV is responsible for 80% of the cases of mixed cryoglobulinemia (Rieu et al., 2002). Identification of these latter secondary vasculitic syndromes is important because of their better outcome when a specific (and effective) treatment of the underlying cause is prescribed, and because the use of immunosuppressants may be deleterious in virus-related vasculitides.

Table 1
Names and definitions of vasculitides adopted by the Chapel Hill Consensus Conference (Jennette et al., 1994) on the Nomenclature of Systemic Vasculitis

	Large vessel vasculitis
Giant cell (temporal) arteritis	Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery. Often involves the temporal artery. *Usually occurs in patients older than 50 and often is associated with polymyalgia rheumatica*
Takayasu's arteritis	Granulomatous inflammation of the aorta and its major branches. *Usually occurs in patients younger than 50*
	Medium-sized vessel vasculitis
Polyarteritis nodosa	Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules
Kawasaki disease	Arteritis involving large, medium-sized, and small arteries, and associated with mucocutaneous lymph node syndrome. *Coronary arteries are often involved. Aorta and veins may be involved. Usually occurs in children*
	Small vessel vasculitis
Wegener's granulomatosis[a]	Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels (e.g. capillaries, venules, arterioles, and arteries). *Necrotizing glomerulonephritis is common*
Churg–Strauss syndrome[a]	Eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels, and associated with asthma and eosinophilia
Microscopic polyangiitis[a]	Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (i.e. capillaries, venules, or arterioles). *Necrotizing arteritis involving small and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs*
Henoch–Schönlein purpura	Vasculitis with IgA-dominant immune deposits, affecting small vessels (i.e. capillaries, venules, or arterioles). *Typically involves skin, gut, and glomeruli, and is associated with arthralgias or arthritis*
Essential cryoglobulinemic vasculitis	Vasculitis, with cryoglobulin immune deposits, affecting small vessels (i.e. capillaries, venules, or arterioles), and associated with cryoglobulins in serum. *Skin and glomeruli are often involved*
Cutaneous leukocytoclastic angiitis	Isolated leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis

Large vessel refers to the aorta and the largest branches directed toward major body regions (e.g. to the extremities and the head and neck); medium-sized vessel refers to the main visceral arteries (e.g. renal, hepatic, coronary, and mesenteric arteries); small vessel refers to venules, capillaries, arterioles, and the intraparenchymal distal arterial radicals that connect with arterioles. Some small and large vessel vasculitides may involve medium-sized arteries, but large and medium-sized vessel vasculitides do not involve vessels smaller than arteries. Essential components are represented by normal type; italicised type represents usual, but not essential, components. Reproduced with permission.

[a] Strongly associated with antineutrophil cytoplasmic autoantibodies.

3. Pathogenesis

Several pathogenic pathways have been implicated in the development of vasculitides, with the main mechanisms possibly differing according to the type of vasculitis. These mechanisms are only partly understood, and some are probably still unknown.

3.1. Immune complexes

Deposition of circulating immune complexes in the vessel walls seems to be relevant in HBV-related PAN, Henoch–Schönlein purpura, mixed cryoglobulinemic vasculitis and the necrotizing vasculitis of rheumatoid arthritis. In the presence of an excess

amount of antigen, immune complexes would form and be deposited onto vessel walls, where they then facilitate the activation of the complement components and attract activated neutrophils, which together can cause local damage to the endothelium. The detection of HBV-derived antigens and their corresponding antibodies in the vessels of patients with HBV-related PAN (Gower et al., 1978) support this concept of immune complex involvement in its pathogenesis.

3.2. Antineutrophil cytoplasmic antibodies

First detected in a small cohort of patients with pauci-immune glomerulonephritis (Davies et al., 1982), antibodies specific to antigens in the cytoplasm of ethanol-fixed neutrophils have been shown to be strongly associated with three major small vessel vasculitides: WG, MPA and CSS (Falk and Jennette, 1988; van der Woude et al., 1985). ANCA are specific to peptides in neutrophil granules and monocyte lysosomes. Indirect immunofluorescence assays give a C-ANCA, P-ANCA, or diffuse labeling pattern. Antigens recognized, and identified by antigen-specific enzyme-linked immunosorbent assays (ELISA), are proteinase 3 (PR3) for C-ANCA, MPO for 90% of the P-ANCA, and elastase, cathepsin G, lactoferrin and lysozyme for the remaining P-ANCA (Ledford, 1997; Specks et al., 1993). Soon after the release of tumor necrosis factor-alpha (TNFα), at the onset of inflammation, PR3 translocates to the neutrophil plasma membrane, where ANCA may bind to it and further activate neutrophils as a surrogate. Such interactions would contribute directly to vascular damage. Indeed, high numbers of circulating endothelial cells, with a necrotic phenotype, have been observed in patients with active ANCA-associated vasculitides. Their numbers were significantly lower in vasculitis patients in remission or those with ANCA-negative vasculitides (Woywodt et al., 2003). This association is further supported by the development of necrotizing glomerulonephritis in recombinase-activating gene-2-deficient ($rag2^{-/-}$) mice, but also in wild-type C57BL/6J mice, after injection of purified anti-MPO IgG (Heeringa et al., 1998; Xiao et al., 2002). Moreover, ANCA titers seem to fluctuate with the disease activity, at least in WG but, at present, must not be used as a tool to initiate or modify therapy because this relationship is not constant (Girard et al., 2001; Tervaert et al., 1989, 1990).

3.3. Cytokines and adhesion molecules

Many cytokines are present at sites of inflammation, and their circulating levels are high in patients with vasculitis (Sundy and Haynes, 2000; Tesar et al., 1998). Some of them may be responsible for clinical symptoms (fever and weight loss induced by interleukin IL-1, transforming growth factor-alpha (TNFα) and IL-6), some may favor fibrosis and thrombosis (TGFβ), while others may act as chemoattractants for neutrophils, or enhance inflammatory reactions (interferon-gamma (IFNγ)). Adhesion molecules are involved in the interactions between these activated neutrophils and endothelial cells (Moore, 1995; Sundy and Haynes, 2000). In addition, high levels of soluble endothelial cell receptors for neutrophils (intercellular adhesion molecule (ICAM)-1, E-selectin and vascular cell adhesion molecule (VCAM)-1) have been detected in patients with active WG, MPA (Ara et al., 2001; Becvar et al., 1997; Mrowka and Sieberth, 1994, 1995; Ohta et al., 2001; Pall et al., 1994; Stegeman et al., 1994), Takayasu's arteritis (Noguchi et al., 1998) and Henoch–Schönlein purpura (Mrowka et al., 1999), and patients with rheumatoid arthritis complicated by peripheral neuropathy (Salih et al., 1999). These cytokines and adhesion molecule cascades may be dysregulated in vasculitides, but this hypothesis has not yet been clearly established. An imbalance between Th1 and Th2 lymphocyte immune pathways may also be involved, as discussed below.

3.4. Other pathogenic factors

T-cell-mediated immunity may contribute to the development of granulomatous vasculitides, i.e. WG and CSS. Infiltration by T-lymphocytes secreting Th1 pro-inflammatory cytokines, essentially IFNγ, has been observed in granulomatous lesions of the nasal mucosa in patients with WG. Thus, in WG, Th1 lymphocytes would play a major role in localized and granulomatous upper respiratory tract involvement, whereas a shift towards Th2 lymphocytes would tend

to be more predominant in systemic forms (Balding et al., 2001; Csernok et al., 1999), which are thought to have a poorer prognosis (Bligny et al., 2003).

Antibody-mediated immunity is implied in some vasculitides, mainly through ANCA, but other autoantibodies may contribute to the observed vascular damage. Anti-endothelial cell antibodies (AECA) include a group of heterogeneous autoantibodies distinct from ANCA that have been detected in a wide variety of diseases, including systemic lupus erythematosus (Chan and Cheng, 1996), systemic sclerosis (Salojin et al., 1997), Kawasaki disease, Takayasu's arteritis, WG, MPA and small vessel vasculitides (Falcini et al., 1997; Gobel et al., 1996; Praprotnik et al., 2000). AECA target a wide range of extracellular matrix proteins and phospholipids, but their precise identities remain to be determined in vasculitides, and their pathogenic roles are still unproven.

In addition to viral agents, such as HBV in PAN, genetic, hemodynamic and environmental (Lane et al., 2003) factors, and exposure to some drugs may also be involved in the development of various vasculitides, but their respective roles remain to be elucidated.

3.5. Notions of the immunopathogenesis of nervous system involvement in vasculitides

Under normal conditions, the nervous system is protected from immunologic reactions by the blood–brain and blood–nerve barriers. However, the peripheral nerves are affected frequently and early in vasculitides, which might be explained by the lack of a blood–nerve barrier at the precise level of epineurial vessels, in contrast to endoneurial vessels (Lundborg, 1975). Indeed, PNS involvement results from axonal ischemia due to vasculitis of the vasa nervorum in the branches of small epineurial vessels. Conversely, CNS vasculitis is less common, except in association with infections, and mostly occurs later in the course of the vasculitides. In WG, CNS involvement may result from either granulomatous invasion from contiguous sinus, para-sinus and/or orbital granulomas, occasionally from remote granulomas, or, rarely, from true cerebral artery vasculitis (Drachman, 1963). Thus, there may be a distinct and more efficient protective mechanism to minimize immune-mediated damage to the blood–brain barrier and cerebral vascular endothelium. Indeed, CNS endothelial cells are physically and biochemically distinct from those of the PNS. Constitutive expression of major histocompatibility complex (MHC) class I and II molecules and ICAM-1 on cerebral vascular endothelium is low. Although such expression of adhesion molecules, e.g. ICAM-1, can be induced by inflammatory cytokines, such as IFNγ, the kinetics differ from those of other vascular endothelia. Lymphocyte traffic through the CNS is thus limited, and adhesive capacities are constrained (Moore, 1995). Moreover, antigen presentation in the CNS mainly involves microglial cells rather than the more accessible endothelial cells, unlike in the PNS. Finally, several CNS manifestations observed in patients with vasculitis result from non-vasculitic conditions, like hypertension or infections favored by immunosuppressive therapy.

4. Clinical manifestations

Neurologic manifestations may occur in the setting of a previously diagnosed systemic vasculitis, or may be the presenting symptoms of vasculitis, which may first appear to be restricted to the nervous system (Kissel, 1989). In the former situation, the challenge is to differentiate vasculitic neurologic involvement from other causes, e.g. infection, hypertension-related cerebral hemorrhage or steroid-induced psychosis. In the latter, the challenge is to perform the most appropriate diagnostic testing in order to diagnose systemic vasculitis, and then to initiate prompt and adequate treatment.

4.1. Peripheral nervous system involvement

Peripheral neuropathy occurs in 50–75% of PAN patients (Frohnert and Sheps, 1967; Moore and Fauci, 1981), 10.6–67% of WG patients (Fauci et al., 1983; Pinching et al., 1983), 50–78% of CSS patients (Guillevin et al., 1999a; Sehgal et al., 1995), and 10–58% of MPA patients (Guillevin, 1999b; Savage et al., 1985). PNS involvement typically results from focal or multifocal, axonal, ischemic neuropathy due to

arteriolar occlusion of the vasa nervorum, usually of epineurial arteries. In 36.4% (8/22) (Bouche et al., 1986) to 55.6% (15/27) (Castaigne et al., 1984) of patients with systemic necrotizing vasculitides, signs of PNS involvement are the initial symptoms of the disease. Onset is usually acute (mononeuritis multiplex), but may be more progressive, particularly in the elderly. Sensory system involvement is responsible for hypo- or hyperesthesia, dysesthesia or frank pain as the prominent and earliest features (Moore and Calabrese, 1994) related to the relatively long length of these fibers compared to the peripheral motor fibers. Usually, motor deficits start later but also occur abruptly, sometimes preceding the sensory loss. The first manifestations often affect the lower limbs, with one particular nerve initially involved. Later, other nerves become affected, with this pattern being referred to as mononeuritis multiplex. In its late stage, so many nerves can be involved that mononeuritis multiplex can be mistaken for a symmetric process. In these cases, only careful history taking will be able to identify the patchy asymmetric pattern of early involvement.

Less frequently, distal symmetric sensorimotor polyneuropathy and pure sensory neuropathy may occur. Most frequently affected nerves are: the sciatic nerve or its peroneal branch, unilaterally in 62.5–84% of the patients, and bilaterally but asynchronously in one-third; the tibial nerve, unilaterally in 27.5–41% and bilaterally in 5%; the ulnar nerve, unilaterally in 25.5–56% and bilaterally in 8%; the median nerve, unilaterally in 21.5% and bilaterally in 3%; the radial nerve unilaterally in 8–29% and bilaterally in 2%; the femoral nerve unilaterally in 2%; and the proximal sciatic nerve or sciatic root unilaterally in another 2% (Guillevin et al., 1999a; Hattori et al., 1999; Said, 1997, 2002). Guillain–Barré syndrome-like presentation has been described (Suggs et al., 1992), as have radicular syndromes and plexopathies (Allan et al., 1982).

In approximately one-third of the patients with histologically proven peripheral nerve vasculitis (Abgrall et al., 2001), the disease appears to be restricted to the PNS. This form has subsequently been referred to as the term of non-systemic vasculitis (Griffin, 2001; Kissel, 1989). This clinical picture raises some diagnostic and therapeutic difficulties because patients with this non-systemic nerve vasculitis cannot be easily distinguished from those who will later develop systemic vasculitis. Indeed, Said (2002) showed that 37% of the patients with initial isolated peripheral nerve vasculitis subsequently develop systemic manifestations of vasculitis, and that 24% of them experienced neuropathy relapses. Even though some sporadic cases with poor outcome have been reported (Abgrall et al., 2001), most non-systemic vasculitides, clearly restricted to peripheral nerves, evolve favorably under treatment (mainly corticosteroids (CS)) (Dyck et al., 1987; Griffin, 2001), but the improvement may be very slow and sometimes only partial.

In addition to PAN and ANCA-associated and non-systemic nerve vasculitides, vasculitic neuropathies may occur in other diseases, listed in Table 2. Thus, other alternative diagnoses have to be considered in the differential diagnosis when the only sign is peripheral neuropathy, or when extra neurologic symptoms are non-specific or unusual in the context of primary systemic necrotizing vasculitides. PNS vasculitis has been described in Behçet's disease (O'Duffy, 1990), and in a few cases of giant cell arteritis (Nesher et al., 1987). Other connective tissue diseases can occasionally be complicated by secondary vasculitis, like rheumatoid arthritis (Puechal et al., 1995) or systemic lupus erythematosus, in which PNS vasculitis occurs in approximately 1% of the patients with each disease, or in Sjögren syndrome with about 4% PNS vasculitis (Said, 1997). Vasculitis can also complicate cancers, especially some lymphoproliferative disorders (Liebow et al., 1972); infections (other than the above-mentioned HBV-related PAN or HCV-associated mixed cryoglobulinemia) such as HIV (with PNS vasculitis developing in 0.3–1% of HIV-infected subjects (Mahadevan et al., 2001)), cytomegalovirus (CMV), Herpesviridae (Herpes simplex virus (HSV), varicella zoster virus (VZV)), tuberculosis, or Lyme disease (Caniello et al., 2002; Chamouard et al., 1993; Delpla et al., 1993; Lortholary et al., 1999; Mahadevan et al., 2001) and drugs' reactions (carbimazole, amiodarone) (Léger et al., 1988). The proximal inflammatory vasculitis seen in diabetic patients, also called proximal diabetic amyotrophy, is a rare entity that predominantly affects the lower limb nerves, with some signs of necrosis at histopathology (Griffin, 2001).

Table 2
Etiology of vasculitic neuropathies

Systemic necrotizing vasculitides	
Primary	Polyarteritis nodosa
	Churg–Strauss syndrome
	Wegener's granulomatosis
	Microscopic polyangiitis
Others	HBV-related polyarteritis nodosa rheumatoid vasculitis
	HIV infection[a]
	Sjögren's syndrome[a]
	Systemic lupus erythematosus[a]
	Systemic sclerosis[a]
Systemic non-necrotizing vasculitides	
Primary	Cryoglobulinemic neuropathy
	Giant cell arteritis
Others	HCV-associated mixed cryoglobulinemia
	Behçet's disease
Non-systemic vasculitis restricted to the peripheral nerves	
Miscellaneous (associated with or complicated by vasculitic neuropathy)	Cancers, lymphoproliferative disorders, monoclonal gammopathy
	Infections: leprosy, Lyme disease, CMV, HSV, tuberculosis
	Proximal diabetic amyotrophy
	Drugs: carbimazole, amiodarone, almitrine

[a] May also be of the non-necrotizing type.

4.2. Central nervous system involvement

The exact frequency of CNS involvement in vasculitides is not known because the diagnosis is often based on purely clinical grounds, without angiographic, imaging or histologic evidence Unlike PNS involvement, CNS involvement is rarely a presenting symptom of vasculitis, and may result from various mechanisms: vasculitis, granulomatous invasion in WG, hypertension, thrombosis or embolism, infections secondary to immunosuppressive therapy, or other drug side effects (Kissel et al., 1985; Kissel, 1989). In systemic vasculitides, Ford and Sieckert (1965) found exclusively CNS involvement in 12% of systemic vasculitides, while CNS and PNS were affected in 34% of their patients, and PNS alone in 38%. Moore and Fauci (1981) reported up to 40% CNS involvement among their 25 patients with different necrotizing vasculitides, while frequencies of 3–38% have been reported for PAN (Frohnert and Sheps, 1967; Sack et al., 1975). Indeed, CNS involvement specifically related to vasculitis would mainly be observed in small vessel vasculitides (Guillevin et al., 2002). It occurs in 6–13% of the patients with WG (Koldingsnes and Nossent, 2003; Reinhold-Keller et al., 2000), but up to 44% according to one study (Pinching et al., 1983), in 6–25% of CSS patients (Guillevin et al., 1999a; Moore and Calabrese, 1994; Sehgal et al., 1995), and 12–18% of MPA patients (Guillevin et al., 1999b; Savage et al., 1985).

The main characteristic CNS manifestations are diffuse encephalopathy and focal or multifocal disturbances in the brain. All sorts of clinical symptoms have been reported, mostly headaches, then confusion, seizures, hemiparesis, aphasia, hemianopsia, ataxia, chorea, psychosis, hallucinations, dementia, apathy and, finally, coma. Large intracranial vessel involvement is more likely to manifest itself with strokes, subarachnoid or intracerebral hemorrhages, or ischemia. Conversely, signs of microvascular disease include encephalopathy, myelopathy or cerebral parenchymal mass. Mild subclinical cognitive impairment, of still unknown significance and prognostic value, may be observed

in ANCA-associated small vessel vasculitides. Indeed, after excluding patients with other organ involvement(s), which could explain the non-specific cognitive disturbances, Mattioli et al. (2002) found that 30% of the patients without overt neurologic manifestations had subclinical neuropsychologic impairment, more frequently in the areas of non-verbal memory, abstract reasoning, attention and immediate memory, a pattern close to those reported for other subcortical CNS diseases, like Huntington's disease, multiple sclerosis or Parkinson's disease.

4.3. Pachymeningitis

In addition to these above-mentioned manifestations of CNS involvement, characteristic, albeit non-specific, inflammatory pachymeningitis can be seen in 0.6–6.7% of WG patients (Drachman, 1963; Katrib et al., 1998; Nishino et al., 1993b; Tishler et al., 1993). Pachymeningitis can be due to granulomatous inflammation of the meninges either from granulomatous spreading from sinus or orbital sites or from remote granulomas, or more rarely, from true meningeal vasculitis and, more exceptionally, in MPA (Kono et al., 2000). Pachymeningitis usually manifests as subacute or most often chronic meningitis. Its clinical symptoms are non-specific, with headaches, cranial nerve palsies in 20% of the patients, seizures when granulomatous inflammation extends into the cerebral parenchyma, confusion, cerebellar ataxia, and/or hydrocephalus (Scarrow et al., 1998). Photophobia and other classic signs of meningitis (neck stiffness, vomiting) are rarely encountered. Extension to leptomeningitis, pia mater and subarachnoid spaces may occur (Nusbaum et al., 1999), and a secondary subdural chronic hematoma may develop (Yokote et al., 1997). The spinal cord dura can also be involved at different levels, resulting in radiculopathy or compression and myelopathy (Albayram et al., 2002; Murphy et al., 1999). CSF examination can reveal mildly increased proteins (64% of the cases) and a non-specific lymphocytic reaction (36%) (Jinnah et al., 1997). Other causes of pachymeningitis must be ruled out: infections (tuberculosis, syphilis, HTLV-1, candidosis, aspergillosis, Pseudomonas infection), since intense local nasopharynx destruction allows microorganisms easy access to CNS invasion, lymphoma, meningioma, metastases, neurosarcoidosis, mixed connective tissue disease, Sjögren's syndrome, rheumatoid arthritis and, lastly, idiopathic inflammatory cranial hypertrophic pachymeningitis (Masson et al., 2001; Provenzale and Allen, 1996). Distinguishing between this aseptic WG-related pachymeningitis and infective complications of immunosuppressive therapy, including cryptococcal or tuberculous meningitis, may be difficult in patients under treatment (Katrib et al., 1998) and may require meningeal biopsy. Dural biopsy characteristically shows necrotizing granuloma, multinucleated giant cells, lymphocytic infiltration and, subsequently, fibrosis (Tishler et al., 1993; Tojo et al., 1998).

4.4. Cranial nerve involvement

Bridging the PNS and CNS involvements, cranial nerve palsies may also occur in vasculitides, especially affecting the facial (VII), optic (II) and abducens (VI) nerves. In WG, cranial nerve involvement may result from granulomatous extension from sinus, orbital or para-sinus granulomas, with nerve compression against the external wall of the cavernal sinus, or from inflammatory pachymeninigitis with cranial nerve(s) engulfment. Indeed, cranial neuropathies occur in 4.7–13.5% of WG patients (de Groot et al., 2001; Drachman, 1963; Nishino et al., 1993b), but may also be seen in less than 2% of PAN patients (Ford and Sieckert, 1965) and in some CSS patients (Sehgal et al., 1995), suggesting a cranial nerve vasculitic process in PAN and CSS.

4.5. Central endocrinopathy

Pituitary involvement is rare, but can occur, especially in WG, with about 20 reported cases in the literature (Berthier et al., 2000; Drachman, 1963; Goyal et al., 2000; Hajj-Ali et al., 1999; Haynes and Fauci, 1978; Katzman et al., 1999; Rosete et al., 1991; Woywodt et al., 2000), due to granulomatous sellar infiltrate, to contiguous extension, or more rarely to hypophysal vasculitis or remote granuloma. In particular, posterior pituitary involvement can lead to diabetes insipidus (Garovic et al., 2001), and can even be isolated and reveal the disease (Goyal et al., 2000).

Conversely, it may appear late and may be revealed only after starting CS, which inhibit the synthesis and secretion of antidiuretic hormone. Anterior hypophysal involvement is very rare (Lohr et al., 1988), as are panhypopituitarism and amenorrhea. However, hyperprolactinemia associated with diabetes insipidus has been noted in 37.5% of the reported WG cases (Berthier et al., 2000; Haynes and Fauci, 1978). Pituitary gland enlargement may lead to hydrocephalus, hemianopsia and/or visual perturbances caused by chiasma compression and/or granulomatous invasion, which may require neurosurgery to insert a shunt or for decompression, respectively (Bertken and Cooper, 1997). The outcome of pituitary involvement is usually good in 80% of the patients under combined treatment with steroids and immunosuppressant(s) (Berthier et al., 2000) but variable in terms of sequelae, and recovery is not certain, so that hormone(s) replacement is often needed (Guillevin et al., 2002).

4.6. Primary angiitis of the CNS

Granulomatous angiitis of the CNS, an early denomination, was subsequently changed to isolated angiitis of the CNS, and now PACNS, because granulomas are often absent (Kasantikul and Kasantikul, 1995; Moore, 1995). PACNS involves leptomeningeal and cortical small and medium-sized arteries (Calabrese, 1995), and is an extremely rare disease, affecting adults and children, with approximately 50 reported cases. It is difficult to diagnose, of unknown etiology, and carries a poor prognosis (Calabrese and Mallek, 1988; Calabrese, 1995). Symptoms are restricted to the CNS and include: headaches (56–78% of the patients), encephalopathy with intellectual deterioration and/or confusion (47–83%), seizures (24–30%), focal deficits resulting from strokes (13–33%), cerebral hemorrhage (11%), and/or cranial neuropathies (Calabrese, 1995; Hunn et al., 1998). Spinal cord involvement, responsible for myelopathy and paraparesis, is also observed in 14% of the patients (Calabrese, 1995). Evidence of progressive or recurrent disease is useful in making the diagnosis, since patients typically present with subacute and relapsing but ultimately progressive encephalopathy, characterized by cognitive impairment and multifocal deficits (Hunn et al., 1998).

PACNS must be distinguished from other causes of CNS vasculitis: mainly systemic vasculitides with CNS involvement (PAN, giant cell arteritis, WG, CSS, MPA), but also CNS vasculitis secondary to infections (HIV, CMV, HSV or VZV infections, syphilis, Lyme disease, bartonellosis, tuberculosis, aspergillosis, coccidioidomycosis, typhus, rickettsioses, bacterial infections), drug exposure (amphetamine, cocaine, heroin, ephedrine, phenylpropanolamine), lymphoma and lymphoproliferative disorders, systemic lupus erythematosus, Sjögren's syndrome (Calabrese, 1995), neurosarcoidosis or amyloid cerebral angiopathy. Based on a small number of cases, Calabrese and Mallek (1988) and Calabrese et al. (1992) proposed the following diagnostic criteria for PACNS: (1) presence of an unexplained neurologic deficit after thorough clinical and laboratory evaluations; (2) documentation by cerebral angiography and/or histologic examination of an arteritic process within the CNS; and (3) no evidence of systemic vasculitis or any other condition to which the angiographic or histologic features could be secondary. Left untreated, the disease is usually fatal within 1–2 years. Treatment with CS, alone or in combination with cyclophosphamide (CYC), has considerably lowered the mortality rate, so that 50% of the patients improve clinically and 70% survive (Younger et al., 1997).

The existence of an angiographically diagnosed more benign form of cerebral angiopathy has been highlighted, which mostly involves women who experienced a single episode of acute focal neurologic deficits (Calabrese, 1995). However, in light of the rarity of definitive data, this form remains to be further clarified.

4.7. Secondary neurologic manifestations

In addition to the above-listed PNS and CNS involvements directly caused by vasculitis, secondary neurologic manifestations (Moore and Fauci, 1981) may occur as a result of other organ or system involvement (cerebral hemorrhage or encephalopathy due to hypertension, kidney or lung failure, stroke resulting

from endocarditis emboli in WG (Provenzale and Allen, 1996)). Immunosuppression favors opportunistic infections, such as HSV or VZV encephalitis or progressive multifocal leukoencephalopathy in WG (Morgenstern and Pardo, 1995). Other treatment side effects must also be considered, e.g. psychosis induced or aggravated by steroids, cerebral atherosclerosis under long-term steroids, or steroid-induced myopathy, which has been demonstrated electromyographically in some patients (Askari et al., 1976). All these potential causes of neurologic manifestations must not be ignored because they may require specific therapy and carry their own prognoses.

5. Diagnostic investigations

In addition to the complementary examinations ordered to obtain diagnostic clues suggestive of systemic vasculitis (ANCA, visceral angiography, investigations of other affected organs or systems) and to exclude other entities included in the differential diagnoses, several lines of investigation are informative when a clinician is confronted with neurologic manifestations.

5.1. Explorations of peripheral nervous system involvement

Electromyography may help to identify a pattern suggestive of mononeuritis multiplex or reveal subclinical peripheral nerve involvement and is also useful for selecting the most appropriate site for nerve and muscle biopsy. Other investigations are less informative. Cerebrospinal fluid (CSF) is usually normal or may simply show non-specific mildly enhanced protein concentrations, in mononeuritis multiplex, as in the rare cases of Guillain–Barré-like syndrome (Castaigne et al., 1984).

5.1.1. Electromyography

In the context of vasculitic PNS involvement, electromyography and nerve conduction studies typically reveals axonal neuropathy, and may show extensive denervation. Amplitudes of motor and sensory nerve action potentials are markedly decreased, or may even be absent, in the most severely affected nerves, while motor nerve conduction velocities are normal or only slightly diminished. Electromyography can help identify the characteristic asymmetry of mononeuritis multiplex. Mononeuropathy simplex, or symmetric or asymmetric axonal polyneuropathy may also be detected (Bouche et al., 1986). Subclinical PNS involvement is common (Said, 1997) and supported by the observation of more diffuse electrophysiologic involvement than was clinically apparent in all the patients examined by Bouche et al. (1986). Myopathy with fibrillation potentials can sometimes be demonstrated electromyographically resulting from severe neuropathy (Tervaert and Kallenberg, 1993). Conduction block, suggestive of demyelination, like in Guillain–Barré syndrome, nerve entrapment or other acquired demyelinating neuropathies, can be seen sporadically in association with axonal neuropathy. These blocks are often transient and are, when due to vasculitis, a consequence of ischemia-induced segmental demyelination, occurring before Wallerian degeneration (Ropert and Metral, 1990).

5.1.2. Nerve and muscle biopsies

Neuromuscular biopsy is the ‘gold standard’ for the diagnosis of vasculitic nerve involvement, provided that the examination is performed by an experienced neuropathologist. However, because it can itself be responsible for persistent and disabling sensory and/or motor sequelae at the biopsy site, it should only be done when the other investigations fail to establish the diagnosis. Small biopsies of the distal portion of a sensory nerve may not show diagnostic features. Ideally, a combined muscle–nerve biopsy should be obtained. The sample should include a clinically and electromyographically affected sensory nerve. Whole nerve biopsy is preferable to fascicular biopsy, and muscle and nerve (especially the sural nerve) biopsy may yield the diagnosis despite normal electromyography (Davidson and Sundstrom, 1988; Wees et al., 1981). The most appropriate sites for neuromuscular biopsies are superficial peroneal nerve–peroneus brevis muscle or sural nerve–gastrocnemius muscle (Collins et al., 2000). Under these conditions, the sensitivity of superficial peroneal nerve–peroneus brevis muscle biopsy is 60% for systemic vasculitis and 64% for the non-systemic vasculitis

(Collins et al., 2000). Muscle biopsy alone is diagnostic for 38% of the patients with vasculitis and neuropathy, while nerve biopsy alone identifies 35%; neuromuscular biopsy further enhances the yield by 27% (Said et al., 1988). Among diagnostic muscle and/or nerve biopsies, vasculitis features were seen in 80% of the muscle biopsies and 55% of the nerve biopsies. Conversely, the diagnostic yield of nerve biopsies (90%) was higher than that of muscle (50%) in another cohort of patients with peripheral vasculitic neuropathy attributed to non-systemic vasculitis, whereas nerve and muscle biopsies had similar yields for patients with systemic vasculitis, with muscle biopsy being slightly superior for this group (Collins et al., 2000). Serial sections of biopsy samples have to be examined because lesions are focal, segmental and randomly distributed along the nerve. Usually, perivascular inflammatory infiltrates are only mild, which is abnormal but poorly specific, as is myofiber necrosis or regeneration. In this setting, inflammation across blood vessel wall is considered more suggestive. Epineurial arteries and vasa nervorum affected in PAN are often small, ranging from 45 to 210 μm in diameter, so the threshold defining small vessel vasculitis was set at 70 μm (Gherardi et al., 1993; Moore, 1995). Ischemic neuropathy, as an indirect sign of vasculitis, is characterized by a predominantly axonal type of degeneration with fiber loss and patchy fascicular involvement. Lesions are located in the less vascularized nerve parts, i.e. predominantly in the center of fascicles that is more vulnerable to ischemia and its consequences (Castaigne et al., 1984; Vital and Vital, 1985). Proliferations of epineurial capillaries and vascular smooth muscle cells may also be considered indirect signs of vasculitic neuropathy. Segmental demyelination can occasionally be seen, suggesting that factors other than vasculitic ischemia are implicated in the development of neuropathy in these patients, and has been observed in some patients without any associated axonal hypoxic features (Bussone et al., 1986).

5.2. Explorations of central nervous system involvement

Electromyography, CSF examination and neuroimaging may help to identify the pathologic focus, but, at best, provide only suggestive information CSF often demonstrates an inflammatory process, with elevated protein level, lymphocyte pleocytosis and/or hemorrhage. The search for ANCA in the CSF, although intriguing, has not yet provided any support for their potential direct role in CNS involvement (Younger and Kass, 1997), except for one WG patient with meningitis whose CSF ANCA titer fluctuated in relationship with the WG activity (Spranger et al., 1997). It certainly merits further investigations. Although EEG may show diffuse or focal slowing, it does not contribute to the diagnosis of vasculitis (Kissel, 1989).

5.2.1. Neuroimaging

Brain magnetic resonance (MRI) is more sensitive than computed tomography (CT) scanning for ischemic cerebrovascular disease and can demonstrate abnormalities in 65–75% of the patients with vasculitides and clinical signs of CNS involvement (Kissel, 1989). However, there are no pathognomonic MRI findings (Younger and Kass, 1997). The most common MRI abnormalities are multiple bilateral cortical and deep white matter hyperintense signals on intermediate- and T2-weighted sequences generally reflecting ischemic changes (Hurst and Grossman, 1994), and enhancement of the leptomeninges on T1-weighted sequences after contrast-medium injection (Younger and Kass, 1997). T2-weighted hypersignals suggestive of brain vasculitis and/or diffuse encephalopathy (Kasantikul and Kasantikul, 1995) have been observed in PAN patients with only cognitive impairment. The so-called pachymeningitis of WG consists of diffuse 8–10 mm dural thickening, that is enhanced after contrast-medium injection on T1-weighted sequences, as illustrated in Fig. 2A and B (Guillevin et al., 2002; Provenzale and Allen, 1996; Tishler et al., 1993; Weinberger et al., 1993). Dural thickening can be diffuse, focal or nodular, or have a plaque-like pattern with mass effect (Beretta et al., 2001; Murphy et al., 1999; Nishino et al., 1993c; Provenzale and Allen, 1996). When the pituitary gland is involved, in WG, its imaging, especially MRI, may reveal infiltration of the stalk, diffuse enlargement of the gland sometimes exhibiting a pseudotumor-like appearance and/or a disappearance of the normal posterior hypophysis hypersignal, or

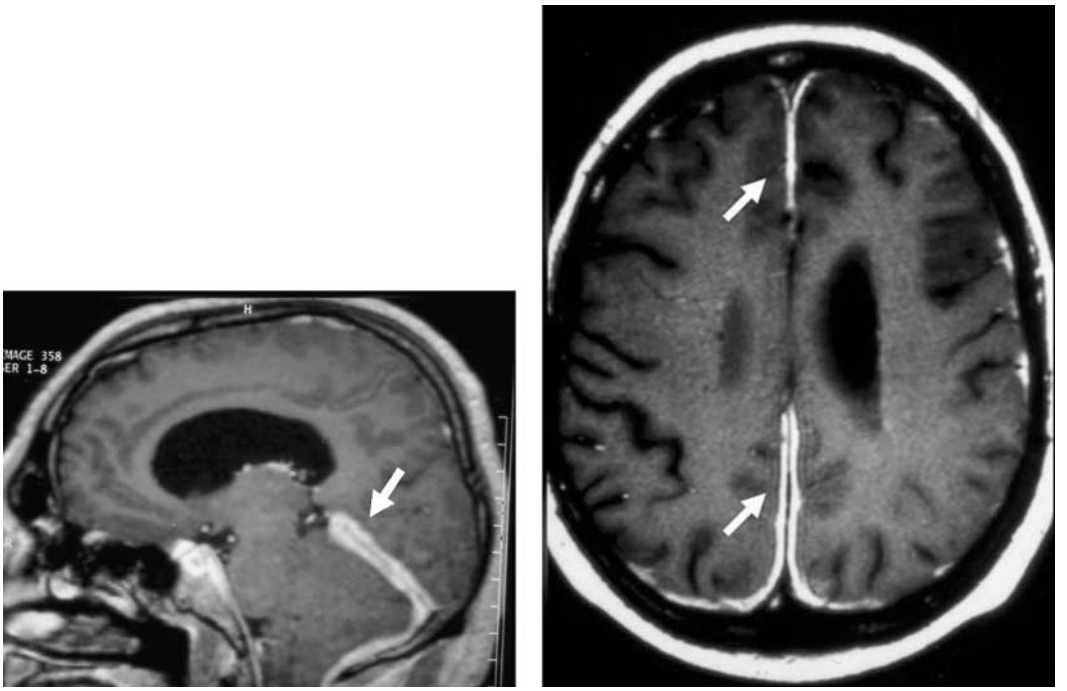

Figure 2. Post-gadolinium T1-weighted MR sequences. Patients with Wegener's granulomatosis. (A) In the parasagittal plane, note the diffuse tentorial thickening attributed to pachymeningitis. (B) In the horizontal plane, note the meningeal thickening and enhancement.

may be normal (Goyal et al., 2000). On brain MR images (Murphy et al., 1999), one can also see infarcts and non-specific white matter lesions with signal hyperintensity on the intermediate- and T2-weighted sequences of 28% of the WG patients, cerebellar granuloma, cerebral and/or cerebellar atrophy of unknown significance and with multiple possible explanations (drugs, senile atrophy, cerebral small vessels vasculitis) (Asmus et al., 1993; Duncker et al., 1993).

Because of the small sizes of the cerebral vessels that can be affected by vasculitis, four-vessel cerebral angiography is often normal, but non-specific focal or diffuse segmental narrowing of the intracranial vessels may occasionally be present (Yamashita et al., 1986) and yield characteristic 'beading' or 'sausage' pattern in multiple vessels (Hurst, 1994; Kissel, 1989; Wynne et al., 1997), as illustrated in Fig. 3. Indeed, despite digital subtraction techniques, small leptomeningeal arteries and veins smaller than 100–200 μm are still not clearly seen. Although the characteristic small bifurcation microaneurysms seen in viscera involved in PAN are much less common in cerebral vessels, they can lead to subarachnoid hemorrhage (Hurst and Grossman, 1994). The complication rate of cerebral angiography is low, but

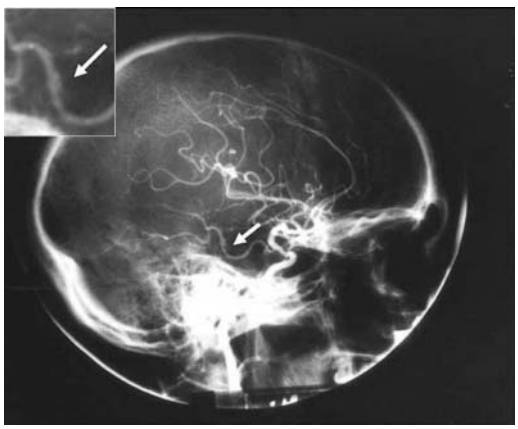

Figure 3. Cerebral angiography in a patient with polyarteritis nodosa. Arterial narrowing with 'beaded' appearance (arrows, and inset).

should be kept in mind for these patients, with 1–11.5% of them experiencing transient deficits, and 0.3–0.8% suffering from permanent deficits (Heiserman et al., 1994; Hurst, 1994).

MR angiography and functional positron-emission-tomography (PET) of the brain provide complementary informations (Hurst, 1994). Single photon emission CT (SPECT) and regional cerebral blood-scintigraphy with flow radiotracers may detect early or preclinical abnormalities due to WG (Marienhagen et al., 1996).

5.2.2. Meningeal and brain biopsies

Meningeal and brain biopsies were able to confirm CNS involvement in some patients with systemic vasculitides, but they are usually not useful to diagnose PAN or ANCA-associated vasculitides, since many other non-invasive explorations (ANCA detection; skin, muscle and nerve biopsies; visceral angiography) may provide sufficient grounds for the diagnosis of vasculitis. Similarly, the diagnosis of CNS involvement may rely on indirect evidence. Brain and meningeal biopsies should generally be taken to exclude alternative diagnoses (mainly infections, malignant tumors or lymphomas), especially in the content of isolated cerebral angiitis.

5.3. Investigations in primary angiitis of CNS

Patients with PACNS present no consistent hematologic or serologic abnormalities. The erythrocyte sedimentation rate (ESR) is elevated in 60% of them but usually only to 30–40 mm/1st h. CSF proteins are usually elevated, ranging from 100 to 200 mg/dl, in 80% of the cases. Two-thirds of the patients have CSF pleocytosis with a lymphocyte predominance in 90% of them, while 30% of them have red blood cells in their CSF. Imaging may be normal at the early stages of the PACNS (Nadeau, 1997). Brain CT is abnormal in 30–65%, but MRI has higher sensitivity, nearly 100%, and can detect focal abnormalities in gray or, predominantly, in white matter, usually with a regional preponderance and asymmetric distribution within the brain. Diffuse lobar or hemispheric edema, poorly defined tumor-like mass in 15% of the patients, contrast-medium enhancement of lesions, diffuse irregular leptomeningeal enhancement and focal or multifocal hemorrhage may be seen (Moore, 1989). Cerebral angiography demonstrates vascular abnormalities, when larger vessels are involved in 50–90% of the patients (Moore, 1989), and/or suggestive features, in 26–40% of them (Younger et al., 1997), typically consisting of fairly abrupt irregularities and segmental constrictions, dilatation of major vessels and their branches, and neovascularization. Similar abnormalities may be seen in cerebral spasm, usually more diffuse and transient, sickle cell disease, mycotic aneurysms, infection, emboli, tumor, drug-induced CNS vasculitis, giant cell arteritis and intracranial atheromatosis. Finally, 20% of arteriographies are normal (Kissel, 1989) and only brain biopsy can yield the definitive diagnosis. However, as PACNS is often quite focal and scattered, small brain samples yield a 26–50% rate of non-diagnostic biopsies, especially needle biopsies (Vollmer et al., 1993; Younger et al., 1997). The preferred site for brain and meningeal biopsy is the temporal tip of the non-dominant hemisphere. Histologic findings may vary widely depending on the size and extent of the vessels involved. Brain and sometimes spinal cord biopsies may show granulomatous angiitis next to areas of necrotizing vasculitis, endothelial cell proliferation and lymphomononuclear cell infiltrates (Moore, 1995).

6. Neurologic manifestations according to the type of vasculitis

6.1. Polyarteritis nodosa

Polyarteritis nodasa affects men and women equally at all ages, with a predominance between 40 and 60 years of age. Its etiology remains unknown for most of the patients, with HBV-related PAN accounting for less than 10% of all currently diagnosed cases (Guillevin et al., 1995b). It is a necrotizing angiitis whose main manifestations are weight loss, fever, asthenia, cutaneous lesions (livedo, cutaneous nodules and/or necrosis), peripheral neuropathy, renal, musculoskeletal and gastrointestinal tract involvement, hypertension and/or cardiac failure, as listed in Table 3.

Peripheral neuropathy is the most frequent finding in PAN patients (50–75%) (Frohnert and Sheps, 1967;

Table 3
Polyarteritis nodosa: clinical features and system or organ involvement, expressed as percentages (%) of the population studied

Reference	No. of patients	CNS	PNS	Heart	HT	Skin	Kidney	GI
Sack et al. (1975)	40	28	38	18	10	55	13	40
Fortin et al. (1995)	45	24	51	18	–	44	44	53
Frohnert and Sheps (1967)	130	3	52	10	–	58	8	14
Guillevin et al. (1988)	165	17	67	23	31	46	29	31

CNS: central nervous system; GI: gastrointestinal tract; HT: hypertension; PNS: peripheral nervous system.

Guillevin et al., 1992; Moore and Fauci, 1981) and it is the earliest symptom of the disease in 23–33% of them (Frohnert and Sheps, 1967; Moore and Fauci, 1981). Indeed, a major variant of PAN exists that exclusively involves peripheral nerve and muscle (Abgrall et al., 2001). Mononeuritis multiplex affects 56.5–61.5% of the patients, mononeuritis (simplex) 16.5% and distal symmetrical sensory, often patchy, or sensorimotor neuropathy 25% of them (Moore and Fauci, 1981; Said, 1997). CSF, when analyzed, is usually normal. Electromyography typically shows axonal neuropathy. Muscle and nerve biopsies may demonstrate characteristic muscle and epineurial artery lesions (Said et al., 1988). Under treatment, mononeuritis multiplex in PAN progressively regresses, and patients may recover without sequelae.

CNS involvement is much less common, noted in 3–38% of PAN patients (Frohnert and Sheps, 1967; Sack et al., 1975) and is usually a late manifestation in the course of the disease. Its common presentations include encephalopathy in 8–20% (Moore and Fauci, 1981; Scott et al., 1982), affecting cognitive function and characterized by disorientation, psychosis and hallucinations or delusion or diminished consciousness, as well as focal or multifocal disturbances of the brain and spinal cord, subarachnoid hemorrhage, seizures and strokes (Moore and Calabrese, 1994), resulting either from vasculitis of a cerebral artery or as a consequence of malignant hypertension. Cerebral angiography is often normal, although non-specific focal or diffuse segmental narrowing of the intracranial vessels may be seen.

Cranial nerve palsies are present in less than 2% of the cases, with the oculomotor (III), trochlear (IV), abducens (VI), facial (VII) and/or acoustic (VIII) nerves being the most affected (Ford and Sieckert, 1965). Blurred vision or visual loss may occur as a result of choroiditis, retinitis, or brain parenchymal arteritis (Moore and Calabrese, 1994). Vasculitis of the optic nerve, optic chiasm and/or occipital cortex have also been well described (Kinyoun et al., 1987). PAN involvement of spinal roots and cauda equina is exceptional.

6.2. ANCA-associated vasculitides

6.2.1. Wegener's granulomatosis

WG is characterized by necrotizing inflammatory lesions of the respiratory tract, usually accompanied by glomerulonephritis and/or systemic vasculitis. Detection of C-ANCA, with anti-PR3 specificity is an important clue to the diagnosis, as is biopsy of paranasal sinus tissue, which is diagnostic for over 50% of the cases, whereas the yield from nasal or laryngeal mucosa biopsy is less than 20% (Devaney et al., 1990). Frequencies of WG clinical manifestations are listed in Table 4.

Neurologic involvement in WG is noted in 11–64% of the cases, but less frequently (18%) in pediatric cases (Orlowski et al., 1978; von Scheven et al., 1998). However, the frequency of neurologic involvement, especially CNS involvement, appears to have decreased over the last two decades, at least in regards to the more recent studies, probably because adequate examinations enable much earlier diagnosis of WG and thus treatment initiation. Main neurologic manifestations are reported in Table 5.

Peripheral neuropathy is seen in 10.6–67% of WG patients (Fauci et al., 1983; Pinching et al., 1983), and develops early, with the first manifestations noted even before the diagnosis of WG in 55.4% of the patients (de Groot et al., 2001). It is sometimes the main presenting symptom. PNS manifestations are represented by mononeuritis multiplex (79% of the patients with peripheral neuropathy), then sensorimotor polyneuropathy (Nishino et al., 1993c).

Table 4
Wegener's granulomatosis: clinical features and organ or system involvement, expressed as percentages (%) of the population studied

Reference	No. of patients	CNS	PNS	NS	Heart	Lung	Kidney	Skin	GI	ENT
Morelli et al. (2000)[a]	9	–	–	44	88	55	44	44	44	78
Pinching et al. (1983)	18	44	67	–	44	100	100	67	–	94
Walton (1958)[b]	56	–/7.4/–	28.6/–/7.4	–	–/11.1/27.8	48/81/78	25/67/78	–/46/17	–/–/24	89/52/26
Koldingsnes and Nossent (2003)	56	13	23	–	20	61	80	34	5	80
Fauci et al. (1983)	85	11.8	10.6	22	12	94	85	45	–	91
de Groot et al. (2001)	128	7	44	50	11	26	38	12	4	58
Reinhold-Keller et al. (2000)	155	6/11[c]	20.6/40[c]	–	12.9	66	70	33	6	99
Hoffman et al. (1992)	158	8	15	–	6	85	72	46	–	92
Lie (1997)	216	8.3	–	–	2.8	69	48	12.4	6.5	87
Anderson et al. (1992)	265	–	–	–	<4	63	60	25	–	75
Nishino et al. (1993c)	324	10	16.4	33.6[d]	–	71	58	–	–	73

CNS: central nervous system; ENT: ear, nose and throat; GI: gastrointestinal tract; NS: nervous system involvement; PNS: peripheral nervous system.

[a] Ultrasonographic study.

[b] 54 out of 56 were autopsied. Frequencies (clinical/granulomatous/arteritis) are, respectively: clinical manifestations noted previously to death, then presence of granulomatous and arteritic features upon histologic examination at autopsy.

[c] Organ or system involvement at onset or diagnosis/over the entire course of the disease.

[d] Difference noted between frequencies of NS and CNS + PNS corresponds to cranial nerve involvement, herpes zoster, myopathy.

Table 5
Wegener's granulomatosis: neurologic manifestations, expressed as percentages (%) of the population studied

Reference	No. of patients	Neurologic manifestations	Peripheral neuropathy	Cranial nerve palsy(ies)	Stroke	Pituitary involvement
Walton (1958)	56	–	28.6	–	–	–
Fauci et al. (1983)	85	22	10.6	9.4	–	–
Drachman (1963)	104	54	21.2	13.5	8.7	3.8
de Groot et al., 2001	128	50	43.8	4.7	–	–
Hoffman et al. (1992)	158	23	15	–	–	–
Nishino et al. (1993c)	324	33.6	16.4	6.5	4	0.3

Nevertheless, PNS involvement, documented in 43.8% of the patients in the clinical and electromyographic study by de Groot et al. (2001) corresponded to mononeuritis multiplex in 'only' 45% of the cases and symmetric polyneuropathy in an unexpectedly higher frequency of 55%, which might be explained by the contribution of other factors (age, medications, end-stage renal failure, diabetes mellitus) (Collins and Periquet, 2002). Indeed, peripheral neuropathy is much more frequent in patients with higher ANCA titers, but also in those older than 50 years at diagnosis, and in those with renal, skin and/or cardiac involvement (de Groot et al., 2001; Nishino et al., 1993b). Vasculitis-associated myopathy was noted in 0.6% of the patients (Nishino et al., 1993b).

CNS involvement of the brain and meninges was found in 6–13% of the patients (Koldingsnes, 2003; Reinhold-Keller et al., 2000), but reached 44% in the study by Pinching et al. (1983), and occurred later at a mean of 8.4 months after WG onset (Nishino et al., 1993b). Neurologic abnormalities may result from contiguous extension of granulomatous lesions and/or remote granulomas from primary sites in the nasopharynx or orbital walls and/or from vasculitis (Drachman, 1963; Moore and Calabrese, 1994). Granulomatous disease often presents as exophthalmia, proptosis, ophthalmoplegia and/or orbital involvement in 20% of the patients (Hurst, 1994), hearing loss, headache, basilar subacute or chronic meningitis (Atcheson and Van Horn, 1977), cranial nerve palsies (Moore and Calabrese, 1994), pituitary and hypothalamic involvement (including diabetes insipidus), intracerebral granulomas and/or granulomas of the skull. CNS vasculitis can present as cerebral infarction, which can be extensive (Satoh et al., 1988), stroke, cerebral vasculitis, cortical blindness (Payton and Jones, 1985), aphasia (Sahn and Sahn, 1976), intracerebral hemorrhage, subarachnoid hemorrhage (Cruz and Segal, 1997), meningitis, cerebritis or seizures in 3% of the patients (Nishino et al., 1993b). Necrotizing cerebral cortex thrombophlebitis leading to extensive venous infarction, requiring surgical intervention along with medical therapy, has also been described (Mickle et al., 1977). Remote granulomas in the brain are the least common form of CNS involvement, but may be severe (Nordmark et al., 1997), with homogeneous and ring-enhancing masses having been observed with signal hyperintensity on T2-weighted images (Murphy et al., 1999; Provenzale and Allen, 1996; Tervaert and Kallenberg, 1993).

In patients with generalized forms of WG, 10% are ANCA-negative. One still moot notion is that CNS manifestations, especially meningeal involvement, appeared to occur more often than expected in these ANCA-negative patients (Reinhold-Keller et al., 2001) or might be associated with P-ANCA rather than C-ANCA (Nagashima et al., 2000).

Pachymeningitis, resulting from granulomatous inflammation of the meninges, was noted in 0.6–6.7% of the patients (Drachman, 1963; Nishino et al., 1993b), but none of those patients examined by Hoffman et al. (1992). This feature may initially be isolated and reveal WG, or often occurs later as a localized manifestation of WG, posing a diagnostic and therapeutic dilemma (Ossi et al., 2002; Shiotani et al., 1997; Weinberger et al., 1993). Detection and quantification of C-ANCA in the CSF might help to diagnose WG and further monitor disease activity under treatment, as reported for one patient with meningeal involvement (Spranger et al., 1997).

Despite effective treatment of WG, substantial residual MRI abnormalities may persist, despite complete symptomatic relief (Specks et al., 2000). Radiolabeled leukocyte scintigraphy may be useful for monitoring the response to therapy in these patients, since it shows abnormal uptake corresponding to active meningeal inflammation (Murphy et al., 2000).

Pituitary involvement is rare (Goyal et al., 2000; Hajj-Ali et al., 1999; Katzman et al., 1999; Rosete et al., 1991; Woywodt et al., 2000) but one of the more characteristic, although non-specific, CNS manifestations of WG, which can lead to diabetes insipidus (Garovic et al., 2001), and occurred early during the course of the disease in 62.5% of the reported cases (Berthier et al., 2000). Even though pituitary involvement has a favorable outcome under combined steroid and immunosuppressant treatment (Haynes and Fauci, 1978), it is unpredictable and may require neurosurgery (Bertken and Cooper, 1997).

Spinal cord involvement with subsequent myelopathy is rare (Kelly et al., 1998; Nishino et al., 1993c) and may be due to compression by meningeal granuloma (Kelly et al., 1998; Nagashima et al., 2000) or to dural vasculitis (Nishino et al., 1993c). Cauda equina syndrome may result from spinal cord involvement (Martens, 1982).

Cranial neuropathies (predominantly II, VI, VII followed by V, VIII, III, IV, XII, IX and X), most often uni- but also bilateral, occur frequently (4.7–13.5%) in WG patients (de Groot et al., 2001; Drachman, 1963; Nishino et al., 1993b). Multiple cranial neuropathies would mostly be the result of granulomatous pachymeningitis (Nishino et al., 1993c), with nerve compression sometimes requiring surgical neurolysis (Nikolaou et al., 2001). Neuroimaging may be crucial to distinguish between visual loss secondary to a compressing granuloma and ischemia of the ophthalmic artery (Moore and Calabrese, 1994). Horner's syndrome has also been reported, attributed to either vasculitis or granulomatous involvement of the oculosympathetic pathway between the hypothalamus and the orbit (Nishino and Rubino, 1993). Notably, among patients with headaches and perturbed vision, temporal artery biopsy may reveal granulomatous giant cell arteritis in 1.4% of WG patients (Nishino et al., 1993a), most likely due to the involvement of large extracranial arteries rather than the coexistence of giant cell arteritis.

6.2.2. Churg–Strauss syndrome

CSS is characterized by pulmonary and systemic small vessel vasculitis, extravascular necrotizing granulomas, and hypereosinophilia occurring in patients with asthma and allergic rhinitis. The frequencies of its clinical manifestations reported in some published studies are listed in Table 6.

Peripheral neuropathy is found in 50–78% (Guillevin et al., 1999b; Lanham et al., 1984; Moore and Calabrese, 1994) and is one of the ACR classification criteria for CSS (Masi et al., 1990). Among patients with peripheral neuropathy, 60–71% have mononeuritis multiplex, whereas 5–29% have asymmetric polyneuropathy and 0–35% have symmetric polyneuropathy (Cavallaro et al., 1988; Hattori et al., 2002; Sehgal et al., 1995). Acute fulminant involvement of all peripheral nerves during the early phase of CSS has also been reported (Ng et al., 1997), with demyelination, as assessed electromyographically, mimicking Guillain–Barré syndrome. Epineurial necrotizing vasculitis was seen

Table 6
Churg–Strauss syndrome: clinical features and organ or system involvement, expressed as percentages (%) of the population studied

References	No. of patients	CNS	PNS	Heart	Asthma	Kidney	Skin	GI	ENT
Lanham et al. (1984)	16	–	66	47	100	49	48	59	70
Haas et al. (2001)	20	–	65	50	100	35	75	50	45
Chumbley et al. (1977)	30	–	63.3	–	100	–	66.6	16.6	70
Sehgal et al. (1995)	47	6.3	53.2	–	100	–	–	–	–
Guillevin et al. (1999a)	96	8.3	78	13.5/22.9[a]	100	26	51	33	61

CNS: central nervous system; ENT: ear, nose and throat; GI: gastrointestinal tract; PNS: peripheral nervous system.
[a] Myocarditis/pericarditis.

in 53% of the sural nerve biopsies from patients with CSS neuropathy, with associated eosinophil invasion in 25% of them, but with no marked IgE deposition, and above all, T-lymphocyte invasion, CD4 as often as CD8 positive cells (Hattori et al., 2002). Granulomas are observed in less than 14% of patients (Hattori et al., 1999; Marazzi et al., 1992). The axonal neuropathy and destruction characteristically observed in CSS would thus result from ischemia rather than from eosinophil degranulation products, such as major basic protein, whose roles have been demonstrated in cardiac or splenic lesions of CSS (Tai et al., 1984). However, in CSS, other mechanisms may be involved in the development of peripheral neuropathy such as immune-complex deposits, with IgM (Lanham et al., 1984) but also IgA and C3 (O'Donovan et al., 1992). Moreover, in a preliminary analysis of 112 CSS patients, we found peripheral neuropathy, unlike heart involvement, to be significantly associated with a higher frequency of ANCA positivity, possibly suggesting different pathogenic mechanisms for each (unpublished data).

CNS involvement was previously reported in 6.3–25% of the patients (Moore and Calabrese, 1994; Sehgal et al., 1995), with fewer case reports concerning CSS than WG or PAN. It mostly occurs late during the course of the disease, as in PAN but a little earlier, probably reflecting the smaller sizes of the vessels involved in CSS (Moore and Calabrese, 1994). However, intracranial and subarachnoid hemorrhage, cerebral infarction due to cerebral vasculitis may also be seen during the early phases of CSS. Some cases of CNS demyelination have been reported in CSS patients vaccinated against hepatitis B (Beretta et al., 2001), which may suggest that, at least, some of the previously reported CNS involvement in CSS may indeed result from various and non-specific pathogenic mechanisms.

Cranial nerve (IX, V) palsies may also occur (Hattori et al., 1999), with ischemic optic neuritis being one of the most frequent signs (Sehgal et al., 1995; Tervaert and Kallenberg, 1993).

6.2.3. Microscopic polyangiitis

MPA is a small vessel vasculitis whose clinical manifestations are similar to those of PAN with the addition of rapidly progressive glomerulonephritis and pulmonary involvement. The average age at onset is 50 years. ANCA are detected in the majority of MPA patients, mostly anti-MPO P-ANCA.

Peripheral neuropathy is found in 10–58% of the patients, less frequently than in PAN (Guillevin et al., 1999b; Jennette et al., 2001; Rodgers et al., 1989; Savage et al., 1985). Mononeuritis multiplex is, as in all other vasculitides, the main feature of PNS involvement, affecting 69% of the patients with such involvement, followed by symmetric polyneuropathy in 12% and asymmetric polyneuropathy in 19% (Hattori et al., 2002). Necrotizing vasculitis can be seen in 81% of the sural nerve biopsies (Hattori et al., 2002).

CNS involvement and cranial neuropathies have been reported in 12–18% of the patients (Guillevin et al., 1999b; Savage et al., 1985), mostly encephalopathy and stroke, reflecting small vessel vasculitis. However, pachymeningitis, thought to result from dural necrotizing vasculitis but with no histological examination, has also been described (Kono et al., 2000).

7. Prognosis

The outcome differs from one vasculitis to another and the relapse rate also varies, from 5% for HBV-related PAN (Guillevin et al., 1995b) to 23.4% for CSS (Guillevin et al., 1999a), 34.1% for MPA (Guillevin et al., 1999a) and about 50% in WG (de Groot et al., 1996; Guillevin et al., 1995c; Hoffman et al., 1992). As would be expected, treatment is more effective when initiated early (Nadeau, 1997).

Peripheral neuropathy does not worsen the prognosis and survival, even though possible neurologic sequelae may be severely incapaciting and relapse(s) may occur. Indeed, peripheral neurologic relapses have been shown to occur in 24% of the patients with non-systemic neuropathies and 31% of the patients with systemic forms of vasculitis (Said, 1997). Conversely, a multivariate analysis of 342 patients with PAN or CSS showed that specific CNS involvement, like renal, gastrointestinal tract and/or cardiac involvements, was associated with a poor outcome (Guillevin et al., 1996). The prognostic five-factor score (FFS; see Table 7) has been devised

Table 7
The five-factor score, as established based on 342 patients with polyarteritis nodosa or Churg–Strauss syndrome (Guillevin et al., 1996)

FFS	5 year survival rate (%)	Relative risk
0	88.1	0.62
1	74.1*	1.35
≧ 2	54.1**	2.40

Proteinuria > 1 g/24 h
Creatininemia > 140 μmol/l
Specific gastrointestinal involvement
Specific cardiomyopathy
Specific CNS involvement

* $p < 0.005$ and ** $p < 0.0001$ as compared to patients with FFS = 0. For each of these five items, 1 point when present.

which includes all these parameters. Five-year mortality was 12% when FFS = 0, 26% when FFS = 1, and 46% when FFS = 2 or more ($p < 0.001$). Application of FFS to MPA patients has been also validated (Gayraud et al., 2001).

Neurologic manifestations have also been included in the Birmingham vasculitis activity score (BVAS; Luqmani et al., 1994), which includes symptoms and signs of nine separate organ systems and is intended to assess the activity of systemic necrotizing vasculitides. The neurologic items assessed in the BVAS are: organic confusion/dementia, seizures (not hypertensive), stroke, spinal cord lesion, peripheral neuropathy and motor mononeuritis multiplex. The revised versions of the BVAS (the so-called BVAS 2000 and BVAS 2001) include: organic confusion/dementia, seizures (not hypertensive), stroke, spinal cord lesion, sensory peripheral neuropathy, cranial nerve palsy and motor mononeuritis multiplex (Stone et al., 2001). However, because this score was designed only to reflect the severity and current extent of active disease, its use should be restricted to the evaluation of therapeutic efficacy in trials.

Neurologic sequelae are frequent but have rarely been studied. Gayraud et al. (2001) found neurologic sequelae in 5.2% of the patients with PAN, MPA or CSS who were still alive after a mean follow-up of 7.3 years. Sensory symptoms persisted longer than motor deficits and could remain indefinitely (Davies, 1994; Davies et al., 1996; de Groot et al., 2001). Even in patients with complete motor deficit at the time of diagnosis, their regression can be seen, albeit slowly under treatment and it is not unusual to wait as long as a year after the disease onset and effective treatment to see improvement. However, the longer they last, the less the neurologic symptoms will regress. Patients with initial involvement of one specific nerve may recover faster, over a 2–4 month period, whereas recovery in those with extensive involvement may take several years (Moore and Fauci, 1981). WG patients with mononeuritis multiplex achieved more complete recovery of nerve function than those with distal symmetrical neuropathy (de Groot et al., 2001). In CSS, the outcome of the early responders was fairly good, while patients responding poorly after 4 weeks of treatment with CS had sustained neurologic deficits and poorer functional scores throughout follow-up (Hattori et al., 1999). As these sequelae can also hamper patients' overall outcomes, a scoring system, the vasculitis damage index (VDI; Exley et al., 1997) has been developed to assess organ damage in systemic necrotizing vasculitides. It includes the following neurologic manifestations: cognitive impairment, major psychosis, seizures, cerebrovascular accident, second cerebrovascular accident, cranial nerve lesion, peripheral neuropathy and transverse myelitis. Mortality was retrospectively shown to be correlated with the VDI.

8. Treatment

In combination with symptomatic drug-based therapies (e.g. antiepileptic drugs for seizures, analgesics for headaches, gabapentin or clonazepam for neurologic dysesthesia), physical therapy, treatment of associated confounding factors (e.g. hypertension), and surgery when required (e.g. ablation of a compressive granulomatous dural mass, CSF shunt for hydrocephalus), specific treatments for these vasculitides should be prescribed for patients with neurologic involvement. Before the introduction of CS in the 1970s, only 10% of untreated PAN patients survived (Frohnert and Sheps, 1967). Since then, survival has increased to 55% with the use of CS alone, and to 82% at 5 years with combined CS and immunosuppressants (Guillevin et al., 1988; Leib et al., 1979). Therapeutic decisions to treat and with

which agents should rely on the presence or not of factor(s) of FFS poor prognosis. Patients' status under treatment and afterwards may be evaluated with BVAS and VDI.

8.1. Polyarteritis nodosa and ANCA-associated vasculitides

The therapeutic armamentarium for systemic necrotizing vasculitides essentially comprises CS and immunosuppressants, mainly cyclophosphamide (CYC). However, the combination of CS and immunosuppressants should be prescribed only for patients with very severe forms of PAN, MPA or CSS. When factors of poor prognosis are absent, CS alone can be prescribed. For WG, the combination of CS and CYC, oral or pulses, should be prescribed, and maintenance therapy with azathioprine or methotrexate is recommended. Alternative treatments using other immunosuppressants or immunomodulating agents can be prescribed for relapses or patients who do not respond to conventional regimens. The different therapeutic modalities should also be adapted to the patient's age and general condition.

8.1.1. Corticosteroids

First-line therapy for all necrotizing vasculitides must include oral prednisone at high dose (at least 1 mg/kg/d), usually preceded by a daily methylprednisolone pulse(s) for 1–3 days (15 mg/kg/d) to rapidly control the more disabling or life-threatening symptoms. The full oral dose should be maintained until clinical and biological improvement are achieved, usually within 1 month, and then gradually tapered over 12–18 months.

8.1.2. Cyclophosphamide

In 1979, Fauci et al. (1979) demonstrated the efficacy of adjunctive CYC for patients whose vasculitides were not controlled with CS alone. Pulse IV CYC should be combined with CS for patients with an FFS $\geqq 1$, like those with specific CNS involvement. Pulse therapy acts more rapidly and engenders fewer side effects (hemorrhagic cystitis, leukopenia) than oral administration. However, oral CYC is also effective as first-line therapy for WG and may achieve remission in patients who did not respond to pulse CYC (Gayraud et al., 1997; Généreau et al., 1994; Reinhold-Keller et al., 1993). Doses, intervals between pulses and duration of CYC treatment have to be adjusted for each patient. Briefly, each CYC pulse (0.5–0.7 g/m^2) is administered every 15 days for the first three boluses, then every 3 weeks (WG and MPA) or monthly (PAN and CSS). When preferred (WG) or needed (e.g. after failure of pulse CYC), oral CYC should be prescribed at the dose of 2 mg/kg/d. The duration of CYC therapy varies according to the patient's status, between 3 (for pulse CYC) and 18 months (for oral CYC), and to the subsequent use or not of maintenance therapy, once the remission is achieved (required for WG and MPA). Many trials have been and/or are still being conducted throughout the world to determine the most accurate, effective and safe regimen for each of these vasculitides.

8.1.3. Intravenous immunoglobulins

Intravenous immunoglobulin efficacy has been demonstrated in Guillain–Barré syndrome, multifocal motor neuropathy, chronic inflammatory demyelinating polyradiculopathy and dermatomyositis, but has not been specifically studied in PNS vasculitis. First reports of its use in patients with refractory systemic vasculitides have yielded encouraging, then mixed, results. Forty to 92% of the patients with refractory disease (Jayne et al., 1991, 2000) responded, at least partially, but complete remission rates and their long-term maintenance have to be more closely analyzed in ongoing trials.

8.1.4. Other therapies

Plasma exchanges may be useful as second-line therapy for refractory PAN or MPA with rapidly progressive glomerulonephritis (Guillevin and Bussel, 2000; Pusey et al., 1991), but are contraindicated for patients with unstable cardiac conditions. However, plasma exchanges may be a rational approach for patients with incapacitating peripheral neuropathy, particularly those with vasculitides associated with immune-complex deposits, like PAN or cryoglobulinemia. Other immunosuppressants (methotrexate, azathioprine, mycophenolate

mofetil) should preferentially be kept for maintenance therapy, when indicated, i.e. for WG and MPA, or for PAN and CSS with multiple relapses (de Groot et al., 1996; Nowack et al., 1999). Cotrimoxazole may be beneficial as adjuvant therapy for patients with WG (Israel, 1988) or limited nasal and oral forms of WG (Lê Thi Huong et al., 1990; Reinhold-Keller et al., 1996; Sangle et al., 2002). Dapsone and colchicine can help control some relapsing cutaneous manifestations of vasculitides (Thomas-Golbanov and Sridharan, 2001). Treatment with anti-TNFα antibodies may be promising for patients with intractable vasculitides (Bartolucci et al., 2002), e.g. those with WG and refractory pachymeningitis, in whom cyclosporin A (Riccieri et al., 2002), anti-CD52 monoclonal antibodies (Lockwood, 1998; Lockwood et al., 1996; Nagashima et al., 2000) and intrathecal methotrexate (Spranger et al., 1997) have also been used and achieved remission for some patients. Other therapeutics are still experimental, in initial trials' phases or of anecdotal use in refractory cases, e.g. bone-marrow auto- or allografts (Thomas-Golbanov and Sridharan, 2001), or anti-CD20 monoclonal antibodies (Specks et al., 2001).

8.2. HBV-related polyarteritis nodosa

Because classical treatment with CS and CYC may aggravate hepatic disease and stimulate viral replication in HBV-related PAN, a specific therapy is needed and has been validated for these patients (Guillevin, 1994, 2001). The therapeutic scheme should be as follows: initial CS to rapidly control life-threatening manifestations of PAN which are common during the first weeks of the disease, and their abrupt withdrawal to enhance immunologic clearance of HBV-infected hepatocytes and favor HBe antigen to anti-HBe antibody seroconversion; plasma exchanges to clear circulating immune complexes and control the course of PAN, in combination with antiviral agents (lamivudine or interferon-alpha-2b) for several months (Guillevin et al., 2001; Gupta, 2001). Immunosuppressants should only be given to those patients whose PAN manifestations worsen despite well-conducted therapy, as recommended.

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Key points

- Neurologic involvement occurs frequently in systemic necrotizing vasculitides.
- PNS involvement usually occurs early during the course of the disease, with frequencies of 50–75% in PAN, 11–67% in WG, 50–78% in CSS and 10–58% in MPA, and is predominantly represented by mononeuritis multiplex. This form of axonal neuropathy results from vasculitis of the vasa nervorum and epineurial arteries.
- CNS involvement is less common and usually occurs later during the course of the disease, i.e. in 3–38% of PAN patients, 6–44% of WG, 6–25% of CSS and 12–18% of MPA. It can result from vasculitis, with encephalopathy, stroke, infarctions and/or cognitive impairment, or from granulomatous extension in WG, with pachymeningitis, cranial nerve palsy and pituitary involvement.
- Alternate diagnoses (mostly infections, and lymphoma) must be ruled out promptly, before initiating specific treatment.
- While PNS manifestations may leave sequelae and functional incapacities, specific CNS manifestations carry a poor prognosis and therefore warrant aggressive therapy.

References

Abgrall, S., Mouthon, L., Cohen, P., Authier, F.J., Nizou, R., Ropert, A., Gherardi, R., Guillevin, L. 2001. Localized neurological necrotizing vasculitides. Three cases with isolated mononeuritis multiplex. J. Rheumatol. 28, 631–633.

Albayram, S., Kizilkilie, O., Adaletli, I., Erdogan, N., Kocer, N., Islak, C. 2002. MR imaging findings of spinal dural involvement with Wegener granulomatosis. Am. J. Neuroradiol. 23, 1603–1606.

Allan, S.G., Towla, H.M., Smith, C.C., Downie, A.W., Clark, J.C. 1982. Painful brachial plexopathy: an unusual presentation of polyarteritis nodosa. Postgrad. Med. J. 58, 311–313.

Anderson, G., Coles, E.T., Crane, M., Douglas, A.C., Gibbs, A.R., Geddes, D.M., Peel, E.T., Wood, J.B. 1992. Wegener's granuloma. A series of 265 British cases seen between 1975 and 1985. A report by a sub-committee of the British Thoracic Society Research Committee. QJM 83, 427–438.

Ara, J., Mirapeix, E., Arrizabalaga, P., Rodriguez, R., Ascaso, C., Abellana, R., Font, J., Darnell, A. 2001. Circulating soluble adhesion molecules in ANCA-associated vasculitis. Nephrol. Dial. Transplant. 16, 276–285.

Arend, W.P., Michel, B.A., Bloch, D.A., Hunder, G.G., Calabrese, L.H., Edworthy, S.M., Fauci, A.S., Leavitt, R.Y., Lie, J.T., Lightfoot, R.W. Jr., 1990. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum. 33, 1129–1134.

Askari, A., Vignos, P.J. Jr., Moskowitz, R.W. 1976. Steroid myopathy in connective tissue disease. Am. J. Med. 61, 485–492.

Asmus, R., Koltze, H., Muhle, C., Spielmann, R.P., Duncker, G., Noelle, B., Beigel, A., Gross, W.L. 1993. MRI of the head in Wegener's granulomatosis. Adv. Exp. Med. Biol. 336, 319–321.

Atcheson, S.G., Van Horn, G. 1977. Subacute meningitis heralding a diffuse granulomatous angiitis: (Wegener's granulomatosis?). Neurology 27, 262–264.

Balding, C.E., Howie, A.J., Drake-Lee, A.B., Savage, C.O. 2001. Th2 dominance in nasal mucosa in patients with Wegener's granulomatosis. Clin. Exp. Immunol. 125, 332–339.

Bartolucci, P., Ramanoelina, J., Cohen, P., Mahr, A., Godmer, P., Le Hello, C., Guillevin, L., 2002. Efficacy of the anti-TNF-alpha antibody infliximab against refractory systemic vasculitides: an open pilot study on 10 patients. Rheumatology (Oxford) 41, 1126–1132.

Becvar, R., Paleckova, A., Tesar, V., Rychlik, I., Masek, Z. 1997. von Willebrand factor antigen and adhesive molecules in Wegener's granulomatosis and microscopic polyangiitis. Clin. Rheumatol. 16, 324–325.

Beretta, L., Caronni, M., Vanoli, M., Scorza, R. 2001. Churg–Strauss vasculitis with brain involvement following hepatitis B vaccination. Clin. Exp. Rheumatol. 19, 757.

Berthier, S., Gil, H., Bonneville, J.F., Magy, N., De Wazieres, B., Mallet, H., Dupond, J.L. 2000. Wegener's disease and central diabetes insipidus (in French). Ann. Endocrinol. (Paris) 61, 531–537.

Bertken, R.D., Cooper, V.R. 1997. Wegener granulomatosis causing sellar mass, hydrocephalus, and global pituitary failure. West J. Med. 167, 44–47.

Bligny, D., Mahr, A., Le Toumelin, P., Mouthon, L., Guillevin, L. 2004. Predicting mortality in systemic Wegener's granulomatosis: a survival analysis based on 93 patients. Arthritis Rheum. 51, 83–91.

Bloch, D.A., Michel, B.A., Hunder, G.G., McShane, D.J., Arend, W.P., Calabrese, L.H., Edworthy, S.M., Fauci, A.S., Fries, J.F., Leavitt, R.Y. 1990. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Patients and methods. Arthritis Rheum. 33, 1068–1073.

Bouche, P., Leger, J.M., Travers, M.A., Cathala, H.P., Castaigne, P. 1986. Peripheral neuropathy in systemic vasculitis: clinical and electrophysiologic study of 22 patients. Neurology 36, 1598–1602. Analysis of electromyography in 22 patients with PNS involvement and systemic vasculitides.

Bussone, G., La Mantia, L., Frediani, F., Tredici, G., Petruccioli Pizzini, M.G. 1986. Vasculitic neuropathy in panarteritis nodosa: clinical and ultrastructural findings. Ital. J. Neurol. Sci. 7, 265–269.

Calabrese, L.H. 1995. Vasculitis of the central nervous system. Rheum. Dis. Clin. North Am. 21, 1059–1076.
Review on primary CNS angiitis.

Calabrese, L.H., Mallek, J.A. 1988. Primary angiitis of the central nervous system. Report of 8 new cases, review of the literature, and proposal for diagnostic criteria. Medicine (Baltimore) 67, 20–39.

Calabrese, L.H., Michel, B.A., Bloch, D.A., Arend, W.P., Edworthy, S.M., Fauci, A.S., Fries, J.F., Hunder, G.G., Leavitt, R.Y., Lie, J.T. 1990. The American College of Rheumatology 1990 criteria for the classification of hypersensitivity vasculitis. Arthritis Rheum. 33, 1108–1113.

Calabrese, L.H., Furlan, A.J., Gragg, L.A., Ropos, T.J. 1992. Primary angiitis of the central nervous system: diagnostic criteria and clinical approach. Cleve. Clin. J. Med. 59, 293–306.

Caniello, M., Baxter, P., Lino, A.M., Lima, L.G., Pinto, W.P. 2002. Confluent peripheral multiple mononeuropathy associated to acute hepatitis B: a case report. Rev. Inst. Med. Trop. Sao Paulo 44, 171–173.

Castaigne, P., Brunet, P., Hauw, J.J., Leger, J.M., Gherardi, R., Guillevin, L. 1984. Peripheral nervous system and panarteritis nodosa. Review of 27 cases (in French). Rev. Neurol. (Paris) 140, 343–352.

Cavallaro, T., Fenzi, F., Lazzarino, L.G., Nicolai, A., Rizzuto, N., Valassi, F. 1988. Peripheral neuropathy associated with allergic granulomatous angiitis (Churg–Strauss syndrome): clinical features and histological findings. Ital. J. Neurol. Sci. 9, 595–598.

Chalk, C.H., Homburger, H.A., Dyck, P.J. 1993. Anti-neutrophil cytoplasmic antibodies in vasculitis peripheral neuropathy. Neurology 43, 1826–1827.

Chamouard, J.M., Smadja, D., Chaunu, M.P., Bouche, P. 1993. Neuropathy caused by necrotizing vasculitis in HIV-1 infection (in French). Rev. Neurol. (Paris) 149, 358–361.

Chan, T.M., Cheng, I.K. 1996. A prospective study on anti-endothelial cell antibodies in patients with systemic lupus erythematosus. Clin. Immunol. Immunopathol. 78, 41–46.

Chomette, G., Auriol, M., Tranbaloc, P. 1983. Anatomopathology of inflammatory arteriopathies. Peculiar aspects of giant cell arteritis (in French). Ann. Méd. Interne (Paris) 134, 421–427.

Chumbley, L.C., Harrison, E.G. Jr., DeRemee, R.A. 1977. Allergic granulomatosis and angiitis (Churg–Strauss syndrome). Report and analysis of 30 cases. Mayo Clin. Proc. 52, 477–484.

Collins, M.P., Periquet, M.I. 2002. Prevalence of vasculitic neuropathy in Wegener granulomatosis. Arch. Neurol. 59, 1333–1334.

Collins, M.P., Mendell, J.R., Periquet, M.I., Sahenk, Z., Amato, A.A., Gronseth, G.S., Barohn, R.J., Jackson, C.E., Kissel, J.T., 2000. Superficial peroneal nerve/peroneus brevis muscle biopsy in vasculitic neuropathy. Neurology 55, 636–643.

Cruz, D.N., Segal, A.S. 1997. A patient with Wegener's granulomatosis presenting with a subarachnoid hemorrhage: case report and review of CNS disease associated with Wegener's granulomatosis. Am. J. Nephrol. 17, 181–186.

Csernok, E., Trabandt, A., Muller, A., Wang, G.C., Moosig, F., Paulsen, J., Schnabel, A., Gross, W.L. 1999. Cytokine profiles in Wegener's granulomatosis: predominance of type 1 (Th1) in the granulomatous inflammation. Arthritis Rheum. 42, 742–750.

Davidson, J.R., Sundstrom, W.R. 1988. Sural nerve biopsy in systemic necrotizing vasculitis. Arthritis Rheum. 31, 149–150.

Davies, L. 1994. Vasculitic neuropathy. Baillieres Clin. Neurol. 3, 193–210.

Davies, D.J., Moran, J.E., Niall, J.F., Ryan, G.B. 1982. Segmental necrotising glomerulonephritis with antineutrophil antibody: possible arbovirus aetiology? Br. Med. J. (Clin. Res. Ed.) 285, 606.

Davies, L., Spies, J.M., Pollard, J.D., McLeod, J.G. 1996. Vasculitis confined to peripheral nerves. Brain 119, 1441–1448.

Delpla, P.A., Delisle, M.B., Arne-Bes, M.C., Archambaud, M., Geraud, G., Bes, A. 1993. Multiple mononeuritis and cerebral meningo-arteritis. Wegener disease or Lyme disease? (in French). Rev. Neurol. (Paris) 149, 411–415.

Devaney, K.O., Travis, W.D., Hoffman, G., Leavitt, R., Lebovics, R., Fauci, A.S. 1990. Interpretation of head and neck biopsies in Wegener's granulomatosis. A pathologic study of 126 biopsies in 70 patients. Am. J. Surg. Pathol. 14, 555–564.

D'Izarn, J.J., Boulet, C.P., Convard, J.P., Bonnin, A., Ledoux-Lebard, G. 1976. Arteriography in polyarteritis nodosa. 15 cases (in French). J. Radiol. Electrol. Med. Nucl. 57, 505–509.

Drachman, D. 1963. Neurological complication of Wegener's granulomatosis. Arch. Neurol. 8, 145–155.
First comprehensive review of neurologic manifestations in WG.

Duncker, G., Nolle, B., Asmus, R., Koltze, H., Rochels, R. 1993. Orbital involvement in Wegener's granulomatosis. Adv. Exp. Med. Biol. 336, 315–317.

Dyck, P.J., Benstead, T.J., Conn, D.L., Stevens, J.C., Windebank, A.J., Low, P.A. 1987. Nonsystemic vasculitic neuropathy. Brain 110, 843–853.

Ewert, B.H., Jennette, J.C., Falk, R.J. 1991. The pathogenic role of antineutrophil cytoplasmic autoantibodies. Am. J. Kidney Dis. 18, 188–195.

Exley, A.R., Bacon, P.A., Luqmani, R.A., Kitas, G.D., Gordon, C., Savage, C.O., Adu, D. 1997. Development and initial validation of the vasculitis damage index for the standardized clinical assessment of damage in the systemic vasculitides. Arthritis Rheum. 40, 371–380.

Falcini, F., Trapani, S., Turchini, S., Farsi, A., Ermini, M., Keser, G., Khamashta, M.A., Hughes, G.R. 1997. Immunological findings in Kawasaki disease: an evaluation in a cohort of Italian children. Clin. Exp. Rheumatol. 15, 685–689.

Falk, R.J., Jennette, J.C. 1988. Anti-neutrophil cytoplasmic autoantibodies with specificity for myeloperoxidase in patients with systemic vasculitis and idiopathic necrotizing and crescentic glomerulonephritis. N. Engl. J. Med. 318, 1651–1657.

Fauci, A., Katz, P., Haynes, B., Wolff, S. 1979. Cyclophosphamide therapy of severe necrotizing vasculitis. N. Engl. J. Med. 301, 235–238.

Fauci, A.S., Haynes, B.F., Katz, P., Wolff, S.M. 1983. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. Ann. Intern. Med. 98, 76–85.

Flores-Suarez, L.F., Cabiedes, J., Villa, A.R., van der Woude, F.J., Alcocer-Varela, J. 2003. Prevalence of antineutrophil cytoplasmic autoantibodies in patients with tuberculosis. Rheumatology (Oxford) 42, 223–229.

Ford, R., Sieckert, R. 1965. Central nervous system manifestations of periarteritis nodosa. Neurology 15, 114–122.

Fortin, P.R., Larson, M.G., Watters, A.K., Yeadon, C.A., Choquette, D., Esdaile, J.M. 1995. Prognostic factors in systemic necrotizing vasculitis of the polyarteritis nodosa group—a review of 45 cases. J. Rheumatol. 22, 78–84.

Fries, J.F., Hunder, G.G., Bloch, D.A., Michel, B.A., Arend, W.P., Calabrese, L.H., Fauci, A.S., Leavitt, R.Y., Lie, J.T., Lightfoot, R.W. Jr., 1990. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Summary. Arthritis Rheum. 33, 1135–1136.

Frohnert, P., Sheps, S. 1967. Long term follow-up study of periarteritis nodosa. Am. J. Med. 43, 8–14.

Garcia-Porrua, C., Llorca, J., Gonzalez-Louzao, C., Gonzalez-Gay, M.A. 2001. Hypersensitivity vasculitis in adults: a benign disease usually limited to skin. Clin. Exp. Rheumatol. 19, 85–88.

Garovic, V.D., Clarke, B.L., Chilson, T.S., Specks, U. 2001. Diabetes insipidus and anterior pituitary insufficiency as presenting features of Wegener's granulomatosis. Am. J. Kidney Dis. 37, E5.

Gayraud, M., Guillevin, L., Cohen, P., Lhote, F., Cacoub, P., Deblois, P., Godeau, B., Ruel, M., Vidal, E., Piontud, M., Ducroix, J.P., Lassoued, S., Christoforov, B., Babinet, P. 1997. Treatment of good-prognosis polyarteritis nodosa and Churg–Strauss syndrome: comparison of steroids and oral or pulse cyclophosphamide in 25 patients. French Cooperative Study Group for Vasculitides. Br. J. Rheumatol. 36, 1290–1297.

Gayraud, M., Guillevin, L., Le Toumelin, P., Cohen, P., Lhote, F., Casassus, P., Jarrousse, B. 2001. Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg–Strauss syndrome: analysis of four prospective trials including 278 patients. Arthritis Rheum. 44, 666–675.

Généreau, T., Lortholary, O., Leclerq, P., Grenet, D., Tubery, M., Sicard, D., Caubarrère, I., Guillevin, L. 1994. Treatment of systemic vasculitis with cyclophosphamide and steroids: daily oral low-dose cyclophosphamide administration after failure of a pulse intravenous high-dose regimen in four patients. Br. J. Rheumatol. 33, 959–962.

Généreau, T., Lortholary, O., Pottier, M.A., Michon-Pasturel, U., Ponge, T., de Wazieres, B., Liozon, E., Pinède, L., Hachulla, E., Roblot, P., Barrier, J.H., Herson, S., Guillevin, L. 1999. Temporal artery biopsy: a diagnostic tool for systemic necrotizing vasculitis. French Vasculitis Study Group. Arthritis Rheum. 42, 2674–2681.

Gherardi, R., Belec, L., Mhiri, C., Gray, F., Lescs, M.C., Sobel, A., Guillevin, L., Wechsler, J. 1993. The spectrum of vasculitis in

human immunodeficiency virus-infected patients. A clinicopathologic evaluation. Arthritis Rheum. 36, 1164–1174.

Girard, T., Mahr, A., Noël, L.H., Cordier, J.F., Lesavre, P., André, M.H., Guillevin, L. 2001. Are antineutrophil cytoplasmic antibodies a marker predictive of relapse in Wegener's granulomatosis? A prospective study. Rheumatology (Oxford) 40, 147–151.

Gisselbrecht, M., Cohen, P., Lortholary, O., Jarrousse, B., Gayraud, M., Gherardi, R., Baudrimont, M., Guillevin, L. 1997. HIV-related vasculitis: clinical presentation and therapeutic approach on six patients. AIDS 11, 121–123.

Gobel, U., Eichhorn, J., Kettritz, R., Briedigkeit, L., Sima, D., Lindschau, C., Haller, H., Luft, F.C. 1996. Disease activity and autoantibodies to endothelial cells in patients with Wegener's granulomatosis. Am. J. Kidney Dis. 28, 186–194.

Gower, R.G., Sausker, W.F., Kohler, P.F., Thorne, G.E., McIntosh, R.M. 1978. Small vessel vasculitis caused by hepatitis B virus immune complexes. Small vessel vasculitis and HBsAG. J. Allergy Clin. Immunol. 62, 222–228.

Goyal, M., Kucharczyk, W., Keystone, E. 2000. Granulomatous hypophysitis due to Wegener's granulomatosis. Am. J. Neuroradiol. 21, 1466–1469.

Griffin, J.W. 2001. Vasculitic neuropathies. Rheum. Dis. Clin. North Am. 27, 751–760.

de Groot, K., Reinhold-Keller, E., Tatsis, E., Paulsen, J., Heller, M., Nolle, B., Gross, W.L. 1996. Therapy for the maintenance of remission in sixty-five patients with generalized Wegener's granulomatosis. Methotrexate versus trimethoprim/sulfamethoxazole. Arthritis Rheum. 39, 2052–2061.

de Groot, K., Schmidt, D.K., Arlt, A.C., Gross, W.L., Reinhold-Keller, E. 2001. Standardized neurologic evaluations of 128 patients with Wegener granulomatosis. Arch. Neurol. 58, 1215–1221.

Analysis of neurologic manifestations in 128 patients with WG, with unexpectedly high PNS involvement frequency of 44%.

Guillevin, L., Bussel, A. 2000. Indications of plasma exchanges in 2000. Ann. Med. Interne (Paris) 151, 123–135.

Guillevin, L., Lhote, F. 1997. Classification and management of necrotising vasculitides. Drugs 53, 805–816.

Guillevin, L., Lê Thi Huong, D., Godeau, P., Jais, P., Wechsler, B. 1988. Clinical findings and prognosis of polyarteritis nodosa and Churg–Strauss angiitis: a study in 165 patients. Br. J. Rheumatol. 27, 258–264.

Guillevin, L., Lhote, F., Jarrousse, B., Fain, O. 1992. Treatment of polyarteritis nodosa and Churg–Strauss syndrome. A meta-analysis of 3 prospective controlled trials including 182 patients over 12 years. Ann. Med. Interne (Paris) 143, 405–416.

Guillevin, L., Lhote, F., Leon, A., Fauvelle, F., Vivitski, L., Trépo, C. 1993. Treatment of polyarteritis nodosa related to hepatitis B virus with short term steroid therapy associated with antiviral agents and plasma exchanges. A prospective trial in 33 patients. J. Rheumatol. 20, 289–298.

Guillevin, L., Lhote, F., Sauvaget, F., Deblois, P., Rossi, F., Levallois, D., Pourrat, J., Christoforov, B., Trepo, C. 1994. Treatment of polyarteritis nodosa related to hepatitis B virus with interferon-alpha and plasma exchanges. Ann. Rheum. Dis. 53, 334–337.

Guillevin, L., Lhote, F., Brauner, M., Casassus, P. 1995a. Antineutrophil cytoplasmic antibodies (ANCA) and abnormal angiograms in polyarteritis nodosa and Churg–Strauss syndrome: indications for the diagnosis of microscopic polyangiitis. Ann. Med. Interne (Paris) 146, 548–550.

Guillevin, L., Lhote, F., Cohen, P., Sauvaget, F., Jarrousse, B., Lortholary, O., Noel, L.H., Trépo, C. 1995b. Polyarteritis nodosa related to hepatitis B virus. A prospective study with long-term observation of 41 patients. Medicine (Baltimore) 74, 238–253.

Guillevin, L., Lhote, F., Jarrousse, B., Cohen, P., Jacquot, C., Lesavre, P., Lortholary, O. 1995c. Treatment of Wegener's granulomatosis: a prospective trial in 50 patients comparing prednisone, pulse cyclophosphamide versus prednisone and oral cyclophosphamide. Clin. Exp. Rheumatol. 101, 43(abstract).

Guillevin, L., Lhote, F., Gayraud, M., Cohen, P., Jarrousse, B., Lortholary, O., Thilbult, N., Casassus, P. 1996.

Prognostic factors in polyarteritis nodosa and Churg–Strauss syndrome. A prospective study in 342 patients. Medicine (Baltimore) 75, 17–28. Five parameters, included in the so-called FFS, five factor score, have poor and significant prognostic values in PAN and CSS.

Guillevin, L., Cohen, P., Gayraud, M., Lhote, F., Jarrousse, B., Casassus, P. 1999a. Churg–Strauss syndrome. Clinical study and long-term follow-up of 96 patients. Medicine (Baltimore) 78, 26–37.

Guillevin, L., Durand Gasselin, B., Cevallos, R., Gayraud, M., Lhote, F., Callard, P., Amouroux, J., Casassus, P., Jarrousse, B. 1999b. Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. Arthritis Rheum. 42, 421–430.

Guillevin, L., Cohen, P., Larroche, C., Queyrel, V., Loustaud-Ratti, V., Imbert, B., Hausfater, P., Ramanoealina, J., Lacombe, F., Roudier, J., Bielefeld, P., Petitjean, P., Smadja, D. 2001. Treatment of HBV-related polyarteritis nodosa (PAN) with lamivudine and plasma exchanges: a prospective, multicenter, pilot trial in 10 patients. Arthritis Rheum. 44, S271.

Guillevin, L., Ramanoelina, J., Mahr, A. 2002. Central nervous system and systemic vasculitides (in French). Rev. Neurol. (Paris) 158, 907–913.

Review of CNS manifestations of vasculitides.

Gupta, S., Piraka, C., Jaffe, M. 2001. Lamivudine in the treatment of polyarteritis nodosa associated with acute hepatitis B. N. Engl. J. Med. 344, 1645–1646.

Ha, H.K., Lee, S.H., Rha, S.E., Kim, J.H., Byun, J.Y., Lim, H.K., Chung, J.W., Kim, J.G., Kim, P.N., Lee, M.G., Auh, Y.H. 2000. Radiologic features of vasculitis involving the gastrointestinal tract. Radiographics 20, 779–794.

Haas, C., Le Jeunne, C., Choubrac, P., Durand, H., Hugues, F.C. 2001. Churg–Strauss syndrome. Retrospective study of 20 cases (in French). Bull. Acad. Natl Med. 185, 1113–1133.

Hagen, E.C., Daha, M.R., Hermans, J., Andrassy, K., Csernok, E., Gaskin, G., Lesavre, P., Ludemann, J., Rasmussen, N., Sinico, R.A., Wiik, A., van der Woude, F.J. 1998. Diagnostic value of standardized assays for anti-neutrophil cytoplasmic antibodies in idiopathic systemic vasculitis. EC/BCR Project for ANCA Assay Standardization. Kidney Int. 53, 743–753.

Hajj-Ali, R.A., Uthman, I.W., Salti, I.A., Zaatari, G.S., Haddad, M.C., Nasr, F.W. 1999. Wegener's granulomatosis and diabetes insipidus. Rheumatology (Oxford) 38, 684–685.

Halbwachs-Mecarelli, L., Nusbaum, P., Noël, L.H., Reumaux, D., Erlinger, S., Grünfeld, J.P., Lesavre, P. 1992. Antineutrophil cytoplasmic antibodies (ANCA) directed against cathepsin G in ulcerative colitis, Crohn's disease and primary sclerosing cholangitis. Clin. Exp. Immunol. 90, 79–84.

Hattori, N., Ichimura, M., Nagamatsu, M., Li, M., Yamamoto, K., Kumazawa, K., Mitsuma, T., Sobue, G. 1999. Clinicopathological features of Churg–Strauss syndrome-associated neuropathy. Brain 122 (Pt 3), 427–439.
Analysis of PNS manifestations in a group of 28 CSS patients.

Hattori, N., Mori, K., Misu, K., Koike, H., Ichimura, M., Sobue, G. 2002. Mortality and morbidity in peripheral neuropathy associated Churg–Strauss syndrome and microscopic polyangiitis. J. Rheumatol. 29, 1408–1414.

Haynes, B.F., Fauci, A.S. 1978. Diabetes insipidus associated with Wegener's granulomatosis successfully treated with cyclophosphamide. N. Engl. J. Med. 299, 764.

Heeringa, P., Brouwer, E., Tervaert, J.W., Weening, J.J., Kallenberg, C.G. 1998. Animal models of anti-neutrophil cytoplasmic antibody associated vasculitis. Kidney Int. 53, 253–263.

Heiserman, J.E., Dean, B.L., Hodak, J.A., Flom, R.A., Bird, C.R., Drayer, B.P., Fram, E.K. 1994. Neurologic complications of cerebral angiography. Am. J. Neuroradiol. 15, 1401–1411.

Hoffman, G.S., Kerr, G.S., Leavitt, R.Y., Hallahan, C.W., Lebovics, R.S., Travis, W.D., Rottem, M., Fauci, A.S. 1992. Wegener granulomatosis: an analysis of 158 patients. Ann. Intern. Med. 116, 488–498.

Hunder, G.G., Arend, W.P., Bloch, D.A., Calabrese, L.H., Fauci, A.S., Fries, J.F., Leavitt, R.Y., Lie, J.T., Lightfoot, R.W. Jr., Masi, A.T. 1990. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Introduction. Arthritis Rheum. 33, 1065–1067.

Hunn, M., Robinson, S., Wakefield, L., Mossman, S., Abernethy, D. 1998. Granulomatous angiitis of the CNS causing spontaneous intracerebral haemorrhage: the importance of leptomeningeal biopsy. J. Neurol. Neurosurg. Psychiatry 65, 956–957.

Hurst, R.W., Grossman, R.I. 1994. Neuroradiology of central nervous system vasculitis. Semin. Neurol. 14, 320–340.
Review of radiologic features of CNS vasculitis.

Israel, H.L. 1988. Sulfamethoxazole–trimethoprim therapy for Wegener's granulomatosis. Arch. Intern. Med. 148, 2293–2295.

Jayne, D.R., Davies, M.J., Fox, C.J., Black, C.M., Lockwood, C.M. 1991. Treatment of systemic vasculitis with pooled intravenous immunoglobulin. Lancet 337, 1137–1139.

Jayne, D.R., Chapel, H., Adu, D., Misbah, S., O'Donoghue, D., Scott, D., Lockwood, C.M., 2000. Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. QJM 93, 433–439.

Jee, K.N., Ha, H.K., Lee, I.J., Kim, J.K., Sung, K.B., Cho, K.S., Kim, P.N., Lee, M.G., Lim, H.K., Choi, C.S., Auh, Y.H. 2000. Radiologic findings of abdominal polyarteritis nodosa. Am. J. Roentgenol. 174, 1675–1679.

Jennette, J.C., Falk, R.J., Andrassy, K., Bacon, P.A., Churg, J., Gross, W.L., Hagen, E.C., Hoffman, G.S., Hunder, G.G., Kallenberg, C.G. 1994. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum. 37, 187–192.

Jennette, J.C., Thomas, D.B., Falk, R.J. 2001. Microscopic polyangiitis (microscopic polyarteritis). Semin. Diagn. Pathol. 18, 3–13.

Jinnah, H.A., Dixon, A., Brat, D.J., Hellmann, D.B. 1997. Chronic meningitis with cranial neuropathies in Wegener's granulomatosis. Case report and review of the literature. Arthritis Rheum. 40, 573–577.

Kallenberg, C.G., Mulder, A.H., Tervaert, J.W. 1992. Antineutrophil cytoplasmic antibodies: a still-growing class of autoantibodies in inflammatory disorders. Am. J. Med. 93, 675–682.

Kasantikul, V., Kasantikul, D. 1995. Localized necrotizing arteritis of the central nervous system. Surg. Neurol. 43, 510–512.

Katrib, A., Portek, I., Corbett, A.J., Hersch, M.I., Zagami, A.S. 1998. Meningeal involvement in Wegener's granulomatosis. J. Rheumatol. 25, 1009–1011.

Katzman, G.L., Langford, C.A., Sneller, M.C., Koby, M., Patronas, N.J. 1999. Pituitary involvement by Wegener's granulomatosis: a report of two cases. Am. J. Neuroradiol. 20, 519–523.

Kelly, P.J., Toker, D.E., Boyer, P., McDonald, C.T., Niles, J. 1998. Granulomatous compressive thoracic myelopathy as the initial manifestation of Wegener's granulomatosis. Neurology 51, 1769–1770.

Kinyoun, J.L., Kalina, R.E., Klein, M.L. 1987. Choroidal involvement in systemic necrotizing vasculitis. Arch. Opthalmol. 105, 939–942.

Kissel, J.T. 1989. Neurologic manifestations of vasculitis. Neurol. Clin. 7, 655–673.
Review of neurologic manifestations of vasculitides.

Kissel, J.T., Slivka, A.P., Warmolts, J.R., Mendell, J.R. 1985. The clinical spectrum of necrotizing angiopathy of the peripheral nervous system. Ann. Neurol. 18, 251–257.

Koldingsnes, W., Nossent, J.C. 2003. Baseline features and initial treatment as predictors of remission and relapse in Wegener's granulomatosis. J. Rheumatol. 30, 80–88.

Kono, H., Inokuma, S., Nakayama, H., Yamazaki, J. 2000. Pachymeningitis in microscopic polyangiitis (MPA): a case report and a review of central nervous system involvement in MPA. Clin. Exp. Rheumatol. 18, 397–400.

Lane, S.E., Watts, R.A., Bentham, G., Innes, N.J., Scott, D.G. 2003. Are environmental factors important in primary systemic vasculitis? A case-control study. Arthritis Rheum. 48, 814–823.

Lanham, J.G., Elkon, K.B., Pusey, C.D., Hughes, G.R. 1984. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg–Strauss syndrome. Medicine (Baltimore) 63, 65–81.

Leavitt, R.Y., Fauci, A.S., Bloch, D.A., Michel, B.A., Hunder, G.G., Arend, W.P., Calabrese, L.H., Fries, J.F., Lie, J.T., Lightfoot, R.W. Jr., 1990. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum. 33, 1101–1107.

Ledford, D.K. 1997. Immunologic aspects of vasculitis and cardiovascular disease. JAMA 278, 1962–1971.

Léger, J.M., Bouche, P., Chaunu, M.P., Hauw, J.J., Brunet, P., Cathala, H.P., Laplane, D. 1988. Peripheral neuropathies with neural vasculitis. Clinical and electrophysiological aspects of 33 cases (in French). Presse Méd. 17, 733–737.

Leib, E.S., Restivo, C., Paulus, H.E. 1979. Immunosuppressive and corticosteroid therapy of polyarteritis nodosa. Am. J. Med. 67, 941–947.

Lê Thi Huong, D., Wechsler, B., De Gennes, C., Raguin, G., Piette, J.C., Blétry, O., Godeau, P. 1990. Treatment of Wegener's granulomatosis with cotrimoxazole (7 cases) (in French). Rev. Méd. Interne 11, 87–89.

Lie, J.T. 1997. Wegener's granulomatosis: histological documentation of common and uncommon manifestations in 216 patients. Vasa 26, 261–270.

Liebow, A.A., Carrington, C.R., Friedman, P.J. 1972. Lymphomatoid granulomatosis. Hum. Pathol. 3, 457–558.

Lightfoot, R.W. Jr., Michel, B.A., Bloch, D.A., Hunder, G.G., Zvaifler, N.J., McShane, D.J., Arend, W.P., Calabrese, L.H., Leavitt, R.Y., Lie, J.T. 1990. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. Arthritis Rheum. 33, 1088–1093.

Lockwood, C.M. 1998. Refractory Wegener's granulomatosis: a model for shorter immunotherapy of autoimmune diseases. J. R. Coll. Physicians Lond. 32, 473–478.

Lockwood, C.M., Thiru, S., Stewart, S., Hale, G., Isaacs, J., Wraight, P., Elliott, J., Waldmann, H. 1996. Treatment of refractory Wegener's granulomatosis with humanized monoclonal antibodies. QJM 89, 903–912.

Lohr, K.M., Ryan, L.M., Toohill, R.J., Anderson, T. 1988. Anterior pituitary involvement in Wegener's granulomatosis. J. Rheumatol. 15, 855–857.

Lortholary, O., Généreau, T., Guillevin, I. 1999. Viral vasculitis not related to HBV, HCV and HIV (in French). Pathol. Biol. (Paris) 47, 248–251.

Lundborg, G. 1975. Structure and function of the intraneural microvessels as related to trauma, edema formation, and nerve function. J. Bone Joint Surg. Am. 57, 938–948.

Luqmani, R.A., Bacon, P.A., Moots, R.J., Janssen, B.A., Pall, A., Emery, P., Savage, C., Adu, D. 1994. Birmingham vasculitis activity score (BVAS) in systemic necrotizing vasculitis. QJM 87, 671–678.

Mahadevan, A., Gayathri, N., Taly, A.B., Santosh, V., Yasha, T.C., Shankar, S.K. 2001. Vasculitic neuropathy in HIV infection: a clinicopathological study. Neurol. India 49, 277–283.

Marazzi, R., Pareyson, D., Boiardi, A., Corbo, M., Scaioli, V., Sghirlanzoni, A. 1992. Peripheral nerve involvement in Churg–Strauss syndrome. J. Neurol. 239, 317–321.

Marienhagen, J., Geissler, A., Lang, B. 1996. High resolution single photon emission computed tomography of the brain in Wegener's granulomatosis. J. Rheumatol. 23, 1828–1830.

Martens, J. 1982. Spinal cord involvement in Wegener's granulomatosis. Clin. Rheumatol. 1, 221.

Masi, A.T., Hunder, G.G., Lie, J.T., Michel, B.A., Bloch, D.A., Arend, W.P., Calabrese, L.H., Edworthy, S.M., Fauci, A.S., Leavitt, R.Y. 1990. The American College of Rheumatology 1990 criteria for the classification of Churg–Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum. 33, 1094–1100.

Masson, C., Boukriche, Y., Colombani, J.M. 2001. Inflammatory hypertrophic cranial pachymeningitis (in French). Presse Med. 30, 411–416.

Mattioli, F., Capra, R., Rovaris, M., Chiari, S., Codella, M., Miozzo, A., Gregorini, G., Filippi, M. 2002. Frequency and patterns of subclinical cognitive impairment in patients with ANCA-associated small vessel vasculitides. J. Neurol. Sci. 195, 161–166.
Analysis of cognitive disturbances in 43 patients with ANCA-associated small vessel vasculitides.

Mickle, J.P., McLennan, J.E., Lidden, C.W. 1977. Cortical vein thrombosis in Wegener's granulomatosis. Case report. J. Neurosurg. 46, 248–251.

Miller, D.L. 2000. Angiography in polyarteritis nodosa. Am. J. Roentgenol. 175, 1747–1748.

Mills, J.A., Michel, B.A., Bloch, D.A., Calabrese, L.H., Hunder, G.G., Arend, W.P., Edworthy, S.M., Fauci, A.S., Leavitt, R.Y., Lie, J.T. 1990. The American College of Rheumatology 1990 criteria for the classification of Henoch–Schönlein purpura. Arthritis Rheum. 33, 1114–1121.

Moore, P.M. 1989. Diagnosis and management of isolated angiitis of the central nervous system. Neurology 39, 167–173.

Moore, P.M. 1995. Neurological manifestation of vasculitis: update on immunopathogenic mechanisms and clinical features. Ann. Neurol. 37 (Suppl. 1), S131–S141.

Moore, P.M., Calabrese, L.H. 1994. Neurologic manifestations of systemic vasculitides. Semin. Neurol. 14, 300–312.

Moore, P.M., Fauci, A.S. 1981. Neurologic manifestations of systemic vasculitis. A retrospective and prospective study of the clinicopathologic features and responses to therapy in 25 patients. Am. J. Med. 71, 517–524.
Analysis of neurologic manifestations in a group of 25 patients with systemic vasculitides.

Morelli, S., Gurgo Di Castelmenardo, A.M., Conti, F., Sgreccia, A., Alessandri, C., Bernardo, M.L., Valesini, G. 2000. Cardiac involvement in patients with Wegener's granulomatosis. Rheumatol. Int. 19, 209–212.

Morgenstern, L.B., Pardo, C.A. 1995. Progressive multifocal leukoencephalopathy complicating treatment for Wegener's granulomatosis. J. Rheumatol. 22, 1593–1595.

Mrowka, C., Sieberth, H.G. 1994. Circulating adhesion molecules ICAM-1, VCAM-1 and E-selectin in systemic vasculitis: marked differences between Wegener's granulomatosis and systemic lupus erythematosus. Clin. Invest. 72, 762–768.

Mrowka, C., Sieberth, H.G. 1995. Detection of circulating adhesion molecules ICAM-1, VCAM-1 and E-selectin in Wegener's granulomatosis, systemic lupus erythematosus and chronic renal failure. Clin. Nephrol. 43, 288–296.

Mrowka, C., Heintz, B., Sieberth, H.G. 1999. VCAM-1, ICAM-1, and E-selectin in IgA nephropathy and Schönlein–Henoch syndrome: differences between tissue expression and serum concentration. Nephron 81, 256–263.

Murphy, J.M., Gomez-Anson, B., Gillard, J.H., Antoun, N.M., Cross, J., Elliott, J.D., Lockwood, M. 1999. Wegener

granulomatosis: MR imaging findings in brain and meninges. Radiology 213, 794–799.
Analysis of MRI findings in 19 patients with WG.

Murphy, J.M., Balan, K.K., Toms, A., Gomez-Anson, B., Lockwood, M. 2000. Radiolabeled leucocyte imaging in diffuse granulomatous involvement of the meninges in Wegener's granulomatosis: scintigraphic findings and their role in monitoring treatment response to specific immunotherapy (humanized monoclonal antilymphocyte antibodies). Am. J. Neuroradiol. 21, 1460–1465.

Nadeau, S.E. 1997. Diagnostic approach to central and peripheral nervous system vasculitis. Neurol. Clin. 15, 759–777.

Nagashima, T., Maguchi, S., Terayama, Y., Horimoto, M., Nemoto, M., Nunomura, M., Mori, M., Seki, T., Matsukawa, S., Itoh, T., Nagashima, K. 2000. P-ANCA-positive Wegener's granulomatosis presenting with hypertrophic pachymeningitis and multiple cranial neuropathies: case report and review of literature. Neuropathology 20, 23–30.

Nakashima, I., Fujihara, K., Endo, M., Seki, H., Okita, N., Takase, S., Itoyama, Y. 1998. Clinical and laboratory features of myelitis patients with anti-neutrophil cytoplasmic antibodies. J. Neurol. Sci. 157, 60–66.

Nesher, G., Rosenberg, P., Shorer, Z., Gilai, A., Solomonovich, A., Sonnenblick, M. 1987. Involvement of the peripheral nervous system in temporal arteritis-polymyalgia rheumatica. Report of 3 cases and review of the literature. J. Rheumatol. 14, 358–360.

Ng, K.K., Yeung, H.M., Loo, K.T., Chan, H.M., Wong, C.K., Li, P.C. 1997. Acute fulminant neuropathy in a patient with Churg–Strauss syndrome. Postgrad. Med. J. 73, 236–238.

Nikolaou, A.C., Vlachtsis, K.C., Daniilidis, M.A., Petridis, D.G., Daniilidis, I.C. 2001. Wegener's granulomatosis presenting with bilateral facial nerve palsy. Eur. Arch. Otorhinolaryngol. 258, 198–202.

Nishino, H., DeRemee, R.A., Rubino, F.A., Parisi, J.E. 1993a. Wegener's granulomatosis associated with vasculitis of the temporal artery: report of five cases. Mayo Clin. Proc. 68, 115–121.

Nishino, H., Rubino, F.A. 1993b. Horner's syndrome in Wegener's granulomatosis: report of four cases. J. Neurol. Neurosurg. Psychiatry 56, 897–899.

Nishino, H., Rubino, F.A., DeRemee, R.A., Swanson, J.W., Parisi, J.E. 1993c. Neurological involvement in Wegener's granulomatosis: an analysis of 324 consecutive patients at the Mayo Clinic. Ann. Neurol. 33, 4–9.
Analysis of neurologic manifestations in a group of 324 WG patients.

Nishino, H., Rubino, F.A., Parisi, J.E. 1993d. The spectrum of neurologic involvement in Wegener's granulomatosis. Neurology 43, 1334–1337.

Noguchi, S., Numano, F., Gravanis, M.B., Wilcox, J.N. 1998. Increased levels of soluble forms of adhesion molecules in Takayasu arteritis. Int. J. Cardiol. 66 (Suppl. 1), S23–S33.

Nordmark, G., Boquist, L., Ronnblom, L. 1997. Limited Wegener's granulomatosis with central nervous system involvement and fatal outcome. J. Intern. Med. 242, 433–436.

Nowack, R., Gobel, U., Klooker, P., Hergesell, O., Andrassy, K., van der Woude, F.J. 1999. Mycophenolate mofetil for maintenance therapy of Wegener's granulomatosis and microscopic polyangiitis: a pilot study in 11 patients with renal involvement. J. Am. Soc. Nephrol. 10, 1965–1971.

Nusbaum, A.O., Morgello, S., Atlas, S.W. 1999. Pial involvement in Wegener's granulomatosis shown on MRI. Neuroradiology 41, 847–849.

O'Donovan, C.A., Keogan, M., Staunton, H., Browne, O., Farrell, M.A. 1992. Peripheral neuropathy in Churg–Strauss syndrome associated with IgA-C3 deposits. Ann. Neurol. 32, 411.

O'Duffy, J.D. 1990. Vasculitis in Behçet's disease. Rheum. Dis. Clin. North Am. 16, 423–431.

Ohta, N., Fukase, S., Aoyagi, M. 2001. Serum levels of soluble adhesion molecules ICAM-1, VCAM-1 and E-selectin in patients with Wegener's granulomatosis. Auris Nasus Larynx 28, 311–314.

Orlowski, J.P., Clough, J.D., Dyment, P.G. 1978. Wegener's granulomatosis in the pediatric age group. Pediatrics 61, 83–90.

Ossi, E., Rossanese, A., Casagrande, F., Rotilio, A., Mingrino, S., Poci, C. 2002. Predictive value of ANCA in atypical primary brain localization of Wegener's granulomatosis. Sarcoidosis Vasc. Diffuse Lung Dis. 19, 78–80.

Pall, A.A., Adu, D., Drayson, M., Taylor, C.M., Richards, N.T., Michael, J. 1994. Circulating soluble adhesion molecules in systemic vasculitis. Nephrol. Dial. Transplant. 9, 770–774.

Payton, C.D., Jones, J.M. 1985. Cortical blindness complicating Wegener's granulomatosis. Br. Med. J. (Clin. Res. Ed.) 290, 676.

Pinching, A.J., Lockwood, C.M., Pussell, B.A., Rees, A.J., Sweny, P., Evans, D.J., Bowley, N., Peters, D.K. 1983. Wegener's granulomatosis: observations on 18 patients with severe renal disease. QJM 52, 435–460.

Praprotnik, S., Rozman, B., Blank, M., Shoenfeld, Y. 2000. Pathogenic role of anti-endothelial cell antibodies in systemic vasculitis. Wien. Klin. Wochenschr. 112, 660–664.

Provenzale, J.M., Allen, N.B. 1996. Wegener granulomatosis: CT and MR findings. Am. J. Neuroradiol. 17, 785–792.

Puéchal, X., Said, G., Hilliquin, P., Coste, J., Job-Deslandre, C., Lacroix, C., Menkes, C.J. 1995. Peripheral neuropathy with necrotizing vasculitis in rheumatoid arthritis. A clinicopathologic and prognostic study of thirty-two patients. Arthritis Rheum. 38, 1618–1629.

Pusey, C.D., Rees, A.J., Evans, D.J., Peters, D.K., Lockwood, C.M. 1991. Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. Kidney Int. 40, 757–763.

Reinhold-Keller, E., Kekow, J., Schnabel, A., Schwarz-Eywill, M., Schmitt, W.H., Gross, W.L. 1993. Effectiveness of cyclophosphamide pulse treatment in Wegener's granulomatosis. Adv. Exp. Med. Biol. 336, 483–486.

Reinhold-Keller, E., de Groot, K., Rudert, H., Nolle, B., Heller, M., Gross, W.L. 1996. Response to trimethoprim/sulfamethoxazole in Wegener's granulomatosis depends on the phase of disease. QJM 89, 15–23.

Reinhold-Keller, E., Beuge, N., Latza, U., De Groot, K., Rudert, H., Nolle, B., Heller, M., Gross, W.L. 2000. An interdisciplinary approach to the care of patients with Wegener's granulomatosis: long-term outcome in 155 patients. Arthritis Rheum. 43, 1021–1032.

Reinhold-Keller, E., De Groot, K., Holl-Ulrich, K., Arlt, A.C., Heller, M., Feller, A.C., Gross, W. 2001. Severe CNS manifestations as the clinical hallmark in generalized Wegener's granulomatosis consistently negative for anti-neutrophil cytoplasmic antibodies (ANCA). A report of 3 cases and a review of the literature. Clin. Exp. Rheumatol. 19, 541–549.

Case report of 3 patients with CNS involvement and ANCA-negative WG, suggesting that CNS involvement may be preferentially seen in ANCA-negative WG.

Riccieri, V., Spadaro, A., Parisi, G., Benfari, G., Trasimeni, G., Taccari, M.D., Valesini, G. 2002. Imaging evidence of successful multiple immunosuppressive treatment of cerebral involvement in Wegener's granulomatosis. Clin. Exp. Rheumatol. 20, 578–579.

Rieu, V., Cohen, P., André, M.H., Mouthon, L., Godmer, P., Jarrousse, B., Lhote, F., Ferriere, F., Deny, P., Buchet, P., Guillevin, L. 2002. Characteristics and outcome of 49 patients with symptomatic cryoglobulinaemia. Rheumatology (Oxford) 41, 290–300.

Rodgers, H., Guthrie, J.A., Brownjohn, A.M., Turney, J.H. 1989. Microscopic polyarteritis: clinical features and treatment. Postgrad. Med. J. 65, 515–518.

Ropert, A., Metral, S. 1990. Conduction block in neuropathies with necrotizing vasculitis. Muscle Nerve 13, 102–105.

Rosete, A., Cabral, A.R., Kraus, A., Alarcon-Segovia, D. 1991. Diabetes insipidus secondary to Wegener's granulomatosis: report and review of the literature. J. Rheumatol. 18, 761–765.

Sack, M., Cassidy, J.T., Bole, G.G. 1975. Prognostic factors in polyarteritis. J. Rheumatol. 2, 411–420.

Sahn, E.E., Sahn, S.A. 1976. Wegener granulomatosis with aphasia. Arch. Intern. Med. 136, 87–89.

Said, G. 1997. Necrotizing peripheral nerve vasculitis. Neurol. Clin. 15, 835–848.

Review on peripheral nerve vasculitides.

Said, G. 2002. Neurological manifestations of systemic necrotizing vasculitis (in French). Rev. Neurol. (Paris) 158, 915–918.

Said, G., Lacroix-Ciaudo, C., Fujimura, H., Blas, C., Faux, N. 1988. The peripheral neuropathy of necrotizing arteritis: a clinico-pathological study. Ann. Neurol. 23, 461–465.

Salih, A.M., Nixon, N.B., Dawes, P.T., Mattey, D.L. 1999. Soluble adhesion molecules and anti-endothelial cell antibodies in patients with rheumatoid arthritis complicated by peripheral neuropathy. J. Rheumatol. 26, 551–555.

Salojin, K.V., Le Tonqueze, M., Saraux, A., Nassonov, E.L., Dueymes, M., Piette, J.C., Youinou, P.Y. 1997. Antiendothelial cell antibodies: useful markers of systemic sclerosis. Am. J. Med. 102, 178–185.

Sangle, S., Karim, M.Y., Hughes, G.R., D'Cruz, D.P. 2002. Sulphamethoxazole–trimethoprim in the treatment of limited paranasal Wegener's granulomatosis. Rheumatology (Oxford) 41, 589–590.

Satoh, J., Miyasaka, N., Yamada, T., Nishido, T., Okuda, M., Kuroiwa, T., Shimokawa, R. 1988. Extensive cerebral infarction due to involvement of both anterior cerebral arteries by Wegener's granulomatosis. Ann. Rheum. Dis. 47, 606–611.

Savage, C.O., Winearls, C.G., Evans, D.J., Rees, A.J., Lockwood, C.M. 1985. Microscopic polyarteritis: presentation, pathology and prognosis. QJM 56, 467–483.

Saveuse, H., Dorra, M., Dechy, H., Baglin, C., Rouveix, E., Betourne, C. 1988. Temporal arteritis: a syndrome. From Horton's disease to periarteritis nodosa (in French). Presse Med. 17, 517–520.

Scarrow, A.M., Segal, R., Medsger, T.A. Jr., Wasko, M.C. 1998. Communicating hydrocephalus secondary to diffuse meningeal spread of Wegener's granulomatosis: case report and literature review. Neurosurgery 43, 1470–1473.

von Scheven, E., Lee, C., Berg, B.O. 1998. Pediatric Wegener's granulomatosis complicated by central nervous system vasculitis. Pediatr. Neurol. 19, 317–319.

Scott, D.G., Bacon, P.A., Elliott, P.J., Tribe, C.R., Wallington, T.B. 1982. Systemic vasculitis in a district general hospital 1972–1980: clinical and laboratory features, classification and prognosis of 80 cases. QJM 51, 292–311.

Sehgal, M., Swanson, J.W., DeRemee, R.A., Colby, T.V. 1995. Neurologic manifestations of Churg–Strauss syndrome. Mayo Clin. Proc. 70, 337–341.

Shiotani, A., Mukobayashi, C., Oohata, H., Yamanishi, T., Hara, T., Itoh, H., Nishioka, S. 1997. Wegener's granulomatosis with dural involvement as the initial clinical manifestation. Intern. Med. 36, 514–518.

Specks, U., Homburger, H.A., DeRemee, R.A. 1993. Implications of c-ANCA testing for the classification of Wegener's granulomatosis: performance of different detection systems. Adv. Exp. Med. Biol. 336, 65–70.

Specks, U., Moder, K.G., McDonald, T.J. 2000. Meningeal involvement in Wegener granulomatosis. Mayo Clin. Proc. 75, 856–859.

Specks, U., Fervenza, F.C., McDonald, T.J., Hogan, M.C. 2001. Response of Wegener's granulomatosis to anti-CD20 chimeric monoclonal antibody therapy. Arthritis Rheum. 44, 2836–2840.

Spranger, M., Schwab, S., Meinck, H.M., Tischendorf, M., Sis, J., Breitbart, A., Andrassy, K. 1997. Meningeal involvement in Wegener's granulomatosis confirmed and monitored by positive circulating antineutrophil cytoplasm in cerebrospinal fluid. Neurology 48, 263–265.

Case report of pachymeningitis in WG with detection and monitoring of C-ANCA in the CSF.

Stegeman, C.A., Tervaert, J.W., Huitema, M.G., de Jong, P.E., Kallenberg, C.G. 1994. Serum levels of soluble adhesion molecules intercellular adhesion molecule 1, vascular cell adhesion molecule 1, and E-selectin in patients with Wegener's granulomatosis. Relationship to disease activity and relevance during followup. Arthritis Rheum. 37, 1228–1235.

Stone, J.H., Hoffman, G.S., Merkel, P.A., Min, Y.I., Uhlfelder, M.L., Hellmann, D.B., Specks, U., Allen, N.B., Davis, J.C., Spiera, R.F., Calabrese, L.H., Wigley, F.M., Maiden, N., Valente, R.M., Niles, J.L., Fye, K.H., McCune, J.W., St Clair, E.W., Luqmani, R.A. 2001. A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham vasculitis activity score. International Network for the Study of the Systemic Vasculitides (INSSYS). Arthritis Rheum. 44, 912–920.

Suggs, S.P., Thomas, T.D., Joy, J.L., Lopez-Mendez, A., Oh, S.J. 1992. Vasculitic neuropathy mimicking Guillain–Barré syndrome. Arthritis Rheum. 35, 975–978.

Sundy, J.S., Haynes, B.F. 2000. Cytokines and adhesion molecules in the pathogenesis of vasculitis. Curr. Rheumatol. Rep. 2, 402–410.

Tai, P.C., Holt, M.E., Denny, P., Gibbs, A.R., Williams, B.D., Spry, C.J. 1984. Deposition of eosinophil cationic protein in granulomas in allergic granulomatosis and vasculitis: the Churg–Strauss syndrome. Br. Med. J. (Clin. Res. Ed.) 289, 400–402.

Tervaert, J.W., Kallenberg, C. 1993. Neurologic manifestations of systemic vasculitides. Rheum. Dis. Clin. North Am. 19, 913–940.
Review of neurologic manifestations of vasculitides.

Tervaert, J.W., van der Woude, F.J., Fauci, A.S., Ambrus, J.L., Velosa, J., Keane, W.F., Meijer, S., van der Giessen, M., van der Hem, G.K., The, T.H. 1989. Association between active Wegener's granulomatosis and anticytoplasmic antibodies. Arch. Intern. Med. 149, 2461–2465.

Tervaert, J.W., Huitema, M.G., Hene, R.J., Sluiter, W.J., The, T.H., van der Hem, G.K., Kallenberg, C.G. 1990. Prevention of relapses in Wegener's granulomatosis by treatment based on antineutrophil cytoplasmic antibody titre. Lancet 336, 709–711.

Tesar, V., Jelinkova, E., Masek, Z., Jirsa, M. Jr., Zabka, J., Bartunkova, J., Stejskalova, A., Janatkova, I., Zima, T. 1998. Influence of plasma exchange on serum levels of cytokines and adhesion molecules in ANCA-positive renal vasculitis. Blood Purif. 16, 72–80.

Thomas-Golbanov, C., Sridharan, S. 2001. Novel therapies in vasculitis. Expert Opin. Invest. Drugs 10, 1279–1289.

Tishler, S., Williamson, T., Mirra, S.S., Lichtman, J.B., Gismondi, P., Kibble, M.B. 1993. Wegener granulomatosis with meningeal involvement. Am. J. Neuroradiol. 14, 1248–1252.

Tojo, J., Nishimaki, T., Ohyanagi, H., Saito, A., Ohira, H., Saka, M., Kuroda, M., Ishikawa, H., Kasukawa, R. 1998. An autopsy case of Wegener's granulomatosis with pachymeningitis. Intern. Med. 37, 711–715.

Vital, A., Vital, C. 1985. Polyarteritis nodosa and peripheral neuropathy. Ultrastructural study of 13 cases. Acta Neuropathol. (Berl.) 67, 136–141.

Vollmer, T.L., Guarnaccia, J., Harrington, W., Pacia, S.V., Petroff, O.A. 1993. Idiopathic granulomatous angiitis of the central nervous system. Diagnostic challenges. Arch. Neurol. 50, 925–930.

Walton, E.W. 1958. Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). Br. Med. J. 2, 265–270.

Wees, S.J., Sunwoo, I.N., Oh, S.J. 1981. Sural nerve biopsy in systemic necrotizing vasculitis. Am. J. Med. 71, 525–532.

Weinberger, L.M., Cohen, M.L., Remler, B.F., Naheedy, M.H., Leigh, R.J. 1993. Intracranial Wegener's granulomatosis. Neurology 43, 1831–1834.

van der Woude, F.J., Rasmussen, N., Lobatto, S., Wiik, A., Permin, H., van Es, L.A., van der Giessen, M., van der Hem, G.K., The, T.H. 1985. Autoantibodies against neutrophils and monocytes: tool for diagnosis and marker of disease activity in Wegener's granulomatosis. Lancet 1, 425–429.

Woywodt, A., Knoblauch, H., Kettritz, R., Schneider, W., Gobel, U. 2000. Sudden death and Wegener's granulomatosis of the pituitary. Scand. J. Rheumatol. 29, 264–266.

Woywodt, A., Streiber, F., de Groot, K., Regelsberger, H., Haller, H., Haubitz, M. 2003. Circulating endothelial cells as markers for ANCA-associated small-vessel vasculitis. Lancet 361, 206–210.

Wynne, P.J., Younger, D.S., Khandji, A., Silver, A.J. 1997. Radiographic features of central nervous system vasculitis. Neurol. Clin. 15, 779–804.
Review of radiologic features of CNS vasculitis.

Xiao, H., Heeringa, P., Hu, P., Liu, Z., Zhao, M., Aratani, Y., Maeda, N., Falk, R.J., Jennette, J.C. 2002. Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. J. Clin. Invest. 110, 955–963.

Yamashita, Y., Takahashi, M., Bussaka, H., Miyawaki, M., Tosaka, K. 1986. Cerebral vasculitis secondary to Wegener's granulomatosis: computed tomography and angiographic findings. J. Comput. Tomogr. 10, 115–120.

Yokote, H., Terada, T., Nakai, K., Itakura, T. 1997. Subdural and meaningful involvement related to Wegener's granulomatosis: case report. Neurosurgery 40, 1071–1073.

Younger, D.S., Kass, R.M. 1997. Vasculitis and the nervous system. Historical perspective and overview. Neurol. Clin. 15, 737–758.

Younger, D.S., Calabrese, L.H., Hays, A.P. 1997. Granulomatous angiitis of the nervous system. Neurol. Clin. 15, 821–834.
Review on primary CNS angiitis.

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CHAPTER 9

Large Vessel Vasculitis—Temporal (Giant Cell) Arteritis and Polymyalgia Rheumatica

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1. Introduction

Temporal (giant cell) arteritis is a systemic vasculitis of medium and large vessels. The clinical manifestations of this disease relate both to the systemic inflammatory features as well as local ischemic complications of vasculitis. While relatively rare in the population, it is important for clinicians to be aware of the varied clinical presentations of temporal arteritis as failure to establish the correct diagnosis and initiate treatment may lead to irreversible visual loss or other morbid complications.

Neurologic manifestations and complications are among the most important features of temporal arteritis and are the subject of this chapter. In this discussion, we will include neurologic manifestations as well as the most feared complications of visual loss and other visual symptoms. Polymyalgia rheumatica (PMR) is a related and more common condition that is a proximal tenosynovitis and bursitis associated with morning stiffness and aching in the shoulders, neck, and hips. While PMR occurs in approximately one third of patients with temporal arteritis, it is not a form of vasculitis and most patients with PMR never develop temporal arteritis. When PMR occurs in isolation, without coexisting temporal arteritis, neurologic complications do not occur. It is, however, important for clinicians to be alert to potential symptoms of temporal arteritis in patients with PMR so as to guide proper diagnosis and treatment. As neurologic features do not exist in isolated PMR, we will restrict our further discussion of this entity to its usefulness in the diagnosis of temporal arteritis.

2. Prevalence

Many studies have reported the incidence of temporal arteritis in varied populations. The incidence varies by geographic location but has ranged from 1 to 22 per 100,000 individuals over age 50 years (Table 1). As an example, Bengtsson and Malmvall (1981b) reviewed the pathology laboratory's records for all individuals in Goteburg, Sweden in addition to a medical record review for all patients with a diagnosis of temporal arteritis or PMR. In this city, the population was almost entirely of Scandinavian origin. Over a 3-year period, 126 patients were diagnosed with temporal arteritis. The average annual incidence for the entire population was 4.6 per 100,000; for individuals 50 years of age or older the incidence was 14.0 per 100,000. PMR is more common than temporal arteritis. Prevalence estimates

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Table 1
Incidence of polymyalgia rheumatica (PMR) and temporal arteritis in population-based studies

Study and Year	Locale	Incidence of PMR per 100,000 people over age 50			Incidence of temporal arteritis per 100,000 people over age 50		
		Men	Women	Total	Men	Women	Total
Bengtsson and Malmvall (1981)	Sweden	11.4	27.9	20.3	8	13.7	14
Friedman et al. (1982)	Israel				0.5	0.47	0.49
Smith et al. (1983)	Tennessee				0.43	2.43	1.58
Boesen and Sorensen (1987)	Denmark	28	104.9	68.3	3.5	38.2	21.6
Salvarani et al. (1991)	Italy	9.7	14.9	12.7	5.8	7.8	6.9
Gonzalez-Gay et al. (1992)	Spain				6.9	5.1	6
Salvarani et al. (1995a)	Olmsted County, Minnesota	39.9	61.7	52.5			
Salvarani et al. (1995a)	Olmsted County, Minnesota				8.2	24.2	17.8
Gran and Myklebust (1997)	Norway	83.2	137.7	112.6	16.3	39.9	29
Petursdottir et al. (1999)	Sweden				12.5	29.8	22.2

range from 13 to 112 per 100,000 individuals over age 50 years.

While temporal arteritis is a rare condition compared with other illnesses in older patients, its morbidity and clinical consequences justify a high level of suspicion of the disease when patients present with a variety of potential compatible symptoms. In one autopsy series, the author found evidence for healed temporal arteritis in 16 of 1097 patients (1.5%) (Ostberg, 1971). The diagnosis was established before death in only two of these cases. This much higher prevalence than is clinically apparent suggests that many cases of temporal arteritis remain undetected, perhaps because they are asymptomatic. The natural history and prognosis of these patients are unknown.

3. Epidemiology

Temporal arteritis is a disease of older individuals. Patients under age 50 years with a histologically confirmed diagnosis of temporal arteritis are largely restricted to case reports and small case series. In our recent review of the value of the clinical examination for the diagnosis of temporal arteritis, we identified 26 studies that provided detailed descriptions of patient age ranges (Smetana and Shmerling, 2002). Among 1435 patients with a positive temporal artery biopsy, only two were less than 50 years of age. Unless the clinical picture is compelling, clinicians may discard the possibility of temporal arteritis when evaluating patients under age 50 years.

The prevalence rises with each additional decade. For example, in a study of the annual incidence rates of temporal arteritis in a Swedish population, overall incidence rates per 100,000 for patients aged 50–59, 60–69, 70–79, and $\geq$80 years were 6.6, 27.7, 62.9, and 70.1, respectively (Bengtsson and Malmvall, 1981a,b). In addition, temporal arteritis has been two to three times as common in women than in men in epidemiologic studies (Table 1) and was 2.1 times more prevalent in women than in men in an analysis of pooled data of 40 studies that provided clinical information on patients with positive temporal artery biopsies (Smetana and Shmerling, 2002).

Temporal arteritis is more common in higher latitudes. This is illustrated by the data in Table 1. For example, the overall prevalence for individuals over age 50 in Sweden was 21.6 per 100,000 while the prevalence was only 6.0 per 100,000 in a population study in Spain. In the United States, the disease is ten times more prevalent in Minnesota than in Tennessee (Smith et al., 1983; Salvarani et al., 1995b). The basis for this clustering is unknown but may be due to a genetic predisposition among ethnic groups more common in northern latitudes, the relative ethnic homogeneity in certain population samples or even to an environmental or infectious trigger more prevalent in higher latitudes.

Temporal arteritis is much more common in Caucasians than in African-Americans. Few African

Americans are represented in the published experience of temporal arteritis. In one study in Tennessee that reported race of affected individuals, the incidence of temporal arteritis was seven times greater in whites than in blacks (Smith et al., 1983).

Periodic clustering exists in new diagnoses of temporal arteritis. Salvarani et al. (1995) reported the trends in the incidence of temporal arteritis over a period of four decades in Olmsted County, Minnesota. They found peak clusters at approximately 7-year intervals during which the incidence of new diagnoses of temporal arteritis doubled. Other authors have also reported cyclic fluctuations (Petursdottir et al., 1999).

4. Etiology/pathogenesis

The underlying etiology and pathogenesis of temporal arteritis remains unknown. Any mechanism proposed to explain the development of this condition must address its remarkable propensity to affect older, Caucasian persons of Northern European descent living in higher latitudes of Europe and the United States. In addition, a genetic influence on pathogenesis is suggested by reports of familial cases (Mathewson and Hunder, 1986), an increased risk of disease among persons with HLA-DR4 and among those who have certain polymorphisms of the intercellular adhesion molecule-1 (ICAM-1) gene. One study of patients with temporal arteritis identified polymorphisms of HLA-DRB1 gene involved in antigen binding of HLA-DR molecules arguing that genetic alterations in antigen binding play a key role in disease development (Weyand et al., 1992). The intriguing cyclic incidence of the disease every 5–7 years (Salvarani et al., 1995a,b) and its propensity to affect persons in higher latitudes have led some investigators to favor an infectious cause (Liozon et al., 2001b; Nordborg and Nordborg, 2003). However, despite studies identifying evidence of present or past infection with chlamydia, parvovirus, parainfluenza virus and other organisms in patients with temporal arteritis, no single infectious agent has been conclusively linked to the development of the disease.

Whether triggered by an exogenous factor such as infection or solar radiation, as suggested by O'Brien and Regan (1998), or by some other mechanism, the immune system is active in persons with temporal arteritis. Biopsy specimens of temporal arteries from patients with temporal arteritis sometimes demonstrate immunoglobulin deposition along the internal elastic lamina, but most evidence points to cellular, rather than humoral, immunity as the more important pathogenic component. Lymphocytes present in the inflammatory infiltrate of temporal arteries are CD4-positive T cells, including clones of identical T cells arguing that their arrival was in response to a particular antigen. The infiltrate also contains macrophages and multinucleated giant cells, sometimes creating the classic granulomatous inflammation noted in the original pathologic descriptions of the disease. Recent studies suggest that cytokines, such as interferon gamma, interleukin-1, and interleukin-6 may play important roles in the inflammatory and ischemic features of temporal arteritis (Roche et al., 1993; Weyand et al., 1997).

Grossly, the temporal artery is enlarged and may demonstrate areas of ectasia, stenosis and even aneurysm formation. As noted above, histologic evaluation reveals an inflammatory infiltrate, often patchy or intermittent along the course of the artery. The inflammatory infiltrate may narrow or obliterate the lumen and is especially prominent in the media and near the internal elastic lamina. The inflammation contains CD4 lymphocytes and macrophages; thickening of the intima and disruption of the internal elastic lamina are common. While giant cells and granulomatous inflammation are classic, they are not routinely present and are not required for diagnosis. Similar histologic changes may be seen in the aorta and other branches of the external carotid system. Of note, intracranial vasculitis is highly unusual in temporal arteritis. Studies demonstrate that even after several weeks of corticosteroid therapy, histologic evidence of temporal arteritis often persists (Achkar et al., 1994).

In some cases, vasculitis involving the temporal artery may be due to a disease other than temporal arteritis. For example, arteritis of the temporal artery and vasculitic mononeuritis multiplex should raise the possibility of polyarteritis nodosa (PAN); careful histologic examination may help to sort out whether temporal arteritis or another form of vasculitis is present, especially because other vasculitides that

involve medium-sized vessels (such as PAN, Wegener's Granulomatosis, Churg-Strauss vasculitis or microscopic Polyangiitis) may have clinical features that overlap with temporal arteritis.

5. Clinical manifestations

5.1. Non-neurologic manifestations

The classic presentation of temporal arteritis may be divided into arteritic and systemic manifestations. Arteritic symptoms include headache, jaw claudication, scalp tenderness, and visual deficits while constitutional symptoms include proximal myalgia (as is typical of PMR), morning stiffness, fever, malaise, anorexia, and weight loss. Symptoms are typically acute in onset and severe enough that patients seek medical care. Patients may complain of the sudden onset of scalp pain so severe that it is uncomfortable to wear their glasses or comb their hair. Jaw claudication develops due to ischemia of the masseter and temporalis muscles that results from vasculitic narrowing of branches of the external carotid artery. Pain develops with prolonged chewing or even talking; painful dysphagia may be prominent. It is not rare for the initial workup to focus on the possibility of occult malignancy or infection, especially because fever may be prominent (Hu et al., 2000).

For the 10–15% of patients with large vessel involvement, such as thoracic aorta, subclavian or axillary artery arteritis, symptoms may include chest pain, arm claudication, paresthesias, and vasospastic or ischemic distal upper extremity symptoms. With aortitis, the risk of aneurysm in increased markedly although there may be no symptoms or symptoms may develop years after the diagnosis is established; thoracic aortic aneurysm rupture or dissection related to active or past temporal arteritis may lead to ischemic arm symptoms or sudden death (Evans et al., 1994).

In our review of all studies between 1966 and 2000 that included at least 10 patients of whom 90% or more had temporal artery biopsies, only symptoms of jaw claudication (present in 34% of patients with temporal arteritis) and diplopia (present in 9% of patients with temporal arteritis) were significant independent predictors of a positive biopsy (Smetana and Shmerling, 2002). Vasculitis of branches of the pulmonary artery may be responsible for a chronic, non-productive cough which infrequently may be a presenting symptom of temporal arteritis (Lim et al., 1999; Desmet et al., 1990). Less common symptoms include eye pain, facial swelling, and extremity swelling.

5.2. Neurologic manifestations

We consider here both neurologic and visual complications of temporal arteritis and will categorize these manifestations as common, infrequent, and rare. Table 2 lists the neurologic complications of temporal arteritis.

Table 2
Neurologic manifestations of temporal arteritis

Common (>30% prevalence)
Headache
Temporal headache
Any visual symptom
Infrequent (10–30% prevalence)
Visual loss
Vertigo
Rare (<10% prevalence)
Diplopia
Hearing loss
Stroke or TIA
Peripheral neuropathy
Mononeuritis multiplex
Brachial plexopathy
Cervical radiculopathy
Visual hallucinations
Spinal cord infarction
Organic affective disorder
Psychosis
Dementia
Tremor
Lingual or facial paralysis
Seizures
Anosmia
Hypopituitarism
Diabetes insipidus

5.2.1. Common manifestations (>30% prevalence)

5.2.1.1. Headache. Common neurologic manifestations include headache and visual symptoms. Table 3 cites published studies with the largest number of included patients that characterize the prevalence of the most common symptoms among patients with temporal arteritis. In each of these studies, at least 90% of patients classified as temporal arteritis were subjected to a temporal artery biopsy and had a positive result. Headache is the most common symptom of temporal arteritis. The prevalence of this symptom among patients with biopsy-confirmed temporal arteritis ranges from 56 to 93%. In our recent review of all eligible studies, the overall sensitivity of this finding for the prediction of a positive temporal artery biopsy among patients suspected having the disease was 75% (Smetana and Shmerling, 2002). Among the subset of studies in the literature that further characterize the location of the headache, the mean prevalence of temporal headache is 52%; the range is 28–95%.

The nature of the headache of temporal arteritis is varied. Few studies offer sufficient detail to allow

Table 3
Frequency of common neurologic manifestations among patients with biopsy confirmed temporal arteritis

Study	Number of patients with symptom	Number of patients	Frequency of symptom
Any headache			
Gonzalez-Gay et al. (1998)	198	239	0.83
Duhaut et al. (1999)	171	207	0.83
Cid et al. (1998)	153	200	0.77
Gabriel et al. (1995)	117	172	0.68
Baldursson et al. (1994)	84	108	0.78
Hayreh et al. (1997)	59	106	0.56
Hall et al. (1983)	32	46	0.70
Vilaseca et al. (1987)	36	45	0.80
McDonnell et al. (1986)	36	42	0.86
Chmelewski et al. (1992)	28	30	0.93
Temporal headache			
Hunder et al. (1990)	138	214	0.64
Duhaut et al. (1999)	86	207	0.42
Fauchald et al. (1972)	25	61	0.41
Fainaru et al. (1979)	13	47	0.28
Myklebust and Gran (1996)	15	39	0.38
Desmet et al. (1990)	12	34	0.35
Dare and Byrne (1980)	21	25	0.84
Hauser et al. (1971)	18	19	0.95
Dimant et al. (1980)	11	14	0.79
Any visual symptom			
Hunder et al. (1990)	45	212	0.21
Duhaut et al. (1999)	65	207	0.31
Gabriel et al. (1995)	51	172	0.30
Jonasson et al. (1979)	81	124	0.65
Fauchald et al. (1972)	4	61	0.07
Hall et al. (1983)	11	46	0.24
Vilaseca et al. (1987)	14	45	0.31
McDonnell et al. (1986)	29	42	0.69
Chmelewski et al. (1992)	18	30	0.60
Fernandez-Herlihy (1989)	8	29	0.28

a detailed description of the 'classic' headache of temporal arteritis. As a practical consideration, clinicians should entertain the possibility of temporal arteritis in any patient with the new onset of headache or change in the pattern of a chronic headache after age 50. However, some general observations are appropriate. While the location of the headache can be anywhere, two thirds of patients with temporal arteritis and headache note temporal headache (Table 3). In a review of headache characteristics among 317 patients with temporal arteritis, Solomon and Cappa (1987) noted that 50% of patients reported headache limited to the temples and that generalized headache occurred in only 6.5% of patients. The pain involved the face and neck in 8% of patients. The most common headache descriptor was that of a throbbing pain; less common descriptors were sharp, dull, or burning. The pain was equally likely to be constant or intermittent and was more likely to be severe than mild or moderate.

In our review of the diagnostic value of clinical features of temporal arteritis, temporal headache, surprisingly, did not significantly predict the likelihood of a positive temporal artery biopsy among patients suspected of having the disease (Smetana and Shmerling, 2002). The positive and negative likelihood ratios for this feature were 1.5 (CI 0.78-3.0) and 0.82 (CI 0.64-1.0), respectively. This reflects the preselection among clinicians in determining which patients to refer for biopsy and the awareness among referring clinicians of the importance of this symptom and does not imply that this symptom is unhelpful in suggesting the possibility of temporal arteritis. On the other hand, even though its presence is characteristic, the absence of a headache in patients with other suggestive features is not reliable enough to rule out the diagnosis.

5.2.1.2. Visual symptoms. Among studies that lumped all visual symptoms of temporal arteritis together, the prevalence ranged from 7 to 69%; the mean was 35% (Table 3). This feature is therefore one half as common as headache among patients with biopsy-proven temporal arteritis. We discuss the individual features below.

5.2.2. Infrequent manifestations (10–30%)

5.2.2.1. Visual loss. Visual loss is the most feared consequence of unrecognized and untreated temporal arteritis. Eye pain is rarely reported. Table 4 cites the prevalence of unilateral or bilateral visual loss among patients with biopsy-proven temporal arteritis. Unilateral visual loss occurs in 24% of patients; the range is 3–54%. The wide variation in the reported incidence of this symptom is due in part to the referral bias in the primary studies related to the locus of patient recruitment (i.e. primary care practice vs. rheumatology practice vs. ophthalmology practice). Bilateral visual loss occurs in 15% of patients (range 2–39%).

Visual loss, either transient or permanent, may be the first symptom of temporal arteritis but more commonly occurs after other characteristic features are present. Visual loss is most commonly the result of posterior ciliary artery inflammation and/or occlusion, as may be demonstrated by fluorescein evaluation of the fundus (Hayreh et al., 1998). Clinicians should consider the possibility of temporal arteritis in any patient over age 50 with the sudden onset of painless visual loss, even in the absence of other features of temporal arteritis. Gonzalez-Gay et al. (2000) recently reviewed their experience with 161 patients with biopsy-proven temporal arteritis in Lugo, Spain. Visual manifestations occurred in 42 (26%) of patients. Twenty-three patients had transient visual loss and 24 experienced permanent visual loss. Half of the patients with permanent visual loss reported transient visual loss (amaurosis fugax) that preceded permanent visual loss. This observation points out the importance of considering temporal arteritis when faced with a patient over age 50 years with transient visual loss. Among the 24 patients with permanent visual loss, 22 were due to anterior ischemic optic neuritis, 2 to central retinal artery occlusion, and one to occipital infarction. When the authors compared the clinical manifestations of patients with and without visual manifestations, patients with visual manifestations were less likely to report constitutional manifestations or fever.

Hayreh et al. (1998) described visual manifestations among 170 patients with temporal arteritis who had been referred to their ophthalmology department and who were therefore more likely to

Table 4
Frequency of less common manifestations among patients with biopsy confirmed temporal arteritis

Study	Number of patients with symptom	Number of patients	Frequency of symptom
Unilateral visual loss			
McDonnell et al. (1986)	19	42	0.45
Hunder et al. (1990)	16	213	0.08
Cid et al. (1998)	14	200	0.07
Jonasson et al. (1979)	54	124	0.44
Hedges et al. (1983)	1	31	0.03
Whitfield et al. (1963)	16	72	0.22
Fainaru et al. (1979)	11	47	0.23
Glutz von Blotzheim and Borruat (1997)	12	47	0.26
Jacobson and Slamovits (1987)	13	24	0.54
Bilateral visual loss			
Hunder et al. (1990)	5	213	0.02
Jonasson et al. (1979)	27	124	0.22
Whitfield et al. (1963)	28	72	0.39
Fainaru et al. (1979)	3	47	0.06
Hamilton et al. (1971)	7	25	0.28
Jacobson and Slamovits (1987)	4	24	0.17
Dimant et al. (1980)	2	14	0.14
Vertigo			
Jonasson et al. (1979)	6	124	0.05
Fernandez-Herlihy (1988)	4	29	0.14
Fauchald et al. (1972)	11	61	0.18
Gonzalez et al. (1989)	0	10	0

have ocular features than unselected patients. In this selected cohort, one half of patients had ocular involvement. These authors also found a lower incidence of some constitutional manifestations including fever, myalgia among patients with ocular manifestations. Among the 85 patients with ocular symptoms, 38 had bilateral involvement, 26 had amaurosis fugax and 83 had either transient or permanent visual loss. Findings on ophthalmologic examination included anterior ischemic neuropathy (69 patients), central retinal artery occlusion (12 patients), cilioretinal artery occlusion (12 patients), and posterior ischemic optic neuropathy. In our review of studies of all patients with biopsy-proven temporal arteritis, optic atrophy or ischemic optic neuropathy occurred in 29% of patient; 31% of patients had an abnormal funduscopic examination (Smetana and Shmerling, 2002). The finding of an abnormal funduscopic examination did not, however, significantly change the likelihood of temporal arteritis among patients suspected of having the disease.

Clinical predictors of visual loss have been reported in case series of patients with temporal arteritis. For example, transient visual loss, stroke and high platelet count were associated with permanent visual loss (Gonzalez-Gay et al., 2000; Liozon et al., 2001a), while constitutional symptoms (including weight loss, anorexia, and fatigue), PMR and an elevated C-reactive protein were associated with reduced risk of visual loss (Liozon et al., 2001a,b).

The visual prognosis of patients with ocular manifestations of temporal arteritis has been well studied. Aiello and colleagues studied 245 patients with temporal arteritis who were treated with glucocorticoids and who had a ophthalmologic examination early in the course of their illness (Aiello et al., 1993). Thirty-four (14%) had permanent visual loss. Visual loss occurred before

diagnosis in 32 patients; only 3 patients had additional visual loss after institution of glucocorticoid treatment. They estimated the probability of additional visual loss after treatment to be 13% at 5 years among patients who presented with visual loss at the time of diagnosis and only 1% among patients with no ocular symptoms at the time of diagnosis. Hayreh et al. (2002) reported on 84 consecutive patients (114 eyes) with visual loss and biopsy-proven temporal arteritis. Improvement in visual acuity occurred in only five eyes after initiation of glucocorticoid therapy. Foroozan et al. (2003) similarly observed a low likelihood of improvement of existing visual loss due to temporal arteritis after initiation of corticosteroid therapy. In their report, improvement in visual acuity occurred in only 5 of 39 eyes. These observations reinforce the importance of the prompt diagnosis and treatment of temporal arteritis among patients with a compatible clinical picture. The importance of early treatment in patients who present with permanent visual loss, given the low rate of improvement with glucocorticoid therapy, is to preserve vision in the contralateral eye.

5.2.2.2. Audiovestibular manifestations. Vertigo occurs in 11% of patients with temporal arteritis. This symptom does not, however, significantly change the likelihood of temporal arteritis among patients suspected of having the disease (Smetana and Shmerling, 2002). The presence of vertigo in a patient with other nonspecific symptoms of temporal arteritis may influence the decision to proceed to temporal artery biopsy. Hearing loss may also accompany temporal arteritis. In a 1989 review, 14 cases had been described in the literature (Sonnenblick et al., 1989).

Amor-Dorado et al. (2003) prospectively evaluated 44 patients with temporal arteritis and performed detailed testing including audiograms and video nystagmography on all patients. In this study specifically designed to determine the prevalence of audiovestibular manifestations of temporal arteritis, the authors found a much higher prevalence of vertigo and other audiovestibular symptoms than reported in unselected clinical series. The prevalence of vertigo, dizziness, dysequilibrium, subjective hearing loss, and tinnitus were 50, 55, 50, 61, and 50%, respectively. On detailed testing, 39 of 44 patients (89%) had abnormal vestibular tests. Most cases of vestibular dysfunction reversed with glucocorticoid treatment. At 3 months after diagnosis, the prevalence of tinnitus, vertigo, and abnormal vestibular test results was 14, 2, and 30%, respectively. The mechanism for the development of vertigo is unknown but may relate to either ischemia of the vertebrobasilar system or terminal cochleovestibular vessels or to the effects of autoantibodies (Amor-Dorado et al., 2003).

5.2.3. Rare manifestations (< 10%)

5.2.3.1. Diplopia. Among the rare neurologic manifestations of temporal arteritis, diplopia is the most useful to clinicians. Diplopia occurs in 9% of patients with temporal arteritis (Smetana and Shmerling, 2002). Its presence significantly increases the likelihood of temporal arteritis among patients suspected of the disease and confers a positive likelihood ratio of 3.4. In our review of the diagnostic value of symptoms of temporal arteritis, only jaw claudication conferred a higher positive likelihood ratio. This does not imply that diplopia is common, but rather that its presence, in the correct clinical context, substantially increases the probability of temporal arteritis. Diplopia may result from several different pathophysiologic mechanisms. Reports exist of internuclear ophthalmoplegia (Ahmad and Zaman, 1999), ocular muscle paresis (Goldberg, 1983), and vasculitis of orbital arteries including the ophthalmic and posterior ciliary arteries (Barricks et al., 1977). Ptosis and miosis may rarely accompany ophthalmoplegia (Dimant et al., 1980).

5.2.3.2. Stroke. Stroke is a rare but morbid complication of temporal arteritis. While the overall mortality for patients with temporal arteritis does not differ from age matched controls over follow up periods up to 12 years (Bengtsson and Malmvall, 1981a,b; Matteson et al., 1996; Gonzalez-Gay et al., 1997), a disproportionate number of deaths due to temporal arteritis are the result of strokes.(Caselli et al., 1988a) As in other neurologic complications of temporal arteritis, it can occasionally be the initial presenting symptom. It is difficult to determine the prevalence of stroke as a complication of temporal arteritis as the older population at risk for temporal

arteritis also has a high stroke risk given the prevalence of atherosclerotic disease or risk factors for the same. In the absence of pathologic confirmation from autopsy material, it is difficult to conclude from case series whether temporal arteritis was the definite cause of a cerebrovascular event. Casselli et al. 1988 reviewed the Mayo Clinic experience with temporal arteritis and reported neurologic findings in 51 of 166 consecutive patients. Twelve patients (7%) had a TIA or stroke; 8 in the carotid system and 4 in the vertebrobasilar system. Eight of these events occurred in patients already taking corticosteroids. In two patients, transient symptoms occurred 1–2 years after diagnosis in the setting of a corticosteroid taper and resolved with increasing corticosteroid dosage.

The vertebrobasilar system is affected proportionately to a greater degree in temporal arteritis than for disease due to atherosclerosis. Clinical syndromes include ataxia, lateral medullary syndrome, hemianopsia, and hearing loss (Monteiro et al., 1984; Reich et al., 1990). Reports exist of bilateral vertebral artery occlusion due to temporal arteritis (Ruegg et al., 2003). This particular stroke syndrome is sufficiently rare due solely to atherosclerotic vascular disease that its occurrence should raise suspicion of temporal arteritis.

5.2.3.3. Peripheral neuropathy. Peripheral neuropathies may accompany temporal arteritis. These may occur in the form of isolated mononeuropathies, mononeuritis multiplex, brachial plexopathy, cervical radiculopathy, and diffuse peripheral neuropathies. Affected nerves in mononeuropathy have included the median, radial, peroneal, sural, tibial, and sciatic nerves (Caselli et al., 1988a,b). The actual prevalence is unknown. In a 1987 review of the literature, only 24 cases of neuropathies associated temporal arteritis existed, (Golbus and McCune, 1987) but subsequent reviews of consecutive patients suggest a higher frequency of neuropathy.

In a series of 166 consecutive patients with histologically confirmed temporal arteritis at they Mayo Clinic, 23 (14%) had clinically diagnosed neuropathies (Caselli et al., 1988a,b). In this series, 11 had diffuse peripheral neuropathies, 9 had mononeuritis multiplex, and 3 had an isolated mononeuropathy. In most cases, the neuropathies improved with treatment. In one case (and in two case from the 1987 review), histologic evidence was found of vasculitis of medium-sized vessels with ischemic necrosis of nerve fascicles suggesting that vasculitis plays a direct role in the development of the neuropathy. The frequency of multiple simultaneous mononeuropathies (mononeuritis multiplex) also suggests ischemic complications of vasculitis as the likely cause of neuropathies in at least some patients with this complication of temporal arteritis.

5.2.3.4. Visual hallucinations. Visual hallucinations may precede the development of visual loss in patients destined to develop visual loss due to temporal arteritis. In a small series of 31 patients with temporal arteritis, 4 of 5 patients with permanent visual loss reported preceding visual hallucinations (Nesher et al., 2001). In these patients, the hallucinations were complex and each patient felt that they did not misinterpret a real image. Hallucinations in this small cohort of patients included carriages and horses, flowers, cats and mice, and colorful rays.

5.2.3.5. Spinal cord infarction. Fruchter and colleagues reported a case of an 80-year-old man with classic symptoms of temporal arteritis and a positive temporal artery biopsy who 2 days after initiation of corticosteroid therapy developed sudden onset of back pain and paraplegia (Fruchter et al., 2002). Examination and spinal MR findings were consistent with a spinal cord infarction that only partially improved with continued treatment. The authors identified five additional cases through a review of the previous literature. Another case of transverse myelitis was reported in a series of patients with neurologic manifestations (Caselli et al., 1988a,b). In addition, a case report exists of meningoradiculitis due to temporal arteritis (Roelcke et al., 2002).

5.2.3.6. Neuropsychiatric manifestations. Varied psychiatric syndromes have been described due to temporal arteritis. The literature experience consists primarily of case reports and small case series. In their recent case report, Johnson and colleagues identified 130 case reports before 1997

(Johnson et al., 1997). Reports exist of depression (organic affective disorder), psychosis, impaired memory, disorientation, dementia, and hallucinations. Case reports of temporal arteritis presenting with cognitive dysfunction suggest that this may be an under-recognized and treatable cause of dementia (Caselli et al., 1988a,b). Encephalopathy may rarely complicate temporal arteritis (Caselli and Hunder, 1997). In most of the reported cases of psychiatric syndromes, the symptoms resolved fully with corticosteroid therapy suggesting a causal relationship rather than a coincidence. Clinicians must distinguish psychiatric manifestations of temporal arteritis from those due to corticosteroid side effects in the patient who is already being treated for the disease. The case report literature describes psychiatric manifestations in previously untreated patients.

5.2.3.7. Miscellaneous neurologic manifestations. Several other neurologic features of temporal arteritis have been described at the case report level. Their etiologic relationship to the diagnosis of temporal arteritis is less well established. In the largest series to examine neurologic disease in biopsy-proven temporal arteritis, Caselli and colleagues identified neurologic manifestations in 51 of 166 consecutive patients (Caselli et al., 1988a,b). In addition to the above-described features, tremor occurred in 6 patients. In three cases this was a cerebellar tremor, in two cases an essential tremor, and in the remaining case a rest tremor. The authors also reported tongue numbness in three patients. Case reports also exist of lingual paralysis, (Caselli and Hunder, 1997) and facial pain due to facial artery vasculitis (Caselli and Hunder, 1997). In a recent review of neurologic manifestation of systemic vasculitis, Nadeau also identified case reports of the following in temporal arteritis: seizures (3 patients), anosmia (2 patients), hypopituitarism (4 patients), and diabetes insipidus (1 patient) (Nadeau, 2002).

5.3. Physical examination

The physical examination is often normal. In our review, however, approximately 65% of 1559 patients with biopsy-proven temporal arteritis had temporal artery abnormalities noted on examination, including thickening, beading, erythema, tenderness, or pulselessness. Shoulder and hip range of motion may be limited or painful on joint examination and fever may be present. Although a number of other physical findings have been reported in temporal arteritis (see below), in our meta-analysis, only the presence of an abnormal temporal artery (such as beading, prominence or tenderness) increased the likelihood of a positive biopsy; the absence of a temporal artery abnormality significantly decreased the likelihood (Smetana and Shmerling, 2002). The funduscopic examination may be particularly helpful as it may demonstrate ischemic optic neuropathy (Wakakura and Ishikawa, 1994) and/or central retinal artery occlusion. While these findings are not specific for temporal arteritis (and may, for example, be seen in diabetes or as an idiopathic process), they may, in the proper clinical setting, provide strong evidence of temporal arteritis.

Rarer manifestations noted on physical examination include wrist synovitis, scalp or tongue necrosis, thoracic bruits, and blood pressure differences in the arms (due to thoracic aorta or branch dissection or stenosis).

6. Diagnostic investigations

6.1. Radiological

While biopsy is the reference ('gold') standard for the diagnosis of temporal arteritis, other non-invasive diagnostic studies have been investigated (and advocated by some) including ultrasound of the temporal arteries (Schmidt et al., 1997; Murgatroyd et al., 2003), fluorescein retinal angiography, gallium scan (Reitblat et al., 2003), PET scan (Turlakow et al., 2001), and MRA. Convincing evidence does not yet exist of adequate sensitivity or specificity for these tests to supplant artery biopsy as the standard means for diagnosis. For example, a study of ultrasound suggested that a 'halo' of edema within the temporal artery was highly specific for temporal arteritis (Schmidt et al., 1997); however, the study was small, not all patients had temporal artery biopsy

performed and in most medical settings, ultrasonographers are unwilling to make a confident diagnosis of temporal arteritis using this technique.

6.2. Biochemistry/serology

The key to diagnosis of temporal arteritis is clinical suspicion. For patients older than age of 50 with appropriate symptoms and/or physical examination findings, an erythrocyte sedimentation rate (ESR) is an important initial diagnostic test. Other studies, including blood counts, chemistry studies, and imaging tests may be appropriate to rule out other possible causes of symptoms. In at least 90–95% of patients, the ESR will be elevated, often markedly so. However, cases of normal ESR in biopsy-proven disease are well documented; for example, Salvarani and Hunder, (2001) found normal ESRs in 5% of 167 patients with histological evidence of temporal arteritis and in our review, 4% of patients had normal ESRs and some patients with 'elevated' ESRs were only mildly abnormal (Smetana and Shmerling, 2002). For example, 19% of patients had ESRs less than 50 mm/hr (Table 5). Although a markedly elevated ESR (e.g. >100) is strongly supportive of the diagnosis of temporal arteritis in the proper clinical setting, we found only one-third of patients had such elevations (Table 6). Because two-thirds of patients with a negative biopsy had ESRs >50 mm/hr (Table 5) and 19% of these patient had ESRs >100 mm/hr (Table 6), the ESR cannot be used alone to predict the results of the temporal artery biopsy.

Other typical, but nonspecific findings include anemia, thrombocytosis, elevated alkaline phosphatase, polyclonal elevation in gamma globulin, and low serum albumin. The antinuclear antibody (ANA), rheumatoid factor (RF), and ANCA tend to be negative (absent) in patients with temporal arteritis. Because testing for these serologic markers is generally unhelpful and positive results may be misleading, these tests are not recommended for patients with suspected temporal arteritis.

6.3. Biopsy

Temporal artery biopsy is the gold standard for the diagnosis of temporal arteritis. While the results of the clinical evaluation and ESR may change the probability that a given patient has the disease, only a biopsy can confirm the diagnosis. If treatment were benign, one could argue that a highly compatible clinical picture in association with an elevated ESR would be sufficient to justify empiric treatment with corticosteroids without the need for biopsy (Nadeau, 2002). However, the usual duration of glucocorticoid therapy is at least 1–2 years and this duration

Table 5
Frequency of ESR >50 mm/hr among patients with suspected temporal arteritis stratified by biopsy results

	No. of patients with positive biopsy and ESR >50	No. of patients with positive biopsy	No. of patients with negative biopsy and ESR >50	No. of patients with negative biopsy
Baldursson et al. (1994)	103	118		
Branum et al. (1987)	62	62		
Brittain et al. (1991)	13	15	4	16
Chmelewski et al. (1992)	25	30	58	68
Cid et al. (1998)	14	25		
Fainaru et al. (1979)	46	46		
Gur et al. (1996)	30	30	0	9
Healey and Wilske (1980)	73	74		
Hunder et al. (1990)	179	207		
Jacobson and Slamovits (1987)	19	24		
Machado et al. (1988)	44	94		
Whitfield et al. (1963)	39	72		
Total	647 (81%)	797	62 (67%)	93

Table 6
Frequency of ESR >100 mm/hr among patients with suspected temporal arteritis stratified by biopsy results

	No. of patients with positive biopsy and ESR >100	No. of patients with positive biopsy	No. of patients with negative biopsy and ESR >100	No. of patients with negative biopsy
Brittain et al. (1991)	7	15	0	16
Chmelewski et al. (1992)	12	30	16	68
Dare and Byrne (1980)	9	25		
Desmet et al. (1990)	21	34		
Glutz von Blotzheim and Borruat (1997)	15	45		
Jacobson and Slamovits (1987)	7	24		
Whitfield et al. (1963)	11	72		
Total	82 (33%)	245	16 (19%)	84

of therapy is associated with a high likelihood of morbidity including risk for avascular necrosis of joints, infection, and osteoporosis. In addition, one risks overlooking the true diagnosis if the clinical diagnosis of temporal arteritis is incorrect.

For example, it has been suggested that one can use the American College of Rheumatology (ACR) 1990 criteria for the classification of temporal arteritis (Hunder et al., 1990) to clinically identify patients with a sufficient probability of temporal arteritis that no biopsy would be necessary. According to these criteria, at least three of the following criteria must be present to establish a diagnosis of temporal arteritis: (1) age at disease onset of ≥ 50 years, (2) new headache, (3) temporal artery abnormality on examination, (4) ESR ≥ 50 mm/hr., and (5) abnormal temporal artery biopsy. It would be possible, therefore, to diagnose temporal arteritis even without a temporal artery biopsy confirmation. These criteria were developed primarily as inclusion criteria for studies of temporal arteritis, not as a definition of disease in an individual patient; as such, they help standardize patients who are enrolled in studies, but are not necessarily reliable in clinical practice. Patients who meet criteria for temporal arteritis but have a negative temporal artery biopsy may have a better prognosis (e.g. less visual loss) than those with a positive biopsy (Gonzalez-Gay et al., 2001).

In the original series of 214 patients with temporal arteritis that constituted the derivation sample for these criteria, the presence of at least 3 criteria conferred a sensitivity of 93.5% and a specificity of 91.2%. It is not possible from the original case series to determine the sensitivity and specificity among patients who did not undergo a biopsy and who met criteria by having three of the first four criteria only. While the sensitivity and specificity are high, we feel that the morbidity of glucocorticoid treatment and the risk of overlooking another potentially treatable cause for a patient's symptoms warrant a higher degree of diagnostic certainty. In the example of this derivation set, 9% of patients would receive a clinical diagnosis of temporal arteritis despite a negative temporal artery biopsy and therefore would be subject to the morbidity of glucocorticoid therapy; the natural history of such patients is uncertain. We note also that the ACR criteria test characteristics were developed by comparing the clinical features of patients with temporal arteritis with those of patients with other forms of vasculitis. In clinical practice, the differential diagnosis extends to a broader range of possibilities than vasculitis.

In our review of the value of clinical features of temporal arteritis, even the most highly predictive factors had positive likelihood ratios in the 3–4 range for predicting a positive temporal artery biopsy. Their presence would not be sufficiently diagnostic to 'rule in' the diagnosis of temporal arteritis.

Several investigators have used decision analytic methods to address the question of the need for temporal artery biopsy. This approach is based on assumptions as to the diagnostic value of particular

clinical and laboratory features. Nadeau (1988) concluded that biopsy is most useful in patients with a high likelihood of developing glucocorticoid side effects and in those with a low pre-test probability of the disease. Buchbinder and Detsky (1992), in a separate decision analysis, concluded that biopsy followed by treatment for patients with positive results would be preferred for patients with an intermediate prior probability (50%) of disease and recommended consideration of treatment without biopsy only if the prior probability of disease exceeded 90%. The authors used an assumption of temporal artery biopsy sensitivity of 83%. In each of these decision analyses, the value of temporal artery biopsy would increase if the sensitivity of biopsy increased.

The choice of which artery to biopsy depends on the clinical findings. The yield may be higher on the symptomatic side for patients with lateralizing symptoms such as temporal headache or unilateral visual loss. If one vessel is particularly tender, beaded or has a diminished pulsation compared with the other, the yield for biopsy may be greater on this side. Bilateral temporal artery biopsies may increase the sensitivity and detection rate compared with clinically directed unilateral biopsies. Ponge et al. (1988) prospectively performed bilateral temporal artery biopsies in 200 patients suspected of having the disease. Of 42 positive biopsies, 22 were only unilaterally positive and 20 were positive bilaterally. Retrospective reviews of pathologic specimens suggest less value of bilateral biopsies. Hall and colleagues found only 2 cases of discordance between results among 59 patients who had either sequential unilateral or simultaneous biopsies (Hall et al., 2003). Boyev and colleagues reviewed the records of 186 patients who underwent bilateral simultaneous or sequential biopsies and found identical results on both sides in 176 patients. Clinicians should consider a contralateral biopsy for patients with a high prior probability of temporal arteritis who have a negative result of a unilateral temporal artery biopsy. If corticosteroid therapy is planned even with bilateral temporal artery biopsies (presumably because the diagnosis seems so certain by clinical presentation), it may still prove useful to perform the second biopsy—it might be positive, a highly useful finding if the diagnosis or the risks of therapy are questioned later.

Because the disease can be patchy within arteries, the yield of arterial biopsy may be increased by resecting a large segment (e.g. a 2–3 cm temporal artery) and by histologic analysis of fine cuts. Skip lesions in temporal arteritis, where a segment of an involved artery is normal, occurred in 8.5% of cases in one pathologic review (Poller et al., 2000). One can increase the sensitivity of temporal artery biopsy, and its value as a diagnostic test, by examining the biopsy specimen at multiple levels. The likelihood of a positive biopsy is not clearly diminished by prior corticosteroid treatment as long as the biopsy is performed within 2 weeks of initiation of therapy (Achkar et al., 1994) and the yield does not fall to zero even several weeks after therapy has begun. The morbidity of temporal artery biopsy, an outpatient procedure, is low.

While we acknowledge the lack of consensus among all authors and clinicians, we recommend a temporal artery biopsy for all patients suspected of having temporal arteritis. This approach is supported by a number of leading researchers in the field of temporal arteritis (Ghanchi and Dutton, 1997; Hunder, 1997; Evans and Hunder, 1998; Salvarani et al., 2002). If the prior probability is high and a unilateral biopsy returns negative results, we recommend consideration of a contralateral biopsy. Clinicians should strongly consider corticosteroid therapy for all patients suspected of having the disease while awaiting the biopsy results. If the results are negative, we recommend discontinuation of glucocorticoid therapy and continuing to search for an alternative diagnosis, unless the clinical prior probability is very high and no reasonable alternative diagnosis is apparent.

7. Differential diagnosis

The differential diagnosis of temporal arteritis in patients >50 years of age includes infectious, neoplastic, vascular, and other rheumatic diseases. One approach to the study of the differential diagnosis is to determine the ultimate or correct diagnoses among patients with a suspicion of disease whose temporal artery biopsy proved to be negative. Chmelewski et al., 1992 reviewed the records of 68 patients who had been referred for a temporal

artery biopsy and had negative results. Subsequent diagnoses for these patients included: (1) neurologic disorders (15 patients) including migraine, stroke, optic neuropathy and Parkinson's disease, (2) PMR (14 patients) without evidence for temporal arteritis, (3) other rheumatologic disorders (10 patients) including other vasculitides, rheumatoid arthritis, systemic lupus erythematosus, and CREST syndrome, (4) fever of unknown origin (4 patients), (5) infections (3 patients), and (6) malignancy (4 patients). Roth and colleagues determined the ultimate diagnosis for 33 patients who had negative temporal artery biopsy results (Roth et al., 1984). In their series, approximately equal numbers of patients had degenerative or rheumatoid arthritis, lymphoma, atherosclerotic carotid artery disease, diabetes mellitus, and ischemic optic neuropathy.

The differential diagnosis depends on the nature of the presenting symptoms. In series of patients referred to ophthalmologists for visual loss, the ultimate potential diagnoses will differ than for patients whose presenting feature was fever. As clinicians entertain the diagnosis of temporal arteritis in older patients, the differential diagnosis includes other illnesses more common in the elderly such as atherosclerotic vascular disease and malignancy. Any chronic infection may potentially mimic temporal arteritis but endocarditis is one that deserves particular mention.

8. Treatment

8.1. Corticosteroids

Standard therapy of temporal arteritis includes high dose corticosteroids. The recommended treatment schedule is oral corticosteroids, such as prednisone, 1 mg/kg/day for one month, tapering slowly over several months (by 10% every 1–2 weeks) to a range of 15–20 mg/day followed by an even slower taper. If visual loss has occurred or is occurring, initial therapy should include high dose intravenous corticosteroids, such as methylprednisolone, 1 gm daily for 3 days, followed by oral treatment as above (Chan et al., 2001). The typical duration of therapy in observational studies is 1–2 years because symptoms often recur during the corticosteroid taper, including the development of PMR, or because the clinician slows the taper in response to a rising ESR. The ideal duration of therapy is unknown because it is not possible to accurately estimate the risk of complications of therapy or the risks of recurrent disease and its complications. However, it may be possible to safely discontinue treatment in as little as 4–6 months in certain cases.

Prompt diagnosis and institution of therapy is essential because once visual loss develops, normal vision is unlikely to return (Hayreh et al., 2002). On the other hand, once corticosteroids are started, visual loss is rare (Aiello et al., 1993). The rate of taper varies widely in different studies and by different clinicians; for example, there is no consensus regarding the management of the corticosteroid taper in the face of a rising ESR. Some clinicians slow the taper when the ESR rises, others continue with the taper if the patient is without symptoms while still others increase the corticosteroids. Patients with the highest inflammatory markers, such as fever, high ESR (e.g. >84 mm/hr in one recent study) and anemia may have higher corticosteroid requirements and need longer duration of therapy than those with a more modest inflammatory response (Hernandez-Rodriguez et al., 2002).

8.2. Steroid sparing therapies

Three recent studies evaluated the role of methotrexate as a steroid-sparing agent in patients with temporal arteritis (Jover et al., 2001; Spiera et al., 2001; Hoffman et al., 2002) and came to different conclusions, arguing for and against a role for methotrexate in this disease. Such treatment is not yet the standard of care and additional research will likely be necessary to determine whether corticosteroids alone or with methotrexate (or another immunomodulatory agent) is best. Many clinicians prescribe other immunosuppressive or immunomodulatory agents in an effort to minimize corticosteroid exposure, but none has proven efficacy. These agents include hydroxychloroquine, leflunomide, and the anti-TNF biologic agents, among others. Studies are ongoing to determine the role of these agents in temporal arteritis.

Therapy to prevent osteoporosis should be considered early in the treatment course because most patients require many months or years of therapy. In addition to weight-bearing exercise, adequate calcium intake and vitamin D, anti-resorptive agents, including alendronate or risedronate, may be appropriate first-line therapies for this purpose.

8.3. Monitoring and follow-up

The most important feature to monitor in follow-up is the patient's symptoms and signs; a recurrence of PMR, for example, may require a slight increase in the prednisone dose or a slower tapering schedule. Clinicians should not rely on the ESR as the only determination of disease activity, because mild to moderate elevations are non-specific and do not necessarily predict disease activity or impending complications. Once the diagnosis is well established and treatment has been started, integration of the clinical information and ESR help drive the pace of the corticosteroid taper. Some experts recommend regular chest radiographs, CT-angiograms or MRA of the thoracic aorta looking for evidence of vasculitis of the great vessels, aneurysm formation, or dissection. Whether this approach prevents morbidity and how often such screening should be performed are not known. As treatment to prevent osteoporosis continues as above, monitoring bone density with DEXA scanning should be considered for patients requiring long-term corticosteroid therapy, including patients with temporal arteritis.

Key points

- Temporal arteritis is uncommon but is important to recognize due to the morbidity of permanent visual loss or stroke in untreated patients. The incidence of temporal arteritis is approximately 20 per 100,000 individuals over age 50.
- Temporal arteritis is rare in individuals <50 years of age.
- Symptoms include arteritic and constitutional. The prominence of constitutional symptoms in an older individual commonly suggests malignancy or infection in the differential diagnosis.
- Jaw claudication carries the highest positive predictive value of any symptom when considering the possible diagnosis of temporal arteritis.
- Neurologic features are common in temporal arteritis and represent the major source of morbidity of the disease. Neurologic manifestations do not occur in isolated PMR.
- Headache is the most common symptom of temporal arteritis; it may either be temporal or diffuse in location. It is commonly, but not invariably, throbbing.
- Visual loss, the most feared complication, may be unilateral or bilateral, transient or permanent. In half of cases of permanent visual loss, transient visual loss occurs first and provides an opportunity to correctly establish the diagnosis and begin treatment.
- Vertigo or diplopia may be prominent early symptoms of temporal arteritis.
- Stroke may accompany temporal arteritis; a predisposition exists for the vertebrobasilar system.
- Less common neurologic manifestations include peripheral neuropathy, visual hallucinations, spinal cord infarction, and neuropsychiatric manifestations.
- Among physical findings, temporal artery tenderness, beading, or pulselessness and funduscopic abnormalities are most useful in increasing the probability of temporal arteritis.
- The ESR is elevated in approximately 90% of cases; an ESR of <50 makes the diagnosis unlikely and should prompt consideration of other diagnoses.
- Temporal artery biopsy remains the gold standard for diagnosis; consider a contralateral biopsy if clinical suspicion is high and the initial biopsy is normal.
- Systemic corticosteroid therapy remains the standard therapy for temporal arteritis. Initiate systemic corticosteroid therapy promptly, while awaiting biopsy results, when temporal arteritis is suspected.

References

Achkar, A.A., Lie, J.T., Hunder, G.G., O'Fallon, W.M., Gabriel, S.E. 1994. How does previous corticosteroid treatment affect the biopsy findings in giant cell (temporal) arteritis? Ann. Intern. Med. 120, 987–992.
Biopsy results are unlikely to be affected by previous treatment with up to one week of systemic corticosteroids.

Ahmad, I., Zaman, M. 1999. Bilateral internuclear ophthalmoplegia: an intitial presenting sign of giant cell arteritis. J. Am. Geriatr. Soc. 47, 734–736.

Aiello, P.D., Trautman, J.C., McPhee, T.J., Kunselman, A.R., Hunder, G.G. 1993. Visual prognosis in giant cell arteritis. Ophthalmology 100. 550–555.
The probability of developing permanent visual loss after initiation of systemic corticosteroid therapy is 1%.

Amor-Dorado, J.C., Llorca, J., Garcia-Porrua, C., Costa, C., Perez-Fernandez, N., Gonzalez-Gay, M.A. 2003. Audiovestibular manifestations in giant cell arteritis. A prospective study. Medicine 82, 13–26.

Baldursson, O., Steinsson, K., Bjornsson, J., Lie, J.T. 1994. Giant cell arteritis in Iceland. An epidemiologic and histopathologic analysis. Arthritis Rheum. 37, 1007–1012.

Barricks, M.E., Traviesa, D.B., Glaser, J.S. 1977. Opththalmoplegia in cranial arteritis. Brain 100, 209–221.

Bengtsson, B., Malmvall, B. 1981a. Prognosis of giant cell arteritis including temporal arteritis and polymyalgia rheumatica. Acta Med. Scand. 209, 337–345.

Bengtsson, B.A., Malmvall, B.E. 1981b. The epidemiology of giant cell arteritis including temporal arteritis and polymyalgia rheumatica. Incidences of different clinical presentations and eye complications. Arthritis Rheum. 24, 899–904.

Boesen, P., Sorensen, S. 1987. Giant cell arteritis, temporal arteritis, and polymyalgia rheumatica in a Danish county. A prospective investigation. Arthritis Rheum. 30, 294–299.

Branum, G., Massey, E.W., Rice, J. 1987. Erythrocyte sedimentation rate in temporal arteritis. South. Med. J. 80, 1527–1528.

Brittain, G., McIlwaine, G., Bell, J., Gibson, J. 1991. Plasma viscosity or erythrocyte sedimentation rate in the diagnosis of giant cell arteritis? Br. J. Ophthalmol. 75, 656–659.

Buchbinder, R., Detsky, A.S. 1992. Management of suspected giant cell arteritis: a decision analyses. J. Rheumatol. 19, 1220–1228.

Caselli, R.J., Hunder, G.G. 1997. Giant cell (temporal) arteritis. Neurol. Clin. 15, 893–902.

Caselli, R., Hunder, G., Whisnant, J. 1988a. Neurologic disease in biopsy-proven giant cell (temporal) arteritis. Neurology 38, 352–359.
Neurologic findings occurred in 51 (31%) of 166 consecutive patients. Most common were neuropathy (23), TIA or stroke (12), neuro-otologic syndromes (11), tremor (6), and neuropsychiatric syndromes (5).

Caselli, R.J., Daube, J.R., Hunder, G.G., Whisnant, J.P. 1988b. Peripheral neuropathic syndromes in giant cell (temporal) arteritis. Neurology 38, 685–689.

Chan, C., Paine, M., O'Day, J. 2001. Steroid management in giant cell arteritis. Br. J. Ophthalmol. 85, 1061–1064.

Chmelewski, W.L., McKnight, K.M., Agudelo, C.A., Wise, C.M. 1992. Presenting features and outcomes in patients undergoing temporal artery biopsy. A review of 98 patients. Arch. Intern. Med. 152, 1690–1695.
Among patients with suspected temporal arteritis who had negative biopsies, the most common ultimate diagnoses were migraine, stroke, polymyalgia rheumatica, other types of vasculitis, rheumatoid arthritis, fever or unknown origin, and malignancy.

Cid, M.C., Font, C., Oristrell, J., de la Sierra, A., Coll-Vinent, B., Lopez-Soto, A., Vilaseca, J., Urbano-Marquez, A., Grau, J.M. 1998. Association between strong inflammatory response and low risk of developing visual loss and other cranial ischemic complications in giant cell (temporal) arteritis. Arthritis Rheum. 41, 26–32.

Dare, B., Byrne, E. 1980. Giant-cell arteritis. A five-year review of biopsy proven cases in a teaching hospital. Med. J. Aust. 1, 372–373.

Desmet, G., Knockaert, D., Bobbaers, H. 1990. Temporal arteritis: the silent presentation and delay in diagnosis. J. Intern. Med. 227, 237–240.

Dimant, J., Grob, D., Brunner, N.G. 1980. Ophthalmoplegia, ptosis, and miosis in temporal arteritis. Neurology 30, 1054–1058.

Duhaut, P., Pinede, L., Bornet, H., Demolombe-Rague, S., Dumontet, C., Ninet, J., Loire, R., Pasquier, J. 1999. Biopsy proven and biopsy negative temporal arteritis: differences in clinical spectrum at the onset of the disease. Groupe de Recherche sur l'Arterite a Cellules Geantes. Ann. Rheum. Dis. 58, 335–341.

Evans, J.M., Hunder, G.G. 1998. Polymyalgia rheumatica and giant cell arteritis. Clin. Geriatr. Med. 14, 455–473.

Evans, J., Bowles, C., Bjornsson, J., Mullany, C., Hunder, G. 1994. Thoracic aortic aneurysm and rupture in giant cell arteritis. A descriptive study of 41 cases. Arthritis Rheum. 37, 1539–1549.

Fainaru, M., Friedman, G., Friedman, B. 1979. Temporal arteritis in Israel. A review of 47 patients. J. Rheumatol. 6, 330–335.

Fauchald, P., Rygvold, O., Oystese, B. 1972. Temporal arteritis and polymyalgia rheumatica. Clinical and biopsy findings. Ann. Intern. Med. 77, 845–852.

Fernandez-Herlihy, L. 1988. Temporal arteritis: clinical aids to diagnosis. J. Rheumatol. 15, 1797–1801.published erratum appears in J. Rheumatol. Feb;16(2):260.

Foroozan, R., Deramo, V.A., Buono, L.M., Jayamanne, D.G.R., Sergott, R.C., Danesh-Meyer, H., Savino, P.J. 2003. Recovery of visual function in patients with biopsy-proven giant cell arteritis. Ophthalmology 110, 539–542.

Friedman, G., Friedman, B., Benbassat, J. 1982. Epidemiology of temporal arteritis in Israel. Isr. J. Med. Sci. 18, 241–244.

Fruchter, O., Ben-Ami, H., Schapira, D., Gallimidi, Z., Gaitini, D., Goldsher, D. 2002. Giant cell arteritis complicated by spinal cord infarction: a therapeutic dilemma. J. Rheumatol. 29, 1556–1558.

Gabriel, S.E., O'Fallon, W.M., Achkar, A.A., Lie, J.T., Hunder, G.G. 1995. The use of clinical characteristics to predict

the results of temporal artery biopsy among patients with suspected giant cell arteritis. J. Rheumatol. 22, 93–96.

Ghanchi, F.D., Dutton, G.N. 1997. Current concepts in giant cell (temporal) arteritis. Surv. Ophthalmol. 42, 99–123.

Glutz von Blotzheim, S., Borruat, F.X. 1997. Neuro-ophthalmic complications of biopsy-proven giant cell arteritis. Eur. J. Ophthalmol. 7, 375–382.

Golbus, J., McCune, W.J. 1987. Giant cell arteritis and peripheral neuropathy: a report of 2 cases and review of the literature. J. Rheumatol. 14, 129–134.

Goldberg, R.T. 1983. Ocular muscle paresis and cranial arteritis. An unusual case. Ann. Ophthalmol. 15, 240–243.

Gonzalez, E.B., Varner, W.T., Lisse, J.R., Daniels, J.C., Hokanson, J.A. 1989. Giant-cell arteritis in the southern United States. An 11-year retrospective study from the Texas Gulf Coast. Arch. Intern. Med. 149, 1561–1565.

Gonzalez-Gay, M.A., Alonso, M.D., Aguero, J.J., Bal, M., Fernandez-Camblor, B., Sanchez-Andrade, A. 1992. Temporal arteritis in a northwestern area of Spain: study of 57 biopsy proven patients. J. Rheumatol. 19, 277–280.

Gonzalez-Gay, M.A., Blanco, R., Abraira, V., Garcia-Porrua, C., Ibanez, D., Garcia-Pais, M.J., Rigueiro, M.T., Sanchez-Andrade, A., Guerrero, J., Casariego, E. 1997. Giant cell arteritis in Lugo, Spain, is associated with low longterm mortality. J. Rheumatol. 24, 2171–2176.

Gonzalez-Gay, M.A., Blanco, R., Rodriguez-Valverde, V., Martinez-Taboada, V.M., Delgado-Rodriguez, M., Figueroa, M., Uriarte, E. 1998. Permanent visual loss and cerebrovascular accidents in giant cell arteritis: predictors and response to treatment. Arthritis Rheum. 41, 1497–1504.

Gonzalez-Gay, M.A., Garcia-Porrua, C., Llorca, J., Hajeer, A.H., Branas, F., Dababneh, A., Gonzalez-Louzao, C., Rodriguez-Gil, E., Rodriguez-Ledo, P., Ollier, W.E. 2000. Visual manifestations of giant cell arteritis. Trends and clinical spectrum in 161 patients. Medicine 79, 283–292.

Gonzalez-Gay, M., Garcia-Porrua, C., Llorca, J., Gonzalez-Louzao, C., Rodriguez-Ledo, P. 2001. Biopsy-negative giant cell arteritis: clinical spectrum and predictive factors for positive temporal artery biopsy. Semin. Arthritis Rheum. 30, 249–256.

Gran, J.T., Myklebust, G. 1997. The incidence of polymylagia rheumatica and temporal arteritis in the county of Aust Agder, South Norway: a prospective study 1987–94. J. Rheumatol 24, 1739–1743.

Gur, H., Rapman, E., Ehrenfeld, M., Sidi, Y. 1996. Clinical manifestations of temporal arteritis: a report from Israel. J. Rheumatol. 23, 1927–1931.

Hall, S., Persellin, S., Lie, J.T., O'Brien, P.C., Kurland, L.T., Hunder, G.G. 1983. The therapeutic impact of temporal artery biopsy. Lancet 2, 1217–1220.

Hall, J.K., Volpe, N.J., Galetta, S.L., Liu, G.T., Syed, N.A., Balcer, L.J. 2003. The role of unilateral temporal artery biopsy. Ophthalmology 110, 543–548.

Hamilton, C.R., Shelley, W.M., Tumulty, P.A. 1971. Giant cell arteritis: including temporal arteritis and polymyalgia rheumatica. Medicine 50, 1–27.

Hauser, W., Ferguson, R., Holley, K., Kurland, L. 1971. Temporal arteritis in Rochester, Minnesota, 1951 to 1967. Mayo Clin. Proc. 46, 597–602.

Hayreh, S.S., Podhajsky, P.A., Raman, R. 1997. Giant cell arteritis: validity and reliability of various diagnostic criteria [see comments]. Am. J. Ophthalmol. 123, 285–296.

Hayreh, S.S., Podhajsky, P.A., Zimmerman, B. 1998. Ocular manifestations of giant cell arteritis. Am. J. Ophthalmol. 125, 509–520.

Among patients with ocular manifestations of biopsy proven temporal arteritis, most common were visual loss (98%), amaurosis fugax (31%), eye pain (8%) and diplopia (6%).

Hayreh, S.S., Zimmerman, B., Kardon, R.H. 2002. Visual improvement with corticosteroid therapy in giant cell arteritis. Report of a large study and review of the literature. Acta Ophthalmol. Scand. 80, 355–367.

Healey, L.A., Wilske, K.R. 1980. Presentation of occult giant cell arteritis. Arthritis Rheum. 23, 641–643.

Hedges, T.R.D., Gieger, G.L., Albert, D.M. 1983. The clinical value of negative temporal artery biopsy specimens. Arch. Ophthalmol. 101, 1251–1254.

Hernandez-Rodriguez, J., Garcia-Martinez, A., Casademont, J., Filella, X., Esteban, M., Lopez-Soto, A., Fernandez-Sola, J., Urbano-Marquez, A., Grau, J., Cid, M. 2002. A strong initial systemic inflammatory response is associated with higher corticosteroid requirements and longer duration of therapy in patients with giant-cell arteritis. Arthritis Rheum. 47, 29–35.

Hoffman, G., Cid, M., Hellmann, D., Guillevin, L., Stone, J., Schousboe, J., Cohen, P., Calabrese, L., Dickler, H., Merkel, P., Fortin, P. 2002. A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. Arthritis Rheum. 46, 1309–1318.

Hu, Z., Yang, Q., Zheng, S., Tang, J., Lu, W., Xu, N., Shong, X., Jang, B. 2000. Temporal arteritis and fever: report of a case and a clinical reanalysis of 360 cases. Angiology 51, 953–958.

Hunder, G.G. 1997. Giant cell arteritis and polymyalgia rheumatica. Med. Clin. N. Amer. 81, 195–219.

Hunder, G.G., Bloch, D.A., Michel, B.A., Stevens, M.B., Arend, W.P., Calabrese, L.H., Edworthy, S.M., Fauci, A.S., Leavitt, R.Y., Lie, J.T., Lightfoot, R.W., Masi, A.T., McShane, D.J., Mills, J.A., Wallace, S.L., Zvaifler, N.J. 1990. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum. 33, 1122–1128.

Jacobson, D.M., Slamovits, T.L. 1987. Erythrocyte sedimentation rate and its relationship to hematocrit in giant cell arteritis. Arch. Ophthalmol. 105, 965–967.

Johnson, H., Bouman, W., Pinner, G. 1997. Psychiatric aspects of temporal arteritis: a case report and review of the literature. J. Geriatr. Psychiatry Neurol. 10, 142–145.

Jonasson, F., Cullen, J.F., Elton, R.A. 1979. Temporal arteritis. A 14-year epidemiological, clinical and prognostic study. Scott. Med. J. 24, 111–117.

Jover, J., Hernandez-Garcia, C., Morado, I., Vargas, E., Banares, A., Fernandez-Gutierrez, B. 2001. Combined treatment of giant-cell arteritis with methotrexate and prednisone. a randomized, double-blind, placebo-controlled trial. Ann. Intern. Med. 134, 106–114.

Lim, K., Liam, C., Vasudevan, A., Wong, C. 1999. Giant cell arteritis presenting as chronic cough and prolonged fever. Respirology 4.

Liozon, E., Herrmann, F., Ly, K., Robert, P., Loustaud, V., Soria, P., Vidal, E. 2001a. Risk factors for visual loss in giant cell (temporal) arteritis: a prospective study of 174 patients. Am. J. Med. 111, 211–217.
Risk factors for permanent visual loss were transient visual loss (OR 6.3), and high platelet count (OR 3.7). Factors that made permanent visual loss less likely included constitutional symptoms (OR 0.14) and polymyalgia rheumatica (OR 0.04).

Liozon, E., Loustaud, V., Ly, K., Vidal, E. 2001b. Association between infection and onset of giant cell arteritis: can seasonal patterns provide the answer. J. Rheumatol. 28, 1197–1198.

Machado, E.B., Michet, C.J., Ballard, D.J., Hunder, G.G., Beard, C.M., Chu, C.P., O'Fallon, W.M. 1988. Trends in incidence and clinical presentation of temporal arteritis in Olmsted County, Minnesota, 1950–1985. Arthritis Rheum. 31, 745–749.

Mathewson, J., Hunder, G. 1986. Giant cell arteritis in two brothers. J. Rheumatol. 13, 190–192.

Matteson, E.L., Gold, K.N., Block, D.A., Hunder, G.G. 1996. Long-term survival of patients with giant cell arteritis in the American College of Rheumatology giant cell arteritis classification criteria cohort. Am. J. Med. 100, 193–196.

McDonnell, P.J., Moore, G.W., Miller, N.R., Hutchins, G.M., Green, W.R. 1986. Temporal arteritis. A clinicopathologic study. Ophthalmology 93, 518–530.

Monteiro, M.L.R., Coppeto, J.R., Greco, P. 1984. Giant cell arteritis of the posterior cerebral circulations presenting with ataxia and ophthalmoplegia. Arch. Ophthalmol. 102, 407–409.

Murgatroyd, H., Nimmo, M., Evans, A., MacEwen, C. 2003. The use of ultrasound as an aid in the diagnosis of giant cell arteritis: a pilot study comparing histological features with ultrasound findings. Eye 17, 415–419.

Myklebust, G., Gran, J.T. 1996. A prospective study of 287 patients with polymyalgia rheumatica and temporal arteritis: clinical and laboratory manifestations at onset of disease and at the time of diagnosis. Br. J. Rheumatol. 35, 1161–1168.

Nadeau, S. 1988. Temporal arteritis: a decision-analytic approach to temporal artery biopsy. Acta Neurol. Scand. 78, 90–100.

Nadeau, S.E. 2002. Neurologic manifestations of systemic vasculitis. Neurol. Clin. 20, 123–150.

Nesher, G., Nesher, R., Rozenman, Y., Sonnenblick, M. 2001. Visual hallucinations in giant cell arteritis: association with visual loss. J. Rheumatol. 28, 2046–2048.

Nordborg, E., Nordborg, C. 2003. Giant cell arteritis: epidemiological clues to its pathogenesis and an update on its treatment. Rheumatology (Oxford) 42, 413–421.

O'Brien, J., Regan, W. 1998. Actinically degenerate elastic tissue: the prime antigen in the giant cell (temporal) arteritis syndrome? New data from the posterior ciliary arteries. Clin. Exp. Rheumatol. 16, 39–48.

Ostberg, G. 1971. Temporal arteritis in a large necropsy series. Ann. Rheum. Dis. 30, 224–235.

Petursdottir, V., Johansson, H., Nordborg, E., Nordborg, C. 1999. The epidemiology of biopsy-positive giant cell arteritis: special reference to cyclic fluctuations. Rheumatology (Oxford) 38, 1208–1212.
Variation in annual and seasonal incidence of temporal arteritis suggest the possibility of exogenous triggering factors such as infection.

Poller, D., van Wyk, Q., Jeffrey, M. 2000. The importance of skip lesions in temporal arteritis. J. Clin. Pathol. 53, 137–139.

Ponge, T., Barrier, J.H., Grolleau, J.Y., Ponge, A., Vlasak, A.M., Cottin, S. 1988. The efficacy of selective unilateral temporal artery biopsy versus bilateral biopsies for diagnosis of giant cell arteritis. J. Rheumatol. 15, 997–1000.

Reich, K.A., Giansiracusa, D.F., Strongwater, S.L. 1990. Neurologic manifestations of giant cell arteritis. Am. J. Med. 89, 67–72.

Reitblat, T., Ben-Horin, C., Reitblat, A. 2003. Gallium-67 SPECT scintigraphy may be useful in diagnosis of temporal arteritis. Ann. Rheum. Dis. 62, 257–260.

Roche, N.E., Fulbright, J.W., Wagner, A.D., Hunder, G.G., Goronzy, J.J., Weyand, C.M. 1993. Correlation of interleukin-6 production and disease activity in polymyalgia rheumatica and giant cell arteritis. Arthritis Rheum. 9, 1286–1294.

Roelcke, U., Eshcle, D., Kappos, L., Moschopulos, M., Laeng, R.H., Buettner, U.W. 2002. Meningoradiculitis associated with giant cell arteritis. Neurology 59, 1811–1812.

Roth, A.M., Milsow, L., Keltner, J.L. 1984. The ultimate diagnoses of patients undergoing temporal artery biopsies. Arch. Ophthalmol. 102, 901–903.

Ruegg, S., Engelter, S., Jeanneret, C., Hetzel, A., Probst, A., Steck, A.J., Lyrer, P. 2003. Bilateral vertebral artery occlusion resulting from giant cell arteritis. Report of 3 cases and review of the literature. Medicine 82, 1–12.

Salvarani, C., Cantini, F., Boiardi, L., Hunder, G.G. 2002. Polymyalgia rheumatica and giant-cell arteritis. N. Engl. J. Med. 347, 261–271.

Salvarani, C., Hunder, G. 2001. Giant cell arteritis with low erythrocyte sedimentation rate: frequency of occurence in a population-based study. Arthritis Rheum. 45, 140–145.

Salvarani, C., Macchioni, P., Zizzi, F., Mantovani, W., Rossi, F., Castri, C., Capozzoli, N., Baricchi, R., Boiardi, L., Chiaravalloti, F., Portioli, I. 1991. Epidemiology and immunogenetic aspects of polymyalgia rheumatica and giant cell arteritis in northern Italy. Arthritis Rheum. 34, 351–356.

Salvarani, C., Gabriel, S.E., O'Fallon, W.M., Hunder, G.G. 1995a. Epidemiology of polymyalgia rheumatica in Olmsted County, Minnesota. Arthritis Rheum. 38, 369–373.

Salvarani, C., Gabriel, S.E., O'Fallon, W.M., Hunder, G.G. 1995b. The incidence of giant cell arteritis in Olmsted county, Minnesota: apparent fluctuations in a cyclic pattern. Ann. Intern. Med. 123, 192–194.

Schmidt, W., Kraft, H., Vorpahl, K., Volker, L. 1997. Color duplex ultrasonography in the diagnosis of temporal arteritis. N. Engl. J. Med. 337, 1336–1342.

Smetana, G.W., Shmerling, R.H. 2002. Does this patient have temporal arteritis? JAMA 287, 92–101.
In a systematic review of clinical features of temporal arteritis, jaw claudication (LR + 4.2), diplopia (LR + 3.4), and an enlarged temporal artery on exam (LR + 4.3) predicted

the correct diagnosis of temporal arteritis to the greatest extent. An ESR <50 (LR- 0.2) made temporal arteritis unlikely.

Smith, C.A., Fidler, W.J., Pinals, R.S. 1983. The epidemiology of giant cell arteritis. Report of a ten-year study in Shelby County, Tennessee. Arthritis Rheum. 26, 1214–1219.

Solomon, S., Cappa, K.G. 1987. The headache of temporal arteritis. J. Am. Geriatr. Soc. 35, 163–165.
The headache of temporal arteritis is most commonly temporal (50%); nuchal, occipital, facial, and generalized headaches also occur. Headache is commonly throbbing but may also be sharp, dull, or burning.

Sonnenblick, M., Nesher, G., Rosin, A. 1989. Nonclassical organ involvement in temporal arteritis. Sem. Arthritis Rheum. 19, 183–190.

Spiera, R., Mitnick, H., Kupersmith, M., Richmond, M., Spiera, H., Peterson, M., Paget, S. 2001. A prospective, double-blind, randomized, placebo controlled trial of methotrexate in the treatment of giant cell arteritis (GCA). Clin. Exp. Rheumatol. 19, 495–501.

Turlakow, A., Yeung, H., Pui, J., Macapinlac, H., Liebovitz, E., Rusch, V., Goy, A., Larson, S. 2001. Fludeoxyglucose positron emission tomography in the diagnosis of giant cell arteritis. Arch. Intern. Med. 161, 1003–1007.

Vilaseca, J., Gonzalez, A., Cid, M.C., Lopez-Vivancos, J., Ortega, A. 1987. Clinical usefulness of temporal artery biopsy. Ann. Rheum. Dis. 46, 282–285.

Wakakura, M., Ishikawa, S. 1994. Neuro-ophthalmic aspects of vascular disease. Curr. Opin. Ophthalmol. 5, 18–22.

Weyand, C., Hicok, K., Hunder, G., Goronzy, J. 1992. The HLA-DRB1 locus as a genetic component in giant cell arteritis. Mapping of a disease-linked sequence motif to the antigen binding site of the HLA-DR molecule. J. Clin. Invest. 90, 2355–2561.

Weyand, C.M., Tetzlaff, N., Bjornsson, J., Brack, A., Younge, B., Goronzy, J.J. 1997. Disease patterns and tissue cytokine profiles in giant cell arteritis. Arthritis Rheum. 40, 19–26.

Whitfield, A., Bateman, M., Cooke, W. 1963. Temporal arteritis. Br. J. Ophthalmol. 47, 555–566.

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CHAPTER 10

Large Vessel Vasculitis—Takayasu Arteritis

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1. Introduction

Takayasu's arteritis (TA) is a chronic systemic inflammatory disorder that preferentially involves the aorta and its main branches. Synonyms for this disorder include 'pulseless disease' and 'aortic-arch syndrome'. Reports of this disorder exist as early as 1761 (Di Giacomo, 1984). The description by Mikito Takayasu, a Japanese ophthalmologist, in 1908 led to Caccamise and Okuda honoring Takayasu by applying his name to 'pulseless disease' in 1954 (Cacamise et al., 1954). TA was initially thought to be a disorder of young Far Eastern females. However, TA has been recognized throughout the world. It affects females 8–10 times more often than males (Kerr et al., 1994). Chronic large vessel vasculitis may lead to myointimal proliferation and stenosis, or attenuation of the vessel wall and aneurysm formation. Some authors have observed that TA follows a predictable triphasic course: systemic illness with constitutional symptoms, vascular inflammation and subsequent 'burnt out' disease with fixed vascular abnormalities (Lupi-Herrera et al., 1977). However, it is now recognized that patients may never exhibit systemic symptoms and disease may remain chronically active. Patients may present with only ischemic symptoms and findings or have asymptomatic bruits or asymmetric pulses.

2. Prevalence/Epidemiology

TA is a rare disorder that most commonly occurs in the Far East. A case series from Japan revealed evidence of TA in 1 of every 3000 autopsies (Nasu, 1975). TA is also seen in other areas, but at a much lower rate. The incidence in Olmstead County, Minnesota has been reported as 2.6 cases/million yearly, and in Sweden, about 1.2 cases/million yearly (Hall et al., 1985; Waern et al., 1983).

Despite its unique course in any individual patient, there are certain patterns of vascular involvement that are most common. Interestingly, there are also variations in patterns of disease that are peculiar to certain regions of the world. For example, in the United States and Japan, involvement of the ascending and transverse aorta and its primary branches is common, with most symptoms resulting from impaired perfusion of the brain and upper extremities. In India, TA patients have more frequent involvement of the supra-renal abdominal aorta and renal arteries leading to a very high frequency of hypertension (Ganguly et al., 1996). These ethnic-regional differences imply genetic or environmental influences on disease expression.

TA can manifest at any age. The peak incidence of disease is in the third decade of life (Hall et al., 1985). The rarity of TA, variations in patterns of presentation and nonspecific symptoms may lead to significant delays in diagnosis. In the National Institute of Health (NIH) cohort, the median time from initial symptoms to diagnosis was 10 months (Kerr et al., 1994). In a Mexican cohort of 107 patients, the time from onset of

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symptoms to diagnosis ranged from 2 to 11 years in 78% of cases (Lupi-Herrera et al., 1977).

TA may coexist with other autoimmune disorders. The concurrence of TA and inflammatory bowel disease is well documented (Levitsky et al., 2002; Morita et al., 1996).

3. Etiology/Pathogenesis

The etiology of TA is unknown. Attempts have been made to identify genetic predispositions to TA through HLA analysis. While some authors have identified either over or under representation of certain alleles in specific ethnic subsets, no definite associations have been demonstrated in most cohorts of TA.

Potential infectious triggers have been studied, but none have been consistently identified by either serologic or histologic techniques. There is ongoing debate about the possible role of tuberculosis in TA. In certain regions where mycobacterial infections are relatively common, and PPD reactivity is frequent, some authors have suggested a pathogenic link. However, in countries with a low prevalence of TB, TA clearly exists in the absence of mycobacterial infection. While these observations do not rule out a possible role for TB initiating an aberrant immunologic-vascular injury response, they imply that other etiologic factors are more likely and more significant.

The predisposition of this disorder for young females suggests that hormonal factors may influence disease pathogenesis or expression. However, there are no data that convincingly demonstrate mechanisms to support this hypothesis.

Vessel injury occurs primarily as a result of mononuclear cell mediated immunologic mechanisms. Initially, the inflammatory process results from circulating leukocytes entering the adventitia through vasa vasora. This is followed by infiltration of the media and later intima by macrophages that may form giant cells and various subpopulations of lymphocytes and dendritic cells. Infiltrating lymphocytes include gamma delta T cells, alpha beta T cells, natural killer cells, T helper cells, and CD8 cytotoxic lymphocytes (Seko, 2000).

The most common vessel response to immunologic injury is wall thickening that results from myointimal proliferation. Smooth muscle cell and elastic fiber destruction in certain sites may dominate vessel wall alterations, leading to aneurysm formation (especially of aortic root and arch), while in most other sites myointimal proliferation leads to luminal stenosis.

Antiendothelial cell antibodies have been detected in a minority of patients with TA. However, because they also occur in various other autoimmune disorders with similar frequency, they are most likely a epiphenomenon of doubtful significance.

4. Clinical manifestations

In most series, about 90% of TA patients are female. However, in India, only 63% of patients are female. Over 50% of patients do not experience systemic symptoms. The most common presentations are acute, subacute, or chronic regional ischemia (light headedness, vertigo, claudication), and pulselessness or bruits that may be detected as an incidental finding. In the United States and Japanese cohorts, hypertension occurs in 40–60% of cases. Indian patients have a higher frequency of abdominal aortic and renal artery involvement, accounting for hypertension occurring in up to 90% of that ethnic subset (Numano, 1997).

Systemic symptoms and signs, when present, are nonspecific and are common to many inflammatory disorders. Fever, weight loss, malaise, and generalized arthralgias and myalgias can be seen at presentation or later in the disease course (Table 1).

Although the entire aorta and all of its branches can be involved, aortic arch vessels are affected in over 90% of patients. Lesions are found most frequently in the subclavian and innominate, common carotid, and vertebral arteries (Table 2) (Fig. 1). Stenosis of these vessels generally develops slowly, leading to the insidious onset of lightheadedness and/or claudicatory symptoms. Lower extremity symptoms most often result from stenoses of the abdominal aorta or ilio-femoral disease. It is rare for ischemia to be so severe as to produce rest pain, gangrene, or ulcerations.

Several classification schemes exist for TA, based on sites of arterial involvement. One of the most

Table 1
Clinical manifestations of TA (from Kerr et al., 1994)

	Onset (%)	Total (%)
Extremities	65	97
Limb fatigue	35	70
Arms	28	62
Legs	8	32
CNS	23	58
Lightheaded/dizzy	18	35
Visual aberration	10	28
Visual loss	2	8
Stroke	5	8
TIA	0	8
Cardiac	17	38
Angina	2	13
Chest pain/MI	0	2
SOB/CHF	2	5
Pericardial pain	3	3
Musculoskeletal	18	53
Chest wall pain	8	30
Arthralgias	10	30
Myalgias	5	15
Constitutional	33	43
Malaise	22	33
Fever	20	27
Weight loss (>10%)	12	17
Night sweats	2	2
Other		
Carotidynia	17	32
Headache	18	42
Rash (*E. nodosum*)	5	8
Numbness (peripheral neuropathy)	2	3

MI: myocordial infarction, SOB: shortness of breath, CHF: congestive heart failure.

Table 2
Distribution of vascular lesions (60 patients) (from Kerr et al. (1994))

Vessel	% involved
Aorta	65
Subclavian	93
Common carotid	58
Renal	38
Vertebral	35
Innominate	27
Axillary	20

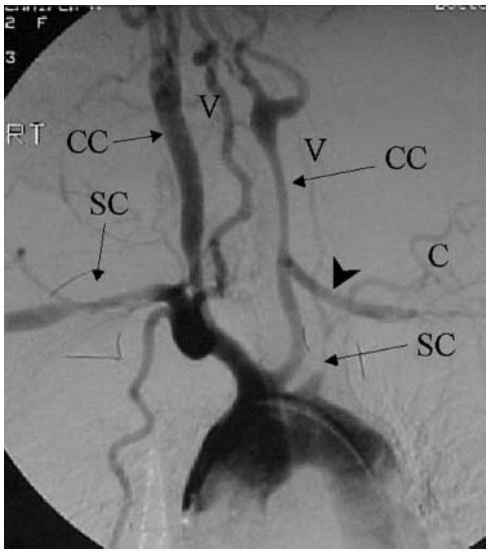

Figure 1. Bilateral subclavian (SC) artery stenoses, with near occlusion on the left. Graft (arrow head) from left common carotid (CC) to distal left SC. Right CC dilated. Note the strategic error in selecting the vulnerable carotid, now stenotic as the origin for the distal SC graft. Unfortunately, the distal SC later occluded and thus the graft was not effective. (V, vertebral arteries, C, collateral vessels).

widely used divides patients into one of five types:

(1) *Type I*: branches of the aortic arch
(2) *Type IIa*: ascending aorta, aortic arch and its branches
(3) *Type IIb*: Type IIa plus thoracic descending aorta
(4) *Type III*: thoracic descending aorta, abdominal aorta, and/or renal arteries
(5) *Type IV*: only abdominal aorta and/or renal arteries
(6) *Type V*: segments of the entire aorta and its branches

Type V is the most common pattern.

The most common clinical findings are blood pressure asymmetry in extremities (96%) and bruits (94%) (Kerr et al., 1994; Johnston et al., 2002). In 60 patients evaluated in an NIH study, 80% had at least one bruit (Hall et al., 1985). The most common sites were over the carotid, subclavian, and aortic vessels; diminished, asymmetric, or absent pulses are frequently noted. In patients with bilateral subclavian artery involvement, peripheral cuff measurements of upper extremity blood pressure may not reflect true

central aortic pressure, and even severe or malignant hypertension may not be recognized. Determination of blood pressure in all extremities is essential, as is anatomic imaging of the entire aorta and its primary branches. If flow is impeded from the aorta to the extremities by stenotic lesions, one must determine which extremity (if any) provides a reliable measure of central aortic pressure. Because about 40% of patients have bilateral subclavian stenosis (Hall et al., 1985), the lower extremities may be the only sites that reflect true central aortic pressure. However, in others, distal thoracic aortic, abdominal aortic, or iliofemoral stenoses may compromise reliability of blood pressure recordings in any limb (Fig. 2). In such cases, it is essential to perform catheter directed angiography with intravascular blood pressure readings to assess peripheral site reliability. The patient should be informed which extremity provides a reliable measure of aortic root pressure. In the setting of severe central hypertension in the absence of a reliable peripheral monitoring site, surgical anatomic correction of a stenotic lesion should be considered.

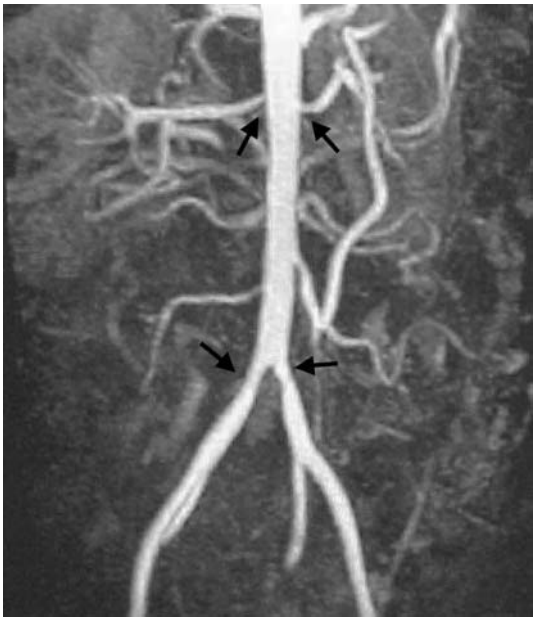

Figure 2. Bilateral renal and iliac artery stenoses. Note how this anatomy, combined with bilateral subclavian or innominate stenosis may make all extremities an unreliable reference for aortic pressure (MRA).

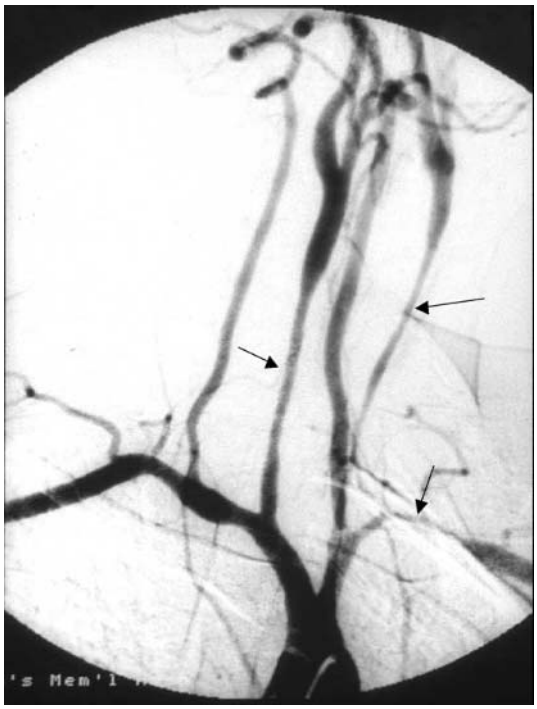

Figure 3. Bilateral common carotid and subclavian artery stenoses (catheter-directed angiogram).

Central nervous system manifestations (50–60%) of TA may be due to lesions that produce ischemia, e.g. common carotid, vertebral, subclavian arteries proximal to the vertebral origins, and/or intracerebral medium-sized vessel stenoses (Figs. 3 and 4).

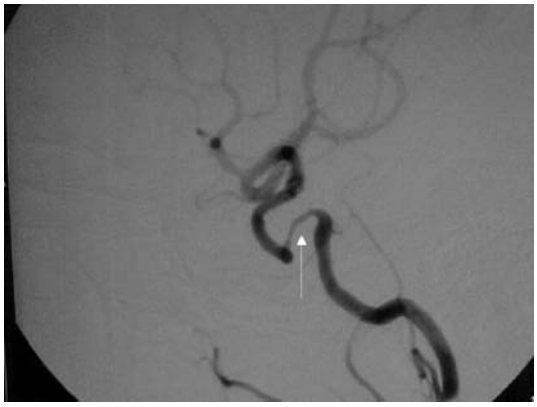

Figure 4. Stenosis of the distal internal carotid artery (catheter-directed angiogram).

Cerebrovascular insufficiency may present as TIAs (20%), stroke (5%), lightheadedness (35%), visual aberration or amaurosis (about 25%), and blindness (<5%) (Kerr et al., 1994; Kerr, 1995). It has been suggested that syncope may occur as a result of carotid sinus hypersensitivity, but this is less certain.

The report by Takayasu highlighted blindness in a young woman with abnormal retinal epipapillary arteriovenous communications progressing from the mid-peripheral retina to surround the optic disc, now known as Takayasu's retinopathy. These findings result from compromised internal carotid artery circulation leading to hypoperfusion of the central retina. Vasodilatation and capillary aneurysms may progress to vascular obliteration and neovascularization. Retinal arteriovenous shunts most commonly manifest as preferential circulatory channels, shunting at AV crossings, or peripapillary neovascularity (Kiyosawa and Baba, 1998). The Uyama classification of retinal changes in TA is as follows (Ishikawa et al., 1983):

Stage 1: enlarged, irregular darkly discolored retinal veins
Stage 2: sludging of retinal veins with microaneurysms
Stage 3: neovascularization and arteriovenous anastamoses
Stage 4: rubeosis (reddish discoloration)

A Japanese study examining the relationship between cervical arterial stenosis, retinal artery pressure, and retinal vascular changes, found that retinal artery pressures and retinal vascular changes generally did not occur in the absence of significant stenosis of both vertebral and both common carotid arteries (Ishikawa et al., 1983).

Other retinal changes include dilation and tortuosity of vessels, and optic nerve atrophy. Exudates and hemorrhage are much less common. However, with hypertension, a common sequelae of this disorder, hypertensive retinopathy can be present in up to 40% of cases (Sharma et al., 1998). Takayasu's retinitis is most commonly found in Japan, where it has been reported in more than 25% of patients in one study (Kiyosawa and Baba, 1998). It has been detected in only 3.6% of patients in India. Blindness in TA can result from causes other than retinopathy, including steroid-induced cataract formation and glaucoma.

The major causes of visual impairment in a Japanese cohort of 65 patients included cataracts, vitreous hemorrhages, macular degeneration, secondary glaucoma, central serous retinopathy, and retinal detachment (Kiyosawa and Baba, 1998). Thirty-five percent of these patients had fundoscopic abnormalities. Twenty percent had no associated clinical symptoms, and 25% noted blurred vision or photophobia. Anterior ischemic optic neuropathy and scleritis have also occasionally been noted in TA (Malik et al., 2002; Smith and Rosenbaum, 2001).

Renal artery stenosis occurs in 40–80% of patients and is the most common cause of hypertension and ischemic nephropathy (Lupi-Herrera et al., 1977; Johnston et al., 2002; Kerr et al., 1994; Kerr, 1995) (Fig. 5). Hypertension may be undetected and untreated as a result of the high frequency of extremity vessel stenoses or distal aortic stenoses. This may lead to congestive heart failure, hemorrhagic stroke, hypertensive encephalopathy, nephropathy, or acute myocardial infarction.

Most frequently, renal artery stenosis is proximal, and is often amenable to catheter-mediated intervention/angioplasty. Coarctation of the supra-renal abdominal aorta can also be a source of renal-mediated hypertension. Rarely TA has been associated with IgA nephropathy, membranoproliferative glomerulonephritis, crescentic glomerulonephritis, and renal amyloidosis (Cavatorta et al., 1995; Koumi et al., 1990; Hellmann et al., 1987; Jain et al., 1992).

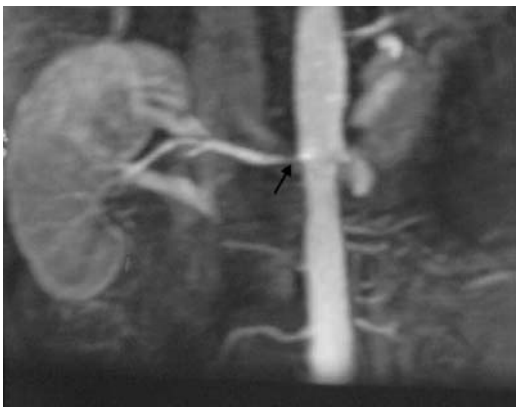

Figure 5. Renal artery stenosis (MRA).

Heart disease in TA may lead to secondary neurologic abnormalities as the result of severe aortic regurgitation (up to 25% of patients), congestive heart failure (about 10%), coronary arteritis (< 5%) leading to ischemia and arrhythmias, angina, myocarditis and cardiomyopathy.

Symptoms of pulmonary involvement include cough, dyspnea, or hemoptysis. These features each occur in less than 25% of patients. However, multiple studies have revealed that pulmonary angiographic abnormalities are present in up to 70% of TA patients (Yamada et al., 1992). Infrequently described pulmonary manifestations include interstitial changes, pulmonary hemorrhage, pleural effusion, and systemic-pulmonary artery communication (Kreidstein et al., 1993; Koyabu et al., 1993; Kumar and Sherman, 1997; Ishikawa et al., 1977), and pulmonary artery stenoses (Clark and Hoffman, 2004) (Fig. 6).

Mesenteric artery involvement may occur, but associated symptoms are infrequent. Lesions of the celiac trunk or superior and/or inferior mesenteric arteries and stenosis of the thoracic or suprarenal aorta can result in ischemia of the abdominal organs (Fig. 7). The frequent absence of symptoms usually reflects the insidious onset of stenoses, with collateral circulation preserving organ perfusion. Generally, findings suggestive of arterial involvement

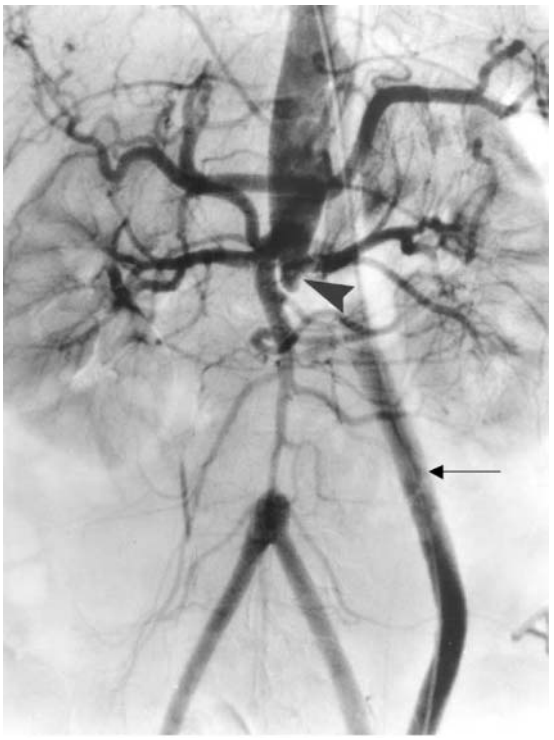

Figure 7. Occlusion of the abdominal aorta (arrow head). Thoracic aorta-femoral artery bypass graft (arrow). (catheter-directed angiogram).

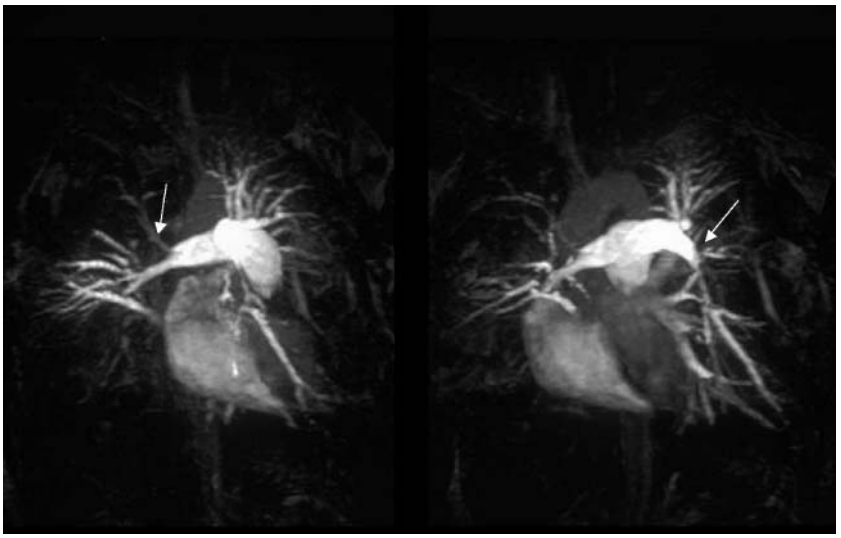

Figure 6. Severe bilateral stenosis of primary branches of the main pulmonary arteries (MRA).

of the gut in an asymptomatic patient warrant careful observation, with intervention only in the setting of intestinal ischemia.

Dermatologic manifestations of TA are estimated to occur in up to 28% of patients. The more commonly reported skin lesions include erythema nodosum, erythema induratum, pyoderma gangrenosum, and tuberculoid-like eruptions (Werfel et al., 1996). Cutaneous necrotizing and granulomatous vasculitis have also been described.

5. Differential diagnosis

Other inflammatory disorders of large vessels with neurologic manifestations include giant cell arteritis (GCA), Behçet's disease, Cogan's disease, syphilis and sarcoidosis. Aortic root aneurysms rarely occur in systemic lupus erythematosus, rheumatoid arthritis, and spondyloarthropathies. However, these illnesses are usually not associated with stenosis of arch vessels and can be distinguished by other disease manifestations.

Distinguishing TA from GCA may be difficult, especially in patients presenting at 40–50 years of age. Although older age, Caucasian race, headache, polymyalgia rheumatica, visual symptoms, or scalp tenderness may suggest GCA, more overlap than is generally appreciated exists in the clinical symptoms and vascular lesions in these disorders.

6. Diagnostic investigations

6.1. Radiological

No one imaging study is flawless in assessing TA diagnosis and vascular change. The gold standard remains conventional catheter angiography. A distinct advantage of this procedure lies in its ability to provide high-resolution imaging. One of the most compelling reasons to utilize catheter-directed imaging, especially early in the clinical course, is to include measurement of central aortic pressure for patients in whom hemodynamically significant stenoses may be present in extremity vessels or the abdominal aorta. Catheter recorded pressures should be compared with blood pressure cuff measurements to assess reliability of cuff pressures. This is essential in patients with subclavian and/or innominate artery involvement, and becomes even more crucial when there are also stenoses of the abdominal aorta, iliac and femoral arteries. Without such data, accurate diagnosis and treatment of hypertension is not possible. It cannot be over-emphasized that considerable morbidity in TA may be a consequence of either unrecognized or untreated hypertension. Another advantage of catheter-directed angiography is the ability to perform interventions at the time of the procedure.

There are also disadvantages of using catheter-directed angiography for evaluation of TA. It does not reveal whether the vessel wall is inflamed. While a lesion in a newly involved site, since the prior study, suggests disease activity, isolated progressive stenosis of a previously documented lesion may be from active disease, or merely indicate bland myointimal proliferation in an area of turbulent flow. Catheter-directed angiography also is limited by its inability to assess the status of the vessel wall. It is a 'lumenogram' for which characteristics of the vessel wall are implied, but not visualized. Although imaging of the vascular lumen is helpful, being able to assess wall thickness or inflammatory changes in the wall would add another measure of insight. The invasiveness of this procedure, with associated radiation exposure, is not an insignificant consideration in the context of patients who require periodic vascular imaging studies.

Computed tomography angiography (CTA) also is useful in detecting vascular lesions and monitoring disease activity. This modality also has the capability of assessing vascular stenosis, occlusion, dilatation and aneurysm formation in large vessels. When CTA was compared to the 'gold standard', catheter-directed angiography, in a controlled trial, only 2% of lesions were either overestimated or underestimated. This study also reported a sensitivity of 93%, specificity of 98%, and accuracy of 97% for evaluation of arterial luminal changes in the thoracic aorta and major branches (Yamada et al., 1998). In addition, mural changes of calcification, thickening, and thrombus formation can be evaluated by CTA. These features are not visualized as well with catheter-directed angiography. CTA is limited by

poor visualization of branch vessel lesions remote from the aortic arch. This is most significant in the distal common carotid and subclavian arteries, where lesions commonly occur. CTA does not spare radiation exposure.

Magnetic resonance imaging (MRI) and arteriography (MRA) offer good spatial resolution and have the capacity to assess wall thickness, without the use of radiation or invasive means. The resolution, although good, is of lesser quality than catheter-directed angiography, especially in smaller vessels. The use of 'edema-weighted' images is handicapped by the lack of correlation between the presence of edema and subsequent changes in vascular anatomy in about one-third of patients (Tso et al., 2002). The implications of wall edema in patients who do not develop new lesions are still uncertain.

Ultrasound has limited application in the assessment of TA. It is limited by its inability to image deep vessels located beneath bony structures, and the number of vessels that can be accurately imaged in the course of followup. Because TA can involve new sites in a clinically overt or covert manner, it is important to follow the anatomy of the entire aorta and its branch vessels.

PET scanning has been utilized for detection of increased metabolic activity in inflammatory disorders such as GCA and polymyalgia rheumatica. This imaging technique has limited use for evaluation of distinct vascular lesions because of poor resolution. However, combining this technique with other imaging modalities (such as CTA or MRA) is currently being investigated as a potential future means of imaging vascular anatomy and assessing TA activity simultaneously.

6.2. Serology/immunology

There are no sensitive or specific serologic markers for diagnosis or monitoring of disease activity in TA. Only about 50% of patients with active TA have leukocytosis, thrombocytosis, anemia of chronic disease, or an increased erythrocyte sedimentation rate (ESR). This is a significant obstacle in following disease activity in TA. One study demonstrated an ESR elevation in 72% of patients with known disease activity, and elevation in 56% of patients who were in apparent remission (Kerr et al., 1994; Hoffman, 1996). This study also demonstrated that 44% of patients with presumed clinically inactive disease, who underwent a vascular bypass procedure, were found to have evidence of vasculitis within the surgical specimen. An evaluation of multiple markers including von Willebrand factor, sedimentation rate, tissue factor, C-reactive protein, and cellular adhesion molecules was performed in 29 patients and compared with 26 controls. None of these markers reliably correlated with measurable disease activity (Hoffman and Ahmed, 1998). A more recent small study did show a correlation of RANTES (regulated upon activation, normal T cell expressed and secreted) and interleukin-6 levels with disease activity (Noris et al., 1999), but these markers are not routinely available in clinical practice. Larger studies will be required to assess the merits of these cytokines for disease monitoring.

7. Treatment

TA is one of the most challenging vasculitides to treat. This in part relates to the cryptic nature of disease activity in many patients. The criteria of Kerr et al. defines active disease as any *two* or more of the following:

New or worsening:

(1) Signs and symptoms of vascular ischemia or inflammation
(2) Increase in sedimentation rate
(3) Angiographic features
(4) Systemic symptoms not attributable to another disease

Although these findings are useful when present, their absence does not assure disease quiescence Since histopathologic data are not routinely available, using these criteria as a means of discernment in combination with information provided by sequential laboratory and imaging studies is currently the best, albeit imperfect means for monitoring TA activity.

The goals of treatment are control of vascular inflammation, relief of symptoms, and detection and treatment of ischemia-related disease. Unfortunately achieving remission is often followed by relapse, in

over half of patients, concurrent with tapering of medical therapy (Hoffman, 1996).

Corticosteroids are the cornerstone of therapy. Prednisone administered at 1 mg/kg/day is initiated and maintained for about 1 month; followed by a slow taper with the goal of discontinuation over the next 6 to 12 months. Improvement must be interpreted in the context of ultimate maintenance of remission or relapse. Almost all patients improve following the initiation of high doses of prednisone. Remission may be achieved in about 60% of patients. However, despite a good initial response, half of these patients relapse after steroid treatment is tapered. The considerable side effects and morbidities associated with long-term steroid therapy are well documented. A desired goal in all patients is to minimize steroid therapy, employing the lowest possible dose to control disease. If steroids cannot be reduced to less than 10 mg of prednisone daily or if life-threatening features of disease are present, the addition of a cytotoxic agent may provide greater efficacy. Daily treatment with cyclophosphamide (2 mg/kg) has been shown to induce and maintain remission in such patients, but significant toxicities associated with long-term use of this agent limit its utility. In addition, there are no prospective controlled studies that have compared this agent to other cytotoxic drugs in TA. In an NIH study, 13/16 patients who were steroid-resistant or steroid-dependent attained remission using low dose weekly methotrexate in combination with glucocorticoids (Hoffman et al., 1994). Nearly half were able to discontinue steroid therapy during the follow up period (mean 2.8 years). Mycophenolate mofetil has been reported to have clinical benefit, with steroid-sparing effect and no significant toxicity, in three patients who were steroid-dependent (Daina et al., 1999). However, in our experience with six patients (unpublished observations), this agent has not been useful. Although there are no published trials regarding the use of biologic agents (e.g. etanercept or infliximab) in TA, case reports and small series document their efficacy in patients with other forms of systemic granulomatous vasculitis. We have demonstrated efficacy for anti-TNF agents in 14/15 patients with TA (Hoffman et al., 2004). Further studies of the agents in TA are needed before their use can be generally endorsed.

The therapy of TA must address hypertension if present. The importance of knowing how well central aortic pressure correlates with extremity cuff pressures cannot be overemphasized. In most cases hypertension is related to renal artery stenosis, which may be amenable to surgical correction and eradication of high renin hypertension. If hypertension is not surgically correctable, medical therapy is key in the prevention of stroke, congestive heart failure, and progressive renal failure. However, it is important to be mindful of the potential deleterious impact of extreme lowering of blood pressure in the setting of stenoses of cerebral and coronary arteries. Ideally, blood pressure should be slowly corrected. However, in the setting of malignant hypertension, options are limited. The high incidence of renal artery stenosis in this population implies the need for cautious use of and careful monitoring with angiotensin-converting enzyme inhibitor therapy. In the few hypertensive patients where vascular stenoses affects all extremities, preventing peripheral measurement of blood pressure that is representative of central aortic pressure, one should consider surgical correction so that blood pressure in at least one extremity can be used to guide therapy.

Along with hypertension and steroid use, vascular inflammation and its physiologic consequences contribute to atherogenesis in TA. Treatment of other cardiovascular risk factors is important to reduce disease-associated morbidity and mortality.

Anatomic diversity of lesions, in regard to severity and distribution, requires that surgical intervention be highly individualized. Bypass surgery or angioplasty should be considered for hypertension with critical renal artery stenosis, cerebrovascular ischemia or critical stenosis of three or more vessels supplying the cerebral circulation, extremity claudication that severely limits normal activity, and cardiac ischemia. Enlarging aortic root aneurysms often lead to clinically significant aortic regurgitation, resulting in congestive heart failure and cardiac ischemia due to inadequate coronary artery filling. When worsening hemodynamic parameters favor aortic root reconstruction, valve replacement may also be required. Vascular and cardiac procedures are best performed during a period of disease inactivity. The care of such patients often requires a close working relationship

between rheumatologists, cardiologists, vascular and cardiothoracic surgeons and imaging specialists.

The greatest success in achieving and maintaining vessel patency occurs when autologous grafts are available and suitable based on length of stenotic lesions and caliber of the donor vessel. Failure rates are progressively greater for synthetic grafts and with angioplasty. It is important to avoid use of arteries prone to involvement by TA for anastamoses. For example, when bypass is performed for carotid artery stenosis, a patent subclavian artery should not be used as the origin of a graft. The subclavian artery will become stenotic in over 90% of patients with TA. Should that occur following a subclavian to common carotid bypass, the graft will be lost. Bypass is not without risks. In a cohort of ninety-one patients with a total of two hundred fifty-nine anastamoses, the incidence of anastamotic aneurysms was 8.5%, compared to 4.7% in patients with atherosclerotic disease (Miyata et al., 1998). When factors influencing aneurysm formation were studied, the same factors important in aneurysm formation in grafts in patients with atherosclerosis were also important in TA patients: wall weakness, compliance mismatch between graft and vessel, graft dilatation, hypertension, mechanical stress, and suture degradation. As expected, aneurysm formation was more likely to occur if the initially bypassed area was aneurysmal, rather than stenotic. Steroid use or features of systemic inflammation did not appear to have a major influence on this process. Unlike atherosclerotic aneurysms, the likelihood of rupture in these patients is low.

Percutaneous angioplasty has also been utilized in the treatment of TA. The most successful and sustained results are noted for renal artery stenosis. The initial patency rate for renal artery PTCA has been reported as high as 81% (Deyu et al., 1998). Sustained patency, however, occurs in less than 60%. Complications with this procedure are rare, but may include dissection, pseudoaneurysm, or the creation of an intimal flap. Angioplasty of other vessels has not proven as successful; the diffuse vascular thickening is less amenable to dilation than an atheromatous plaque, and high rates of restenosis have been the rule rather than the exception. Data on the use of intravascular stents is limited. Initial experience has thus far been disappointing in our center.

Key points

- TA is a chronic form of vasculitis that has a predilection for the aorta and its first order branches.
- Although diagnosed most frequently in young Asian women, this disorder occurs worldwide in both men and women.
- The presentation of this disease is highly variable. Patients may have an acute systemic illness with overt inflammatory signs and symptoms, or have asymptomatic findings of pulselessness or bruits.
- Central nervous system sequelae of this disorder include strokes. Contributing factors include unrecognized and uncontrolled hypertension, and stenoses of the carotid, proximal subclavian/innominate, and vertebral arteries. Anatomic definition of all lesions is essential. This is to ensure that the physician and patient are aware of areas of critical stenosis and to identify which extremity provides cuff blood pressure recordings that are representative of central thoracic aortic pressure.
- The gold standard for diagnosis is catheter-guided angiography. Other less invasive imaging modalities may be useful for monitoring disease activity.
- Laboratory studies may reveal nonspecific features of inflammation in 50% of patients with active TA. They are not reliable indicators of disease activity. Treatment should not be based on these findings alone.
- Therapy should address not only the control of inflammation, but should encompass monitoring and treatment of associated vascular complications. Surgical interventions should be preceded by careful preoperative assessment and, when possible, performed when the disease is in remission.

References

Cacamise, W.C., Okuda, K. 1954. Takayasu's or pulseless disease. Am. J. Ophthalmol. 37, 748.

Cavatorta, F., Campisi, S., Tabassi, E., Zollo, A., Salvidio, G. 1995. IgA nephropathy associated with Takayasu's arteritis: report of a case and review of the literature. Am. J. Nephrol. 15, 165–167.

Clark, T., Hoffman, G.S. 2004. Pulmonary artery involvement in Wegener's granulomotosis. Clin. Exp. Rheum. 21 (5), 124–126.

Daina, E., Schieppati, A., Remuzzi, G. 1999. Mycophenolate mofetil for the treatment of Takayasu arteritis: report of three cases. Ann. Intern. Med. 130, 422–426.

Deyu, Z., Lisheng, L., Ruping, D., Haiying, W., Guozhang, L. 1998. Percutaneous transluminal renal angioplasty in aortoarteritis. Int. J. Cardiol. 66 (Suppl.), S205–S211.

Di Giacomo, V. 1984. A case of Takayasu's disease occurred over 200 years ago. Angiology 35, 170.

Ganguly, N.K., Jain, S., Kumari, S. 1996. Current status of Takayasu arteritis in India. Int. J. Cardiol. 54, 155–163.

Hall, S., Barr, W., Lie, J.T., Stanson, A.W., Kazmier, F.J., et al. 1985. Takayasu arteritis. A study of 32 North American patients. Medicine 64, 89–99.

A 13 year observational study of clinical features, response to therapy and prognosis in a cohort of clinical features, response to therapy and prognosis in a cohort of 32 patients with Takayasu's arteritis.

Hellmann, D.B., Hardy, K., Lindenfeld, S., Ring, E. 1987. Takayasu's arteritis associated with crescentic glomerulonephritis. Arthritis Rheum. 30, 451–454.

Hoffman, G.S. 1996. Takayasu arteritis: lessons from the American National Institutes of Health experience. Int. J. Cardiol. 54 (Suppl.), S83–S86.

A discussion of key points determined and important questions derived from the NIH prospective study of 60 patients with Takayasu's arteritis over a 20 year period.

Hoffman, G.S., Ahmed, A.E. 1998. Surrogate markers of disease activity in patients with Takayasu arteritis. A preliminary report from The International Network for the Study of Systemic Vasculitides (INSSYS). Int. J. Cardiol. 66 (Suppl.), S191–S194.

An important investigation that highlighted the discordance between serologic markers and disease activity in Takayasu's arteritis.

Hoffman, G.S., Leavitt, R., Kerr, G., Rottem, M., Sneller, M., et al. 1994. Treatment of glucocorticoid-resistant or relapsing Takayasu arteritis with methotrexate. Arthritis Rheum. 37, 578–582.

Hoffman et al. 2004. Arthritis Rheum. (in press).

Ishikawa, T. 1977. Systemic artery-pulmonary communication in Takayasu's arteritis. Am. J. Roentgenol. 128, 389–393.

Ishikawa, K., Uyama, M., Asayama, K. 1983. Occlusive thromboaortopathy (Takayasu's disease): cervical artery stenoses, retinal artery pressure, retinal microaneurisms and prognosis. Stroke 14, 730–735.

Jain, S., Taraphdar, A., Joshi, K., Malik, N., Sakhuja, V., et al. 1992. Renal amyloidosis complicating Takayasu's arteritis: a rare association. Nephr. Dial. Transplant. 7, 1133–1135.

Johnston, S.L., Lock, R.J., Gompels, M.M. 2002. Takayasu arteritis: a review. J. Clin. Path. 55, 481–486.

Kerr, G. 1995. Takayasu arteritis. Rheum. Dis. Clin. N. Am. 21, 1041–1057.

Kerr, G., Hallahan, C., Giordano, J., Leavitt, R., Fauci, A., et al. 1994. Takayasu arteritis. Ann. Int. Med. 120, 919–929.

A prospective study of clinical features, angiographic findings, and response to therapy in 60 patients with Takayasu's arteritis.

Kiyosawa, M., Baba, T. 1998. Ophthalmological findings in patients with Takayasu disease. Int. J. Cardiol. 66 (Suppl. 1), S141–S147.

Koumi, S., Endo, T., Okumura, H., Yoneyama, K., Fukuda, Y., et al. 1990. A case of Takayasu's arteritis associated with membranoproliferative glomerulonephritis and nephrotic syndrome. Nephron 54, 344–346.

Koyabu, S., Isaka, N., Yada, T., Konishi, T., Nakano, T. 1993. Severe respiratory failure caused by recurrent pulmonary hemorrhage in Takayasu's arteritis. Chest 104, 1905–1906.

Kreidstein, S., Lytwyn, A., Keystone, E. 1993. Takayasu arteritis with acute interstitial pneumonia and coronary vasculitis:expanding the spectrum. Arthritis Rheum. 36, 1175–1178.

Kumar, S., Sherman, C. 1997. Unusual pulmonary manifestations of Takayasu's arteritis. J. Rheum. 24, 1661–1662.

Levitsky, J., Harrison, J., Cohen, R. 2002. Crohn's disease and Takayasu's arteritis. J. Clin. Gastroenterol. 34, 454–456.

Lupi-Herrera, E., Sanchez-Torrez, G., Marchushamer, J., et al. 1977. Takayasu's arteritis. Clinical study of 107 cases. Am. Heart J. 93, 94–103.

Malik, K., Kapoor, K., Mehta, A., Dadeya, S., Guliani, B., et al. 2002. Bilateral anterior ischaemic optic neuropathy in Takayasu arteritis. Ind. J. Ophthalmol. 50, 52–54.

Miyata, T., Sato, O., Deguchi, J., Kimura, H., Namba, T., et al. 1998. Anastamotic aneurysms after surgical treatment of Takayasu's arteritis: a 40-year experience. J. Vasc. Surg. 27, 438–445.

Morita, Y., Yamamura, M., Suwaki, K., Mima, A., Ishizu, T., et al. 1996. Takayasu's arteritis associated with ulcerative colitis; genetic factors in this association. Int. Med. 35, 574–577.

Nasu, T. 1975. Takayasu's truncoarteritis in Japan: a statistical observation of 76 autopsy cases. Pathol. Microbiol. 43, 140–146.

Noris, M., Daina, E., Gamba, S., Bonazzloa, S., Remuzzi, G. 1999. Interleukin-6 and RANTES in Takayasu arteritis: a guide for theraputic decisions? Circulation 100, 55–60.

Seko, Y. 2000. Takayasu arteritis. Insights into immunopathology. Jpn. Heart J. 41, 15–26.

Sharma, B.K., Jain, S., Radotra, B.D. 1998. An autopsy study of Takayasu arteritis in India. Int. J. Cardiol. 66 (Suppl. 1), S85–S90.

Smith, J., Rosenbaum, J. 2001. Scleritis occurring in association with Takayasu disease. Arch. Ophthalmol. 119, 778–779.

Tso, E., Flamm, S., White, R., Schvartzman, P., Mascha, E., et al. 2002. Takayasu arteritis. Utility and limitations of magnetic resonance imaging in diagnosis and treatment. Arthritis Rheum. 46, 1634–1642.

Waern, A.U., Anderson, P., Hemmingsson, A. 1983. Takayasu's arteritis: a hospital-region based study on occurrence, treatment, and prognosis. Angiology 34, 311–320.

Werfel, T., Kuipers, J., Zeidler, H., Kapp, A., Kiehl, P. 1996. Cutaneous manifestations of Takayasu arteritis. Acta Derm. Venereol. (Stockh.) 76, 496–497.

Yamada, I., Shibuya, H., Matsubara, O., Umehara, I., Makino, T., et al. 1992. Pulmonary artery disease in Takayasu's arteritis: angiographic findings. AJR 159, 263–269.

Yamada, I., Nakagawa, T., Himeno, Y., Numano, F., Shibuya, H. 1998. Takayasu arteritis: evaluation of the thoracic aorta with CT angiography. Radiology 209, 103–109.

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CHAPTER 11

Behçet's Syndrome

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1. Introduction

The skeptic would challenge the inclusion of Behçet's syndrome (BS) in a textbook of systemic autoimmune disease (Yazıcı, 1997). Starting from the unique geographic distribution, there are many features that differ from a classic autoimmune disease like the lack of autoantibodies, no association with Sjögren's syndrome, and the absence of clinical manifestations like serosal disease and Raynaud's phenomenon. On the other hand, the lumper would argue that there is enough clinical similarity and backup from the immunology laboratory to justify such an inclusion.

BS, a systemic vasculitis of unknown cause, affects many organs and systems. Among these are the mucocutaneous lesions, a uveitis sometimes resulting in blindness, central nervous system (CNS) pathology (the main substance of this chapter), major vessel disease that may be fatal, musculoskeletal problems, gastrointestinal involvement and many others. The diagnosis remains clinical. A course of exacerbations and remissions is usually seen and the syndrome, in the majority of the cases, goes into a remission with the passage of time. In fact, only about one-fourth of an inception cohort would have been diagnosed as BS when reevaluated 20 years later (Kural-Seyahi et al., 2003).

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2. Prevalence

In Turkey, among the population aged 10 years or older, the prevalence ranges from 4/10,000 to 39/10,000 (Yurdakul et al., 1988; Idil et al., 2002). A similar frequency has been reported among the ethnic Arabs in Israel (Jaber et al., 2002). Judging from the clinical cases being reported, probably a near frequency is true for other Mid-eastern countries like Iran. Case registries show frequencies of 1/10,000 in Japan (Shimizu et al., 1979) while much lower frequencies are reported from the Western countries (Gonzalez-Gay et al., 2000).

BS is rare among children. In one survey among 45,000 children in Turkey no such cases were found (Ozen et al., 1998). This puts 95% of the upper limits of the estimated frequency to 1/15,000 (Yazıcı et al., 2001). On the other hand, there is certainly an increased awareness of the pediatric cases (Kone-Paut et al., 1998).

3. Epidemiology

For unexplained reasons, the geographic distribution of BS shows considerable variation. The Silk Route that extends from the Mediterranean to Japan has been proposed as the genetic common denominator. A similar variation in the population frequency of HLA-B51, strongly associated with the disease in the high prevalence areas supports this notion

(Ohno et al., 1982; Verity et al., 1999). Overall the male:female ratio is approximately equal but the syndrome has a more severe course among men (Kural-Seyahi et al., 2003).

The reported frequency of neurological involvement among BS patients ranges from 2.2 to 49.0%, and it was found to be 4.8% in our non-selected series from the Behçet's Disease Research Center with the mean age of onset for BS and neuro-Behçet's syndrome (NBS) to be 26.7 ± 8.0 and 32.0 ± 8.7 years, respectively (Siva et al., 2001). This is consistent with some other series (Akman-Demir et al., 1999; Kidd et al., 1999). However, these are frequency estimates from cross-sectional studies. When we evaluated the frequency of neurological involvement prospectively, the frequency became 13.0% among the males and 5.6% among the females after two decades of follow-up (Kural-Seyahi et al., 2003).

When the patients with neurological disease were stratified according to the two major types of neurological involvement, the age of onset for patients with cerebral venous sinus thrombosis (CVST) was significantly earlier than that of CNS–parenchymal involvement (24.7 ± 8.8 vs. 32.7 ± 7.4 years) (Siva et al., 2003). Among the small number of females studied, such a trend was not observed.

Neurological complications in BS occur more commonly in males. In our reported series of 164 well-documented cases with neurological involvement, the male to female ratio was 3.8:1, whereas the corresponding ratio in the total BS population in our center was 1.8:1 at that time (Siva et al., 2001). Such a significant male predominance is also noted for other vascular complications of BS (Kural-Seyahi et al., 2003).

4. Etiology/pathogenesis

The hallmark of BS is an increased inflammatory response with vasculitis as its main clinical consequence. Pathogenesis is yet unclear and, as underlined in the introduction, there are a number of reasons why BS cannot be easily explained as another 'autoimmune' disease. As is true for many diseases of unknown etiology, the popular theory is that of environmental factors causing disease in the genetically susceptible host.

In the areas like Turkey where the disease is endemic, the sibling recurrence risk ratio (λ_s) has been estimated to be between 11 and 53 and this suggests a rather strong genetic influence on disease expression (Gul et al., 2000). However, the inheritance pattern is non-Mandelian, with more severe disease in subsequent generations among the familial cases being proposed (Fresko et al., 1998).

The HLA-B51 association was first described in 1973 (Ohno et al., 1973). We still do not know its biological meaning. A recent theory suggests that a HLA-B51 related peptide might function as a cross-reactive antigen with the retinal S antigen in disease pathogenesis, akin to a similar role some assume for HLA-B27 in the pathogenesis of ankylosing spondylitis (Kurhan-Yavuz et al., 2000). Also, for some time, a group of genes in linkage with HLA-B51-like MICA was proposed as the true genetic markers, but further work established that the real marker was HLA-B51 itself (Salvarani et al., 2001; Gul et al., 2001a). Recently, a new locus outside the MHC has also been shown to be BS associated (Gul et al., 2001b).

Autoantibodies, including ANCA (Tunc et al., 2003) and anticardiolipin antibodies (Tokay et al., 2001) are not usually present in BS. Recently, and as what had been reported for Crohn's disease, antibodies to *Saccharomyces cerevisiae* has been reported among patients with BS from Israel (Krause et al., 2002). The same group has also recently reported antibodies to alpha-tropomysin and, when the target antigen alpha-tropomysin was injected into the Lewis rat, uveitis was induced (Mor et al., 2002). These two novel and interesting observations of increased B-cell activity in BS remain to be confirmed further by more work.

T-cell mediated aberrations have frequently been reported in BS. The proportion of $\gamma\delta+$ T-cells are certainly increased (Fortune et al., 1990). There is also a strong Th-1 polarization in the cytokine release (Frassanito et al., 1999).

There is an increased T and B-cell response to mycobacterial heat shock proteins (HSP) and to their human homologues in BS. In the past, this had been thought to be quite specific and even diagnostically useful (Hasan et al., 1996). In Lewis rats, uveitis have been produced with these proteins and a mechanism

of molecular mimicry had been proposed between bacterial and self-HSP molecules in the pathogenesis of BS (Stanford et al., 1994). We, however, now know that the specificity of the HSP response is not specific for BS. On the other hand, HSP might still be important in the pathogenesis through functions as molecular chaperons or adjuvants that facilitate and augment the immune response (Direskeneli and Saruhan-Direskeneli, 2003).

Herpes simplex virus (HSV) type I has also been implicated in pathogenesis and BS-like symptoms were produced in ICR mice with HSV inoculation (Sohn et al., 1998), an observation also in need of further study.

About one-third of all patients with BS have thrombophlebitis (Kural-Seyahi et al., 2003). There is ample evidence both for thrombophilia—without any one specific coagulation abnormality apart from a decrease in fibrinolysis—(Espinosa et al., 2002) and endothelial dysfunction (Chambers et al., 2001). It is more likely that endothelial dysfunction is the proximal event (Yazıcı, 2002). Like in many vasculitides, antiendothelial antibodies (AECA) had been reported in BS, with little insight into their target antigen. Recent work from Korea has shown that α-enolase is the target antigen in the majority of the instances when AECA is positive in BS. Furthermore, the early data show that this antibody might also have some specificity for BS, as well (Lee et al., 2003).

An increased frequency of Factor V Leiden and prothrombin G → A20210 mutations have been proposed but their individual contributions to pathogenesis are not clear (Gul, 2001).

The pathergy reaction is almost unique to BS. It is clinically demonstrated as a papule or a pustular reaction of the skin to a dermal pinprick after 48 h. The pathogenetic role of pathergy, on the other hand, is not known.

A neutrophil hyperreactivity has also been reported in BS and even it has been tied up with HLA-B51 in an animal model (Takeno et al., 1995). The specificity of the neutrophil hyperreactivity, however, has been challenged (Tuzun et al., 1999).

Finally, the discovery of the MEFV gene in association with familial Mediterranean fever, a disease with a few clinical manifestations similar to Behçet's, but certainly common in the Middle East where BS is also common, has led some investigators to consider whether the two conditions were pathogenetically related. This concept was initially based on some patients with co-existent disease (Schwartz et al., 2000) and later with the demonstration of a somewhat increased MEFV disease associated mutations among the BS patients (Touitou et al., 2000). This certainly is an interesting concept that still needs more data to back it up (Ben-Chetrit and Yazıcı, 2002).

Studies specifically addressed to the pathogenesis of brain involvement in BS have been very few. One such study reported, increased cerebrospinal fluid (CSF) antibody response to mycobacterial HSP (Tasci et al., 1998).

5. Systemic manifestations of Behçet's syndrome

Although various different criteria have previously been used for the diagnosis, currently the most widely used diagnostic criteria is the International Study Group's classification, according to which, a definitive diagnosis requires recurrent oral ulcerations plus two of the following: recurrent genital ulcerations, skin lesions, eye lesions and a positive pathergy test (International Study Group for Behçet's Disease, 1990, 1992) (Table 1). The clinical manifestations of BS, along with the usual frequency with which they are noted, are shown in Table 2.

5.1. Skin—mucosa findings

5.1.1. Oral ulcers

Practically all patients with Behçet's disease have oral ulcers. The majority of the oral ulcers are indistinguishable from ordinary canker sores, however, they are more frequent, multiple and perhaps more painful. They begin as red, slightly raised areas in the oral mucosa that turn into round or oval ulcers within a day or two. Oral ulcers are usually the first manifestations of Behçet's disease. Since oral ulceration is also common in the general population, it usually is matter of debate whether one can consider oral ulceration as the initial manifestation of the disease in any one patient.

It is customary to classify the ulcers as (a) minor, (b) major or (c) herpetiform. Ninety percent of the oral

Table 1
Criteria for diagnosis of Behçet's syndrome

Finding	Definition
Recurrent oral ulceration	Minor aphtous, major aphtous, or herpetiform ulcers observed by the physician or reliably described by the patient, which recurred at least three times over a 12-month period
Recurrent genital ulceration	Aphtous ulceration or scarring observed by the physician or reliably described by the patient
Eye lesions	Anterior or posterior uveitis or cells in the vitreous body on slit-lamp examination; or retinal vasculitis detected by an ophthalmologist
Skin lesions	Erythema nodosum, pseudofolliculitis, papulopustular lesions or acneiform nodules not related to glucocorticoid treatment or adolescence
Positive pathergy test	Test interpreted as positive by the physician at 24–48 h

For a clinical definite diagnosis of BD, patient must have recurrent oral ulceration plus at least two of the other findings in the absence of any other clinical explanations (International Study Group for Behçet's disease, 1990).

ulcers are of the minor form. They are round/oral shallow ulcers less than 10 mm in diameter. There is usually a surrounding, red, inflammatory halo. The inner lips, gingival mucosa, cheeks and tongue are more commonly involved than the palate and the pharynx. In contrast to the herpetic lesions, the outer portions of the lips are spared. They usually heal in about 15 days without scarring. The major aphthous ulcers are bigger than 10 mm in diameter and can involve any region. They are more painful and usually heal with a scar. Sometimes they can lead to dysphagia, pharyngeal stenosis or even death. Patients with major ulcers have significantly more relapses, and more ulcers per relapse. These ulcers, when compared to the minor forms, also last longer (Krause et al., 1999). The herpetiform ulcers, the least common form are small crusts, 2–3 mm in diameter. They heal in a few days without scarring.

The histopathology of the oral ulcers is usually indistinguishable from the histopathology of the ordinary canker sore.

Table 2
Frequency of clinical manifestations of Behçet's syndrome (Mediterranean countries and Japan)

Manifestation	Frequency (%)
Oral ulcers	97–100
Genital ulcers	~85
Eye disease	~50
Skin lesions	
Papulopustular lesions	~85
Erythema nodosum	~50
Pathergy reaction	~60[a]
Arthritis	~50
Thrombophlebitis	25
Involvement of major arteries/veins	~4
CNS disease	~5–10
Epididymitis	~5
Gastrointestinal lesions	1–30 (more prevalent in Far East)

[a] Mediterranean countries and Japan.

5.1.2. Genital ulcers

With the same histology as the oral ulcers, the genital ulcers of BS are a much more specific finding. The ulcer is usually round or oval with a base covered with grayish fibrin. There is a punched-out appearance with a surrounding edema with induration. Secondary infection is common, especially among the females. The ulcers usually heal, in a size dependent fashion, mostly within 3 weeks and commonly leave scars. In males they are usually localized on the scrotum and less frequent on the shaft and the glans penis, inguinal area, the pubis, and the perineum. Perianal lesions can also be seen. In females, they are commonly found on the labiae with decreasing frequency in the vagina and the cervix. It is important to note that genital ulcers may go unnoticed among the females, especially if they are not infected with secondary discharge.

This mandates a gynecologic examination in all female patients with suspected BS.

The scrotal ulceration of BS is a rather unique finding. No such lesions are usual in other connective diseases or vasculitides. Furthermore, it is well known that the scrotal skin is one of the androgen sensitive areas of the body and this peculiar localization might just be representative of an increased end-organ responsiveness in a condition in which males have a more severe disease course in almost all aspects (Kural-Seyahi et al., 2003).

5.1.3. Skin lesions

The dermal lesions of BS are mainly of three types: the nodular lesions (erythema nodosum-like lesions and superficial thrombophlebitis); papulopustular lesions; and other dermal lesions such as skin ulcers, Sweet's syndrome, or pyoderma gangrenosum.

The main two types of nodular lesions—each occurring with almost the same frequency—can cause problems in differential diagnosis, especially for the uninitiated. On the other hand, this distinction can be important both from the standpoint of target organ associations and in management. Erythema nodosum-like lesions look like idiopathic erythema nodosum, or erythema nodosum-associated with other diseases. On closer inspection, these lesions tend to be less well demarcated and deeper with a tendency to leave some pigmentation as they heal. Our group and others have recently shown (Kim and LeBoit, 2000; Demirkesen et al., 2001) that when the histology of the erythema nodosum-like lesions of BS are compared to erythema nodosum idiopathic or associated with other diseases, the BS lesions may show areas of frank vasculitis. Superficial thrombophlebitis: lesions morphologically look very much like the erythema nodosum lesions. The superficial thrombophlebitis lesion obviously has a thrombosed vein as the central lesion on biopsy. We have preliminary evidence that we can perhaps differentiate between the two, in short of a biopsy, by dermal ultrasound. The correct differentiation between the superficial thrombophlebitis and erythema nodosum lesions is important in that the former is associated with major vessel disease (Tunc et al., 2002), which in turn is associated with dural sinus thrombi (Siva et al., 2003).

The acne-like lesions of BS (the papulopustular lesions) are both clinically and pathologically indistinguishable from ordinary acne (Ergun et al., 1998). On the other hand, it is common for the papulopustular lesions of BS also to appear in the arms and legs sites uncommon for ordinary acne. Acne are androgen dependent lesions and one can speculate that the abundance of these lesions in BS represent an end-organ hypersensitiveness in line with more severe disease among the male patients in general.

One recent interesting observation is the association of acne lesions with the presence of arthritis (Diri et al., 2001; Tunc et al., 2002), reminiscent of an acne–arthritis type of disease mechanism in the joint involvement in BS (Winchester, 1999).

5.2. Eye involvement

Eye involvement, the most frequent cause of serious morbidity, is a non-granulomatous panuveitis and retinal vasculitis. It runs with a course of exacerbations and remissions with the eventual outcome of blindness in some patients, if not treated. The overall frequency is about 50%, with higher frequencies in the young male and much lower frequencies in the older female. Becoming eventually bilateral in 90% of the patients, it is usually an early manifestation. It is quite rare for patients to develop eye disease after the initial 4–5 years of disease course (Kural-Seyahi et al., 2003).

Patients usually complain of ocular pain, ocular discomfort and visual blurring. The primary lesion in eye involvement is a retinal vasculitis, mainly on the venous side. This results in exudates, hemorrhages, venous thrombosis, papilloedema, macular disease and pars planitis. With an acute flare there is a marked influx of fibrin, inflammatory cells, and cellular debris into the vitreous, and after each flare there is usually some residual structural damage in the form of retinal changes, vitreal opacities, posterior synechiae, and cataracts. Secondary glaucoma frequently develops. The extent of these structural changes determinates the course of eye disease in BS.

Conjunctivitis and episcleritis are rare in BS.

5.3. Cardiovascular and pulmonary involvement

Venous disease is a key manifestation of BS. Thrombophlebitis is seen in about one-third of all patients. Both the peripheral and the central veins (vena cavea) can be involved. Occlusion of the suprahepatic veins can cause Budd–Chiari syndrome with a high mortality.

Pulmonary embolism is rare in BS. This is probably due to the fact that the thrombi are secondary to an inflamed vessel wall and are thus adherent.

Aneurysms of both the abdominal aorta and other carotid, femoral and the popliteal arteries can be seen. The basic pathology is thought to be a vasculitis of the vasa vasorum. Pulmonary artery aneurysms are the leading cause of mortality in BS (Kural-Seyahi et al., 2003). They invariably present with hemoptysis and are seen in radiographs of the chest as homogenous masses. The vast majority of the patients are male and peripheral thrombophlebitis is also very common. This leads to an erroneous diagnosis of pulmonary emboli by the uninitiated. The diagnosis is usually made by (CT) tomography scans.

Endocarditis, myocarditis, pericarditis, intracardiac thrombi along with endomyocardial fibrosis, coronary vasculitis and ventricular aneurysms have also been documented in BS but are quite rare (Kaklamani et al., 1998).

5.4. Gastrointestinal disease

Gastrointestinal disease is one of the manifestations of BS that shows geographical variation. Common among the patients from the Far East (Lee et al., 2001), it is quite rare among patients in Turkey (Yurdakul et al., 1996). Mucosal ulcerations are seen in the ileum, caecum and other parts of the colon. The common symptoms are abdominal pain and melena and a mass is often palpable in the abdomen. Intestinal perforation is the feared complication.

Unlike inflammatory bowel disease, ano-rectal involvement is uncommon in BS.

5.5. Musculoskeletal system

Arthritis or arthralgia is seen in about one-half of the patients. Usually a few joints are involved. Erosions and deformity are rare. Back pain and sacroiliitis are unusual and an association of the arthritis with acne is noted (Diri et al., 2001; Tunc et al., 2002).

A local myositis is occasionally seen in BS (Serdaroglu, 1998a,b). Rarely generalized forms can be encountered. The muscle enzymes are not raised in the local form and the histological features are indistinguishable from those of polymyositis.

5.6. Other clinical features

Renal involvement is uncommon for a systemic vasculitis but is seen especially when searched for (Akpolat et al., 2002). Epididymitis and voiding dysfunction are well-recognized symptoms (Çetinel et al., 1998). Amyloidosis is seen sporadically and, when present, usually presents with a nephrotic syndrome. It is of the AA type and carries a grave prognosis (Melikoglu et al., 2001).

6. Neurologic manifestations of Behçet's syndrome

6.1. Clinical manifestations

Patients with BS may present with different neurological problems, related either directly or indirectly to the disease (Table 3).

Table 3
The neurological spectrum of Behçet's syndrome

Headache (non-structural)
Cerebral venous sinus thrombosis (extra-axial NBS)
Central nervous system involvement (intra-axial NBS)
Neuro-psycho-Behçet syndrome
Peripheral nervous system involvement
Complications of treatments
Secondary neurological involvement
(i.e. cerebral emboli from cardiac complications of BS)
Coincidental neurological involvement

NBS; neuro-Behçet syndrome. Modified from Siva, A., Fresko, I., 2000. Behçet's disease. 59.

Headache is the most common neurological involvement in BS. There is a non-structural, recurrent, vascular-type headache that starts after the onset of the systemic manifestations of BS, and sometimes associated with their exacerbations. This is relatively common and we are not sure whether this is directly related to the syndrome. On the other hand, a tension-type headache, depression and neurologic complications of BS treatment (i.e. with cyclosporine and thalidomide use) are surely among the indirect neuro-psychiatric consequences of the syndrome (Siva et al., 2000).

The two major forms of neurological disease seen in BS are the CNS–parenchymal involvement or CVST. The common clinical presentations are brainstem or corticospinal tract syndromes in the former and of increased intracranial pressure in the latter form. Some authors like to call isolated CNS–parenchymal involvement as NBS, and include CVST within the spectrum of so-called vasculo-Behçet (Wechsler et al., 1992; Serdaroglu, 1998a). However, as both have neurological consequences they will be reviewed here as 'neuro-Behçet syndrome' and will be identified as 'intra-axial NBS' and 'extra-axial NBS', respectively.

Clinical and neuroimaging evidence also, we believe, justify this sub-classification of NBS. CNS-NBS or intra-axial NBS is due to small vessel disease and causes the focal or multifocal CNS involvement seen in the majority of patients with CNS involvement. The second form, CVST or extra-axial NBS, which is due to large vessel disease in the form of CVST, has limited symptoms, a better prognosis and generally an uncomplicated outcome (Siva et al., 2001). These two types of involvement occur in the same individual rarely, and presumably have a different pathogenesis. Many of the CNS-NBS patients with small vessel inflammation have a relapsing–remitting course initially, with some ultimately developing a secondary progressive course later, and a few will have a progressive CNS dysfunction from the onset. In our series of patients with neurological manifestations related to BS, the rate of CNS-NBS was 75.6%, and CVST 12.2%, with the remaining having other or indefinite diagnoses (Siva et al., 2001).

Peripheral nervous system (PNS) involvement is rare. Neurophysiological studies may demonstrate non-specific findings in some patients. The limited number of patients, who have been reported with PNS involvement, had clinical and electrophysiological findings consistent with mononeuritis multiplex, a peripheral neuropathy prominent in the lower extremities, and a poly-radiculoneuritis (Namer et al., 1987; Takeuchi et al., 1989).

6.1.1. Headache and Behçet's Syndrome

The most common neurological symptom among patients with BS is headache, which may be due to a variety of causes (Table 4). Some patients with BS report a paroxysmal migraine-like pain, which is bilateral, frontal, of moderate severity and throbbing. This type of headache generally starts after the onset of the systemic findings of BS, and may be seen during exacerbations of systemic findings such as oral ulcerations or skin lesions, though this is not always the rule. This non-structural headache of BS is not associated with primary neurological involvement.

However, a substantial number of patients with BS may report a severe headache of recent onset not apparently consistent with a co-existing primary headache or ocular inflammatory pain. These patients require further evaluation, even if they do not have neurological signs, as such a symptom may indicate the onset of NBS, of either intra or extra-axial type. Such patients require further evaluation when the reported headache is severe and incapacitating, if it is the first or worst headache of their life, if their symptoms began after or within 6 months of onset of other systemic symptoms, if there is a change in character of the headache after the onset of systemic disease, or needless to say, when they have objective findings in neurological examination or the fundoscopic examination discloses papilledema. Almost approximately 10% of patients presenting with

Table 4
The differential diagnosis of 'headache' in patients with Behçet's syndrome

Headache due to central nervous system parenchymal involvement
Headache due to cerebral venous sinus thrombosis
Headache in association with ocular inflammation
The non-structural headache of BS
Co-exiting primary headaches (i.e. migraine; tension-type headache)

an isolated severe headache will turn out to have a neurological syndrome due to BS (Siva et al., 2001).

6.1.2. The spectrum of NBS

In addition to headache by itself, NBS may present with focal or multifocal CNS dysfunction with or without headache. The most common symptoms detected at onset in our series were: headache (61.6%), weakness of upper motor neuron type (53.7%), brainstem and cerebellar (49%), and cognitive/behavioral (16%) (Siva et al., 2001). Rare presentations that we have personally observed or were reported by others include isolated optic neuritis, psychiatric manifestations referred to as Neuro-Psycho-Behçet syndrome, aseptic meningitis, intracerebral hemorrhage due to ruptured aneurysms, extrapyramidal syndromes, eight nerve involvement leading to hearing loss and peripheral neuropathy (Adler et al., 2002; Akman-Demir et al., 1999; Bogdanova et al., 1998; Bussone et al., 1982; Kidd et al., 1999; O'Duffy et al., 1971; Pellechia et al., 1999; Perniciaro and Molina, 1991; Namer et al., 1987; Siva et al., 1986, 1991, 2001; Takeuchi et al., 1989). Our suggested criteria for diagnosis of NBS are outlined in Table 5.

6.1.3. Intra-axial NBS

The onset of a sub-acute brainstem syndrome that includes cranial nerve findings, dysarthria, uni or bilateral corticospinal tract signs, cerebellar findings (i.e. ataxia) and a mild confusion should raise the probability of 'NBS'. If this patient is a young man, especially of Mediterranean (or Middle East, or oriental) origin, the probability increases. Such a patient should always (if a reliable history cannot be obtained from the patient, then his family member(s) need to) be interviewed for the presence of systemic findings of BS. In the case of BS, a past or present history of oral aphtous ulcers and some other systemic manifestations of the disease will likely be present. Some patients with NBS would never consult a physician because of the mild nature of their systemic symptoms and thus the correct diagnosis might be missed. As mentioned above, it will be quite unlikely to see NBS cases without oral ulcers and all our patients with NBS had a history of recurrent oral ulcers and at least one of the other systemic manifestations of the disease by the time that they have developed their neurological symptoms. On the other hand, the MRI findings of NBS are highly suggestive (Koçer et al., 1999). There are some clinical series in which the onset of neurological disease was reported to be the first manifestation of the disease in some of the patients of the study cohort (Akman-Demir et al., 1999; Kidd et al., 1999; Al-Araji et al., 2003). In such cases, however, the diagnosis was made retrospectively, as at the time of the initial presentation none of the systemic symptoms of BS was detected to enable the clinician to reach the diagnosis. MRI, as already noted may be suggestive, but in the absence of systemic findings it will not be possible to diagnose NBS. Therefore, it is still a possibility that oral aphtous ulcers and probably some other systemic findings were already present at the time of the initial admission with the neurological problem but had not been specifically sought for.

It should be kept in mind that parenchymal-NBS (intra-axial NBS) do not always present with brainstem signs and symptoms. A hemiparesis, cognitive-behavioral changes, emotional lability, a self-limited or progressive myelopathy, as well as other CNS manifestations such as extrapyramidal signs and seizures, may be seen, but are less common.

Various types of voiding dysfunction related to bladder and sphincteric components in both phases of micturition can be seen in BS. Voiding dysfunction can be due to either neurological or direct bladder involvement. Augmentation ileocystoplasty is a good

Table 5
Suggested diagnostic criteria for neuro-Behçet syndrome

(A) Fulfilling the International Diagnostic Criteria for Behçet's Disease
(B) Onset of neurological symptoms not otherwise explained by any other known systemic or neurological disease or treatment
(C) Presence of at least one of the following:
(1) Objective abnormalities on neurological examination (clinical evidence)
(2) Abnormal neuroimaging findings suggestive of NBS (imaging evidence)
(3) Abnormal cerebrospinal fluid findings suggestive of NBS (laboratory evidence)
(4) Abnormal neurophysiological (electromyography or evoked potentials) studies consistent with the current neurological symptoms (neuro-physiological evidence)

The diagnosis of NBS requires both A and B, and at least one of the C criteria. Modified from Siva and Altintas, 2000.

treatment option in BS with severe bladder involvement (Cetinel et al., 1999).

6.1.4. Neuro-psycho-Behçet syndrome

Some patients with BS develop a neurobehavioral syndrome, which consists of euphoria, loss of insight, disinhibition, indifference to their disease, psychomotor agitation or retardation, with paranoid attitudes and obsessive concerns. The development of such psychiatric symptoms may be seen with or without other neurological symptoms of NBS, or independently. This syndrome should not be confused with psychosis associated with the use of glucocorticosteroid or other therapy. We have named this syndrome 'Neuro-Psycho-Behçet Syndrome' (Siva et al., 1991). Others have also observed a similar neurobehavioral syndrome (Oktem-Tanor et al., 1999).

In a prospective neuropsychological study of 12 patients with NBS, memory impairment was found to be the major finding (Oktem-Tanor et al., 1999). The most severely affected memory process was delayed recall, being impaired in all the patients either in the verbal and/or visual modalities. An impairment in the process of acquisition and storage; attention deficit and deficits of executive functions of the frontal system were other cognitive functions involved in a declining order. Neuropsychological status deteriorated insidiously, regardless of the neurological attacks during the follow-up period in most of the patients, and the presence of cognitive decline was not directly related to detectable lesions on neuroimaging at early stages of the disease. However, an enlargement of the third ventricle and atrophy of the posterior fossa structures were observed in the late stages of the disease, which correlated with memory loss (Oktem-Tanor et al., 1999).

6.1.5. Aseptic meningitis

In earlier studies, and using CT scans as the primary imaging modality, aseptic meningitis had been reported as a relatively frequent form of neurological involvement (Serdaroglu et al., 1989). Our experience has not been such, and we suspect that in some patients, parenchymal disease had been misclassified as aseptic meningitis due to lack of sensitive imaging data. In a recent update from the same institution, aseptic meningitis was reported only in 1 out of 200 cases studied (Akman-Demir et al., 1999). Similarly, in another recent study of 50 patients from the UK (Kidd et al., 1999), four cases were reported to have meningitis symptoms, while two of these patients had parenchymal lesions and two had normal MRIs. There was no discussion of meningeal enhancement and the CSF findings were within the same range as with patients who had brainstem parenchymal involvement. In support of this, in our experience, we have always observed inflammatory findings in CSF in patients who had findings consistent with CNS parenchymal disease on their MRIs. Taken together, we conclude that pure aseptic meningitis is quite rare within the clinical spectrum of neurological involvement in BS (Siva et al., 2001).

6.1.6. Extra-axial NBS

CVST is seen in 10–20% of BS patients in whom neurologic involvement occurs. Higher rates have been reported in a limited number of clinical studies from different geographical regions and ethnic backgrounds causing difficulty in interpreting these rates (Wechsler et al., 1992; Al-Araji et al., 2003). The co-occurrence of intra-axial and extra-axial NBS in the same patient is uncommon (Siva et al., 2003).

Thrombosis of the venous sinuses may cause increased intracranial pressure with severe headache, mental changes and motor ocular cranial nerve palsies, but in some patients the only manifestation may be a moderate headache. It is well known that the clinical manifestations resulting from thrombosis of the intracranial venous system vary according to the site and rate of venous occlusion and its extent. Our experience suggests that the CVST in BS may evolve relatively slowly in most patients with this form of involvement, as in none of our patients we have observed a fulminating syndrome of violent headache, convulsions, paralysis and coma.

Hemorrhagic venous infarcts or other parenchymal CNS lesions on MRI in patients with CVST (extra-axial NBS) are rare (Akman-Demir et al., 1999; Siva et al., 2001; Wechsler et al., 1992). This observation also suggests that the CVST in BS is probably usually not an acute process that also produces a complete block in venous drainage.

However, acute onset cases have been reported in whom seizures and focal neurologic signs also occurred besides headache (Wechsler et al., 1992). Papilledema and sixth nerve paresis are the most common signs reported and hemiparesis may develop in some patients (Akman-Demir et al., 1999; Siva et al., 2001; Wechsler et al., 1992).

Any of the dural sinuses may be affected, but the superior sagittal sinus is the most commonly thrombosed, with a substantial number of these patients also disclosing lateral sinus thrombosis (Akman-Demir et al., 1999; Siva et al., 2003; Wechsler et al., 1992). The thrombus may be limited to the lateral sinus in up to 20% of patients (Wechsler et al., 1992). Intracranial hypertension without any demonstrable neuroimaging pathology have been reported, with some of them developing neuroimaging findings consistent with CVST in further attacks later (Akman-Demir et al., 1996).

The extension of the clot into the cerebral veins causing focal venous hemorrhagic infarction is uncommon in extra-axial NBS. This may be explained by the slow and incomplete occlusion of the cerebral venous dural sinuses in BS, but such a probability needs to be confirmed. The co-occurrence of CVST with primary CNS involvement (CNS-NBS) is rare (Akman-Demir et al., 1996; Siva et al., 2001; Wechsler et al., 1992). However, such a mixed pattern of presentation was recently reported in four patients among a group of 20 with neurological disease from Iraq (Al-Araji et al., 2003).

We have recently reported that CVST in BS is strongly associated with systemic major vessel disease and tends to occur earlier in the disease course compared to the parenchymal CNS type of neurological involvement (Siva et al., 2003). We believe that these observations also support the notion that two forms of CNS disease in BS might have different pathogenic mechanisms. It is also well established that neurological disease in the form of CVST has a better neurological prognosis than that of CNS–parenchymal involvement. However, considering the fact that patients with major vessel disease have a higher rate of morbidity and mortality, a diagnosis of CVST in a patient with BS may not be associated with a favorable outcome.

6.2. Neuro-pathology

Vasculitis is regarded as the key feature in BS in biopsy specimens from skin and mucosa lesions (Matsumoto et al., 1991). Arterial and venous large vessel involvement such as narrowing, occlusion and aneurysm formation is reported in up to 27–35% of patients, with 12% being arterial and 88% venous (Koç et al., 1992). Even a greater proportion of patients may have small vessel vasculitis and this is taken as the pathological basis of various histological changes observed in different organ systems. It is also usually considered that CNS lesions are due to a vasculitis as well with a venous predominance (Mc Menemey and Lawrence, 1957; Kawakita et al., 1967; Koçer et al., 1999). However, the pathology in NBS with CNS involvement is not always uniform and covers a wide spectrum that includes vasculitis, a low-grade inflammation, demyelination and degenerative changes (Fig. 1). A definite vasculitis, on the other hand, is not observed in all cases (Hadfield et al., 1997). Radiological studies do not support a strictly arterial vasculitis in that lesions seen in imaging studies are not compatible with arterial territories in general (Koçer et al., 1999). Furthermore, there is a peri-lesional large edema with a tendency to disappear or leave disproportional small residua in follow-up studies that is consistent with venous infarctions since all intensity changes seen in venous occlusive disease do not necessarily present infarction, but rather

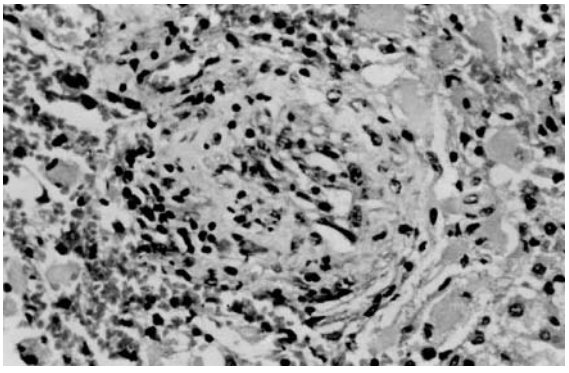

Figure 1. Small vessel vasculitis in the brain of a patient with Behçet syndrome. The lymphositic infiltration of the vessel wall and the occlusion of the lumen are seen. There is also hemorrhage around the vessel wall and some gemistocytic-type astrocytic proliferation. (H + E × 400). (Courtesy of Professor Buge Oz.)

represent accumulation of water within interstitial space (Yuh et al., 1994). This information supports the probable inflammatory-venous (small vessel) etiology for the CNS lesions seen in BS. If one considers the possible venous territories where brain stem lesions appear in NBS, it is clear that the affected venous structures are indeed intra-axial small brainstem veins (Duvernoy, 1978), and as suggested by Koçer et al., it is likely that the anatomical variability of venous anatomic arrangements at different levels of the CNS might explain the predilection of lesions toward different regions and the occurrence of clinical and imaging findings (Koçer et al., 1999). It is well known that telencephalic structures are drained by superficial and deep venous systems, both systems anastomose via medullary veins. They interconnect superficial pial veins to the internal cerebral vein and the basal vein of Rosental, the former being more common than the latter (Bracard et al., 1996), whereas in brain stem, intra-parenchymal radial and longitudinal anastomatic channels are nearly absent (Duvernoy, 1978). This may explain that despite of a wider involvement throughout the brain, as reported in earlier pathology studies, the vascular involvement may cause more damage in the brainstem structures whereas the hemispheric structures may relatively be spared due to their anastomotic drainage systems.

6.3. Neuroimaging

Neuroimaging studies in CNS-NBS have shown that cranial magnetic resonance imaging (MRI) is both more specific and sensitive than CT in demonstration of the typical reversible inflammatory parenchymal lesions (Koçer et al., 1999). Lesions are generally located within the brainstem, occasionally with extension to the diencephalon, or less commonly within the periventricular and sub-cortical white matter (Figs. 2–4).

The most commonly affected region is the mesodiencephalic junction, followed by the ponto-bulbar region. This pattern of involvement was seen in 46 and 40% of our patients with intra-axial NBS, respectively (Koçer et al., 1999). Hypothalamo-thalamic region, basal ganglia, cerebral hemispheres, cerebellum and the spinal cord are also involved, but less commonly. Most patients who do have meso-diencephalic junction lesions also show an upward extension involving the diencephalic structures and/or a downward extension involving the ponto-bulbar region. Hemispheric lesions are not seen commonly in intra-axial NBS, and almost always are associated with diencephalic and brainstem lesions.

A frequent finding is the resolution or the decrease in the size of the lesions, when follow-up imaging studies are available (Koçer et al., 1999; Siva et al., 1991). Such studies may also disclose the appearance of new 'silent' lesions without corresponding clinical symptoms and signs. Arterial involvement, as noted above, is rare, and a limited number of patients with primary or secondary intracerebral hemorrhage have been reported (Altinörs et al., 1987; Nagata, 1985). The hemorrhagic lesions seen in our patients (Koçer et al., 1999) most likely resulted from 'diapedesis of red cells around veins' as already reported and were not of arterial origin (Kawakita et al., 1967). A non-specific, mostly but not necessarily nodular-type gadolinium enhancement may be seen when the study is performed in the acute or sub-acute phase.

With the exception of the rarely occurring lesions only affecting periventricular and sub-cortical white matter, cranial MRIs in intra-axial NBS are rarely confused with MS. The prominence of brainstem lesions, which are large and do not have distinct borders, and their extending nature help to differentiate intra-axial NBS from multiple sclerosis by MRI. The cranial MRI findings of NBS are also dissimilar from thrombotic or embolic stroke.

Spinal cord involvement is not common, but can be seen. The usual site is the cervical spinal cord, with the myelitis-like inflammatory lesion continuing more than two segments, extending to the brainstem in some (Green and Mitchell, 2000; Siva et al., 1991; Morrissey et al., 2000) (Fig. 5). Gadolinium enhancement, resolution of these lesions, and thoracic cord involvement has also been reported.

We have observed one patient with optic neuropathy, who had an enhancing isolated optic nerve lesion (Koçer et al., 1999).

Magnetic resonance-venography is the preferred imaging technique to diagnose or confirm CVST in Behçet's disease. In addition T1 and T2-weighted images also help to identify venous sinus thrombosis (Fig. 6a and b).

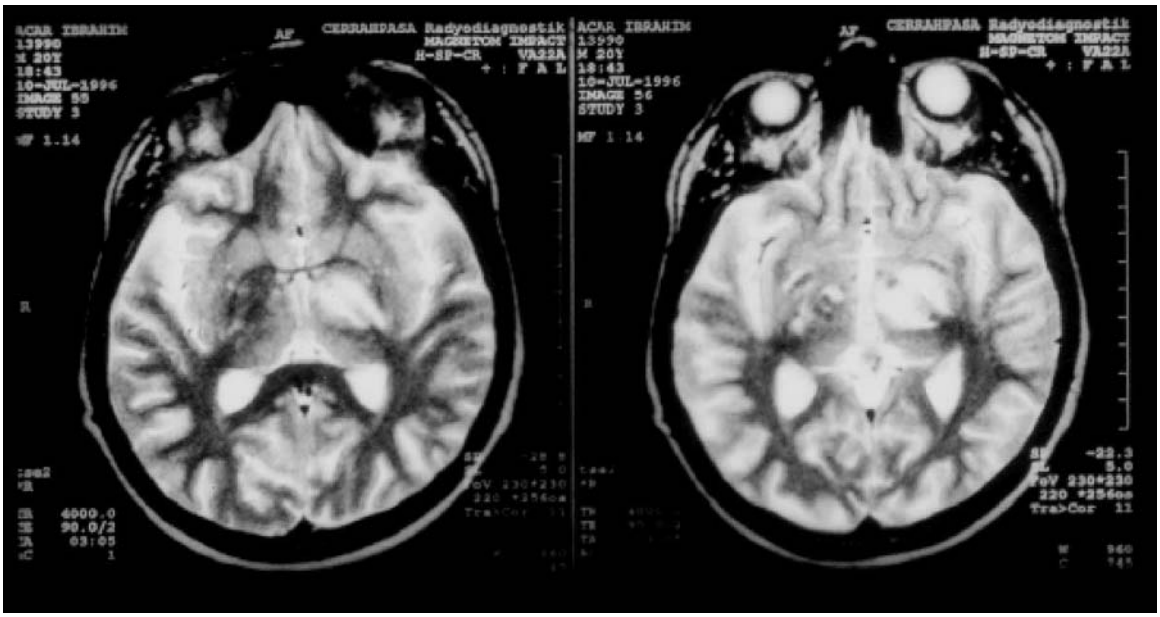

Figure 2. Neuro-Behçet disease: axial T2W images showing the most common pattern of CNS involvement as seen on MRI in a patient with intra-axial NBS. Involvement of the mesodiencephalic region, the most commonly affected region in intra-axial NBS, with extension to the basal ganglia and external capsule.

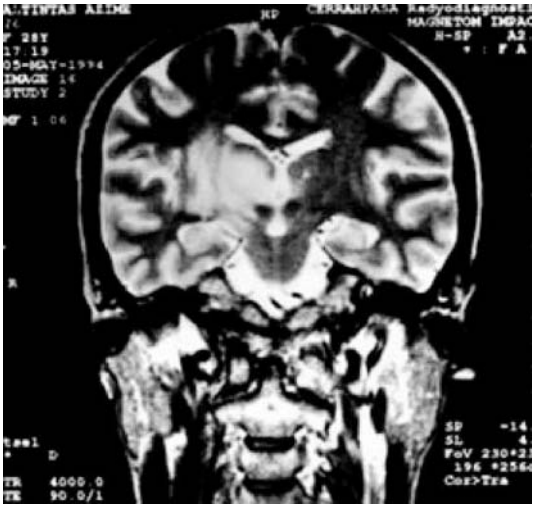

Figure 3. Neuro-Behçet disease: coronal T2W images in another patient with NBS, showing the involvement of the mesodiencephalic region, the most commonly affected region in intra-axial NBS, with prominent extension to the basal ganglia and external capsule.

Cerebral or spinal arteriography may serve to demonstrate vasculitis, dissection or aneurysms, and also have been used to monitor treatment effects in patients with vascular involvement (Bahar et al., 1993; Krespi et al., 2001; Zelenski et al., 1989). However, the probability of detecting a significant finding in the cerebral arteriography is low, as in most cases with CNS parenchymal disease, the vascular involvement is most prominent in the postcapillary venules. Therefore, it is our impression that cerebral arteriography is not a cost-effective diagnostic tool in CNS-NBS, unless the patient presents with sub-arachnoid hemorrhage or an overt cerebral arterial lesion.

6.4. Cerebrospinal fluid in Behçet's syndrome

If performed during the acute stage, CSF studies usually show inflammatory changes in most cases of CNS-NBS, such as elevated protein content, a mild to moderate lymphocytic pleocytosis, and at times a cellular reaction up to a few thousand cells mainly composed of neutrophils (Akman-Demir et al., 1996;

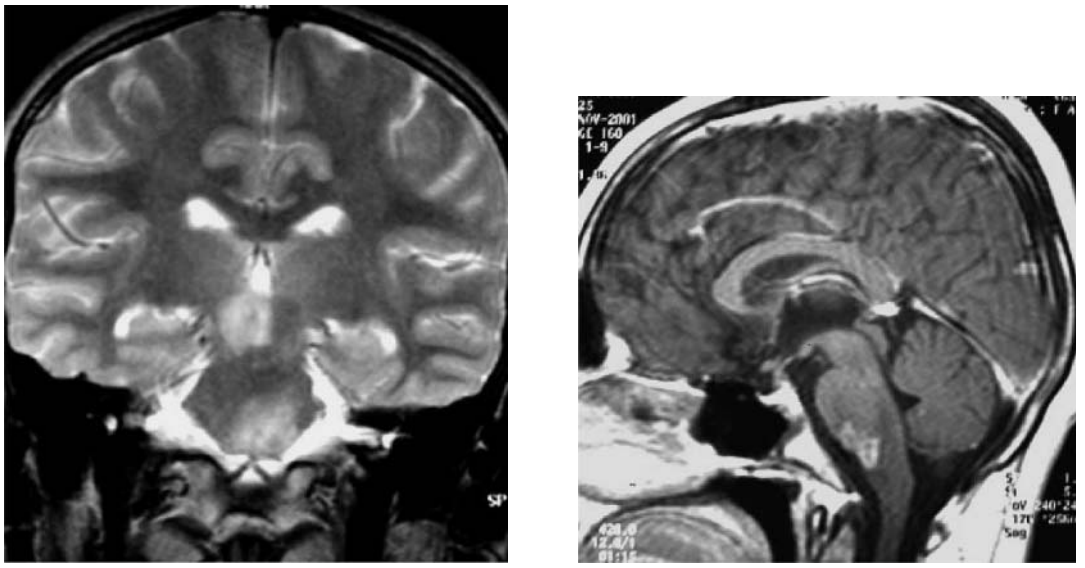

Figure 4. Neuro-Behçet disease: coronal and axial T2W images in a patient with acute onset brainstem syndrome. Two separate edematous lesions involving the brainstem and the mesodiencephalic region are seen, with the lower one enhancing after gadolinium. (Courtesy of Professors Civan Islak and Naci Kocer.)

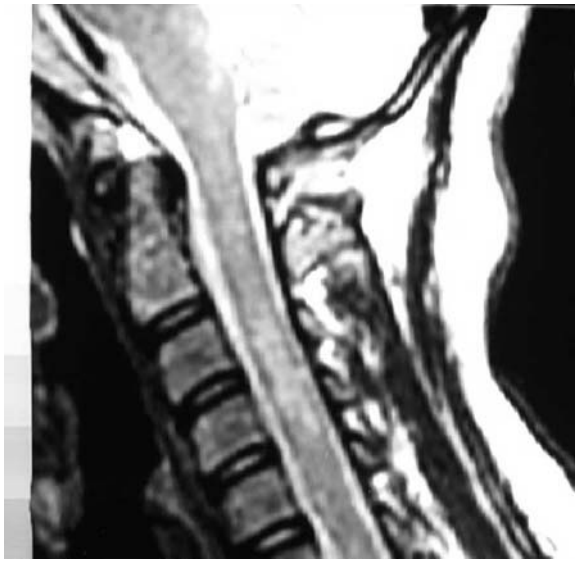

Figure 5. Neuro-Behçet disease (intra-axial NBS): cervical spinal involvement—myelitis extending over a few segments. (Courtesy of Professors Civan Islak and Naci Kocer.)

Kidd et al., 1999; Serdaroglu, 1998b; Siva et al., 2001). More severe forms of NBS disease are usually associated with more inflammatory changes in the CSF (Akman-Demir et al., 1999).

Oligoclonal bands can be detected, but this will be an infrequent finding (Akman-Demir et al., 1996; Kidd et al., 1999; McLean et al., 1995; Siva et al., 2001). Loss of oligoclonal bands following treatment with corticosteroids were reported in one study (Gille et al., 1990). Furthermore, the use of CSF oligoclonal IgM and IgA bands or the CSF IgM index to monitor disease activity was suggested by some (Hirohata et al., 1986; Sharief et al., 1991). We think that the prognostic value of looking at oligoclonal bands in BS does not justify its routine clinical use.

CSF in patients with CVST shows increased pressure, but the cellular and chemical composition may be normal (Siva et al., 2001).

6.5. Neurophysiology

Peripheral nervous system (PNS) involvement in BS, as already mentioned, is rare. A limited number of patients with PNS involvement, however, have been reported with clinical and electrophysiological findings consistent with mononeuritis multiplex,

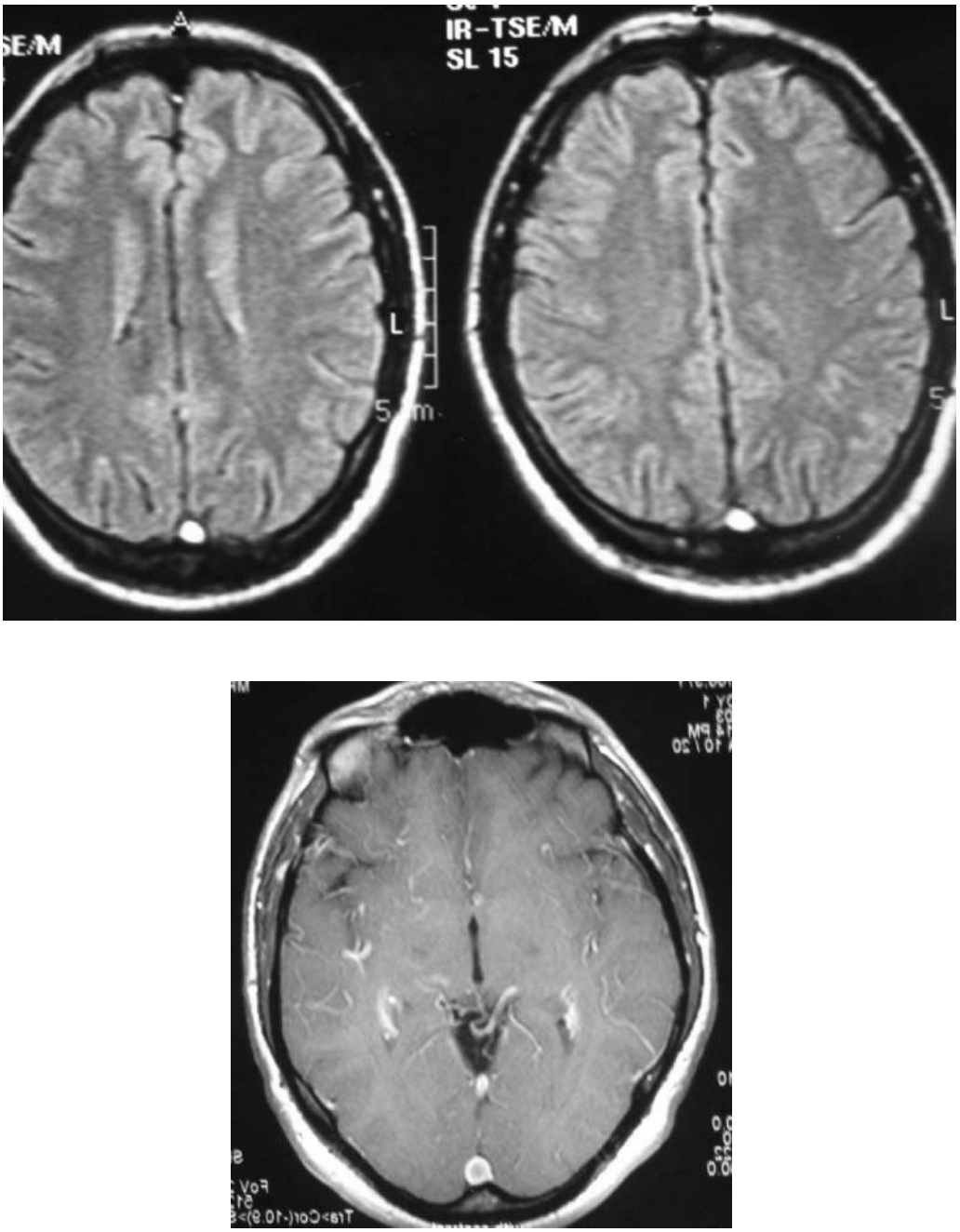

Figure 6. Neuro-Behçet disease (extra-axial NBS): superior sagital sinus thrombosis as seen on proton-weighted and gadolinium-enhancing T1W images.

a peripheral neuropathy prominent in the lower extremities and poly-radiculoneuritis (Namer et al., 1987; Takeuchi et al., 1989). Electroneuromyographic studies disclosed demyelination, chronic denervation, and even myogenic involvement in the reported cases (Baslo et al., 1979; Namer et al., 1987; Takeuchi et al., 1989). However, electroneuromyographic studies may disclose a sub-clinical neuropathy in patients who do not report symptoms suggestive of neuropathy. Besides, it should be kept in mind, that the neuropathy may develop secondary to various drugs (i.e. thalidomide and colchicine) used in the treatment of BS, or may also be coincidental.

Brainstem auditory and somatosensory-evoked potentials, and transcranial magnetic stimulation were studied in patients with CNS-NBS in several studies and showed a wide range of abnormalities, mainly due to the involvement the basal parts of the brainstem and corticospinal tracts (Nakamura et al., 1989; Parisi et al., 1996; Rizzo et al., 1989; Stigsby et al., 2000). The demonstration of sub-clinical involvement, by detection of abnormal responses in examined areas without corresponding clinical symptoms and signs in some of these patients, is noteworthy in providing information about the extent of the CNS involvement. In another recent study, sub-clinical involvement was investigated by using P300 in BS patients without neurological manifestations (Kececi and Akyol, 2001). The P300 cerebral event-related potential is an electrophysiological correlate of cognitive decision-making processes that can be measured in response to either an auditory or visual stimulus and the findings in this study suggested that the P300 measures and motor response time may reflect sub-clinical neurologic involvement in BS. However, the prognostic value of these findings currently is not clear.

6.6. Differential diagnosis of intra-axial (parenchymal) NBS

The major diseases to be included in the differential diagnosis of parenchymal NBS are shown in Table 6. Patients with NBS are young and frequently present with an acute or sub-acute brainstem syndrome or hemiparesis, as well as with other various neurological manifestations. Hence, multiple sclerosis and stroke in the young population are the commonest entities in the differential diagnosis of BS. This is especially true in patients with BS where the symptoms other than those related to the CNS are not very pronounced.

Table 6
The differential diagnosis of intra-axial (CNS) neuro-Behçet's syndrome

Firstline syndromes and diseases to be considered
Multiple sclerosis
Stroke in young adults
Primary CNS vasculitis
Secondary CNS vasculitis
Syndromes and diseases to be considered less commonly
Neuro-sarcoidosis
CNS-tuberculosis
Brainstem glioma
Primary CNS lymphoma
Rare syndromes
Vogt–Koyanagi–Harada syndrome
Reiter syndrome
Eales' disease
Cogan's syndrome
Susac syndrome
Sweet syndrome

Multiple sclerosis is more common in women, whereas NBS is seen frequently in men. Optic neuritis, sensory symptoms and spinal cord involvement, which are common in MS, are rarely seen in NBS (Table 7). However, sometimes the clinical presentation of NBS may be confused with MS, but the neuroimaging —MRI— findings are clearly different. The pattern of brainstem involvement in NBS, which commonly extends to involve basal ganglia and diencephalic structures, are not seen in MS. Furthermore, periventricular and ovoid lesions suggestive of MS are not expected to be seen in NBS, and when hemispheric white matter lesions are present in NBS they are more likely to be sub-cortical than periventricular, and these are almost always associated with the brainstem-diencephalic lesions (Koçer et al., 1999). Brain stem lesions in MS are usually small even in the acute stage, and prominent brain stem and cerebellar atrophy without cerebral volume loss that is seen in the chronic phase of NBS is unusual in MS (Miller et al., 1987; Morrissey et al., 1993). When one considers spinal cord involvement, this rarely extends more than a few vertebral segments in MS

Table 7
The differential diagnosis of multiple sclerosis and intra-axial (CNS) neuro-Behçet's syndrome

	Multiple sclerosis	CNS-neuro-Behçet syndrome
Gender	Female > male	Male > female
Symptoms at onset		
Common	ON; sensory; spinal cord; BS/INO; motor; cerebellar	Headache; motor; cerebellar; BS/Cr neuropathies
Uncommon	Headache; BS/Cr neuropathies	ON; Sensory; spinal cord; BS/INO
MRI		
PV and SC lesions	(+++)	(±)
Brainstem lesions	Small, discrete, up/downward extension (−)	Large, diffuse, up/downward extension (+)
Spinal cord lesions	(++)	(±)
CSF		
Inflammatory changes	(±)	(++)
OCB (+)	>90%	<20%

CNS: central nervous system; MRI: magnetic resonance imaging; CSF: cerebrospinal fluid; OCB: oligoclonal bands; ON: optic neuritis; BS: brainstem; INO: internuclear opthalmoplegia; Cr: cranial; PV: periventricular; SC: sub-cortical. From Siva et al. (2004).

(Nijeholt et al., 1997), contrary to the more extensive lesions that were observed in the few cases of NBS (Green and Mitchell, 2000; Koçer et al., 1999). The CSF also reveals different patterns, with a more prominent pleocytosis and low rate of positivity for oligoclonal bands in NBS (Serdaroglu, 1998b).

Co-morbidity of BS and MS is a possibility, and we have observed a few such cases in whom systemic BS and MS co-existed. These patients had clinical and imaging features consistent with MS, had OCBs in their CSF, and also had the systemic manifestations of BS. The systemic symptoms and signs of BS preceded the onset of MS in all, but some were admitted because of their neurological symptoms and a detailed history and physical examination revealed the presence of BS. On the other hand, in patients with a known diagnosis of BS, the onset of the neurological symptoms raised the possibility of NBS. However, based on the clinical and neuroimaging differential diagnosis (Table 6) we could rule out CNS-NBS. An acute stroke-like onset is not common in NBS, and MRI lesions compatible with classical arterial territories are also not expected. The absence of systemic symptoms and signs will serve to differentiate the primary CNS vasculitic disorders from NBS, and the difference in the systemic symptoms and signs from the secondary CNS vasculitides, as well as the MRI findings (Koçer et al., 1999; Siva, 2001).

Sarcoidosis can be taken for BS due to its uveitis, arthritis, and CNS involvement, but the absence of oral and genital ulcers, and the presence of peripheral lymphadenopathy, and bilateral hilar lymph nodes on chest X-ray, as well as pathological examination of the non-caseating granulomatous lesions of sarcoidosis, help in the differential diagnosis. In some patients with sarcoidosis, however, involvement of the nervous system may be the presenting and only manifestations of the disease (Said, 2000). Cranial neuropathies, seventh nerve involvement being the most common, seizures; peripheral neuropathy, diabetes insipidus and other symptoms related to chronic meningitis and hydrocephalus as well as a myopathy are among the manifestations of sarcoidosis (Said, 2000). These are not common in NBS, and MRI findings are unlikely to be a source of confusion between the two diseases.

Brainstem glioma, and primary CNS lymphoma come into the differential diagnosis of NBS, as well, but the absence of systemic findings and the MRI findings will be helpful in the differential diagnosis.

Due to their ophthalmologic and some other systemic manifestations diseases as Vogt–Koyanagi–Harada (VKH) syndrome; Reiter Syndrome; Eales' disease; Cogan's syndrome (CS); and Susac syndrome are other considerations in the differential diagnosis of BS. All may present with nervous system manifestations and, therefore, are included in the differential diagnosis. However, apart from the clinical findings, a complete ophthalmologic examination will reveal the true nature of eye involvement in each of these syndromes, all quite distinct from the findings in BS.

The VKH syndrome is a bilateral, diffuse granulomatous uveitis associated with poliosis, vitiligo, alopecia, and CNS and auditory signs. Symptoms of meningeal irritation and occasional encephalopathy are most common in the prodromal phase of the illness and a CSF pleocytosis has been noted to be even more common than symptomatic meningitis, but it rarely causes significant focal neurologic disease (Goodwin, 2003). This inflammatory syndrome, which occurs more commonly among heavily pigmented populations such as Asians, Hispanics, Native Americans, and Indians, is probably the result of an autoimmune mechanism, influenced by genetic factors, and appears to be directed against melanocytes.

Ocular inflammation, arthritis, and urethritis are seen in Reiter syndrome, but conjunctivitis is much more prominent than uveitis—and that, unlike BS, most commonly an anterior uveitis— in this disease. The genital lesions are also different with urethritis, most unusual BS, being a hallmark of Reiter's. Furthermore, genital ulceration is not seen in the latter condition.

Eales' disease, a syndrome of retinal perivasculitis and recurrent intraocular hemorrhages, is infrequently associated with neurologic abnormalities (Atabay et al., 1992).

Cogan's syndrome (CS) is an idiopathic inflammatory disease in which the major symptoms are ocular and cochleovestibular. The eye inflammation consists of interstitial keratitis and uveitis, and inner ear inflammation will cause symptoms clinically indistinguishable from Meniere's disease (St. Clair and McCallum, 1999). Almost three-quarters of the patients develop systemic manifestations, and a vasculitis involving large vessels, similar to Takayasu's arteritis or involving medium vessels resembling periarteritis nodosa may develop in 10–15% of the patients (Nazarian, 2003; St. Clair and McCallum, 1999). Nervous system involvement is not common, but when present the neurologic manifestations may include headache, psychosis, stroke, cerebral sinus thrombosis, seizures, encephalopathy, myelopathy, cranial neuropathies, mononeuropathies and polyneuropathy (Nazarian, 2003; St. Clair and McCallum, 1999). Susac syndrome is a non-inflammatory vasculopathy causing small infarcts in the retina, the cochlea, and the brain, resulting in the clinical triad of retinopathy, hearing loss, and encephalopathy (O'Halloran et al., 1998; Susac, 1994).

6.7. Differential diagnosis of extra-axial NBS (CVST)

In patients who present with symptoms of intracranial hypertension, and in whom neuroimaging reveals thrombosis in one or more of the cerebral venous sinuses, BS needs to be included in the differential diagnosis. The presence of its systemic findings is the only clue to the association of CVST with BS, and their absence will exclude this possibility. As already mentioned, observation of hemorrhagic venous infarcts or other parenchymal CNS lesions on MRI in patients with extra-axial NBS is exceptional. Lupus erythematosus, sarcoidosis, ulcerative colitis and Crohn's disease are some other conditions, which may be associated with cerebral venous thrombosis, and may have systemic symptoms which may cause problems in differential diagnosis.

7. Prognosis

In a recent study from our center the long-term mortality and morbidity of Behçet Syndrome was studied over two decades (Kural-Seyahi et al., 2003). The 'disease burden' of Behçet syndrome was found to be usually confined to the early years of its course, and it was shown that in many patients the syndrome burnt out over the years. However, major vessel disease and CNS involvement were found to be exceptions and could appear for the first time relatively late in the course. Furthermore most of the deaths seen in this cohort were due to these two conditions. Neurological involvement in BS is also a remarkable cause of morbidity and approximately 50% of the NBS patients are moderate to severely disabled after 10 years of disease (Siva, 2001). We rated the neurological disability of our patients with BS by using the Expended Disability Status Scale (EDSS) of Kurtzke, which was originally devised for multiple sclerosis-associated disability (Kurtzke, 1983). Taking into consideration that the visual disability is most commonly due to uveitis in BS, the visual function was eliminated from the original

scale. By 10 years after the onset of neurological symptoms and signs, 78.2% of our patients developed at least mild (EDSS ≥ 3), and 45.1% moderate to severe neurological disability (EDSS ≥ 6). An EDSS score of 3 represents full ambulation despite neurological moderate disability on neurological examination, and a score of 6 represents patients requiring assistance in walking such as one-sided support to walk for 100 m, and during other activities of daily life. However, when patients were evaluated separately, all with CVST had EDSS scores of either 1 or 2 (minimal disability) (Siva et al., 2001).

Onset with cerebellar symptoms and a progressive course were unfavorable factors, while onset with headache, a diagnosis of CVST, and disease course limited to a single episode were neurologically favorable (Siva et al., 2001; Akman-Demir et al., 1999). An elevated protein level and pleocytosis in the CSF were also reported to be associated with a poorer prognosis (Akman-Demir et al., 1999).

In a recent study completed in our center, CVST in BS was found to be strongly associated with systemic major vessel disease and tended to occur earlier in disease course compared to the parenchymal CNS type of neurological involvement. Considering the fact that patients with major vessel disease have a higher rate of morbidity and mortality, a diagnosis of CVST in a patient with BS may not be associated always with a favorable outcome (Siva et al., 2003).

8. Treatment

Neurological involvement in BS is not uniform and it is difficult to predict its course and prognosis, and response to treatment. Therefore, it is not possible to reach a conclusion on the efficacy of any treatment unless properly designed, double masked, placebo controlled studies are carried out for each form. However, this is difficult to accomplish, as even in large centers the yearly numbers of new neuro-cases are limited. Most studies, which report some kind of efficacy with various treatments in BS with neurological involvement have not included uniform cases, have not followed their patients for long periods and did not have controls. So, currently we have no hard evidence for the efficacy of the various treatment modalities for any form of neurological treatment in BS. Empirical impressions are the basis for our current guidelines in management.

8.1. Intra-axial NBS—acute episodes

Corticosteroids are used to treat acute CNS involvement with in BS, but their effects are short-lived and they do not prevent further attacks or progression. Acute episodes of intra-axial NBS are treated with either oral prednisolone (1 mg/kg for up to 4 weeks, or until improvement is observed) or with high-dose intravenous methylprednisolone (IVMP-1 g/day) for 3–7 days (Kantarci and Siva, 2003). Both forms of treatment should be followed with an oral tapering dose of corticosteroids over 2–3 months in order to prevent early relapses (Siva and Fresko, 2000). There is no apparent difference between the two regimens, but our impression is that the high dose IVMP regimen is associated with earlier improvement. Our current practice is to give IVMP, 1 g/day for 7 days, followed by the oral regimen in patients with clinical and imaging evidence of CNS involvement.

8.2. Intra-axial NBS—long-term treatment

Colchicine, azathioprine, cyclosporine-A, cyclophosphamide, methotrexate, chlorambucil, immunomodulatory agents such as interferon-alpha, pentoxyphilline, and more recently, thalidomide have been shown to be of benefit in treating some of the systemic manifestations of BS, none of these agents have been shown effective in NBS in a properly designed study (Bang, 1997; Hamuryudan et al., 1998; Kaklamani and Kaklamanis, 2001; Sakane et al., 1999; Siva and Fresko, 2000).

In a small, retrospective study, Chlorambucil was reported to have some efficacy in meningoencephalitis of BS (O'Duffy et al., 1984). As most patients were treated prior to the CT/MRI era, there is no information on neuroimaging correlates of treatment. However, lessening in the CSF pleocytosis was documented in patients treated with chlorambucil. Although limited, our experience with chlorambucil in NBS, is not encouraging, and its serious side effects including increased risk of malignancy, excludes it from our use. However, we do use other

immunosuppressive drugs such as azathioprine, cyclosporine A and cyclophosphamide either alone or in combination for extraneural systemic manifestations of BS, with no proven evidence of their efficacy in preventing the development or halting the progression of intra-axial NBS (Siva and Fresko, 2000).

Cyclosporine was reported to cause neurotoxicity or to accelerate the development of CNS symptoms and, therefore, its use in NBS is not recommended (Schwartz et al., 1995; Kotake et al., 1999). In six patients with BS in whom progressive neuro-psychiatric manifestations were observed, an open 12-month trial with low-dose weekly methotrexate was carried out, and the authors suggested that this regimen might have a beneficial effect in the treatment of progressive neurological disease, but the results were not conclusive (Hirohata et al., 1998).

A common clinical practice is to add an immunosuppressant drug, such as azathioprine or monthly pulse cyclophosphamide to corticosteroids in progressive NBS cases, however, the efficacy of such a combination has also not been demonstrated.

Successful treatment of ocular and other systemic manifestations of BS with monoclonal anti-TNF alpha antibody treatment with infliximab in a few patients was reported recently (Fresko, 2002; Goossens et al., 2001; Rozenbaum et al., 2002; Triolo et al., 2002), none of these patients however, had significant neurologic problems. The same is hold true for etanercept, another drug with TNF-α blocker properties, which some recent studies revealed that this drug was also beneficial in suppressing ocular and some other systemic manifestations of BS, but the effect was not sustained when the drug was stopped (Fresko, 2002). Mycophenolate mofetil (CellCept) and Tacrolimus (Prograf) are other immunosuppressant/immunomodulator agents that was used to treat ocular inflammation and significant systemic manifestations in patients with BS (Russell et al., 2001), but there is no information regarding the potential effect of all these drugs in preventing CNS involvement or new neurologic attacks.

In theory, intravenous immunoglobulin (IVIG) would be expected to have a possible regulatory effect in the reported immunologic abnormalities of BS and its CNS involvement. However, in our limited experience with a few cases with progressive CNS involvement, we have not observed any significant improvement (Siva and Altintas, 2000). We are not aware of beneficial effects of plasma exchange in the slowly progressive forms of NBS, but this treatment may be considered as an option for acute severe episodes that are resistant to corticosteroid therapy or for rapidly progressive disease (Kantarci and Siva, 2003). There is a single case report of the successful treatment of NBS with interferon alpha (Nichols et al., 2001), a drug commonly used to treat severe eye disease in BS.

8.3. Cerebral venous sinus thrombosis

There is a tendency to treat deep venous thrombosis in BS with anticoagulants and antiplatelet agents in combination with intermediate doses of corticosteroids (Sakane et al., 1999). However, there is no consensus on the treatment of CVST. Some authors use a combination of anticoagulation with corticosteroids (Wechsler et al., 1992), while others administer corticosteroids alone (Akman-Demir et al., 1996). When anticoagulation therapy is considered in the treatment of CVST, the presence of pulmonary or other aneurysms needs to be ruled out first, as it was shown that CVST in BS was strongly associated with systemic major vessel disease. In our current practice to treat CVST we sometimes use a combination of sub-cutaneous low molecular weight heparin with corticosteroids (Siva and Fresko, 2000). Low molecular weight heparin is given for 14–21 days and IVMP, 1 g/day, for 7 days followed by an oral regimen of corticosteroids, which are given for 3 weeks. Patients are evaluated every 2 weeks with neuro-ophthalmic examination that includes visual fields and visual-evoked potentials. Such an evaluation is only feasible in the absence of ocular involvement due to BS. If the patient continues to report headache and visual symptoms, CSF analysis is repeated at week 4 or earlier. When the opening pressure is found to be elevated, the oral corticosteroid treatment is continued until the patient improves and stabilizes in terms of clinical symptomatology, CSF pressure and on neuro-ophthalmic examination. The CVST in BS is rarely severe to require systemic or thrombolytic treatment.

Recurrence of CVST is uncommon after the initial episode. Therefore, we do not recommend any form of long-term treatment in extra-axial NBS.

9. Conclusion

There has not been a consensus and a major advance in the agents used for the treatment of the various forms of NBS, as most of the currently used drugs are not specific to the disease process, and none have been shown to be effective in a controlled trial. A major problem is the identification of the type of the neurological disease and choosing the most appropriate corresponding treatment. Another problem is when to stop treatment in patients receiving long-term glucocorticoids or other immunosuppressive treatment for their neurological problems particularly when they are doing well.

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Key points

- *Epidemiology*. Prevalence of BS: USA and Northern Europe: $1/10^5$; Turkey: $80-370/10^5$; Japan and Far-East countries $10-20/10^5$. Prevalence of NBS: 5–10% of BS patients.
- *Demographics*. Mean age of onset of BS: 27 ± 8.0. Mean age of onset of NBS: 32.0 ± 8.7 (younger age for extra-axial NBS/older for intra-axial NBS). Male to female ratio in BS: 1.8:1; NBS: 3.8:1.
- *Major neurological symptoms and syndromes seen in NBS*. Headache (non-structural) (most common), CNS involvement (intra-axial NBS), CVST (extra-axial NBS), neuro-psycho-Behçet syndrome.
- *Central nervous system involvement (intra-axial NBS)*. Clinical features: brainstem syndrome—cranial neuropathies with (asymmetrical) corticospinal tract ± cerebellar findings (ataxia); confusion or neurobehavioral syndromes.
- *Cerebral venous sinus thrombosis (extra-axial NBS)*. Clinical features: headache and other symptoms of intracranial hypertension.

References

Adler, Y.D., Jovanovic, S., Jivanjee, A., Krause, L., Zouboulis, C.C. 2002. Adamantiades-Behcet's disease with inner ear involvement. Clin. Exp. Rheumatol. 20 (Suppl. 26), S40.

Akman-Demir, G., Bahar, S., Baykan-Kurt, B., Gürvit, I.H., Serdaroğlu, P. 1996. Intracranial hypertension in Behçet's Disease. Eur. J. Neurol. 3, 66.

Akman-Demir, G., Serdaroglu, P., Tasçı, B. The Neuro-Behçet Study Group. 1999. Clinical patterns of neurological involvement in Behçet's disease: evaluation of 200 patients. Brain 122, 2171.
This article, in which the clinical features, evoked potentials, cerebrospinal fluid and imaging studies, and prognostic factors of patients with Behcet syndrome and neurological involvement are evaluated retrospectively, is the largest case series of its kind.

Akpolat, T., Akkoyunlu, M., Akpolat, I., Dilek, M., Odabas, A.R., Ozen, S. 2002. Renal Behcet's disease: a cumulative analysis. Semin. Arthritis Rheum. 31, 317.

Al-Araji, A., Sharquie, K., Al-Rawi, Z. 2003. Prevalence and patterns of neurological involvement in Behcet's disease: a prospective study from Iraq. J. Neurol. Neurosurg. Psychiatry 74 (5), 608.

Altınörs, N., Senveli, E., Arda, N., Türker, A., Kars, Z., Çınar, N., Özkan, S. 1987. Intracerebral hemorrhage and hematoma in Behçet's disease. Neurosurgery 21, 582.

Atabay, C., Erdem, E., Kansu, T., Eldem, B. 1992. Eales' disease with internuclear ophthalmoplegia. Ann. Ophthalmol. 24, 267.

Bahar, S., Çoban, O., Gürvit, I.H., Akman-Demir, F., Gökyiğit, A. 1993. Spontaneus dissection of the extracranial vertebral artery with spinal subarachnoid hemorrhage in a patient with Behcet's disease. Neuroradiology 35, 352.

Bang, D. 1997. Treatment of Behçet's disease. Yonsei Med. J. 38, 401.

Baslo, P., Kara, I., Eker, E., Kotogyan, A., Kayali, H., Ozdamar, E., Seckin, I. 1979. Clinical, electrophysiological, immunological and electron microscopic investigation of Behcet's disease. In: N. Dilsen, M. Konice, C. Ovul (Eds.), Behcet's Disease. Excerpta Medica International Congress Series, Amsterdam, vol. 467, p. 178.

Ben-Chetrit, E., Yazıcı, H. 2002. Thoughts on the proposed links between Behcet's disease and familial Mediterranean fever. Clin. Exp. Rheumatol. 20 (Suppl. 26), S1.

Bogdanova, D., Milanov, I., Georgiev, D. 1998. Parkinsonian syndrome as a neurological manifestation of Behcet's disease. Can. J. Neurol. Sci. 25, 82.

Bracard, S., Braun, M., Meder, J.F., Velut, S. 1996. Anatomie et radioanatomie du systeme veineux intracranien. Neurochirurgie 42 (Suppl. 1), 11.

Bussone, G., La Mantia, L., Boiardi, A., Giovannini, P. 1982. Chorea in Behçet's syndrome. J. Neurol. 227, 89.

Çetinel, B., Öbek, C., Solok, V., Yaycıoğlu, O., Yazıcı, H. 1998. Urologic screening for men with Behcet's syndrome. Urology 52, 863.

Çetinel, B., Akpinar, H., Tufek, I., Uygun, N., Solok, V., Yazıcı, H. 1999. Bladder involvement in Behcet's syndrome. J. Urol. 161, 52.

Chambers, J.C., Haskard, D.O., Kooner, J.C. 2001. Vascular endothelial function and oxidative stress mechanisms in patients with Behçet's syndrome. J. Am. Coll. Cardiol. 37, 517.

Demirkesen, C., Tüzüner, N., Mat, C., Senocak, M., Buyukbabani, N., Tuzun, Y., Yazıcı, H. 2001. Clinicopathological evaluation of nodular lesions of Behçet syndrome. Am. J. Clin. Pathol. 116, 341.

Direskeneli, H., Saruhan-Direskeneli, G. 2003. The role of heat shock proteins in Behcet's disease. Clin. Exp. Rheumatol. 21 (4 Suppl. 30), S44.

Diri, E., Mat, C., Hamuryudan, V., Yurdakul, S., Hizli, N., Yazıcı, H. 2001. Papulopustular lesions are seen more frequently in patients with Behçet's syndrome who have arthritis: a controlled and masked study. Ann. Rheum. Dis. 60, 1074.

Duvernoy, H.M. 1978. Human Brainstem Vessels. Springer, Berlin, p. 2.

Ergun, T., Gurbuz, O., Dogusoy, G., Mat, C., Yazıcı, H. 1998. Histopathologic features of the spontaneous pustular lesions of Behcet's syndrome. Int. J. Dermatol. 37, 194.

Espinosa, G., Font, J., Tassies, D., Vidaller, A., Deulofeu, R., Lopez-Soto, A., Cervera, R., Ordinas, A., Ingelmo, M., Reverter, J.C. 2002. Vascular. involvement in Behçet's disease: relationship with thrombophilic factors, coagulation activation and thrombomodulin. Am. J. Med. 112, 37.

Fortune, F., Walker, J., Lehner, T. 1990. The expression of gamma delta T cell receptor and the prevalence of primed, activated and IgA-bound T cells in Behcet's syndrome. Clin. Exp. Immunol. 82, 326.

Frassanito, M.A., Dammacco, R., Cafforio, P., Dammacco, F. 1999. Th1 polarization of the immune response in Behcet's disease: a putative pathogenetic role of interleukin-12. Arthritis Rheum. 42, 1967.

Fresko, I. 2002. Highlights of the 10th International Congress on Behçet's disease (editorial). Clin. Exp. Rheumatol. 4 (Suppl. 26), S59.

Fresko, I., Soy, M., Hamuryudan, V., Yurdakul, S., Yavuz, S., Tumer, Z., Yazıcı, H. 1998. Genetic anticipation in Behcet's syndrome. Ann. Rheum. Dis. 57, 45.

Gille, M., Sindic, C.J.M., Laterre, P.F., De Hertogh, P., Hotermans, J.M., Selak, I., Laterre, C. 1990. Atteintes neurologiques révélatrices d'une maladie de Behcet: quatres observations cliniques. Acta Neurol. Belg. 90, 233.

Gonzalez-Gay, M.A., Garcia-Porrua, C., Branas, F., Lopez-Lazaro, L., Olivieri, I. 2000. Epidemiologic and clinical aspects of Behcet's disease in a defined area of Northwestern Spain, 1988–1997. J. Rheumatol. 27, 703.

Goodwin, J. 2003. The Vogt–Koyanagi–Harada syndrome. In: S. Gilman (editor-in-chief) (Ed.), MedLink Neurology on CD ROM. MedLink Corporation, San Diego, First 2003 edition.

Goossens, P.H., Verburg, R.J., Breedveld, F.C. 2001. Remission of Behcet's syndrome with tumour necrosis factor alpha blocking therapy. Ann. Rheum. Dis. 60 (6), 637.

Green, A.L., Mitchell, P.J. 2000. Spinal cord neurobehçet's disease detected on magnetic resonance imaging. Australas. Radiol. 44, 201.

Gul, A. 2001. Behçet's disease: an update on the pathogenesis. Clin. Exp. Rheumatol. 19 (Suppl. 24), 6.

Gul, A., Aslantas, A.B., Tekinay, T., Konice, M., Ozcelik, T. 1999. Procoagulant mutations and venous thrombosis in Behcet's disease. Rheumatology (Oxford) 38, 1298.

Gul, A., Inanc, M., Ocal, L., Aral, O., Konice, M. 2000. Familial aggregation of Behcet's disease in Turkey. Ann. Rheum. Dis. 59, 622.

Gul, A., Hajeer, A.H., Worthington, J., Barrett, J.H., Ollier, W.E., Silman, A.J. 2001a. Evidence for linkage of the HLA-B locus in Behcet's disease, obtained using the transmission disequilibrium test. Arthritis Rheum. 44, 239.

Gul, A., Hajeer, A.H., Worthington, J., Ollier, W.E., Silman, A.J. 2001b. Linkage mapping of a novel susceptibility locus for Behçet's disease to chromosome p.22-23. Arthritis Rheum. 44, 2693.

Hadfield, M.G., Aydın, F., Lippman, H.R., Sanders, K.M. 1997. Neuro-Behçet's disease. Clin. Neuropathol. 16, 55.

Hamuryudan, V., Mat, C., Saip, S., Ozyazgan, Y., Siva, A., Yurdakul, S., Zwingenberger, K., Yazıcı, H. 1998. Thalidomide in the treatment of the mucocutaneous lesions of the Behcet syndrome. A randomized, double-blind, placebo-controlled trial. Ann. Intern. Med. 128 (6), 443.

Hasan, A., Fortune, F., Wilson, A., Warr, K., Shinnick, T., Mizushima, Y., van der Zee, R., Stanford, M.R., Sanderson, J., Lehner, T. 1996. Role of gamma delta T cells in pathogenesis and diagnosis of Behcet's disease. Lancet, 347 (9004), 789.

Hirohata, S., Takeuchi, A., Miyamoto, T. 1986. Association of cerebrospinal fluid IgM index with central nervous system involvement in Behcet's disease. Arthritis Rheum. 29, 793.

Hirohata, S., Suda, H., Hashimoto, T. 1998. Low-dose weekly methotrexate for progressive neuropsychiatric manifestations in Behcet's disease. J. Neurol. Sci. 14, 159.

Idil, A., Gurler, A., Boyvat, A., Caliskan, D., Ozdemir, O., Isik, A., Tuncbilek, A., Kocyigit, P., Calikoglu, E. 2002. The prevalence of Behcet's disease above the age of 10 years. The results of a pilot study conducted at the Park Primary Health Care Center in Ankara, Turkey. Ophthalmic Epidemiol. 9 (5), 325.

International Study Group for Behçet's Disease, 1990. Criteria for diagnosis of Behçet's disease. Lancet 335, 1078.

International Study Group for Behçet's Disease, 1992. Evaluation of diagnostic (classification) criteria in Behçet's disease—towards internationally agreed criteria. Br. J. Rheumatol. 31, 299.

Jaber, L., Milo, G., Halpern, G.J., Krause, I., Weinberger, A. 2002. Prevalence of Behcet's disease in an Arab community in Israel. Ann. Rheum. Dis. 61, 365.

Kaklamani, V.G., Kaklamanis, P.G. 2001. Treatment of Behçet's disease—an update. Semin. Arthritis Rheum. 30 (5), 299.

Kaklamani, V.G., Vaiopoulos, G., Kaklamanis, P.G. 1998. Behçet's disease. Semin. Arthritis Rheum. 27, 197.

Kantarci, O., Siva, A. 2003. Behçet's disease: diagnosis and management. In: J. Noseworthy (Ed.), Neurological Therapeutics: Principles and Practice. Martin Dunitz Publishers, London, p. 1084, Chapter 95.

Kawakita, H., Nishimura, M., Satoh, Y., Shibata, N. 1967. Neurological aspects of Behçet's disease: a case report and clinico-pathological review of the literature in Japan. J. Neurol. Sci. 5, 417.

Kececi, H., Akyol, M. 2001. P300 in Behcet's patients without neurological manifestations. Can. J. Neurol. Sci. 2, 66.

Kidd, D., Steuer, A., Denman, A.M., Rudge, P. 1999. Neurological complications in Behcet's syndrome. Brain 122, 2183.
This case series of 50 patients describes the clinical, imaging, laboratory and neurophysiological features as well as prognostic factors of Behçet's disease patients with neurological involvement.

Kim, B., LeBoit, P.E. 2000. Histopathologic features of erythema nodosum-like lesions in Behcet disease: a comparison with erythema nodosum focusing on the role of vasculitis. Am. J. Dermatopathol. 22, 379.

Koç, Y., Güllü, I., Akpek, G., Akpolat, T., Kansu, E., Kiraz, S., Batman, F., Kansu, T., Balkancı, F., Akkaya, S. 1992. Vascular involvement in Behçet's disease. J. Rheumatol. 19, 402.

Koçer, N., Islak, C., Siva, A., Saip, S., Akman, C., Kantarci, O., Hamuryudan, V. 1999. CNS involvement in Neuro-Behçet's syndrome: an MR study. AJNR 20, 1015.
This article reports the imaging findings of central nervous system involvement seen in Behçet's disease and emphasizes its differential diagnosis in a large case-series. The findings are also correlated with the current understanding on the pathophysiology of this form of neurological involvement.

Kone-Paut, I., Yurdakul, S., Bahabri, S.A., Shafae, N., Ozen, S., Ozdogan, H., Bernard, J.L. 1998. Clinical features of Behcet's disease in children: an international collaborative study of 86 cases. J. Pediatr. 132, 721.

Kotake, S., Higashi, K., Yoshikawa, K., Sasamato, Y., Okamoto, T., Matsuda, H. 1999. Central nervous system symptoms in patients with Behçet disease receiving cyclosporine therapy. Ophthalmology 106, 586.

Krause, I., Rosen, Y., Kaplan, I., Milo, G., Guedj, D., Molad, Y., Weinberger, A. 1999. Recurrent aphthous stomatitis in Behcet's disease: clinical features and correlation with systemic disease expression and severity. J. Oral Pathol. Med. 28, 193.

Krause, I., Monselise, G., Milo, G., Weinberger, A. 2002. Anti Saccharomyces antibodies: a novel serologic marker for Behçet's disease. Clin. Exp. Rheumatol. 20 (Suppl.), S21.

Krespi, Y., Akman-Demir, G., Poyraz, M., Tugcu, B., Coban, O., Tuncay, R., Serdaroglu, P., Bahar, S. 2001. Cerebral vasculitis and ischaemic stroke in Behcet's disease: report of one case and review of the literature. Eur. J. Neurol. 8 (6), 719.

Kural-Seyahi, E., Fresko, I., Seyahi, N., Ozyazgan, Y., Mat, C., Hamuryudan, V., Yurdakul, S., Yazıcı, H. 2003. The long-term mortality and morbidity of Behcet syndrome: a 2-decade outcome survey of 387 patients followed at a dedicated center. Medicine (Baltimore) 82 (1), 60.
A comprehensive study on the long-term mortality and morbidity of Behcet syndrome. This study concludes that the disease is more severe among young and male patients, and tends to become less severe with the passage of time.

Kurhan-Yavuz, S., Direskeneli, H., Bozkurt, N., Ozyazgan, Y., Bavbek, T., Kazokoglu, H., Eksioglu-Demiralp, E., Wildner, G., Diedrichs-Mohring, M., Akoglu, T. 2000. Anti-MHC autoimmunity in Behcet's disease. T cell responses to an HLA-B-derived peptide cross-reactive with retinal-S antigen in patients with uveitis. Clin. Exp. Immunol. 120, 162.

Kurtzke, J.F. 1983. Rating neurological impairment in MS: an expended disability status scale (EDSS). Neurology 33, 1444.

Lee, C.R., Kim, W.H., Cho, Y.S., Kim, M.H., Kim, J.H., Park, I.S., Bang, D. 2001. Colonoscopic findings in Behçet's disease. Inflamm. Bowel Dis. 7, 243.

Lee, K.H., Chung, H.S., Kim, H.S., Oh, S.H., Ha, M.K., Baik, J.H., Lee, S., Bang, D. 2003. Human alpha-enolase from endothelial cells as a target antigen of anti-endothelial cell antibody in Behcet's disease. Arthritis Rheum. 48, 2025.

McLean, B.N., Miller, D., Thompson, E.J. 1995. Oligoclonal banding of Ig G in CSF. Blood–brain barrier function, and MRI findings in patients with sarcoidosis, systemic lupus erythematosus, and Behçet's disease involving the nervous system. J. Neurol. Neurosurg. Psychiatry 58 (5), 548.

Mc Menemey, W.H., Lawrence, B.J. 1957. Encephalomyelopathy in Behçet's disease: report of necropsy findings in two cases. Lancet 24, 353.

Melikoglu, M., Altiparmak, M.R., Fresko, I., Tunc, R., Yurdakul, S., Hamuryudan, V., Yazıcı, H. 2001. A reappraisal of amyloidosis in Behcet's syndrome. Rheumatology (Oxford) 40, 212.

Miller, D.H., Ormerod, I.E.C., Gibson, A., DuBoulay, E.P.G.H., Rudge, P., McDonald, W.I. 1987. MRI brain scanning in patients with vasculitis: differentiation from multiple sclerosis. Neuroradiology 29, 226.

Mor, F., Weinberger, A., Cohen, I.R. 2002. Identification of alpha tropomyosin as a target self-antigen in Behçet's syndrome. Eur. J. Immunol. 32, 356.

Morrissey, S.P., Miller, D.H., Harmszewski, R., et al. 1993. Magnetic resonance imaging of the central nervous system in Behçet's disease. Eur. Neurol. 33, 287.

Matsumoto, T., Uekusa, T., Fukuda, Y. 1991. Vasculo-Behçet's disease: a pathologic study of eight cases. Hum. Pathol. 22, 45.

Nagata, K. 1985. Recurrent intracranial hemorrhage in Behçet's disease (letter). J. Neurol. Neurosurg. Psychiatry 48, 190.

Nakamura, Y., Takahashi, M., Kitaguchi, M., Imaoka, H., Tarui, S. 1989. Brainstem auditory and somatosensory evoked potentials in neuro-Behcet's syndrome. Jpn. J. Psychiatry Neurol. 43, 191.

Namer, I.J., Karabudak, R., Zileli, T., et al. 1987. Peripheral nervous system involvement in Behçet's disease. Eur. Neurol. 26, 235.

Nazarian, S. 2003. Cogan's syndrome. In: S. Gilman (editor-in-chief) (Ed.), MedLink Neurology on CD ROM. San Diego, MedLink Corporation, First 2003 edition.

Nichols, J.C., Ince, A., Akduman, L., Mann, E.S. 2001. Interferon-alpha 2a treatment of neuro-Behcet disease. J. Neuroophthalmol. 21, 109.

Nijeholt, G.J.L., Barkhof, F., Scheltens, P., et al. 1997. MR of the spinal cord in multiple sclerosis: relation to clinical subtype and disability. Am. J. Neuroradiol. 18, 1041.

O'Duffy, J.D., Carney, A., Deodhar, S. 1971. Behçet's Disease. Report of 10 cases, 3 with new manifestations. Ann. Intern. Med. 75, 561.

O'Duffy, J.D., Robertson, D.M., Goldstein, N.P. 1984. Chlorambucil in the treatment of uveitis and meningoencephalitis of Behçet's disease. Am. J. Med. 76, 75.

O'Halloran, H.S., Pearson, P.A., Lee, W.B., Susac, J.O., Berger, J.R. 1998. Microangiopathy of the brain, retina, and cochlea (Susac syndrome). A report of five cases and a review of the literature. Ophthalmology 105, 1038.

Ohno, S., Aoki, K., Sugiura, S., Nakayama, E., Itukara, K., Aizawa, M. 1973. HLA-5 Behcet's disease 2, 1383.

Ohno, S., Ohguchi, M., Hirose, S., Matsuda, H., Wakisaka, A., Aizawa, M. 1982. Close association of HLA-Bw51 with Behcet's disease. Arch. Ophthalmol. 100, 1455.

Oktem-Tanor, O., Baykan-Kurt, B., Gurvit, I.H., Akman-Demir, G., Serdaroglu, P. 1999. Neuropsychological follow-up of 12 patients with neuro-Behcet disease. J. Neurol. 246, 113.

Ozen, S., Karaaslan, Y., Ozdemir, O., Saatci, U., Bakkaloglu, A., Koroglu, E., Tezcan, S. 1998. Prevalence of juvenile chronic arthritis and familial Mediterranean fever in Turkey: a field study. J. Rheumatol. 25 (12), 2445.

Parisi, L., Terracciano, M.E., Valente, G.O., Calandriello, E., Accorinti, M., Spadaro, M. 1996. Pre-symptomatic neurological involvement in Behcet's disease: the diagnostic role of magnetic transcranial stimulation. Electroencephalogr. Clin. Neurophysiol. 101, 42.

Pellechia, M.T., Cuomo, T., Striano, S., et al. 1999. Paroxysmal dystonia in Behçet's disease. Mov. Disord. 14, 177.

Perniciaro, C., Molina, J. 1991. Cerebrovascular aneurysms in patients with Behçet's disease. In: J.D. O'Duffy, E. Kökmen (Eds.), Behçet's Disease: Basic and Clinical Aspects. Marcel Dekker, New York, p. 119.

Rizzo, P.A., Valle, E., Mollicda, M.A., Sanarelli, L., Pozzessere, G. 1989. Multimodal evoked potentials in neuro-Behçet: a longitudinal study of two cases. Acta Neurol. Scand. 79, 18.

Rozenbaum, M., Rosner, I., Portnoy, E. 2002. Remission of Behcet's syndrome with TNF alpha blocking treatment. Ann. Rheum. Dis. 61 (3), 283.

Russell, A.I., Lawson, W.A., Haskard, D.O. 2001. Potential new therapeutic options in Behcet's syndrome. BioDrugs 15, 25.

Said, G., 2000. Sarcoidosis of the nervous system. Neurological manifestations in systemic diseases. ENS Teaching Course 12, Syllabus, p. 74.

Sakane, T., Takeno, M., Suzuki, N., Inaba, G. 1999. Behcet's disease. N. Engl. J. Med. 341, 84.
This article reviews some of the concepts on the causation and pathophysiology of Behçet's disease. In addition, clinical manifestations and treatment strategies of Behçet's disease were reviewed.

Salvarani, C., Boiardi, L., Mantovani, V., Olivieri, I., Ciancio, G., Cantini, F., Salvi, F., Malatesta, R., Molinotti, C., Govoni, M., Trotta, F., Filippini, D., Paolazzi, G., Viggiani, M. 2001. Association of MICA alleles and HLA-B51 in Italian patients with Behcet's disease. J. Rheumatol. 28, 1867.

Schwartz, R.B., Bravo, S.M., Klufas, R.A., Hsu, L., Barnes, P.D., Robson, C.D., Antin, J.H. 1995. Cylosporin neurotoxicity and its relation to hypertensive neuropathy: CT and MR findings in 16 cases. Am. J. Roentgenol. 165, 627.

Schwartz, T., Langevitz, P., Zemer, D., Gazit, E., Pras, M., Livneh, A. 2000. Behçet's disease in familial Mediterranean fever: characterization of the association between the two diseases. Semin. Arthritis Rheum., 286.

Serdaroglu, P. 1998a. Neuromuscular manifestations in the course of Behçet's disease. Acta Myol. 2, 41.

Serdaroglu, P. 1998b. Behçet's disease and the nervous system. J. Neurol. 245 (4), 197.

Serdaroglu, P., Yazıcı, H., Özdemir, C., et al. 1989. Neurological involvement in Behçet's syndrome: a prospective study. Arch. Neurol. 46, 265.

Sharief, M.K., Hentges, R., Thomas, E. 1991. Significance of CSF immunoglobulins in monitoring neurologic disease activity in Behcet's disease. Neurology 41, 1398.

Shimizu, T., Ehrlich, G.E., Inaba, G., Hayashi, K. 1979. Behcet disease (Behcet syndrome). Semin. Arthritis Rheum. 8, 223.

Siva, A. 2001. Vasculitis of the nervous system. J. Neurol. 248, 451.

Siva, A., Altıntaş, A. 2000. Neuro-Behçet syndrome. In: G. Said (Ed.), Intravenous Immunoglobulins in the Treatment of Neurological Disorders. Martin Dunitz Publishers, London, p. 115.

Siva, A., Fresko, I. 2000. Behçet's disease. Curr. Treat. Options Neurol. 2, 435.

Siva, A., Özdogan, H., Yazıcı, H., et al., 1986. Headache, neuropsychiatric and computerized tomography findings in Behçet's syndrome. In: T. Lehner, C.G. Barnes (Eds.), Recent Advances in Behçet's Disease. Royal Society of Medicine Service, London, p. 247.

Siva, A., Necdet, V., Yurdakul, S., et al., 1991. Neuroradiological findings in neuro-Behçet syndrome. In: J.D. O'Duffy, E. Kökmen (Eds.), Behçet's Disease: Basic and Clinical Aspects. Marcel Dekker, New York, p. 323.

Siva, A., Kantarci, O.H., Saip, S., Altintas, A., Hamuryudan, V., Islak, C., Kocer, N., Yazıcı, H. 2001. Behcet's disease: diagnostic and prognostic aspects of neurological involvement. J. Neurol. 248, 95.
Clinical, diagnostic and prognostic features of well documented 164 neuro-Behcet syndrome patients were discussed. This study introduces some new clinical concepts in understanding the patterns of neurological involvement in Behcet's syndrome.

Siva, A., Tunc, R., Masatlioglu, S., Saip, S., Yazıcı, H. 2003. Cerebral venous thrombosis is associated with major vessel disease in Behçet's syndrome. Neurology 60, 5 (Suppl. 1), A181.

Siva, A., Altintaş, A., Saip, S. 2004. Behçet's syndrome and the nervous system. Curr. Opin. Neurol. 17, 347.

Sohn, S., Lee, E.S., Bang, D., Lee, S. 1998. Behcet's disease-like symptoms induced by the Herpes simplex virus in ICR mice. Eur. J. Dermatol. 8 (1), 21.

St. Clair, E.W., McCallum, R.M. 1999. Cogan's syndrome. Curr. Opin. Rheumatol. 11, 47.

Stanford, M.R., Kasp, E., Whiston, R., Hasan, A., Todryk, S., Shinnick, T., Mizushima, Y., Dumonde, D.C., van der Zee, R., Lehner, T. 1994. Heat shock protein peptides reactive in patients with Behcet's disease areuveitogenic in Lewis rats. Clin. Exp. Immunol. 97, 226.

Stigsby, B., Bohlega, S., McLean, D.R., Al-Kawi, M.Z. 2000. Transcranial magnetic stimulation in Behcet's disease: a cross-sectional and longitudinal study with 44 patients comparing clinical, neuroradiological, somatosensory and brain-stem auditory evoked potential findings. Clin. Neurophysiol. 111, 1320.

Susac, J.O. 1994. Susac's syndrome—the triad of microangiopathy of the brain and retina with hearing loss in young women. Neurology 44, 591.

Takeno, M., Kariyone, A., Yamashita, N., Takiguchi, M., Mizushima, Y., Kaneoka, H., Sakane, T. 1995. Excessive function of peripheral blood neutrophils from patients with Behcet's disease and from HLA-B51 transgenic mice. Arthritis Rheum. 38, 426.

Takeuchi, A., Kodama, M., Takatsu, M., et al. 1989. Mononeuritis multiplex in incomplete Behçet's disease: a case report and the review of the literature. Clin. Rheumatol. 8, 375.

Tasci, B., Direskeneli, H., Serdaroglu, P., Akman-Demir, G., Eraksoy, M., Saruhan-Direskeneli, G. 1998. Humoral immune response to mycobacterial heat shock protein (hsp)65 in the cerebrospinal fluid of neuro-Behcet patients. Clin. Exp. Immunol. 113, 100.

Tokay, S., Direskeneli, H., Yurdakul, S., Akoglu, T. 2001. Anticardiolipin antibodies in Behçet's disease: a reassessment. Rheumatology (Oxford) 40, 192.

Touitou, I., Magne, X., Molinari, N., Navarro, A., Quellec, A.L., Picco, P., Seri, M., Ozen, S., Bakkaloglu, A., Karaduman, A., Garnier, J.M., Demaille, J., Kone-Paut, I. 2000. MEFV mutations in Behcet's disease. Hum. Mutat. 16, 271.

Triolo, G., Vadala, M., Accardo-Palumbo, A., Ferrante, A., Ciccia, F., Giardina, E., Citarrella, P., Lodato, G., Licata, G. 2002. Anti-tumour necrosis factor monoclonal antibody treatment for ocular Behcet's disease (letter). Ann. Rheum. Dis. 61, 560.

Tunc, R., Keyman, E., Melikoglu, M., Fresko, I., Yazıcı, H. 2002. Target organ associations in Turkish patients with Behçet's disease: a cross sectional study by exploratory factor analysis. J. Rheumatol. 29, 2393.

Tunc, R., Ozbakir, F., Caglayan, A., Altiparmak, M.R., Yalgan, P., Fresko, I., Yazıcı, H. 2003. Absence of ANCA in Behçet's syndrome with large vessel involvement. Angiology 2001 (10), 260.

Tuzun, B., Tuzun, Y., Yurdakul, S., Hamuryudan, V., Yazıcı, H., Ozyazgan, Y. 1999. Neutrophil chemotaxis in Behcet's syndrome. Ann. Rheum. Dis. 58, 658.

Verity, D.H., Marr, J.E., Ohno, S., Wallace, G.R., Stanford, M.R. 1999. Behcet's disease, the Silk Road and HLA-B51: historical and geographical perspectives. Tissue Antigens 54, 213.

An in-depth discussion of the HLA 51 association with BS.

Wechsler, B., Vidailhet, M., Bousser, M.G., et al. 1992. Cerebral venous sinus thrombosis in Behçet's disease: long term follow-up of 25 cases. Neurology 42, 614.

Winchester, R. 1999. Psoriatic arthritis and the spectrum of syndromes related to the SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome. Curr. Opin. Rheumatol. 11, 251.

Yazıcı, H. 1997. The place of Behçet's syndrome among the autoimmune diseases. Intern. Rev. Immunol. 14, 1.

Yazıcı, H. 2002. Behçet's syndrome: where do we stand? Am. J. Med. 112, 75.

Yazıcı, H., Bıyıklı, H., Van der Linden, S., Schouten, H.J.A. 2001. The 'zero patient' design to compare the prevalences of rare diseases. Rheumatology (Oxford) 40, 121.

Yuh, W.T.C., Simonson, M.T., Wang, A. 1994. Venous sinus occlusive disease: MRI findings. Am. J. Neuroradiol. 15, 309.

Yurdakul, S., Gunaydin, I., Tuzun, Y., Tankurt, N., Pazarli, H., Ozyazgan, Y., Yazıcı, H. 1988. The prevalence of Behcet's syndrome in a rural area in northern Turkey. J. Rheumatol. 15, 820.

Yurdakul, S., Tuzuner, N., Yurdakul, I., Hamuryudan, V., Yazıcı, H. 1996. Gastrointestinal involvement in Behçet's syndrome: a controlled study. Ann. Rheum. Dis. 55, 208.

Zelenski, J., Capraro, J.A., Holden, D., Calabrese, L.H. 1989. Central nervous system vasculitis in Behçet's syndrome: angiographic improvement after therapy with cytotoxic agents. Arthritis Rheum. 32, 217.

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CHAPTER 12

Vasculitides—Miscellaneous Vasculitides

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1. Introduction

Vasculitis refers to the inflammation of the vessel wall. Segmental involvement results in stenosis and occlusion of the affected vessel with subsequent infarction of the adjacent tissue. Alternatively, the inflammatory process can lead to necrosis of the vessel wall resulting in aneurysms, rupture of the vessel, and hemorrhage.

Primary vasculitis refers to intrinsic vessel disease, which can be classified according to the size of the predominantly affected vessels (large-, medium- and small-vessel vasculitis) and its pattern of distribution (systemic or localized vasculitis) (Jennette et al., 1994). Secondary vasculitides encompass vasculitides which occur in the setting of connective tissue disorders, neoplastic diseases, infections, drugs, or toxins.

Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides, Temporal (giant-cell) arteritis, Takayasu arteritis, and Behçet's Syndrome were discussed in previous chapters. The purpose of this chapter is to discuss some of the other vasculitides that physicians may face with in the clinical practice (Table 1). Although the primary angiitis of the central nervous system (CNS) (PACNS) is not a *systemic* autoimmune disorder, we prefer to include PACNS in our discussion as the recent increased recognition of PACNS has created much interest among physicians.

2. Primary angiitis of the central nervous system (PACNS)

2.1. Introduction

Primary angiitis of the CNS, in the past also known as isolated CNS angiitis or noninfectious granulomatous angiitis of the CNS, is a primary vasculitis restricted to the CNS. Cases of PACNS were first described in 1959 by Cravioto and Feigin (1959). Until the early 90's only 108 cases were published in the English literature (Lie, 1992). Since then, increased recognition of the disease has been facilitated by the increasing availability of sophisticated neuroimaging techniques such as magnetic resonance imaging (MRI), angiography and brain biopsy.

2.2. Prevalence

Although regarded as a very rare disease, PACNS is the most common CNS vasculitis (Moore, 2000). Accurate numbers regarding prevalence of PACNS are not available because of lack of adherence to strict diagnostic criteria in the published literature.

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Table 1
Miscellaneous vasculitides

Primary angiitis of the central nervous system (PACNS)[a]
Relapsing polychondritis
Cogan's syndrome

[a] Although PACNS is not a *systemic* autoimmune disorder, we prefer to include PACNS in our discussion as the recent increased recognition of PACNS has created much interest among physicians.

2.3. Epidemiology

Primary angiitis of the CNS may occur at any age but is predominantly diagnosed in the fourth to sixth decades (Newman, 1998). In earlier series, males prevailed but recent studies showed an equal sex ratio (Newman, 1998; Moore and Richardson, 1998).

2.4. Etiology/Pathogenesis

Primary angiitis of the CNS has a predilection for small and medium sized arteries and veins located in the leptomeninges, cortical and subcortical brain parenchyma. The chronic phase of the inflammatory process may exhibit granulomatous changes of the vessel with infiltration of the vessel wall by monocytes, histiocytes, lymphocytes and plasma cells. However, these histological features are often absent, especially in antemortem studies (Moore and Richardson, 1998). The etiology and pathogenesis of PACNS are still unknown. An autoimmune etiology is suspected, but the primary immunopathogenic events that initiate vascular inflammation are poorly understood.

2.5. Clinical manifestations

In accordance with the pathological changes, which exclusively affect cerebral vessels, clinical symptoms and signs are restricted to the CNS. Clinical presentation is variable but multifocal neurological deficits that occur in the setting of diffuse encephalopathy, accompanied by persistent headache are the most common clinical presentations of PACNS. Symptoms of encephalopathy typically comprise cognitive impairment, altered level of consciousness, and psychiatric or behavioral changes. Cranial neuropathies and myelopathy may predominate the clinical picture in some patients. Ischemic stroke is an uncommon presenting symptom of PACNS (Vollmer et al., 1993) and intracranial hemorrhage is a more frequent finding. Subarachnoid hemorrhage has been associated with PACNS and is usually minor. Seizures occur in about 5% of patients and are usually focal in nature. Since PACNS exclusively affects the CNS, presence of systemic features affecting joints, skin or other organs should alert the physician to investigate an alternative diagnosis (Moore and Richardson, 1998).

The clinical course of PACNS is highly variable. Initially PACNS was considered to be an inexorably progressive disease rapidly resulting in major disability and death within the first 9 to 12 months after diagnosis, implying the necessity for intense immunosuppressive therapy. However, more recently the striking variability of the clinical course even in untreated cases has been recognized: onset can be acute or subacute; and clinical course may be slowly progressive, relapsing—remitting over several years, or even monophasic (Calabrese et al., 1993; Moore and Richardson, 1998; Alreshaid and Powers, 2003). In 1993, Calabrese et al. introduced for the first time the term of 'Benign angiopathy of the nervous system' (BACNS) based on subgroup analysis of angiographically diagnosed patients, advocating that this subgroup would require less intense immunosuppressive therapy. Distinctive clinical features of this subgroup were female sex, acute onset of symptoms, prevailing headache, normal or near normal cerebrospinal fluid (CSF), and a high probability angiogram. This clinical subgroup had a monophasic and benign clinical course relative to patients with pathologically documented PACNS (Calabrese et al., 1993). However, the concept of BACNS has been controversial ever since (Woolfenden et al., 1998). Recently, a long-term follow up study of a cohort of 16 patients matching the criteria of BACNS with a favorable outcome, requiring less intensive treatment has been published (Hajj-Ali et al., 2002).

2.6. Diagnostic investigation

All diagnostic tests and procedures, including laboratory tests, different imaging modalities like MRI,

cerebral angiography, or histopathological studies lack specificity. Therefore, final diagnosis of PACNS relies heavily on careful evaluation of clinical symptoms and signs, correlation with radiological findings, performance of a broad battery of serologic tests mainly to exclude other causes of vasculitis and histopathological confirmation by brain biopsy (Moore, 1994).

2.6.1. Laboratory tests

Hematological work up usually demonstrates lack of inflammatory markers: complete blood count, erythrocyte sedimentation rate (ESR), and C-reactive protein can be normal. However, elevated ESR is still compatible with the diagnosis of PACNS as half of the patients have elevated ESR. Serologic markers of vasculitis (secondary to connective tissue disorders) such as cryoglobulins, ANCA, anti-Ro (SSA) and anti-La (SSB) antibodies, rheumatoid factor (RF), angiotensin converting enzyme, anticardiolipin antibodies should be negative. Serum complement levels and protein electrophoresis should be normal (Goldberg et al., 1997). Antinuclear antibodies are usually negative but mildly elevated titers do not exclude the diagnosis of PACNS. CNS vasculitis of infectious etiology should be ruled out with serological studies testing for Varicellazoster virus (VZV), human immunodeficiency virus (HIV), cytomegalovirus (CMV), treponema pallidum, mycobacterium tuberculosis, borrelia burgdorferi (Siva, 2001) as well as hepatitis B and hepatitis C infection (Heckmann et al., 1999).

2.6.2. Lumbar puncture

CSF analysis is abnormal in 80–90% of pathological confirmed cases (Calabrese et al., 1997). Consequently, a normal CSF study is considered to have a high negative predictive value. Abnormalities of the CSF typically comprise mild lymphocytic pleocytosis and hyperproteinemia. In a study of Calabrese et al. mean CSF cell count was 77/mm^3 and mean protein was reported to be 177 mg% (Calabrese et al., 1997). Occasionally, increased IgG synthesis with oligoclonal bands can be detected. CSF analysis should include adequate stains, cultures and cytological exams to rule out CNS infection or neoplasm.

2.6.3. Imaging

(i) *MRI*: MRI is a highly sensitive diagnostic tool for PACNS, but findings lack specificity. In the vast majority of histological confirmed PACNS, MR imaging exhibits positive findings (Calabrese et al., 1997; Greenan et al., 1992). There exists a substantial variation in number, size and location of the lesion. Lesions attributed to PACNS are usually multifocal, bilateral and distributed nearly equally among cortical, subcortical and deep gray matter structures (Pomper et al., 1999). Brainstem, cerebellum and spinal cord are typically less frequently affected (Shoemaker et al., 1994). After administration of contrast material, lesions and the meninges may exhibit enhancement (Calabrese et al., 1997), indicating inflammation (Shoemaker et al., 1994). The most important radiological differential diagnosis is atherovascular or demyelinative diseases and neoplasms such as low grade glioma.

(ii) *MR angiography*: Despite the important value of MR angiography in the diagnosis of medium- and large-vessel vasculitis, the resolution of MR angiography is insufficient to depict the morphological changes of the small vessels predominantly affected in PACNS (Dagirmanjian et al., 1995; Stellar, 1995; Stock et al., 1995).

(iii) *Angiography*: Cerebral angiography is the most sensitive imaging study in the diagnosis of PACNS, although angiography may be completely normal in up to 10% of pathologically proven cases (Moore and Richardson, 1998). Correlations between MR imaging and angiography seem to be modest: only a minority of angiographic lesions correlate with MR imaging findings (Pomper et al., 1999; Greenan et al., 1992), emphasizing the additional value of angiography in delineating the extent of the disease beyond that detected by MR imaging.

Although sensitive, angiographic changes are not specific for PACNS and can be demonstrated in a variety of different vasculitis involving the CNS. Positive findings on angiography include: segmental or widespread changes in vessel contour and caliber resulting in beading, abrupt vessel termination, hazy vessel margins, and neovascularization. The most important angiographic differential diagnosis apart from the secondary CNS vasculitis are vascular abnormalities secondary to atherosclerotic changes,

vasospasm, fibromuscular dysplasia, hypertensive vasculopathy, or CNS infection (Calabrese and Duna, 1995; Calabrese et al., 1997; Greenan et al., 1992).

(iv) *Functional imaging*: Functional imaging like single-photon-emission computed tomography (SPECT) and positron emission tomography (PET) may exhibit unspecific diffuse perfusion abnormalities. Their value is currently restricted to research purposes.

2.6.4. Biopsy

Brain biopsy remains the golden standard for the diagnosis of PACNS. It is essential for corroborating the diagnosis of PACNS and for excluding conditions mimicking it (Moore, 1994; Alrawi et al., 1999; Calabrese, 2001). In consideration of the significant side effects of prolonged therapy with glucocorticoids and cyclophosphamide, and the potential to misdiagnose a condition which requires a different treatment strategy, brain biopsy with its usually low complication rate remains an invaluable diagnostic tool. Probably because of the focal and segmental nature of the inflammation, brain biopsies yield a high false negative rate, which may exceed 20% (Alhalabi and Moore, 1994; Duna and Calabrese, 1995; Greenan et al., 1992). Therefore, a negative biopsy does not rule out vasculitis (Chu et al., 1998; Duna and Calabrese, 1995). Selection of the biopsy site in accordance with enhancement of the lesion on MR imaging after administration of contrast significantly increases the diagnostic yield of the procedure (Calabrese, 1997).

Biopsy material should include leptomeninges, cortical and subcortical brain parenchyma (Chu et al., 1998), although a recent study failed to demonstrate that sampling of leptomeningeal tissue increases the sensitivity of brain biopsy in PACNS (Alrawi et al., 1999).

Primary angiitis of the CNS was initially described in 1959 as noninfectious granulomatous angiitis because of granulomatas present in postmortem studies (Cravioto and Feigin, 1959). However, antemortem granulomata are a variable and frequently absent histological feature (Moore, 1994). The histopathological hallmark of PACNS is a predominantly mononuclear inflammation in and around the walls of small- to medium sized leptomeningeal and intracerebral vessels, affecting small arteries and arterioles much more frequently than small veins and venules (Parisi et al., 1994). The pattern of distribution of inflammation is segmental and affected arteries exhibit intimal proliferation and fibrosis with sparing of the media. In some cases giant multinucleate Langerhans cells can be demonstrated (Lie, 1997; Parisi et al., 1994).

2.7. Differential diagnosis

Since the exclusion of an underlying systemic inflammatory, infectious, or neoplastic process by appropriate laboratory studies belongs to the diagnostic criteria of PACNS (Moore and Richardson, 1998), careful evaluation of the differential diagnosis of PACNS is essential. Corresponding to the impressive variability of its clinical presentation and features on imaging and pathology, PACNS has a broad differential diagnosis (Table 2). A rare but distinct differential diagnosis of PACNS is the only recently described Susac's syndrome, a noninflammatory vasculopathy causing microinfarcts in the retina, cochlea and brain, resulting in the clinical triad of retinopathy, hearing loss and encephalopathy. The most frequent manifestation of this disease are headache, however, cognitive and psychiatric changes accompanied by multifocal neurological deficits that may progress during the disease (Susac, 1994). It is important to note that angiographically PACNS can mimic vascular changes suggestive of atherosclerotic disease, fibromuscular dysplasia or vasospasm.

Table 2
Differential diagnosis of primary angiitis of central nervous system

Vasculitis (e.g. giant cell arteritis, PAN, Churg Strauss, Wegner's granulomatosis, Behçet's disease, cryoglobulinemia, sympathamemetic use)
Connective tissue disease (e.g. systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, scleroderma)
Infectious disease (especially VZV, HIV, CMV, *Treponema Pallidum*, *Mycobacterium Tuberculosis*, *Borrelia Burgdorferi* and progressive multifocal leukoencephalopathy)
Neoplastic disease (especially low-grade glioma, meningeal carcinomatosis, primary brain lymphoma, intravascular lymphoma)
Demyelinating disease (e.g. multiple sclerosis)
Reversible cerebral vasoconstriction sydnromes
Others (Susac's syndrome)

2.8. Treatment

So far, no randomized clinical trials have been conducted to validate current treatment protocols for PACNS. Establishing evidence based treatment strategies for PACNS has been difficult because of rarity of the disease, its heterogeneous clinical and histopathological manifestations, and the variant criteria according to which the diagnosis of PACNS has been made. It is generally agreed, that patients require long-term, combined immunosuppressive therapy consisting of glucosteroids and cytotoxic drugs. Because of the severity of side effects and the cumulative risk associated with immunosuppressive therapy, many authors agree that brain biopsy should be performed prior to administration of treatment (Siva, 2001). Several treatment regimens have been proposed, but the most established current protocol consists of high dose intravenous methylprednisolone (1 g/day for three to seven days followed by oral prednisolone 60 mg daily), together with oral (2–2.5 mg/kg/day) or intravenous cyclophosphamide. Intravenous cyclophosphamide is given at a dosage of 500–1000 mg/m^2 of body surface. It is administered every second week for the first three times and then at monthly intervals (Calabrese, 1997). Required length of treatment is still controversial, but a period of at least 12 months after clinical remission seems advisable with a corresponding relapse rate lower than 10% (respective relapse rate after only 6 months of treatment being 30%) (Moore and Richardson, 1998). Concurrent administration of antiaggregant therapy is recommended (Zivkovic et al., 2000). Treatment response can be monitored noninvasively by serial MR imaging with contrast administration. Until now no convincing evidence exists that conventional immune modulatory therapy like intravenous immunoglobulins (IVIG), plasmapheresis, or interferon-α (INF-α) are effective in the treatment of PACNS (Calabrese, 1997; Gross, 1999; Siva, 2001). The efficacy of new immunosuppressant and immunomodulatory drugs such as mycophenolate mofetil and leflunamide, which has been demonstrated in experimental models of autoimmune diseases and systemic vasculitis such as Wegener's granulomatosis and vasculitis secondary to rheumatoid arthritis, has yet to be established in PACNS (Zivkovic et al., 2000).

3. Relapsing polychondritis

3.1. Introduction

Relapsing polychondritis (RP) is an episodic and progressive inflammatory disease of cartilaginous structures, affecting primarily the ear, nose, peripheral joints and the tracheobronchial tree. In most patients, RP is associated with a fluctuating but progressive course in which recurrent exacerbation of inflammation eventually leads to permanent destruction of the involved structures (Table 3).

3.2. Epidemiology

RP is a rare disease. By 1997 only 600 cases had been reported worldwide. Diagnosis is usually made in adulthood, but onset of the disease has been described as early as the age of 5 and as late as the age of 84 years. Apparently there is no significant gender predisposition.

3.3. Etiology

The etiology of the disease is unknown. Based on pathological studies demonstrating lymphocytic infiltration and presence of antigen–antibody complexes in the affected cartilage, the pathogenesis is considered to be autoimmune, involving the humoral and cellular system. In addition, the efficacy of immunosuppressive therapy and the association of RP with other autoimmune diseases are strongly indicative of an autoimmune etiology (McAdam et al., 1976; Trentham et al., 1998).

Table 3
McAdam criteria for the diagnosis of relapsing polychondritis (at least three features should be present)

Bilateral auricular chondritis
Nonerosive seronegative inflammatory polyarthritis
Nasal chondritis
Ocular inflammation
Respiratory tract chondritis
Audiovestibular damage

3.4. Clinical manifestation

The onset is generally sudden, followed by a relapsing-remitting but generally progressive course. Corresponding to the distribution of cartilage, RP is a multisystem disease with diverse clinical presentation. Most frequent clinical manifestation are auricular, nasal and respiratory tract chondritis, polyarthritis and ocular inflammation.

Neurological manifestations are uncommon, but may precede the classic signs of RP. There is conclusive evidence that neurological symptoms are caused by vasculitis affecting the central and peripheral nervous system. The first case of CNS vasculitis was reported by Stewart and Ashzawa (1988). Postmortem studies demonstrated diffuse small and medium artery vasculitis of the brain. Corresponding to the site of involvement, neurological symptoms are characterized by a wide diversity including headache, encephalopathy, seizures, stroke, focal motor or sensory deficit and neuropathy. The course is usually acute or subacute. (Willis et al., 1984).

3.5. Diagnostic criteria

The diagnosis of RP is usually made on the basis of clinical findings alone. Generally the criteria of McAdam have been used to confirm the diagnosis of RP (Table 3) (McAdam et al., 1976).

3.5.1. Laboratory tests

No specific laboratory test exists for the diagnosis of RP. Hematological markers of inflammation like anemia, leukocytosis or thrombocytosis may be present. Serological tests for evaluation for other autoimmune diseases including RF, antinuclear antibodies, ANCA and complement levels should be performed.

Anti-collagen type 2 antibodies are found in the acute phase of RP, but lack specificity for the disease, although their serum level seems to correlate with disease severity (Foidart et al., 1978).

3.5.2. Imaging

Radiographs may show calcification of the pinna, nasal or tracheal cartilage. Tracheal stenosis may be observed on plain chest radiographs. Spiral CT is a noninvasive test that readily identifies tracheal and bronchial thickening, stenosis and calcifications.

When CNS vasculitis is suspected, brain magnetic resonance (MR) imaging with contrast should be performed and a CT-angio scan or cerebral angiography should be considered to identify and delineate the extent of small and medium size vasculitis.

3.5.3. Functional diagnostic tests

Pulmonary function tests, in the presence of respiratory involvement, demonstrates a nonreversible obstructive pattern, collapse and stenosis of the airways.

3.5.4. Histopathology

Affected cartilage exhibits in the early stages of the disease lymphocytic infiltrates and decreased numbers of chondrocytes, which are replaced in later stages of the disease by fibroblastic granulation tissue (Valanzuela et al., 1980). Brain biopsy of RP with CNS involvement typically demonstrates diffuse vasculitis, involving medium and small arteries and veins, with thickening of the vascular wall, perivascular cuffing with neutrophils and lymphocytes, resulting in focal ischemia, thrombosis and reactive astrocytosis. Areas of necrotizing vasculitis may also be seen (Trentham et al., 1998).

3.6. Differential diagnosis

Major differential diagnosis for the classical presentation of RP are other autoimmune diseases affecting eyes, ears and joints like Wegener's granulomatosis, polyarteritis nodosa (PAN), rheumatoid arthritis, sarcoidosis, and Cogan's syndrome.

Differential diagnosis for the neurological manifestations of RP comprises all primary and secondary vasculitides affecting the central or peripheral nervous system like: Giant cell atrteritis, Takayasu arteritis, PAN, WG and other connective tissue diseases.

3.7. Treatment

Because of paucity of the data about RP and its course, a standardized therapeutic protocol for RP has not yet been established. Mild inflammation of the joints,

ear or nose usually benefits from dapsone (25–200 mg/day) or colchichine.

The mainstay of treatment is systemic corticosteroids. Prednisone (20–60 mg/day) is administered in the acute phase and is tapered to 15–25 mg/day for maintenance. Severe flares may require 80–100 mg/day. McAdam et al. (1976) found that continuous prednisone decreased disease severity, frequency and durations of relapses.

Other medications reported to control symptoms and progression of the disease include cytotoxic drugs like methotrexate (7.5–22.5 mg/week), azathioprine, cyclophosphamide and cyclosporin A.

4. Cogan's syndrome

4.1. Introduction

Cogan's syndrome, originally described in 1945, by David Cogan, is a multisystem inflammatory vascular disease, characterized by ocular symptoms, typically interstitial keratitis and vestibulocochlear symptoms as well as involvement of other organ systems (Haynes and Kaiser, 1980). Cody and Williams defined atypical Cogan's syndrome as the presence of an inflammatory eye lesion in addition to, or instead of interstitial keratitis (Cody and Williams, 1962). The distinction between the typical and atypical subtypes has become less important, as both have now been associated with systemic vasculitis (St. Clair and McCallum, 1999).

4.2. Epidemiology

Cogan's syndrome is considered a rare syndrome, but no accurate estimate of its incidence or prevalence is available. Until now only 300 patients have been reported in the world literature. The disease occurs in young adults and older children, with a median age at onset of 25 (range 4–63). There is no gender predominance and the disease has been described in all races. In the majority of cases clinical manifestation begins in the eyes or in the audiovestestibular system, less frequently in another organ system (Vollertsen and Mc Donald, 1986).

4.3. Etiology

The etiology of Cogan's syndrome is still elusive. However, pathology studies and the strong association of the disease with vasculitis indicates an autoimmune origin (Haynes and Kaiser, 1980), possibly with participation of humoral immunity in the pathogenesis of the disease as indicated by detection of autoantibodies directed against the mesenchymal structures of the inner ear and the epithelial cells of the cornea (Majoor et al., 1992).

Recently, Lunardi and Bason (2002) used pooled IgG immunoglobulins derived from eight patients with Cogan's syndrome to randomly screen a peptide library in search of the relevant autoantigen peptide. One immunodominant peptide that shows similarity with autoantigens such as SSA/Ro and with retrovirus three major core protein lambda 1 was recognized by all the patients' sera. The peptide's sequence also showed with the cell-density enhanced protein tyrosine phosphatase-1, which is expressed on the sensory epithelia of the inner ear and on endothelial cells. The spectrum of pathological findings described in patients with Cogan's disease encompasses lymphocyte and plasma cells infiltration into the deeper layers of the cornea, with evidence of neovascularization (Leff, 1967; Haynes and Kaiser, 1980; Majoor et al., 1992), vasculitis of the optic and vestibulocochlear nerves (Haynes and Kaiser, 1980) and retrograde degeneration of vestibular and auditory nerves (Schuknecht and Nadol, 1994).

4.4. Clinical manifestations

The first clinical manifestation usually involves either the eye or ear alone. The mean interval between involvement of the two organs ranges from 3 months in the typical form, to 11 years in the atypical form of the disease. The acute phase of ocular and vestibulocochlear involvement lasts months to years, followed by a chronic phase of relatively low disease activity.

Vestibulocochlear involvement: Involvement of the vestibulochochlear system presents as Menière- like attacks of severe vertigo, nausea, emesis, and tinnitus and hearing loss. The course is progressive or intermittent for several days or months. As a general rule the vestibular syndrome regresses, while

the auditory deficit leads to progressive hearing loss and deafness in 60% of patients (Haynes and Kaiser, 1980).

Ocular involvement: The initial symptoms of acute interstitial keratitis include redness, photophobia, lacrimation, eye pain and usually transient decrease in visual acuity. The inflammatory process affects mainly the posterior part of the cornea, which may subsequently develop into a site of neovascularization. Also conjunctivitis, uveitis, episcleritis or scleritis have been described. However, while affection of the vestibulochochlear system results relative frequently in deafness, ocular involvement only rarely leads to blindness.

Systemic manifestations: Nonspecific systemic findings are fever, weight loss, fatigue and headache. One third of the patients have musculoskeletal complaints including arthralgia, myalgia or arthritis, and gastrointestinal symptoms.

Two thirds of the patients develop systemic vasculitis within a year from the onset of ocular or vestibulochochlear symptoms (Vollertsen and Mc Donald, 1986). Life-threatening complications occur as a result of systemic necrotizing vasculitis that may affect vital organs such as the aorta, aortic valves, brain and kidneys.

Cardiac involvement: Cardiac manifestations are vasculitic in nature and were reported in 25% of patients. Aortic insufficiency, present in 15% of patients might develop into a severe complication requiring valve replacement in almost half of the patients. Other cardiac manifestations include myocarditis, pericarditis, myocardial infarction. (Cheson and Bluming, 1976).

Neurological manifestations are seen in about 25% of patients. CNS involvement predominates and results from cerebral vasculitis, subarachnoid hemorrhage and sinus venous thrombosis, giving rise to a diverse clinical picture, including seizures, stroke and myelopathy Affection of the peripheral nervous system is expressed by poly- or mononeuropathy. (Bicknell and Holland, 1978; Karni et al., 1991).

4.5. Diagnostic investigation

4.5.1. Laboratory tests

There are no specific diagnostic tests to establish the diagnosis of Cogan's syndrome. Blood tests may reveal a pattern of chronic inflammation like leukocytosis, anemia, thrombocytosis and an elevated ESR. Anti nuclear antibody (ANA) is usually negative, but positive RF and a false positive veneral disease research laboratories (VDRL) test have been reported. CSF analysis is usually normal or shows mild pleocytosis and elevated protein levels (Haynes and Kaiser, 1980; Vollertsen and Conn, 1990).

4.5.2. Imaging

High resolution, gadolinium enhanced, T1-weighted MRI studies have shown enhancement of the vestibule, semicircular canals, vestibular nerve and cochlea in patients with acute disease. In chronic stages of the disease, narrowing or occlusion of the semicircular canal can be depicted (Helmchen et al., 1999). Cerebral angiography in a patient with Cogan syndrome and multiple strokes may reveal alternating segments of stenosis and ectasia of the intracranial arteries compatible with cerebral vasculitis, as well as aneurysm at the vertebrobasilar junction (Albayram et al., 2001).

4.5.3. Pathology

Pathologic findings of necrotizing vasculitis have been demonstrated by biopsy of the skin, kidney, liver, spleen, gastrointestinal tract, muscle, myocardium and coronary arteries.

4.6. Differential diagnosis

Differential diagnosis of Cogan's syndrome includes disorders that cause ocular (especially interstitial keratitis) and vestibulocochlear symptoms in the setting of systemic disease. Congenital or acquired syphilis is one of the most important diseases in the differential diagnosis because of relatively high prevalence and implication for therapy. Broader differential diagnosis comprises a wide variety of systemic autoimmune diseases such as PAN, sarcoidosis, Wegener's granulomatosis, RP, rheumatoid arthritis, systemic lupus erythematosus, giant cell arteritis, Behçet's Syndrome, and Sjogren syndrome. Susac's syndrome (retinocochleocerebral vasculopathy), a vasculopathy affecting the retinal, cochlear and cerebral arterioles, manifested by loss of visual acuity, deafness and central neurological disorders

and Vogt-Koyanagi-Harada syndrome, which is also associated with audiovestibular symptoms are very rare, but should be considered.

Since different infectious diseases like congenital rubella, congenital mumps, viral infections like herpes simplex, herpes zoster, measels, Chlamydial infections and tuberculosis can mimic Cogan's syndrome, the patient should be carefully evaluated for it.

4.7. Treatment

Topical glucocorticoids and atropine generally control the interstitial keratitis of Cogan's syndrome. Ocular symptoms improve in 80% of patients treated with topical or systemic glucocorticoids within 1 week (Vollertsen and Mc Donald, 1986). Oral glucocorticoids are the treatment of choice for prevention of hearing loss, when used early in the course of the disease. Low and middle frequency hearing is best preserved (Haynes and Pikus, 1981). Initial dose of prednisone usually recommended is 1 mg/kg/day with subsequent tapering to low maintenance dose, attempting discontinuation within 2–6 months.

Cytotoxic drugs are useful in protecting hearing in glucocorticoid-unresponsive patients. Methotrexate at dose of 7.5–10 mg/kg/week has been found to be effective (Richardson, 1994), with a dose titrated to up to 17.5 mg/kg over 4–8 weeks. Hearing fluctuations that occur late in the disease respond to oral thiazides (Haynes and Pikus, 1981). Cochlear implantation may be necessary.

Oral glucocorticoids (prednisone 1–2 mg/kg) combined with cytotoxic drugs (e.g. cyclophosphamideare effective in treating vasculitic manifestations of Cogan's syndrome, such as systemic necrotizing vasculitis. Cyclosporin A, at initial dose of 1–10 mg/kg daily followed by maintenance dose of 0.5–2 mg/kg has been shown to be of benefit in cases of severe uveitis, necrotizing vasculitis and aortitis.

Key points

- Primary vasculitis refers to intrinsic vessel disease. Secondary vasculitides encompass vasculitides which occur in the setting of another disease.
- Primary angiitis of the CNS (PACNS), is a rare, probably autoimmune, primary vasculitis restricted to the CNS, affecting predominantly small and medium sized vessels.
- PACNS has a highly variable clinical course and manifestation but most commonly presents as multifocal neurological deficits in the setting of diffuse encephalopathy and headache.
- There are no pathognomonic diagnostic findings in PACNS, therefore the combination of different diagnostic modalities, including laboratory tests, lumbar puncture, MRI, cerebral angiography and brain biopsy are essential.
- Combined long term immunosuppressive therapy consisting of glucosteroids and cytotoxic drugs are indicated in PACNS.
- Cogan's Syndrome, is a multisystem inflammatory vascular disease, characterized by inflammatory eye disease, vestibuloauditory dysfunction associated with systemic vasculitis.
- Relapsing polychondritis is an episodic and progressive inflammatory disease of cartilaginous structures, affecting primarily the ear, nose, peripheral joints and the tracheobronchial tree.

References

Albayram, M.S., Wityk, R. 2001. The cerebral angiographic findings in Cogan syndrome. Am. J. Neuroradiol. 22, 751–754.

Alhalabi, M., Moore, P.M. 1994. Serial angiography in isolated angiitis of the central nervous system. Neurology 44, 1221–1226.

Alrawi, A., Trobe, J.D., Blaivas, M., Musch, D.C. 1999. Brain biopsy in primary angiitis of the central nervous system. Neurology 53 (4), 858–860.

Alreshaid, A.A., Powers, W.J. 2003. Prognosis of patients with suspected primary CNS angiitis and negative brain biopsy. Neurology 61, 831–833.

Bicknell, J.M., Holland, J.V. 1978. Neurologic manifestations of Cogan syndrome. Neurology 28, 278–281.

Calabrese, L.H. 1997. Therapy of systemic vasculitis. Neurol. Clin. 15, 973–991.

Calabrese, L.H. 2001. Primary angiitis of the CNS: the penumbra of vasculitis. J. Rheumatol. 28, 465–466.

Calabrese, L.H., Duna, G.F. 1995. Evaluation and treatment of central nervous system vasculitis. Curr. Opin. Rheumatol. 7, 37–44.

Calabrese, L.H., Gragg, L.A., Furlan, A.J. 1993. Benign angiopathy: a distinct subset of angiographically defined primary angiitis of the central nervous system. J. Rheumatol. 20, 2046–2050.
Important original article describing for the first time a benign form of PACNS.

Calabrese, L.H., Duna, F.G., Lie, J.T. 1997. Vasculitis in the central nervous system. Arthritis Rheum. 40, 1189–1201.

Cheson, B.D., Bluming, A.Z. 1976. Cogan's syndrome: a systemic vasculitis. Am. J. Med. 60, 549–555.

Chu, C.T., Gray, L., Goldstein, L.B., Hulette, C.M. 1998. Diagnosis of intracranial vasculitis: a multi-disciplinary approach. J. Neuropathol. Exp. Neurol. 57, 30–38.

Cody, D.T., Williams, H.L. 1962. Cogan's syndrome. Mayo. Clin. Proc. 37, 372–375.

Cravioto, H., Feigin, I. 1959. Noninfectious granulomatous angiitis with a predilection for the nervous system. Neurology 9, 599–609.

Dagirmanjian, A., Ross, J.S., Obuchowski, N., et al. 1995. High resolution, magnetization transfer saturation, variable flip angle, time-of-flight MRA in the detection of intracranial vascular stenoses. J. Comput. Assist. Tomogr. 19, 700–706.

Duna, G.F., Calabrese, L.H. 1995. Limitation of invasive modalities in the diagnosis of primary angiitis of the central nervous system. J. Rheumatol. 22, 662–667.

Foidart, J.M., Abe, S. 1978. Antibodies to type 2 collagen in relapsing polychondritis. N. Eng. J. Med. 299 (22), 1203–1207.

Goldberg, J.W. 1997. Primary angiitis of the central nervous system. In: L.A. Rolak, Y. Harati (Eds.), Neuroimmunology for the Clinician. Butterworth, London, pp. 177–186.

Greenan, T.J., Grossman, R.I., Goldberg, H.I. 1992. Cerebral vasculitis: MR imaging and angiographic correlation. Radiology 182, 65–72.

Gross, W.L. 1999. New concepts in treatment protocols for severe systemic vasculitis. Curr. Opin. Rheumatol. 11, 41–46.

Hajj-Ali, R.A., Furlan, A., Abou-Chebel, A., Calabrese, L.H. 2002. Benign angiopathy of the central nervous system: cohort of 16 patients with clinical course and long-term follow up. Arthritis Rheum. 47 (6), 662–669.

Haynes, B.F., Kaiser, K.M. 1980. Cogan's syndrome: studies in thirteen patients, long term follow up and a review of the literature. Medicine (Baltimo) 59, 426–441.

Haynes, B.F., Pikus, A. 1981. Successful treatment of sudden hearing loss in Cogan's syndrome with corticosteroids. Arthritis Rheum. 24, 501–503.

Heckmann, J.G., Kayser, C., Heuss, D., et al. 1999. Neurological manifestations of chronic hepatitis C. J. Neurol. 246, 486–491.

Helmchen, C., Arbusow, V., Jager, L., Strupp, M., Stocker, W., Schulz, P. 1999. Cogan's syndrome: clinical significance of antibodies against the inner ear and cornea. Acta Otolaryngol. 119 (5), 528–536.

Jennette, J.C., Falk, R.J., Andrassy, K., et al. 1994. Nomenclature of systemic vasculitides: proposal of an international consensus conference. Arthritis Rheum. 37, 187–192.

Karni, A., Sadeh, M. 1991. Cogan's syndrome complicated by lacunar brain infarcts. J Neurol. Neurosurg. Psychiatry 54, 169–171.

Leff, I.L. 1967. Cogan's syndrome. Ocular pathology. NY State Med. J. 67, 2249–2257.

Lie, J.T. 1992. Primary (granulomatous) angiitis of the central nervous system—clinicopathologic analysis of 15 new cases and a review of the literature. Hum. Pathol. 23 (2), 164–171.

Lie, J.T. 1997. Classification and histopathologic spectrum of central nervous system vasculitis. Neurol. Clin. 15, 805–819.

Lunardi, C., Bason, C. 2002. Autoantibodies to inner ear and endothelial antigens in Cogan's syndrome. Lancet 360, 915–921.

Majoor, M.H., Alber, F.W. 1992. Corneal autoimmunity in Cogan's syndrome: Report of two cases. Ann. Otol. Rhinol. Laryngol. 101, 679–684.

McAdam, L.P., O'Halan, M.A., Bluestone, R., Pearson, C.M. 1976. Relapsing polychondritis—prospective study of 23 patients and a review of the literature. Medicine 55, 193–215.

Moore, P.M. 1994. Vasculitis of the central nervous system. Semin. Neurol. 14, 307–312.

Moore, P.M. 2000. Vasculitis of the central nervous system. Curr. Rheumatol. Rep. 2 (5), 376–382.

Moore, P.M., Richardson, B. 1998. Neurology of the vasculitides and connective tissue disease. J. Neurol. Neurosurg. Psychiatry 65 (1), 10–22.
Excellent review of neurology of vasculitides.

Newman, G.C. 1998. CNS Vasculitis, Clinical neuroimmunology, Education Syllabus. AAN pp. 2FC.005-143–2FC. 005-174.

Parisi, J.E., Moore, P.M. 1994. The role of biopsy in vasculitis of the central nervous system. Semin. Neurol. 14, 341–348.

Pomper, M.J., Miller, T.J., Stone, J.H., Tidmore, W.C., Hellman, D.J. 1999. CNS vasculitis in autoimmune disease: MR imaging findings and correlation with angiography. Am. J. Neuroradiol. 20, 75–85.

Richardson, B. 1994. Methotrexate therapy for hearing loss in Cogan's syndrome. Arthritis Rheum. 37 (10), 1559–1561.

Schuknecht, H.F., Nadol, J.B. 1994. Temporal bone pathology in a case of Cogan's syndrome. Larygoscope 104, 1135–1142.

Shoemaker, E.I., Zwu-Shin, L., Rae-Grant, A.D., Little, B. 1994. Primary angiitis of the CNS: unusual MR appearance. AJNR 15, 331–334.

Siva, A. 2001. Vasculitis of the nervous system. J. Neurol. 248 (6), 451–468.
Most comprehensive review of vasculitis of the nervous system.

St. Clair, E.W., McCallum, R.M. 1999. Cogan's syndrome. Curr. Opin. Rheumatol. 11, 47–52.

Stellar, R.J. 1995. Imaging blood vessels of the head and neck. J. Neurol. Neurosurg. Psychiatry 59, 225–237.

Stewart, S.S., Ashzawa, T. 1988. Cerebral vasculitis in relapsing polychondritis. Neurology 38 (1), 150–152.

Stock, K.W., Radue, E.W., Jacob, A.L., Bao, X.S., Steinbrich, W. 1995. Intracranial arteries: prospective blinded comparative study of MR angiography and DSA in 50 patients. Radiology 195, 451–456.

Susac, J.O. 1994. Susac's syndrome: the triad of microangiopathy of the brain and retina with hearing loss in young women. Neurology 44, 591–593.

Trentham, D.E., Le, C.H. 1998. Relapsing polychondritis. Ann. Intern. Med. 129, 114–122.

Valanzzuela, R., Cooperrider, P.A. 1980. Relapsing polychondritis: immunomicroscopic findings in cartilage of ear biopsy specimens. Hum. Path. 11, 19–22.

Vollertsen, R.S., Conn, D.L, 1990. Vasculitis associated with rheumatoid arthritis. Rheum. Dis. Clin. North Am. 16 (2), 445–461.

Vollertsen, R.S., Mc Donald, T.J. 1986. Cogan's syndrome: 18 cases and a review of the literature. Mayo. Clin. Proc. 61, 344–361.

Vollmer, T.L., Guarnaccia, J., Harrington, W., Pacia, S.V., Petroff, O.A.C., 1993. Idiopathic granulomatous angiitis of the central nervous system; diagnostic challenges. Arch. Neurol. 50, pp. 925–930

Willis, J., Atack, E.A. 1984. Relapsing polychondritis with multifocal neurologic abnormalities. Can. J. Neurol. Sci. 11, 402–404.

Woolfenden, A.R., Tong, D.C., Marks, M.P., et al. 1998. Angiographically defined primary angiitis of the CNS. Is it really benign? Neurology 51, 183–188.

Zivkovic, S., Moore, P.M. 2000. Systemic and Central Nervous System Vasculitides. Curr. Treat. Options Neurol. 2, 459–472.

PART VI

Other Conditions with Neurologic Involvement

Handbook of Systemic Autoimmune Diseases, Volume 3
Neurologic Involvement in Systemic Autoimmune Diseases
D. Erkan and S.R. Levine, editors

CHAPTER 13

Neurosarcoidosis

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1. Introduction

Neurologic complications of sarcoidosis occur in approximately 5% of patients with sarcoidosis (Stern et al., 1985). Neurosarcoidosis is a diagnostic consideration in patients with known sarcoidosis who develop neurological symptoms and signs and in patients without documented sarcoidosis who present with a spectrum of neurological findings consistent with neurosarcoidosis (Krumholz and Stern, 1998). Approximately 50% of patients with neurosarcoidosis present with neurologic disease at the time sarcoidosis is first diagnosed. Three-quarters of patients develop their neurologic problems within two years of becoming ill with sarcoidosis. One-third of those with neurosarcoidosis has or develops more than one neurologic manifestation of their disease. Only rarely do patients have isolated neurosarcoidosis.

2. Prevalence

Sarcoidosis occurs with an approximate incidence of 11 per 100,000 population. (Krumholz and Stern, 1998; Hosoda et al., 2002). The prevalence of sarcoidosis is on the order of 60 per 100,000 population, although in certain groups the incidence and prevalence can be substantially greater. There is a wide range of reported figures which is influenced, in part, by data using surveillance radiographs as opposed to symptomatic disease.

3. Epidemiology

Sarcoidosis occurs throughout the world and can develop in any racial/ethnic population. (Hosoda et al., 2002) It most commonly presents in persons in their 20s or 30s, though individuals of any age can be afflicted. Although there are some indications that sarcoidosis develops most commonly in women, overall there seems to be no sex predilection. Women do seem to have a greater risk for neurological and eye involvement than men (Baughman et al., 2001). There is an increased incidence of sarcoidosis in United States blacks compared to whites. Familial clusters of sarcoidosis exist but as yet there is no defined genetic transmission. A study of familial risk for sarcoidosis among siblings revealed an odds ratio of 5.8 (95% confidence interval = 2.1–15.9) and in a familial multivariate model the adjusted familial relative risk was 4.7 (95% confidence interval = 2.3–9.7) (Rybicki et al., 2001).

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White patients have a higher familial risk (18.0) than African-Americans (2.8).

4. Etiology/Pathogenesis

Non-necrotizing granulomas, the hallmark of sarcoidosis, are composed of epithelioid macrophages, lymphocytes, monocytes, and fibroblasts (Gal et al., 2002). The fusion of epithelioid mononuclear cells leads to the formation of multinucleated Langhans'-type giant cells. Small central foci of necrosis can occur. The inflammation is often perivascular and there can be involvement in the outer aspect of the media and the adventitia. With time, fibrosis can develop as can thickening of the intima and media of blood vessels, leading to ischemic tissue injury.

Moller and Chen (2002) state that "the etiology of … sarcoidosis is linked to genetically determined enhanced Th1 immune responses to a limited number of microbial pathogens". Macrophages are thought to ingest antigenic material and antigenic remnants are displayed in association with class II MHC molecules. The T-cell receptor repertoire is restricted, consistent with an oligoclonal expression (Agostini et al., 2002). With cytokine and chemokine release there is an increase in lymphocyte–endothelium adhesion and an accumulation of Th1 cells, with a subsequent proliferation of Th1 cells. Sarcoidosis is characterized by a dominant Th1 response with expression, for instance, of interferons β and γ, interleukin (IL) 2, IL-6, IL-12, and IL-16. Other inflammatory cytokines, such as tumor necrosis factor-α (TNF), are expressed. Inhibition of apoptosis may lead to persistent inflammation. With time, a Th2 response can develop and lead to fibrosis.

The antigen inciting the inflammatory response remains unknown. Although *Mycobacterium* species, including mycobacterial proteins, have been implicated in the pathogenesis of sarcoidosis, evidence that these organisms are central to the disease remains to be definitively established (Moller and Chen, 2002). *Propionibacterium* species have also been implicated in the pathogenesis of sarcoidosis (Moller and Chen, 2002). There is little robust evidence for a noninfectious environmental or occupational exposure causing sarcoidosis.

5. Clinical manifestations

The neurologic manifestations of sarcoidosis and their approximate frequencies are outlined in Table 1. Many of the diverse presentations of neurosarcoidosis can be approached if they are considered to fit within one of these broad categories (Nowak et al., 2001).

Patients can be classified as having possible, probable, or definite neurosarcoidosis based on the certainty of the diagnosis of multisystem sarcoidosis, the pattern of neurological disease, and the response to therapy. The following is adapted from Zajicek et al. (1999):

Table 1
The clinical manifestations of neurosarcoidosis

Cranial neuropathy	50–75%
Facial palsy	(25–50%)
Meningeal disease	10–20%
Aseptic meningitis	
Mass	
Hydrocephalus	10%
Parenchymal disease	50%
Brain	
Endocrinopathy	(10–15%)
Mass lesion(s)	(5–10%)
Encephalopathy/vasculopathy	(5–10%)
Seizures	(5–10%)
Vegetative dysfunction	
Spinal canal	
Extramedullary or intramedullary disease	
Cauda equina syndrome	
Neuropathy	15%
Axonal neuropathy	
Mononeuropathy	
Mononeuropathy multiplex	
Sensorimotor	
Sensory	
Motor	
Demyelinating neuropathy	
Gullain-Barré syndrome	
Myopathy	15%
Nodule	
Polymyositis	
Atrophy	

Adapted from Stern, B.J. 1992. Neurosarcoidosis. Neurol. Chronicle. 2, and Stern, B.J. Schonfeld, S.H. Neurosarcoidosis. In: A.I. Arieff, R.C. Griggs (Eds.), Metabolic Brain Dysfunction in Systemic Disorders. Little, Brown, Boston, 1992, p. 289.

Possible: The clinical syndrome and neurodiagnostic evaluation are suggestive of neurosarcoidosis. Infection and malignancy have not been rigorously excluded or there is no pathologic confirmation of systemic sarcoidosis.

Probable: The clinical syndrome and neurodiagnostic evaluation are suggestive of neurosarcoidosis and alternate diagnoses have been excluded, especially infection and malignancy. There is pathologic evidence of systemic sarcoidosis.

Definite: (a) The clinical presentation is suggestive of neurosarcoidosis, other possible diagnoses are excluded, and there is the presence of supportive nervous system pathology or (b) The criteria for a 'probable' diagnosis are met and the patient has had a beneficial response to therapy for neurosarcoidosis over a one to two year observation period.

6. Diagnostic investigations

6.1. Radiological

The preferred imaging technique to evaluate central nervous system (CNS) sarcoidosis is magnetic resonance imaging (MRI) without and with contrast enhancement (Christoforidis et al., 1999). T1-weighted images accurately depict hydrocephalus and optic nerve, optic chiasm and spinal cord enlargement. With T2-weighted and FLAIR imaging, areas of increased signal intensity can be appreciated, especially in a periventricular distribution. Contrast administration can demonstrate leptomeningeal enhancement as well as parenchymal abnormalities. Spine MRI can visualize intramedullary disease, which appears as an enhancing fusiform enlargement, focal or diffuse enhancement, or atrophy. Enhancing nodules or thickened or matted nerve roots can be noted with images of the cauda equina.

6.2. Functional

Visual, auditory, or somatosensory evoked potentials can detect abnormalities in patients with optic nerve, eighth nerve, or spinal cord disease, respectively. Occasional patients with CNS sarcoidosis have evoked potential abnormalities without overt clinical disease in the anatomic pathways being studied. Furthermore, rarely, patients with sarcoidosis but no clinically evident CNS disease can have evoked potential abnormalities.

Nerve conduction studies can be of assistance in evaluating the possible presence of a neuropathy. However, there is nothing specific about the spectrum of findings to suggest the diagnosis of sarcoidosis. There can be decreased sensory or motor nerve conduction velocities. The amplitude of the motor or sensory nerve action potentials can be diminished. Localized conduction deficits at the carpal tunnel can be found. Electromyography can demonstrate denervation in appropriate muscles and help characterize patients as having a mononeuritis multiplex or symmetric polyneuropathy. Myopathic changes can be documented in patients with granulomatous myositis.

6.3. Biochemistry/serology/immunology

Clues to the presence of systemic sarcoidosis include an elevated angiotensin-converting enzyme, hypercalcemia, hypercalciuria, elevated immunoglobulins, and anergy. None of these findings are pathognomonic for sarcoidosis but in the proper setting can increase diagnostic suspicion for sarcoidosis. Furthermore, all of these systemic manifestations of sarcoidosis can be absent in the setting of isolated neurosarcoidosis.

Patients with CNS sarcoidosis can have abnormal CSF findings (Nowak et al., 2001). The CSF pressure can be elevated and analysis can reveal an increased total protein, hypoglycorrhachia, and a predominantly mononuclear pleocytosis. The IgG index can be elevated and oligoclonal bands detected. CSF angiotensin-converting enzyme can be elevated in patients with CNS sarcoidosis, although abnormalities are also seen in the presence of infection and malignancy. A normal CSF angiotensin-converting enzyme assay does not exclude the diagnosis of neurosarcoidosis and tracking CSF ACE levels is not particularly helpful in therapeutic decision-making. (Dale et al., 1999).

Currently, there are no cytokine markers or other immunological assays commonly employed for the diagnosis of sarcoidosis or neurosarcoidosis, or to

monitor the response to treatment. (Semenzato et al., 2002).

7. Differential diagnosis

Patients with known systemic sarcoidosis who develop neurologic disease consistent with sarcoidosis should be evaluated for the reasonable exclusion of other disease entities, particularly infection and neoplasia. The patient can then be treated for neurosarcoidosis. If the patient does not respond as expected, the diagnosis should be questioned and a more extensive evaluation pursued to consider other diagnoses.

If a patient without known sarcoidosis develops a clinical syndrome consistent with neurosarcoidosis, the diagnostic challenge can be considerable. Since corticosteroid therapy can mask signs of systemic sarcoidosis or other diseases, treatment should be postponed, if possible, while a search for systemic disease is initiated (Johns et al., 1999). An examination of the skin and lymph nodes may reveal abnormalities that can be biopsied. Sarcoidosis most frequently affects intrathoracic structures (87% of patients), followed by lymph node, skin, and ocular disease (15–28% of patients). If the patient has impaired smell or taste, nasal or olfactory nerve disease might be present. If dry eyes or mouth are noted, lacrimal, parotid, or salivary gland inflammation is possible.

Systemic sarcoidosis can often be demonstrated if a comprehensive approach is followed, using the following tests in a selective manner: serum angiotensin-converting enzyme, serum calcium, chest X-ray, thoracic CT scan, pulmonary function tests including diffusing capacity, ophthalmologic examination, endoscopic nasal examination, whole-body gallium scan, 24 h urinary calcium excretion, anergy screen, muscle MRI, and whole body fluorodeoxyglucose positron emission tomography imaging (FDG PET) (Zhuang and Alavi, 2002).

Patients with possible CNS disease should be questioned about symptoms relating to neuroendocrinologic or hypothalamic dysfunction, since problems in these areas are the most common parenchymal disorders found in CNS sarcoidosis. Inquiry about changes in menses, libido, and potency should be made as well as the presence of galactorrhea. Excessive thirst can be caused by resetting of the hypothalamic osmostat, diabetes insipidus, hypercalcemia, hypercalciuria, and corticosteroid-induced diabetes mellitus. Alterations in body temperature, sleep, and appetite can develop. Patients with suspected CNS sarcoidosis and symptoms other than transient cranial nerve palsies or aseptic meningitis, should undergo neuroendocrinologic evaluation including tests for thyroid function (for consideration of hypothalamic hypothyroidism), prolactin, testosterone or estradiol, follicle-stimulating hormone, luteinizing hormone, and cortisol.

Selected differential diagnostic considerations include: multiple sclerosis, Sjögren syndrome, systemic lupus erythematosus, neurosyphilis, neuroborreliosis, human immunodeficiency virus infection, Behçet's disease, Vogt-Koyanagi-Harada disease, toxoplasmosis, brucellosis, Whipple's disease, lymphoma, germ cell tumors, craniopharyngioma, isolated angiitis of the CNS, primary CNS neoplasia (anaplastic astrocytoma, glioblastoma multiforme), lymphocytic hypophysitis, pachymeningitis, and low CSF pressure/volume meningeal enhancement.

Patients without known systemic sarcoidosis who develop a brain or spinal cord mass are usually biopsied for definitive diagnosis. If pathologic examination suggests noncaseating granulomas, appropriate cultures should be obtained. If a patient with known sarcoidosis develops a CNS mass, an empiric trial of corticosteroid therapy is appropriate, especially if infection and malignancy can be reasonably excluded by CSF examination. If the patient does not respond to corticosteroid therapy, a biopsy should be pursued. In either of these situations, if a mass progressively enlarges in spite of corticosteroid therapy, surgical exploration should be strongly considered to evaluate the possibility of a malignancy. Peripheral nerve and muscle samples can be obtained for pathological examination, thereby increasing diagnostic certainty (Prayson, 1999; Said et al., 2002; Berger et al., 2002). A skin biopsy can document disease of peripheral nerve endings in patients with neuropathic symptoms and otherwise unrevealing nerve conduction and electromyographic studies (Hoitsma et al., 2002).

8. Treatment

There have been no rigorous studies to define the optimal treatment for neurosarcoidosis. Recommendations generally stem from case series and expert opinion. Most authorities recommend corticosteroid therapy as first-line therapy for patients, if there are no contraindications (Johns et al., 1999). Increasingly, adjunct therapy with other immunosuppressive and immunomodulating agents is being utilitzed (Baughman, 2002). Therapeutic decisions should be guided by the patient's clinical course, the expected natural history of the patient's clinical manifestations, and adverse treatment effects.

Approximately two-thirds of patients have a monophasic neurologic illness; the remainder have a chronically progressive or remitting-relapsing course. Patients with a monophasic illness typically have an isolated cranial neuropathy, most often involving the facial nerve, or an episode of aseptic meningitis. Patients with a chronic course usually have CNS disease (parenchymal abnormalities, hydrocephalus, and multiple cranial neuropathies, especially involving cranial nerves II and VIII) (Ferriby et al., 2001), peripheral neuropathy, and myopathy (Luke et al., 1987). Whether treatment changes the natural history of the disease is not proven, though in the short term symptoms can often be alleviated with therapy. A goal of treatment is to diminish the irreversible fibrosis that can develop as well as the tissue ischemia that might result from perivascular inflammation. With time, the inflammatory process can become quiescent, allowing immunosuppressive therapy to be decreased or withdrawn, at least temporarily.

Peripheral facial nerve palsy usually responds to 2 weeks of prednisone therapy. The first week's prednisone dose is usually 0.5–1.0 mg/day (or 40 to 60 mg/day), followed by a taper over the second week. This approach can also be used as initial therapy for other cranial neuropathies and aseptic meningitis. However, even prolonged, aggressive therapy, as discussed below, can fail to prevent irreversible optic and eighth nerve dysfunction. Patients with a peripheral neuropathy or myopathy can respond to a short course of corticosteroid therapy. However, prolonged treatment is often necessary.

Asymptomatic ventricular enlargement probably does not require treatment. Mild, symptomatic hydrocephalus can respond to corticosteroid therapy, although prolonged treatment is often required. Life-threatening hydrocephalus or corticosteroid-resistant hydrocephalus require ventricular shunting. Unfortunately, patients can evolve from mild hydrocephalus to severe life-threatening disease quite rapidly (Scott, 2000). Patients and caregivers should be educated as to when to seek emergent care. Shunt placement is not without risk in these patients, which is why 'prophylactic' shunting is not typically performed. Shunt obstruction from the inflamed CSF and ependyma is common and placement of a foreign object in the CNS of an immunosuppressed host predisposes to infection.

Corticosteroid therapy can improve the status of patients with a diffuse encephalopathy/vasculopathy or a CNS mass lesion. Only rarely does immunosuppressive treatment improve neuroendocrine dysfunction or vegetative symptoms. Seizures occur most commonly in patients with parenchymal disease or hydrocephalus. Control of seizures is usually not difficult if the underlying inflammatory process can be controlled.

Corticosteroid treatment for CNS parenchymal disease and other severe neurologic manifestations of sarcoidosis usually starts with prednisone 1.0 mg/kg/day. These patients often require prolonged therapy and prednisone should be tapered very slowly. The patient might be observed on high dose prednisone for 2–4 weeks to determine the clinical response. The prednisone dose can then be tapered by 5 mg decrements every 2 weeks as the clinical course is monitored. The disease tends to exacerbate at a prednisone dose approximating 10 mg daily (or 0.1 mg/kg/day). Patients often exhibit an individual dosage level below which worsening develops. If a dose of prednisone of 10 mg daily (or 0.1 mg/kg/day) can be achieved, the patient should be evaluated for evidence of subclinical worsening of disease. For patients with CNS disease, an enhanced MRI scan is useful (Dumas et al., 2000). Enhancement suggests that the disease is active and further decreases in corticosteroid dose may lead to a clinical exacerbation. On the other hand, persistent CSF abnormalities are usually not an indication for continuing high-dose corticosteroid therapy, since patients can

remain quite functional in spite of an abnormal CSF. Efforts to 'normalize' the CSF often require intense immunosuppression, with its attendant adverse effects. If the disease appears quiescent at a low prednisone dose, the daily prednisone dose can be further tapered by 1 mg every 2–4 weeks. If a patient has a clinical relapse, the dose of prednisone can be doubled (unless the dose is very modest, in which case prednisone 10–20 mg daily can be prescribed). The patient should be observed for approximately 4 weeks before another taper is begun. Patients may require multiple cycles of higher and lower corticosteroid doses. This effort is usually warranted since the disease can become quiescent and without attempts at withdrawing medication, patients may be needlessly exposed to the harmful long-term side effects of corticosteroids.

A short course of methylprednisolone 20 mg/kg/day intravenously for 3 days, followed by high-dose prednisone for 2–4 weeks, is occasionally warranted. Patients with severe acute neurologic compromise can improve on this regimen. Another potential approach to treating severe disease is the use of infliximab, a monoclonal antibody directed at tumor necrosis factor (Pettersen et al., 2002; Katz et al., 2003).

If it is unclear whether a patient might benefit from more intense immunosuppression, intravenous methylprednisolone or infliximab can be used to judge a response over a relatively short time. One or two target signs or symptoms can be used to assess the clinical response; for instance, the results of psychometric tests or a timed walk. One caveat should be noted: if the patient has a CNS mass lesion unresponsive to high-dose intravenous corticosteroids, surgical resection is probably appropriate in life-threatening situations.

In this author's experience, daily dosing of corticosteroids is usually superior to alternate day therapy in patients with neurosarcoidosis. However, if a patient is doing well on a modest dose of daily prednisone, an attempt can be made to wean the patient slowly onto alternate day therapy.

Alternate or adjunct therapies are occasionally considered for neurosarcoidosis. Experience in this area is limited and firm recommendations are not available. Indications for the use of alternate treatments include the need to avoid corticosteroids as initial therapy, serious adverse corticosteroid effects, and disease activity in spite of aggressive corticosteroid therapy (Agbogu et al., 1995).

Immunosuppressive medications to treat sarcoidosis include azathioprine, methotrexate (Maust et al., 2003), cyclophosphamide, mycophenolate mofetil (Kouba et al., 2003), cyclosporine, and chlorambucil. None of these agents have been studied in a placebo-controlled manner, and none has been rigorously compared with the others. None-the-less, anecdotal experience suggests that these drugs, especially when used in combination with corticosteroid therapy, can provide therapeutic benefit. Patients can incrementally improve beyond that experienced with corticosteroid monotherapy or the corticosteroid dose can be decreased with the addition of an adjunct therapy. Rarely is it possible to withdraw corticosteroid treatment completely; patients tend to do best on a modest dose of corticosteroid combined with an alternate agent.

One way of choosing among the various adjunct agents is to note the organ systems compromised by sarcoidosis and avoid drugs that have notable adverse effects directed at the already compromised organ. For instance, azathioprine, methotrexate, and chlorambucil are associated with liver toxicity, cyclosporine can cause renal impairment, and methotrexate, cyclophosphamide, and chlorambucil can cause pulmonary fibrosis. After the dose of the adjunct agent has been brought to the desired level, the corticosteroid dose can be slowly lowered as the clinical status is monitored. It can take several weeks or months to demonstrate the benefit of the adjunct medication. Monitoring for drug toxicities should be diligently pursued.

Immunomodulatory agents can also be used to treat sarcoidosis and neurosarcoidosis. Experience with these drugs is relatively limited but these agents can be used in conjunction with corticosteroids or corticosteroids and immunosuppressive agents. Hydroxychloroquine, pentoxyfillin, thalidomide (Meierhofer et al., 2001; Baughman, 2002), and infliximab are reported in case reports and small case series to be beneficial. The later three drugs have activity against tumor necrosis factor and thalidomide antagonizes a variety of cytokines and other inflammatory modulators.

If a patient with CNS disease fails or cannot tolerate alternate agents, consideration should be

given to radiotherapy (Kang et al., 1999). Patients may stabilize, at least in the short term. Ultimately, corticosteriods and alternate agents often need to be continued, at least in modest doses.

Patients require close attention to their general medical condition. Potential adverse effects of treatment should be sought. Prescribed exercise and dietary program are often highly beneficial. Rehabilitation services should be utilized as appropriate. Depression is not uncommon and treatment can be helpful.

Therapy of endocrinologic disturbances is important. In particular, hypothyroidism and hypogonadism should be treated. Since patients are often on protracted, low-dose corticosteroid regimens, supplemental corticosteroids are appropriate during surgery or intercurrent illness.

Men and women are at risk for osteoporosis. Screening should be done on a regular basis. Treatment of osteoporosis is often a challenge since sarcoidosis itself can cause hypercalcemia and hypercalciuria. Since the management of osteoporosis is an evolving science, it is best to work closely with an expert in this area.

Patients with refractory neurosarcoidosis not only are prone to the primary effects of the inflammatory process but are also at risk for the long-term complications of treatment. If a patient is not doing well, the diagnosis of sarcoidosis should be questioned, alternate causes investigated, and a search for intercurrent complications begun. Some potential complications include cryptococcal and tuberculous meningitis, toxoplasmosis, progressive multifocal leukoencephalopathy, *Listeria monocytogenes* infection, spinal epidural lipomatosis, corticosteroid-induced myopathy, lymphoma, and inclusion body myositis.

Key points

- The clinical manifestations of sarcoidosis include cranial neuropathies, meningeal disease, hydrocephalus, parenchymal brain and spinal cord disease, neuropathy, and myopathy.
- Key diagnostic tests for CNS disease include MRI and CSF analysis. Nerve conduction studies and electromyography are important for the assessment of nerve and muscle disease. The need for biopsy of neural tissue or muscle should be determined on an individual basis.
- Corticosteroids are the mainstay of therapy for neurosarcoidosis.
- Adjunct or alternative immunosuppressive or immunomodulatory drugs for the treatment of neurosarcoidosis include azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil, cyclosporine, chlorambucil, hydroxychloroquine, pentoxyfillin, thalidomide, and infliximab. Radiation therapy is occasionally used for refractory CNS disease.
- Attention to the patient's general medical care can contribute greatly to the patient's well-being.

References

Agbogu, B.N., Stern, B.J., Sewell, C., Yang, G. 1995. Therapeutic considerations in patients with refractory neurosarcoidosis. Arch. Neurol. 52, 875.

Agostini, C., Meneghin, A., Semenzato, G. 2002. T-Lymphocytes and cytokines in sarcoidosis. Curr. Opin. Pulm. Med. 8, 435.

Berger, C., Sommer, C., Meinck, H.M. 2002. Isolated sarcoid myopathy. Muscle Nerve 26, 553.

Baughman, R.P. 2002. Therapeutic options for sarcoidosis: new and old. Curr. Opin. Pulm. Med. 8, 464.
This is a review of the evolving management strategies for sarcoidosis, and, by extension, neurosarcoidosis.

Baughman, R.P., Teirstein, A.S., Judson, M.A., Rossman, M.D., Yeager, H., Bresnitz, E.A., DePalo, L., Hunninghake, G., Iannuzzi, M.C., Johns, C.J., McLennan, G., Moller, D.R., Newman, L.S., Rabin, D.L., Rose, C., Rybicki, B., Weinberger, S.E., Terrin, M.L., Knatterud, G.L., Cherniak, R. 2001. A case control etiologic study of sarcoidosis (ACCESS) research group. Clinical characteristics of patients in a case control study of sarcoidosis. Am. J. Respir. Crit. Care Med. 164, 1885.

Baughman, R.P., Judson, M.A., Teirstein, A.S., Moller, D.R., Lower, E.E. 2002. Thalidomide for chronic sarcoidosis. Chest 122, 227.

Christoforidis, G.A., Spickler, E.M., Recio, M.V., Mehta, B.M. 1999. MR of CNS sarcoidosis: Correlation of imaging features to clinical symptoms and response to treatment. Am. J. Neuroradiol. 20, 655.

Dale, J.C., O'Brien, J.F. 1999. Determination of angiotensin-converting enzyme levels in cerebrospinal fluid is not a useful

test for the diagnosis of neurosarcoidosis. Mayo Clin. Proc. 74, 535.

Dumas, J.L., Valeyre, D., Chapelon-Abric, C., Belin, C., Piette, J.C., Tandjaoui-Lambiotte, H., Brauner, M., Goldlust, D. 2000. Central nervous system sarcoidosis: follow-up at MR imaging during steroid therapy. Radiology 214, 411.

Ferriby, D., de Seze, J., Stojkovic, T., Hachulla, E., Wallaert, B., Destee, A., Hatron, P.Y., Vermersch, P. 2001. Long-term follow-up of neurosarcoidosis. Neurology 57, 927.
This is a case series describing the clinical course of patients with neurosarcoidosis.

Gal, A.A., Koss, M.N. 2002. The pathology of sarcoidosis. Curr. Opin. Pulm. Med. 8, 445.

Hoitsma, E., Marziniak, M., Faber, C.G., Reulen, J.P.H., Sommer, C., De Baets, M., Drent, M. 2002. Small fibre neuropathy in sarcoidosis. Lancet 359, 2085.
This is a case series highlighting a previously under-recognized clinical manifestation of neurosarcodosis.

Hosoda, Y., Sasagawa, S., Yasuda, N. 2002. Epidemiology of sarcoidosis: new frontiers to explore. Curr. Opin. Pulm. Med. 8, 424.

Johns, C.J., Michele, T.M. 1999. The clinical management of sarcoidosis. A 50-year experience at the Johns Hopkins Hospital. Medicine 78, 65.

Kang, S., Suh, J.H. 1999. Radiation therapy for neurosarcoidosis: report of three cases from a single institution. Radiat. Oncol. Invest. 7, 309.

Katz, J.M., Bruno, M.K., Winterkorn, J.M.S., Nealon, N. 2003. The pathogenesis and treatment of optic disc swelling in neurosarcoidosis: A unique therapeutic response to infliximab. Neurology 60, 2003.
This article highlights a new approach to the treatment of refractory neurosarcoidosis with the tumor necrosis factor alpha antagonist infliximab.

Kouba, D.J., Mimouni, D., Rencic, A., Nousari, H.C. 2003. Mycophenolate mofetil may serve as a steroid-sparing agent for sarcoidosis. Br. J. Dermatol. 148, 147.
This article highlights the use of mycophenolate mofetil for the treatment of sarcoidosis. The author of this chapter has found this drug to be beneficial in neurosarcoidosis.

Krumholz, A., Stern, B.J. 1998. Neurological manifestations of sarcoidosis. In: P.J. Vinkin, G.W. Bruyn (Eds.), Handbook of Clinical Neurology. Systemic Diseases (Part III), Elsevier, Amsterdam, p. 463.

Luke, R.A., Stern, B.J., Krumholz, A., Johns, C.J. 1987. Neurosarcoidosis: the long-term clinical course. Neurology 37, 461.

Maust, H.A., Foroozan, R., Sergott, R.C., Niazi, S., Weibel, S., Savino, P.J. 2003. Use of methotrexate in sarcoid-associated optic neuropathy. Ophthalmology 110, 559.

Meierhofer, C., Dunzendorfer, S., Wiedermann, C.J. 2001. Theoretical basis for the activity of thalidomide. Biodrugs 15, 681.

Moller, D.R., Chen, E.S. 2002. What causes sarcoidosis? Curr. Opin. Pulm. Med. 8, 429.
This article is an excellent review of the pathogenesis of sarcoidosis.

Nowak, D.A., Widenka, D.C. 2001. Neurosarcoidosis: a review of its intracranial manifestation. J. Neurol. 248, 363.
This is a review article of the clinical features of intracranial neurosarcoidosis.

Pettersen, J.A., Zochodne, D.W., Bell, R.B., Martin, L., Hill, M.D. 2002. Refractory neurosarcoidosis responding to infliximab. Neurology 59, 1660.

Prayson, R.A. 1999. Granulomatous myositis. Clinicopathologic study of 12 cases. Am. J. Clin. Pathol. 112, 63.

Rybicki, B.A., Iannuzzi, M.C., Frederick, M.M., Thompson, B.W., Rossman, M.D., Bresnitz, E.A., Terrin, M.L., Moller, D.R., Barnard, J., Baughman, R.P., DePalo, L., Hunninghake, G., Johns, C., Judson, M.A., Knatterud, G.L., McLennan, G., Newman, L.S., Rabin, D.L., Rose, C., Teirstein, A.S., Weinberger, S.E., Yeager, H., Chemiack, R. 2001. The ACCESS Research Group, 2001. Familial aggregation of sarcoidosis. A case-control etiologic study of sarcoidosis (ACCESS). Am. J. Respir. Crit. Care Med. 164, 2085.

Said, G., Lacroix, C., Plante-Bordeneuve, V., Le Page, L., Pico, F., Presles, O., Senant, J., Remy, P., Rondepierre, P., Mallecourt, J. 2002. Nerve granulomas and vasculitis in sarcoid peripheral neuropathy: a clinicopathological study of 11 patients. Brain 125, 264.

Scott, T.F. 2000. Cerebral herniation after lumbar puncture in sarcoid meningitis. Clin. Neurol. Neurosurg. 102, 26.

Semenzato, G., Bortoli, M., Agostini, C. 2002. Applied clinical immunology in sarcoidosis. Curr. Opin. Pulm. Med. 8, 441.

Stern, B.J., Krumholz, A., Johns, C., Scott, P., Nissim, J. 1985. Sarcoidosis and its neurological manifestations. Arch. Neurol. 42, 909.

Zajicek, J.P., Scolding, N.J., Foster, O., Roveris, M., Evanson, J., Moseley, I.F., Scadding, J.W., Thompson, E.J., Chamoun, V., Miller, D.H., McDonald, W.I., Mitchell, D. 1999. Central nervous system sarcoidosis—diagnosis and management. Quart. J. Med. 92, 103.
This article is a very good synthesis of the approach to the patient with CNS sarcoidosis.

Zhuang, H., Alavi, A. 2002. 18-fluorodeoxyglucose positron emission tomographic imaging in the detection and monitoring of infection and inflammation. Semin. Nucl. Med. 32, 47.
This article highlights the potential value of FDG PET for the detection of otherwise occult sites of inflammation. FDG PET can provide a target for biopsy to confirm a diagnosis of sarcoidosis, or provide an alternate diagnosis.

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CHAPTER 14

Nervous System Involvement in Sjogren's Syndrome

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1. Introduction

Sjogren's syndrome (SS) is a chronic, slowly progressive autoimmune disease characterized by lymphocytic infiltration and destruction of the exocrine glands. The salivary and lachrymal glands are mainly involved leading to dry mouth and eyes. The disease affects 2–3% of the adult population with a female preponderance. Two types of SS are recognized, primary and secondary. In primary SS (pSS) the disease exists alone. Secondary SS exists in 30% of patients with other autoimmune rheumatic disorders such as rheumatoid arthritis and systemic lupus erythematosus (SLE). One third of SS patients have systemic disease. Virtually every organ or system of the body can be affected. This includes the lung, the gastrointestinal tract, the liver, the kidneys and the central and peripheral nervous system (PNS) (Moutsopoulos, 2001).

PNS involvement is well documented, affecting approximately one fourth of patients with SS (Andonopoulos et al., 1990). In contrast, the prevalence of central nervous system (CNS) involvement is a matter of controversy (Moutsopoulos et al., 1993). Some investigators consider CNS disease as being almost non-existent, whilst other research groups report it as being quite common. Differences in the diagnostic criteria used and in the selection of patient populations are possible explanations for the discrepancy noted (Ioannidis and Moutsopoulos, 1999).

2. Involvement of the peripheral nervous system

2.1. Prevalence

Henrik Sjogren (1935), in his monograph published in 1935, was the first to describe a patient with peripheral neuropathy associated with SS. Table 1 summarizes the studies, published since 1990, examining the prevalence of PNS disease in pSS. If we leave out the study by Lafitte et al. (2001) whereby possible referral bias in the neurology group of patients may have resulted in the high prevalence of PNS disease reported, then we can calculate an average reported prevalence of PNS disease of approximately 25%. This is in agreement with previous studies of pSS patients (Alexander, 1993).

2.2. Epidemiology

Skopouli et al. (2000) studied the evolution of the clinical picture in a prospective cohort of 261 patients with pSS. The development of PNS disease was found to be a late event, not commonly found at the time of development of the sicca symptoms. This was in contrast to other systemic manifestations of SS, such as pulmonary involvement, interstitial nephritis and

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Table 1
Prevalence of PNS disease in SS

References	No of SS patients studied	% with PNS disease	Nature of PNS disease
Barendregt et al. (2001)	39	23	Sensory polyneuropathy
Lafitte et al. (2001)	25[a]	16	Sensory neuronopathy, carpal tunnel syndrome, trigeminal neuropathy
	11[b]	91	Sensorimotor or sensory polyneuropathy, polyradiculoneuropathy
Garcia-Carrasco et al. (1999)	31	16	Peripheral neuropathy
Govoni et al. (1999)	87	13.8	Sensory or sensory-motor polyneuropathy
Tumiati et al. (1997)	30	46	Sensorineural hearing loss
Tajima et al. (1997)	21	50	Trigeminal neuropathy
Hebbar et al. (1995)	115	5	Sensorimotor polyneuropathy, mononeuritis multiplex
Gemignani et al. (1994)	46	21.7	Sensory polyneuropathy, sensory neuronopathy, autonomic neuropathy, mononeuritis multiplex
Mauch et al. (1994)	20	35	Sensory neuropathy, trigeminal neuropathy, anisocoria
Moll et al. (1993)	45	40	Polyneuropathy, sensory neuronopathy, carpal tunnel syndrome
Hietaharju et al. (1993)	48	14.5	Polyneuropathy, entrapment neuropathy, radiculopathy
Andonopoulos et al. (1990)	63	26	Peripheral sensorimotor/sensory neuropathy, trigeminal, latent motor neuropathy
Hietaharju et al. (1990)	48	27	Polyneuropathy, entrapment neuropathy, cranial neuropathy

[a] Internal medicine group.
[b] Neurology group.

liver disease, which appeared at the same time as the sicca symptoms. It is of interest that glomerulonephritis, another systemic manifestation of SS that occurs late in the disease, shares a common pathogenic mechanism with PNS disease. In both diseases an immune complex mediated small vessel vasculitis has been described (Mellgren et al., 1989; Inoue et al., 1991). This may explain the similarity in the epidemiology between the two diseases.

2.3. Etiology/Pathogenesis

Mellgren et al. (1989) performed sural nerve biopsies in 11 patients with peripheral neuropathy (8 patients with sensorimotor polyneuropathy and 3 patients with sensory neuropathy). They found evidence of vascular or perivascular inflammation of small epineurial arterioles and venules in all 11 specimens. In two nerves the findings were diagnostic of necrotizing vasculitis. In six others the pathologic findings were suggestive but not diagnostic of necrotizing vasculitis. They also found evidence of axonal degeneration in 32% of patients. Grant et al. (1997) found evidence of frank vasculitic neuropathy in 3% patients with peripheral neuropathy studied but non-specific epineural inflammation was present in 70% of nerve biopsies. Furthermore, Molina et al. (1985) studied the clinical features of 50 pSS patients with evidence of peripheral vasculitis.

Cryoglobulins may be implicated in the mechanism of vasculitis. In a study by Hebbar et al. (1995) 83% of pSS patients with peripheral neuropathy had evidence of a cryoglobulinaemia. In a study of 5 patients with peripheral neuropathy confirmed by neurophysiological studies, 2 patients were found to have antibodies against peripheral nerve myelin (Vrethem et al., 1990). Furthermore, Inoue et al. (1991) reported two patients with pSS and peripheral neuropathy who had increased levels of anti-endothelial cell antibodies in their sera. Immunofluorescence staining showed that deposits of immunoglobulin and C3 were present in the vasa vasorum of both patients and histological examination revealed

damage to the endothelial cells in the same vessels. High levels of circulating immune complexes have also been described in a case of SS with mononeuritis (Tanaka et al., 1989). These findings suggest that endothelial cell injury from the presence of immune complexes or endothelial cell antibodies may be the mechanism of vasculitis in PNS disease in SS.

The pathogenesis of sensory neuronopathy has been well delineated. It is caused by a lymphocytic infiltration of the dorsal root ganglia (ganglionitis) (Font et al., 1990; Malinow et al., 1986). The neuronopathy preceded the diagnosis of SS in 4 out of 5 patients with this disorder. Griffin et al. (1990) studied the pathogenesis of sensory neuronopathy associated with autonomic neuropathy in 13 patients with SS. Examination of the dorsal roots and of the ganglia in 3 patients showed evidence of T cell lymphocytic infiltration, whereas half of patients had a perivascular mononuclear infiltrate of the cutaneous nerves without necrotizing vasculitis. A localized ganglionitis is also implicated in trigeminal neuropathy associated with SS (Alexander, 1993).

2.4. Clinical manifestations

Table 2 summarizes the spectrum of PNS disease. The following types of PNS involvement in SS are recognized:

2.4.1. Distal sensory/sensorimotor neuropathy

A distal sensory neuropathy is the most common manifestation of PNS disease (Lafitte, 2001; Alexander, 1993; Grant et al., 1997). It presents with anaesthesia or paresthesia affecting the lower more that the upper limbs in a symmetrical fashion.

Table 2
Spectrum of PNS disease in SS

Distal sensory/sensorimotor polyneuropathy
Sensory neuronopathy
Cranial neuropathy
Entrapment neuropathy
Mononeuritis multiplex
Autonomic neuropathy
Small fiber sensory neuropathy

It is slow to progress and the symptoms are mild and non-disabling. Clinical examination reveals a glove-stocking sensory neuropathy and ankle reflexes are usually absent (Van Dijk and Wokke, 1998; Alexander, 1993). There also exists a mixed sensorimotor neuropathy, which is less common and has a sensory predominance. Both these neuropathies are axonal neuropathies.

2.4.2. Sensory neuronopathy

This type of neuropathy is not common. It is a pure sensory neuropathy characterized by diffuse sensory loss involving the extremities as well as the trunk (Van Dijk and Wokke, 1998; Alexander, 1993). It may be asymmetrical or patchy. Patients may present with sensory ataxia or pseudoathetosis. Clinical examination reveals loss of vibration and joint position sense with preservation of pain and temperature sensation and loss of reflexes. There is a wide variability in the severity and rapidity of progression of sensory neuronopathy and approximately 40% of SS patients improve spontaneously. It is caused by a dorsal root ganglionitis (see immunopathogenesis).

2.4.3. Cranial neuropathies

The trigeminal nerve is the most commonly involved cranial nerve in SS (Tajima et al., 1997). It presents with unilateral or bilateral numbness or paraesthesia in the distribution of the second and/ or third division of the trigeminal nerve. Pain may be present but it is not usually severe. Motor function is normal. Trigeminal neuropathy may be caused by an isolated ganglionitis affecting the Gausserian ganglion (see immunopathogenesis). It can be the first clinical manifestation of SS (Hull et al., 1984). Other cranial nerve palsies have also been described including those of facial, abducent and trochear nerves (Moll et al., 1993; Chu et al., 2000; Matsukawa et al., 1995). Optic neuropathy is of particular importance in the context of a neurological syndrome resembling multiple sclerosis (MS) (see CNS involvement).

2.4.4. Entrapment neuropathies

Carpal tunnel syndrome is a very common PNS manifestation of SS (Alexander, 1993; Moll et al., 1993; Lafitte et al., 2001). It may occur in the setting

of synovitis or hypothyroidism associated with SS or it may occur in the absence of any precipitating factor.

2.4.5. Mononeuritis muliplex

Mononeuritis multiplex is often of acute onset. Patients present with severe neuropathic pain and with progressive weakness and sensory loss (Van Dijk and Wokke, 1998). The underlying pathology is a vasculitis affecting one ore more isolated nerves (see immunopathogenesis).

2.4.6. Autonomic neuropathy

The prevalence of autonomic neuropathy is not clear. Nimela et al. (2003) did not find any evidence of autonomic dysfunction in 30 patients with pSS compared with healthy controls. Similarly, Barendregt et al. (2002) did not find evidence of autonomic involvement in 43 patients with pSS. However, Mandl et al. (2001) reported evidence of both sympathetic and parasympathetic impairment in 30 patients with pSS tested. Furthermore, Wright et al. (1999) tested pSS patients with peripheral neuropathy and found that 87% had evidence of autonomic dysfunction. Griffin et al. (1990) studied 13 patients with sensory neuronopathy who also had symptoms and signs of autonomic neuropathy. Some patients had severe autonomic dysfunction with dilated pupils, tachycardia, and orthostatic hypotension. These controversial findings may be partly due to patient selection bias or to the fact that different tests were used for assessing autonomic dysfunction by the different investigators.

2.4.7. Small fiber neuropathy

Small fiber neuropathies typically present with painful paraesthesia and on clinical examination there is distal loss of pain and temperature perception. Nerve conduction studies are normal since large fiber function is preserved (Van Dijk and Wokke, 1998).

2.5. Diagnostic investigations

2.5.1. Radiological

2.5.1.1. Magnetic resonance imaging (MRI).

MRI studies seem to be useful in the evaluation of PNS disease in SS particularly when symptoms and signs suggestive of sensory neuronopathy are present. In the study of Mori et al. (2001) 12 out of 14 patients with the diagnosis of sensory neuronopathy in the context of SS had increased signal by T2 weighted MRI in the dorsal columns of spinal cord. The extent of neuronal involvement as illustrated by MRI imaging, reflects the severity of this kind of neuropathy.

2.5.2. Functional

2.5.2.1. Electrophysiological studies.

Nerve conduction studies is the investigation of choice in the evaluation of peripheral neuropathy in patients with SS. Depending on the type of fibers involved, motor or sensory, absent motor or sensory response is noted. Decreased, mainly sensory, amplitude is an unequivocal finding. Latencies are usually within normal limits (Alexander, 1993; Mellgren et al., 1989). Hence, in general terms axonal degeneration predominates over demyelination in this group of patients.

In pure sensory neuronopathy a characteristic electrophysiologic pattern is noted consisting of absent or decreased sensory potentials, with motor nerve conduction and F response well preserved. Electromyographic studies are also within normal limits (Alexander, 1993). In small fiber neuropathies, conventional conduction studies are normal since large fibers remain intact. In these cases, quantitative thermal sensory threshold testing and qualitative and quantitative evaluation of skin sweating are adjunctive helpful tests in evaluating small fiber function (Denislic et al., 1994).

2.5.3. Biochemistry/serology/immunology

In the evaluation of peripheral neuropathy in the context of SS, a large number of other treatable disorders should be taken into account and carefully excluded. Thus, a complete blood count, blood glucose, liver and kidney function tests, serum electrophoresis, thyroid function tests, vitamin B12/folate levels, as well as Human Immunodeficiency Virus (HIV) serology should be performed in all patients presenting with symptoms and/or signs of peripheral neuropathy.

Cryoglobulins were detected in 25% of patients and, along with complement levels, should be carefully evaluated in the presence of peripheral neuropathy, since their presence, especially of mixed

monoclonal type, could connote the presence of an underlying lymphoma (Skopouli et al., 2000). If cryoglobulins are present, hepatitis screen should also be performed. Finally, an association was found between anti-Ro/SSA antibodies and peripheral vasculitis (Alexander, 1993).

2.5.4. Nerve biopsy

Sural nerve biopsy, although generally not recommended in clinical practice for diagnostic purposes, can provide useful clues for the pathogenesis of PNS involvement in SS. The main histopathological finding detected is vascular or perivascular inflammation of small epineurial vessels (Mellgren et al., 1989).

2.6. Differential diagnosis

Certain issues should be taken into account, on approaching a patient with SS who presents with peripheral neuropathy. The pattern of neuropathy, which predominates, along with a good clinical history determines the list of differential diagnoses that should be born in mind.

In the presence of sensorimotor/sensory neuropathies, metabolic (diabetes, vitamin B12/folate deficiency, hypothyroidism, renal failure), paraproteinemias, lymphomas, infectious, paraneoplastic, hereditary and toxic causes should be excluded. When motor involvement predominates, lymphoma, porphyria, lead intoxication and motor neuron disease should be considered.

The main differential diagnosis of purely sensory neuronopathy includes drug-induced (ethanol, metronidazole, pyridoxine, cisplatin, thalidomide), hereditary, amyloidosis, HIV and leprosy infection, metabolic (Vitamin E deficiency) and paraneoplastic (anti-Hu/ANNA-1 syndrome), associated with small cell lung cancer.

Differential diagnosis of chronic cases of autonomic dysfunction, manifested as labile blood pressure, orthostatic intolerance, erectile dysfunction, gastroparesis, syncope or bladder dysfunction includes diabetes mellitus, HIV infection, amyloidosis, or paraneoplastic syndromes. In acute cases of autonomic dysfunction, Guillain Barre syndrome is on the top of the list of differential diagnosis. When mononeuropathies occur metabolic causes (amyloidosis, diabetes, hypothyroidism), pregnancy and pressure palsies should be considered. Finally, painful neuropathies implicating involvement of small fibers, should be differentiated by inflammatory, hereditary and metabolic causes such as diabetes and amyloidosis (Wein et al., 2002).

2.7. Treatment

The type of peripheral nerve disease that occurs in patients with SS determines the therapeutic approach, which should be followed. In particular, in cases of distal sensory/sensorimotor neuropathy, the most common form of PNS disease in SS patients, symptoms are generally mild and not disabling and, therefore, no treatment is required. When cryoglobulinemia is found to be the underlying cause of the peripheral neuropathy, a more aggressive treatment, with intravenous and oral corticosteroids and plasma exchange, is used (Hebbar et al, 1995). In contrast, when a pure sensory neuronopathy occurs, intervention with immunosuppressive treatment might be helpful despite the fact that in 40% of patients a spontaneous remission is noted (Alexander, 1993). Anecdotal reports suggest a beneficial role of plasmapheresis, D-Penicillamine, intravenous gamma globulin (IVIG) and anti-TNFα in the management of this type of neuropathy (Chen et al., 2001; Asahina et al., 1998; Molina et al., 1996; Takahashi et al., 2003; Caroyer et al., 2002).

There is paucity of data available for the effective treatment of cranial neuropathy. Steroid use may be of some therapeutic value.

Management of entrapment neuropathies includes conservative measures such as splints, physical therapy, salicylates and non-steroidal anti-inflammatory drugs. In resistant cases corticosteroid therapy or surgical intervention may be of considerable help (Alexander, 1993).

Mononeuritis multiplex, although relatively uncommon, can lead to severe disability due to motor impairment. Although data are scarce, the use of steroids and cytotoxic drugs, such as cyclophosphamide, may have a therapeutic role.

In their report, Mochizuki et al. (2002) have shown for the first time the potentially beneficial role of IVIG

in the management of ascending motor neuropathies in two patients with SS.

Treatment of autonomic neuropathy in SS is not well established. Also in this case, anecdotal reports support a role of IVIG in the management of autonomic dysfunction in patients with SS (Dupond et al., 1999).

Finally, pain control due to peripheral neuropathy in these patients can be achieved by the combined use of sympatholytic and anti-inflammatory agents, suggesting a possible role of alpha-adrenergic receptor in the pathogenesis of pain in this type of neuropathies (Galer et al., 1992).

3. Involvement of the central nervous system

3.1. Prevalence/epidemiology

The prevalence of CNS disease in SS is a matter of controversy. Tables 3 and 4 list the prevalence of CNS disease in SS and as one can see, it ranges from 0 to 100%. Several reasons could account for the enormous variability reported in these studies.

An important reason is that the definition of CNS involvement in SS is not uniform. For example, not all studies include psychiatric disease or mild symptoms (such as headache or mood disturbances) in the definition of CNS disease. In addition, the diagnostic criteria used for SS vary from study to study. In some studies confirmatory salivary gland biopsies were mandatory, whereas in others they were not a necessary criterion for SS and patients with probable SS were also included. Some authors have also included patients suffering from secondary SS. As a result the distinction between CNS involvement in the context of lupus or SS is not clear. This is further complicated by the fact that a true SS–SLE overlap syndrome can occur manifesting CNS disease. Finally, confounding factors that may increase the risk for cerebrovascular disease such as diabetes, hypertension and hyperlipidemia or factors that may be associated with psychiatric disease such as thyroid disease are not always taken in consideration. The latter is particularly important considering that the incidence of autoimmune endocrinopathies, such as autoimmune thyroditis, is known to be increased in SS patients (Perez et al., 1995; Scofield, 1996).

Table 3
Prevalence of CNS manifestations in SS

References	No. of SS patients studied	% with neurological symptoms	Nature of CNS disease
Lafitte et al. (2001)	25	17	Spinal cord dysfunction, transverse myelitis, motor neuron syndrome, seizures + tetrapyramidal + cerebellar syndrome
Anaya et al. (2000)	95	3.2	MS-like illness, optic neuritis + epilepsy, complicated migraine
Coates et al. (1999)	30	0	
Tajima et al. (1997)	21	14	
Escudero et al. (1995)	48	23	Focal neurological deficits
Mauch et al. (1994)	20	10	Hemiparesis, aseptic meningitis
Moll et al. (1993)	45	9	Transverse myelitis, stroke, Bell's palsy, pyramidal signs
Hietaharju et al. (1993)	48	23	Optic neuropathy, movement disorders, aseptic meningitis, seizures
Hietaharju et al. (1990)	43	12.5	Aseptic meningitis, epilepsy, hypereflexia
Andonopoulos et al. (1990)	63	1.6	Cerebrovascular accident
Binder et al. (1988)	50	6	Epilepsy, vertigo, recurrent TIAs
Alexander et al. (1986a,b)		20	MS-like syndrome
Malinow et al. (1985)	40	60	CNS abnormalities
Molina et al. (1985)	50	45	Focal defects, seizures, aseptic meningitis, encephalopathy, myelopathy, neurogenic bladder

MS: multiple sclerosis;
CNS: central nervous system.

Table 4
Psychiatric involvement in SS

References	No. of SS patients	% with psychiatric symptoms	Nature of disease
Lafitte et al. (2001)	25	22	Cognitive dysfunction
Belin et al. (1999)	14	100	Neuropsychological
Govoni et al. (1999)	87	8	Non-focal dysfunction
Escudero et al. (1995)	48	29	Neuropsychiatric
Mauch et al. (1994)	20	70	Cognitive impairment
Moll et al. (1993)	45	7	Psychiatric disorders
Spezialetti et al. (1993)	165	80	Psychiatric symptoms/cognitive impairment
Hietaharju et al. (1990)	43	77	Psychiatric symptoms-depression most common
Drosos et al. (1989)	52	52	Introverted hostility, paranoid ideation, somatization, obsessive compulsive behavior
Malinow et al. (1985)	40	62	Psychiatric disease

The most important factor accounting for the difference in prevalence of CNS disease is the way the study population is selected and whether or not there is referral bias. Referral bias usually occurs in tertiary centers where complex cases with severe disease are referred. These, patients are not representative of the general SS population and, therefore, over-diagnosis of CNS disease can occur. Similarly, the frequency of CNS disease varies between patients seen in a neurology compared to a rheumatology outpatients department. Again selection bias may lead to differences in the observed disease frequencies. Furthermore, under-diagnosis of CNS disease may occur if symptoms such as cognitive impairment are attributed to anxiety or stress. Neurological symptoms may be considered functional in nature and dismissed by the assessing physician. Also, patients may not always report their symptoms. This is of particular relevance to psychiatric symptoms. Moreover, neurological symptoms in patients with SS who are elderly may be attributed to their age, resulting again in under-diagnosis.

Another complicating factor is that due to a problem with classification, some SS patients with CNS involvement may also satisfy the American College of Rheumatology (ACR) criteria for SLE. Hence these patients may be diagnosed as CNS-SLE rather than CNS–SS and again be missed.

It is important to consider that the reported differences in frequency of CNS disease may reflect true differences in frequency of CNS diseases between different populations. This could be due to genetic or environmental factors. This is of particular relevance to diseases like MS. The incidence of MS increases with latitude and, therefore, the probability of coexistence of SS with MS increases. This may partly explain the high incidence of MS-like disease observed in SS patients in North America and Scandinavia compared to the low incidence reported in Southern Europe and Colombia (Sanchez et al., 2000; Sundstrom et al., 2003; Celius and Vandvik, 2001).

Since the prevalence of specific neurological disorders in the general population is low, the only way to solve the question of prevalence of CNS disease in SS is to conduct large prospective, controlled studies. However, this is not an easy task considering that the prevalence of SS in the general population is also low.

3.2. Etiology/Pathogenesis

Despite progress in recent years in the understanding of the pathogenesis of SS, the etiology of CNS involvement is not well understood. However, CSF analysis, histopathology as well as neuroimaging studies can give us some insights into the pathogenesis of CNS–SS.

Based on the CSF analysis of SS patients with active CNS disease, Alexander et al. (1986a,b) proposed that an immunologically mediated mechanism for CNS disease exists in SS. This was based on the findings of lymphocytosis, elevated IgG index and of one or more oligoclonal bands on electrophoresis,

suggesting that there is migration of lymphocytes into the CNS and intrathecal production of antibodies. Moreover, the intrathecal activation of the terminal pathway of complement has been observed in patients with pSS with CNS involvement (Sanders et al., 1987).

Furthermore, several data point towards a small vessel vasculitis being the underlying pathogenic process in CNS–SS. A small-vessel mononuclear inflammatory and ischemic/hemorrhagic vasculopathy was demonstrated in brain biopsies from patients with SS and CNS involvement (Alexander, 1993). In particular, the presence of anti-Ro antibodies correlated with frank necrotizing vasculitis and abnormal angiography findings (Alexander et al., 1994). Furthermore, the presence of active CNS disease was associated with active peripheral vasculitis affecting the skin, muscles and nerves (Molina et al., 1985).

In-vitro studies also point to anti-Ro antibodies being implicated in the pathogenesis of CNS vasculitis, by binding to brain endothelial cells and promoting inflammation that leads to vascular damage (Alexander et al., 1994). However, no association has been reported between CNS–SS and other autoantibodies, such as anti-neutrophil cytoplasmic antibodies or ribosomal P antibodies, the latter classically associated with cerebral lupus (Spezialetti et al., 1993). Anticardiolipin antibodies are reported to occur in 5–14% of pSS patients (Alexander, 1993; Cervera et al., 1997). However, they are not thought to be associated with CNS disease in SS (Alexander, 1993).

Brain perfusion abnormalities may account for some of the clinical manifestations in CNS–SS, as revealed by single photon emission computed tomography (SPECT) scanning. In the study of Kao et al. (1998) Technetium-99m-hexamethylpropyleneamine-oxime (HMPAO) SPECT scanning was performed in 16 pSS patients with neuro-psychiatric manifestations and normal brain MRIs. 81% of patients had abnormal findings on SPECT scanning with the temporal lobes being most commonly involved.

Finally, in the study by Johnson et al. (1998), mood disorders and depression in eight patients with SS were partly attributed to hypofunction of the hypothalamic–pituitary–adrenal (HPA) axis. Hence these patients had significantly lower adrenocorticotropin (ACTH) levels and cortisol levels, as well as a lack of response to corticotropin releasing hormone (CRH) compared to controls.

3.3. Clinical spectrum of CNS disease in SS

The CNS disease reported in SS is diverse and extensive (Tables 3–5), since the brain, spinal cord as well as the cranial nerves can all become involved (Alexander, 1993). Focal involvement of the brain can cause motor and sensory deficits, aphasia, dysarthria, brain stem syndrome, movement disorder, seizures and migraine. Diffuse or non-focal involvement of the brain can result in encephalopathy, aseptic meningitis, cognitive dysfunction and dementia as well as psychiatric disorders. Spinal cord involvement can manifest itself as transverse myelitis, chronic progressive myelopathy, neurogenic bladder, Brown–Sequard syndrome and lower motor neuron disease. Optic neuritis and a MS-like syndrome have also been described (see below).

Table 5
Spectrum of CNS disease in primary Sjogren's syndrome

Brain
Focal
Motor and/or sensory deficit
Aphasia/dysarthria
Brain stem syndrome
Movement disorder
Cerebellar syndrome
Seizures
Migraine
Non-focal
Encephalopathy
Aseptic meningitis
Cognitive dysfunction/Dementia
Psychiatric disorders
Spinal Cord
Transverse myelitis
Chronic progressive myelopathy
Neurogenic bladder
Lower motor neuron disease
Brown–Sequard syndrome
Other
Optic neuritis
Multiple sclerosis-like syndrome

3.4. Diagnostic investigations

3.4.1. Radiological

3.4.1.1. Magnetic resonance imaging. Brain magnetic resonance imaging (MRI) scan is the imaging study of choice in detecting anatomic abnormalities in CNS–SS, since it has a much higher sensitivity than computed tomography (CT) (Alexander et al., 1988). In MRI scans of a large proportion of SS patients with focal CNS disease, multiple areas of increased signal intensity on T2-weighted images were found predominantly in subcortical and periventricular white matter (Govoni et al., 1999; Alexander et al., 1988; Manthorpe et al., 1992). These abnormalities can be due to infarction, ischemia, edema or demyelination. An attempt to correlate MRI findings with neuropathological data has revealed that some of the MRI abnormalities can be associated with myelin pallor, dilated perivascular (Virchow-Robin) spaces, periventricular gliosis, arteriosclerosis and infarction (Coates et al., 1999). In contrast, the prevalence of MRI abnormalities in SS patients with non-focal/diffuse CNS disease, such as frontal lobe syndrome and memory problems, is less clear. Belin et al. (1999) studied 19 such SS patients without detecting any brain MRI abnormalities. However, in a study of Alexander et al. (1988), 5 out of 8 patients with psychiatric or cognitive dysfunction had abnormal findings on brain MRI scans.

The prevalence of MRI abnormalities in SS patients without apparent clinical CNS disease remains to be determined. Studies by Alexander supports that these patients have a very low frequency of abnormal MRI scans (Alexander, 1993). In contrast, Pierot et al. (1993) studied and found abnormalities in 60% on brain MRI of 15 SS patients without clinical evidence of CNS disease. These were mainly punctate areas of high signal in the basal ganglia and the white matter of the basal ganglia. However, it should be noted that the incidence of high signal abnormalities in the MRI scans increases with age. Thus, the interpretation of such findings in a population of SS patients consisting mainly of middle aged women should be done with caution (Awad et al., 1986).

3.4.1.2. Cerebral angiography. The role of cerebral angiography is to exclude other causes of CNS disease such as AV malformations, congenital aneurysms, other vascular abnormalities and cerebrovascular disease. Angiographic findings suggestive of small vessel vasculitis, such as stenosis, dilatation or occlusion of small cerebral blood vessels are found in a considerable proportion of SS patients with active CNS disease (Alexander et al., 1994).

3.4.2. Functional

3.4.2.1. Electrophysiological studies. Abnormal electroencephalographic findings (EEG) are found in approximately one third of SS patients with severe progressive CNS disease. Patients with focal deficits may show focal slow wave activity, decreased amplitude or spikes. In patients with epilepsy, the EEG may show seizure discharges, whereas in patients with encephalopathy or dementia it may show diffuse slow wave activity. The EEG is useful in detecting subclinical abnormalities that antedate the development of clinical manifestations in CNS–SS. However, in patients with obvious CNS manifestations the EEG is of limited value.

Multimodality evoked response testing (MMER), measures the integrity of neuronal circuits from the periphery via the cerebral cortex, via the visual, auditory and peripheral nerve pathways. It seems to be a useful tool for the detection of early subclinical abnormalities and the monitoring of the response to therapy (Alexander, 1993).

3.4.3. Immunology

3.4.3.1. CSF analysis. CSF analysis in SS patients with active CNS disease commonly shows lymphocytosis, elevated IgG index and the presence of one or more oligoclonal bands (Alexander et al., 1986a,b). In patients presenting with acute or subacute encephalopathy, CSF examination is also important to exclude the presence of CNS infection (bacterial or viral). When patients present with MS-like symptoms, CSF analysis is an important investigation for the diagnosis of MS.

3.4.3.2. Serology. CNS disease can occur in anti-Ro positive as well as anti-Ro negative patients with SS. However, anti-Ro positivity is associated with severity of CNS disease and with findings of small vessel angiitis on cerebral angiography. Therefore,

autoantibody testing in SS has more of a prognostic than diagnostic value (Alexander et al., 1994).

The reported prevalence of antiphospholipid antibodies in SS is variable (Alexander, 1993; Kao et al., 1998; Pennec et al., 1991; Jedryka et al., 1992). However, the presence of antiphospholipid antibodies in SS patients does not seem to be of clinical relevance as it does not correlate with thrombotic events or fetal loss (Jedryka et al., 1992).

Nevertheless, testing for antiphospholipid antibodies in a patient with CNS disease is valid, as antiphospholipid syndrome can mimic many other neurological diseases, in particular MS and transverse myelitis.

3.5. Differential diagnosis

All the imitators of demyelinating disease should be included in the differential diagnosis of CNS–SS, such as inflammatory disorders (SLE, vasculitis, sarcoidosis, Behçet's disease), infectious diseases (Lyme disease, syphilis, progressive multifocal leukoencephalopathy, HTLV-1 infection, herpes zoster), genetic disorders (lysosomal disorders, adrenoleukodystrophy, mitochondrial disorders), metabolic disorders (vitamin B12 deficiency), neoplastic diseases (CNS lymphoma) and spinal conditions (degenerative disorders and vascular malformations) (Trojano and Paolicelli, 2001). Moreover, other neurological disorders, such as dementia, amyotrophic lateral sclerosis, Parkinson's disease, dorsal root ganglionitis should also be included in the differential diagnosis (Alexander, 1992).

MS is the main imitator of CNS–SS disease. Both diseases can present with involvement of the spinal cord, the brain and the optic tract, producing symptoms disseminated in time and space (Alexander, 1992; Tesar et al., 1992). As both disorders are relatively common in the general population, Ioannidis and Moutsopoulos (1999) suggested that the co-existence of SS and MS occurs simply by chance. On the other hand, several studies in patients with MS report an incidence of SS that is much higher than the one based on chance alone, although the figures quoted vary from 2 to 16.6% amongst different reports (de Seze et al., 2001; Sandberg-Wollheim et al., 1992; Ellemann et al., 1991; Miro et al., 1990; Metz et al., 1989; Noseworthy et al., 1989).

The distinction between MS and CNS–SS can be very difficult, even by very experienced clinicians. Involvement of peripheral nerves, if present, may serve as a differentiating clinical feature between the two diseases: sensory neuropathy occurs more commonly in patients with SS.

Elevation of the IgG index and the presence of oligoclonal bands are not helpful distinguishing features, as they are found in both disorders. However, the number of oligoclonal bands detected may be useful in distinguishing between the two conditions: patients with CNS–SS have been reported to have less than two oligoclonal bands, whereas MS patients have more than three bands (Alexander, 1992).

Detection of autoantibodies, such as antinuclear, anti-Ro, anti-La, and rheumatoid factor, found in patients with SS, seems to be a useful tool for the distinction between the two entities. However, it should be borne in mind that positive antinuclear antibodies are also commonly found in patients with MS. In a prospective study of patients with MS, a high frequency of antinuclear antibodies, 22.5% was detected (Collard et al., 1997), while anti-Ro/SSA antibodies were reported in a frequency of 7% in another study (de Andres et al., 2001). Periventricular and subcortical lesions are indinguishably found in MRI studies in both disorders. Abnormal MMER testing is also not very helpful in the distinction between the two syndromes, since in CNS–SS approximately 50% of patients have one or more abnormal multimodality-evoked response tests. Therefore, the differential diagnosis should be based mainly on the patient's history, in order to detect features of underlying autoimmune disease, especially sicca symptoms, which, when subtle, go unnoticed by most patients.

In the differential diagnosis of CNS–SS, SLE with CNS involvement should always be included. Although both disorders can have similar neurology, there are several differentiating points that should be noted. Firstly, in lupus neurological disease is of acute onset, whereas in SS it tends to be insidious, subtle, waxing and waning. Secondly, lupus patients have additional features of systemic autoimmune disease e.g. rash, serositis, polyarthritis or nephritis,

whereas SS patients have other distinguishing features, such as, sicca symptoms, parotid gland enlargement or distinctive tongue appearance. Thirdly, SLE patients tend to be younger whereas SS patients tend to be older. Fourthly, the distribution of MRI lesions may be of help in distinguishing between the two conditions: white matter lesions occur mainly in SS, whereas gray matter lesions are more common in CNS lupus. Also, CSF analysis has revealed the presence of atypical mononuclear cells (probably monocytoid B cells) in SS, not observed in patients with lupus. Finally, the autoantibody profile of patients can be helpful even though not always diagnostic (e.g. positivity for anti-Ro/anti-La antibodies in patients with SS, or for anti-Sm/anti-dsDNA antibodies in patients with lupus) (Alexander, 1992).

3.6. Treatment

So far the treatment of CNS–SS has not been evidence-based. There are no large randomized-controlled studies and treatment has mainly been empirical. Protocols have been based on the experience drawn from treating SLE patients with CNS disease and on anecdotal reports of successfully treated SS–CNS patients.

One approach to treatment is to tailor therapy according to disease activity (Govoni et al., 2001). For example, treatment may not be required if there is evidence of resolution of the neurological event and if the CNS disease appears to be self-limiting or stable. However, if there are signs of activity or progression of the CNS disease, for example, new symptomatology, or new MRI findings, or CSF abnormalities of lymphocytosis or raised IgG index, aggressive therapy may be warranted.

Aggressive therapy would typically consist of corticosteroids used in combination with cyclophosphamide. The regimes used typically consist of high dose oral corticosteroids (prednisolone at a daily dose of 0.5–1 mg/kg body weight) or intravenous monthly pulses of methylprednisolone (1 gr/m^2 of body surface area) given together with intravenous pulses of cyclophosphamide (1 gr/m^2 of body surface area) for six to twelve months. Other immunosuppressive drugs used with various degrees of success include azathioprine, methotrexate and cyclosporine (Alexander, 1992). A recent report by Canhao et al. (2000), pointed to a beneficial role of intravenous γ-globulin in the treatment of CNS vascultis in patients with SS. However, the cost-effectiveness of this type of treatment is not well established. Plasmapheresis, may benefit some patients, especially if used together with immunosuppressive therapy. Theoretically it may work by removing the pathogenic antibodies from the circulation of SS patients. However, there are no data to support the use of plasmapheresis in CNS–SS.

Finally, treatment with tricyclic antidepressants should be used with caution in SS patients with depressive symptoms since mucosa dryness could be exacerbated, in view of their anticholinergic action (reviewed in Govoni et al., 2001).

4. Conclusion

In SS PNS involvement is well delineated, whereas CNS involvement is a matter of controversy. PNS disease affects approximately 25% of patients. In contrast, the reported prevalence of CNS disease ranges between 0 and 100%. This variability may be due to lack of consensus on the definition of CNS involvement, variability in the diagnostic criteria used for SS and the presence of selection bias in the populations studied. The most common PNS manifestation is a distal sensory or sensorimotor neuropathy. It is usually mild and non-disabling and does not usually require any treatment. Other types of PNS disease include a pure sensory neuronopathy, cranial neuropathies, mononeuritis muliplex, autonomic and small fiber neuropathies. In the CNS, focal as well as non-focal involvement of the brain and spinal cord has been described, resulting in a wide spectrum of neurological and psychiatric symptoms. Vasculitis causing axonal degeneration is a major pathogenic mechanism of PNS disease and is also thought to be implicated in CNS disease. Treatment of neurological disease in SS is usually reserved for severe or progressive disease and includes the use of immunosuppressants, plasmapheresis and intravenous immunoglobulin, although there is a lack of evidence-based data.

Key points

PNS Disease

- The reported prevalence of PNS disease in pSS is approximately 25%.
- The development of PNS disease is a late event, not commonly found at the time of development of the sicca symptoms in pSS patients.
- Axonal degeneration due to frank necrotizing vasculitis or perivascular inflammation of small epineurial arterioles are the possible immunopathogenic mechanisms of PNS disease.
- Cryoglobulinemia, immune complex formation or the presence of anti-endothelial and anti- myelin antibodies may be implicated in the mechanism of vasculitis.
- Diagnostic evaluation: electrophysiological studies, imaging, serology.
- Differential diagnosis: metabolic, hereditary, neoplastic, neurological disorders.
- Treatment depending on the type of peripheral neuropathy—Steroids, immunosuppressants, IVIG.

CNS Disease

- Involvement of CNS in SS is a controversial topic.
- The reported prevalence of CNS disease is variable (0–100%).
- A small vessel immune-mediated vasculopathy is a possible pathogenetic mechanism of CNS–SS.
- CNS–SS presents with a wide spectrum of clinical manifestations (spinal cord, brain, cranial nerve involvement).
- Useful diagnostic tests: MRI, cerebral angiography, CSF analysis, electrophysiologic studies, serology.
- Differential diagnosis: MS, Cerebral lupus, Other inflammatory, infectious, genetic, metabolic and neoplastic disorders.
- Treatment is empirical: steroids and immunosuppressant are used in severe cases and in active disease.

References

Alexander, E. 1992. Central nervous system disease in Sjogren's syndrome. New insights into immunopathogenesis. Rheum. Dis. Clin. N. Am. 18, 637.

Alexander, E.L. 1993. Neurologic disease in Sjogren's syndrome: mononuclear inflammatory vasculopathy affecting central/peripheral nervous system and muscle. A clinical review and update a thorough review of central nervous system involvement in Sjogren's syndrome of immunopathogenesis. Rheum. Dis. Clin. N. Am. 19, 869.

Alexander, E.L., Lijewski, J.E., Jerdan, M.S., et al. 1986a. Evidence of an immunopathogenic basis for central nervous system disease in primary Sjogren's syndrome. Arthritis Rheum. 29, 1223.

Alexander, E.L., Malinow, K., Lejewski, J.E., et al. 1986b. Primary Sjogren's syndrome with central nervous system disease mimicking multiple sclerosis. Ann. Intern. Med. 104, 323.

Alexander, E.L., Beall, S.S., Gordon, B., et al. 1988. Magnetic resonance imaging of cerebral lesions in patients with the Sjogren syndrome. Ann. Intern. Med. 108, 815.

Alexander, E.L., Ranzenbach, M.R., Kumar, A.J., et al. 1994. Anti-Ro (SS-A) autoantibodies in central nervous system disease associated with Sjogren's syndrome (CNS–SS): clinical, neuroimaging, and angiographic correlates. Neurology 44, 899.

Anaya, J.-M., Villa, L., Restrepo, L., et al. 2000. Nervous system involvement in primary Sjogren's syndrome. Abstract no 1417. 64th ACR Annual Scientific Meeting. Arthritis Rheum. 43 (Suppl.), S303.

Andonopoulos, A.P., Lagos, G., Drosos, A.A., et al. 1990. The spectrum of neurological involvement in Sjogren's syndrome. Br. J. Rheumatol. 29, 2.

Asahina, M., Kuwabara, S., Asahina, M., et al. 1998. D-penicillamine treatment for chronic sensory ataxic neuropathy associated with Sjogren's syndrome. Neurology 51, 1451.

Awad, I.A., Spetzler, R.F., Hodak, J.A., et al. 1986. Incidental subcortical lesions identified on magnetic resonance imaging in the elderly. I. Correlation with age and cerebrovascular risk factors. Stroke 17, 1084.

Barendregt, P.J., van den Bent, M.J., van Raaij-van den Aarssen, V.J., et al. 2001. Involvement of the peripheral nervous system in primary Sjogren's syndrome. Ann. Rheum. Dis. 60, 876.

Barendregt, P.J., Tulen, J.H., van den Meiracker, A.H., et al. 2002. Spectral analysis of heart rate and blood pressure variability in primary Sjogren's syndrome. Ann. Rheum. Dis. 61, 232.

Belin, C., Moroni, C., Caillat-Vigneron, N., et al. 1999. Central nervous system involvement in Sjogren's syndrome: evidence from neuropsychological testing and HMPAO-SPECT. Ann. Med. Intern. (Paris) 150, 598.

Binder, A., Maddison, P.J., Skinner, P., et al. 1988. Sjogren's syndrome: a study of its neurological complications. Br. J. Rheumatol. 27, 275.

Canhao, H., Fonseca, J.E., Rosa, A. 2000. Intravenous immunoglobulin in the treatment of central nervous system vasculitis associated with Sjogren's syndrome. J. Rheumatol. 27, 1102.

Caroyer, J.M., Manto, M.U., Steinfeld, S.D. 2002. Severe sensory neuronopathy responsive to infliximab in primary Sjogren's syndrome. Neurology 59, 1113.

Celius, E.G., Vandvik, B. 2001. Multiple sclerosis in Oslo, Norway: prevalence on 1 January 1995 and incidence over a 25-year period. Eur. J. Neurol. 8, 463.

Cervera, R., Garcia-Carrasco, M., Font, J., et al. 1997. Antiphospholipid antibodies in primary Sjogren's syndrome: prevalence and clinical significance in a series of 80 patients. Clin. Exp. Rheumatol. 15, 361.

Chen, W.H., Yeh, J.H., Chiu, H.C. 2001. Plasmapheresis in the treatment of ataxic sensory neuropathy associated with Sjogren's syndrome. Eur. Neurol. 45, 270.

Chu, K., Kang, D.W., Song, Y.W., Yoon, B.W. 2000. Trochlear nerve palsy in Sjogren's syndrome. J. Neurol. Sci. 177, 157.

Coates, T., Slavotinek, J.P., Rischmueller, M., et al. 1999. Cerebral white matter lesions in primary Sjogren's syndrome: a controlled study. J. Rheumatol. 26, 1301.

Collard, R.C., Koehler, R.P., Mattson, D.H. 1997. Frequency and significance of antinuclear antibodies in multiple sclerosis. Neurology 49, 857.

de Andres, C., Guillem, A., Rodriguez-Mahou, M., Lopez Longo, F.J. 2001. Frequency and significance of anti-Ro (SS-A) antibodies in multiple sclerosis patients. Acta Neurol. Scand. 104, 83.

Denislic, M., Meh, D. 1994. Neurophysiological assessment of peripheral neuropathy in primary Sjogren's syndrome. Clin. Invest. 72, 822.

de Seze, J., Devos, D., Castelnovo, G., et al. 2001. The prevalence of Sjogren syndrome in patients with primary progressive multiple sclerosis. Neurology 57, 1359.

Drosos, A.A., Andonopoulos, A.P., Lagos, G., et al. 1989. Neuropsychiatric abnormalities in primary Sjogren's syndrome. Clin. Exp. Rheumatol. 7, 207.

Dupond, J.L., Gil, H., de Wazieres, B. 1999. Five-year efficacy of intravenous gammaglobulin to treat dysautonomia in Sjogren's syndrome. Am. J. Med. 106, 125.

Ellemann, K., Krogh, E., Arlien-Soeborg, P., Halberg, P. 1991. Sjogren's syndrome in patients with multiple sclerosis. Acta Neurol. Scand. 84, 68.

Escudero, D., Latorre, P., Codina, M. 1995. Central nervous system disease in Sjogren's syndrome. Ann. Med. Intern. (Paris) 146, 239.

Font, J., Valls, J., Cervera, R.F., et al. 1990. Pure sensory neuropathy in patients with primary Sjogren's syndrome: clinical, immunological, and electromyographic findings. Ann. Rheum. Dis. 49, 775.

Galer, B.S., Rowbotham, M.C., Von Miller, K., et al. 1992. Treatment of inflammatory, neuropathic and sympathetically maintained pain in a patient with Sjogren's syndrome. Pain 50, 205.

Garcia-Carrasco, M., Cervera, R., Rosas, J., et al. 1999. Primary Sjogren's syndrome in the elderly: clinical and immunological characteristics. Lupus 8, 20.

Gemignani, F., Marbini, A., Pavesi, G., et al. 1994. Peripheral neuropathy associated with primary Sjogren's syndrome. J. Neurol. Neurosurg. Psychiatry 57, 983.

Govoni, M., Bajocchi, G., Rizzo, N., et al. 1999. Neurological involvement in primary Sjogren's syndrome: clinical and instrumental evaluation in a cohort of Italian patients. Clin. Rheumatol. 18, 299.

Govoni, M., Padovan, M., Rizzo, N., Trotta, F. 2001. CNS involvement in primary Sjogren's syndrome: prevalence, clinical aspects, diagnostic assessment and therapeutic approach. CNS Drugs 15, 597.

Grant, I.A., Hunder, G.G., Homburger, H.A., Dyck, P.J. 1997. Peripheral neuropathy associated with sicca complex. Neurology 48, 855.

Griffin, J.W., Cornblath, D.R., Alexander, E., et al. 1990. Ataxic sensory neuropathy and dorsal root ganglionitis associated with Sjogren's syndrome. Ann. Neurol. 27, 304.

Hebbar, M., Hebbar-Savean, K., Hachulla, E., et al. 1995. Participation of cryoglobulinaemia in the severe peripheral neuropathies of primary Sjogren's syndrome. Ann. Med. Intern. (Paris) 146, 235.

Hietaharju, A., Yli-Kerttula, U., Hakkinen, V., Frey, H. 1990. Nervous system manifestations in Sjogren's syndrome. Acta Neurol. Scand. 81, 144.

Hietaharju, A., Jantti, V., Korpela, M., Frey, H. 1993. Nervous system involvement in systemic lupus erythematosus. Sjogren syndrome and scleroderma. Acta Neurol. Scand. 88, 299.

Hull, R.G., Morgan, S.H., Harding, A.E., Hughes, G.R. 1984. Sjogren's syndrome presenting as a severe sensory neuropathy including involvement of the trigeminal nerve. Br. J. Rheumatol. 23, 301.

Inoue, A., Koh, C.S., Tsukada, N., Yanagisawa, N. 1991. Peripheral neuropathy associated with Sjogren's syndrome: pathologic and immunologic study of two patients. Jpn. J. Med. 30, 452.

Ioannidis, J.P.A., Moutsopoulos, H.M. 1999. Sjogren's syndrome: too many associations too limited evidence. The enigmatic example of CNS involvement. A discussion of the existing controversies of central nervous system involvement in Sjogren's syndrome. Semin. Arthritis Rheum. 29, 1.

Jedryka-Goral, A., Jagiello, P., D'Cruz, D.P., et al. 1992. Isotype profile and clinical relevance of anticardiolipin antibodies in Sjogren's syndrome. Ann. Rheum. Dis. 51, 889.

Johnson, E.O., Vlachoyiannopoulos, P.G., Skopouli, F.N., et al. 1998. Hypofunction of the stress axis in Sjogren's syndrome. J. Rheumatol. 25, 1508.

Kao, C.H., Lan, J.L., ChangLai, S.P., Chieng, P.U. 1998. Technetium-99m-HMPAO brain SPECT in Sjogren's syndrome. J. Nucl. Med. 39, 773.

Lafitte, C., Amoura, Z., Cacoub, P., et al. 2001. Neurological complications of primary Sjogren's syndrome. J. Neurol. 248, 577.

Malinow, K.L., Molina, R., Gordon, B., et al. 1985. Neuropsychiatric dysfunction in primary Sjogren's syndrome. Ann. Intern. Med. 103, 344.

Malinow, K., Yannakakis, G.D., Glusman, S.M., et al. 1986. Subacute sensory neuronopathy secondary to dorsal root ganglionitis in primary Sjogren's syndrome. Ann. Neurol. 20, 535.

Mandl, T., Bornmyr, S.V., Castenfors, J., Jacobsson, L.T., Manthorpe, R., Wollmer, P. 2001. Sympathetic dysfunction

in patients with primary Sjogren's syndrome. J. Rheumatol. 28, 296.

Manthorpe, R., Manthorpe, T., Sjoberg, S. 1992. Magnetic resonance imaging of the brain in patients with primary Sjogren's syndrome. Scand. J. Rheumatol. 21, 148.

Matsukawa, Y., Nishinarita, S., Horie, T. 1995. Abducent and trochlear palsies in a patient with Sjogren's syndrome. Br. J. Rheumatol. 34, 484.

Mauch, E., Volk, C., Kratzsch, G., et al. 1994. Neurological and neuropsychiatric dysfunction in primary Sjogren's syndrome. Acta Neurol. Scand. 89, 31.

Mellgren, S.I., Conn, D.L., Stevens, J.C., Dyck, P.J. 1989. Peripheral neuropathy in primary Sjogren's syndrome. Neurology 39, 390.

Metz, L.M., Seland, T.P., Fritzler, M.J. 1989. An analysis of the frequency of Sjogren's syndrome in a population of multiple sclerosis patients. J. Clin. Lab. Immunol. 30, 121.

Miro, J., Pena-Sagredo, J.L., Berciano, J., et al. 1990. Prevalence of primary Sjogren's syndrome in patients with multiple sclerosis. Ann. Neurol. 27, 582.

Mochizuki, H., Kamakura, K., Masaki, T., Hirata, A., Nakamura, R., Motoyoshi, K. 2002. Motor dominant neuropathy in Sjogren's syndrome: report of two cases. Intern. Med. 41, 142.

Molina, R., et al. 1985. Peripheral inflammatory vascular disease in Sjogren's syndrome. Arthritis Rheum. 28, 1342.

Molina, J.A., Benito-Leon, J., Bermejo, F., et al. 1996. Intravenous immunoglobulin therapy in sensory neuropathy associated with Sjogren's syndrome. J. Neurol. Neurosurg. Psychiatry 60, 699.

Moll, J.W., Markusse, H.M., Pijnenburg, J.J., et al. 1993. Antineuronal antibodies in patients with neurologic complications of primary Sjogren's syndrome. Neurology 43, 2574.

Mori, K., Koike, H., Misu, K., et al. 2001. Spinal cord magnetic resonance imaging demonstrates sensory neuronal involvement and clinical severity in neuronopathy associated with Sjogren's syndrome. J. Neurol. Neurosurg. Psychiatry 71, 488.

Moutsopoulos, H.M. 2001. Sjogren's syndrome, 15th ed., Harrison's Principles of Internal Medicine, McGraw-Hill, New York, p. 1947.

Moutsopoulos, H.M., Sarmas, J.H., Talal, N. 1993. Is central nervous system involvement a systemic manifestation of primary Sjögren's syndrome? Rheum. Dis. Clin. N. Am. 19, 909.

Niemela, R.K., Hakala, M., Huikuri, H.V., Airaksinen, K.E. 2003. Comprehensive study of autonomic function in a population with primary Sjogren's syndrome. No evidence of autonomic involvement. J. Rheumatol. 30, 74.

Noseworthy, J.H., Bass, B.H., Vandervoort, M.K., et al. 1989. The prevalence of primary Sjogren's syndrome in a multiple sclerosis population. Ann. Neurol. 25, 95.

Pennec, Y.L., Magadur, G., Jouquan, J., et al. 1991. Serial measurements of anticardiolipin antibodies in primary Sjogren's syndrome. Clin. Exp. Rheumatol. 9, 165.

Perez, B., Kraus, A., Lopez, G., et al. 1995. Autoimmune thyroid disease in primary Sjogren's syndrome. Am. J. Med. 99, 480.

Pierot, L., Sauve, C., Leger, J.M., et al. 1993. Asymptomatic cerebral involvement in Sjogren's syndrome: MRI findings of 15 cases. Neuroradiology 35, 378.

Sanchez, J.L., Aguirre, C., Arcos-Burgos, O.M., et al. 2000. Prevalence of multiple sclerosis in Colombia. Rev. Neurol. 31, 1101.

Sandberg-Wollheim, M., Axell, T., et al. 1992. Primary Sjogren's syndrome in patients with multiple sclerosis. Neurology 42, 845.

Sanders, M.E., Alexander, E.L., Koski, et al. 1987. Detection of activated terminal complement (C5b-9) in cerebrospinal fluid from patients with central nervous system involvement of primary Sjogren's syndrome or systemic lupus erythematosus. J. Immunol. 138, 2095.

Scofield, R.H. 1996. Autoimmune thyroid disease in systemic lupus erythematosus and Sjogren's syndrome. Clin. Exp. Rheumatol. 14, 321.

Sjogren, H. 1935. Zur Kenntnis deer keratoconjunctivitis sicca II. Allgemeine Syptomatologic und Atiologie. Acta Opthal. (Kbh) 13, 1.

Skopouli, F.N., Dafni, U., Ioannidis, J.P., Moutsopoulos, H.M. 2000. Clinical evolution, and morbidity and mortality of primary Sjogren's syndrome. Semin. Arthritis Rheum. 29, 296.

Sobue, G., Yasuda, T., Kumazawa, K., et al. 1995. MRI demonstrates dorsal column involvement of the spinal cord in Sjogren's syndrome-associated neuropathy. Neurology 45, 592.

Spezialetti, R., Bluestein, H.G., Peter, J.B., Alexander, E.L. 1993. Neuropsychiatric disease in Sjogren's syndrome: anti-ribosomal P and anti-neuronal antibodies. Am. J. Med. 95, 153.

Sundstrom, P., Nystrom, L., Forsgren, L. 2003. Incidence (1988–97) and prevalence (1997) of multiple sclerosis in Vasterbotten County in northern Sweden. J. Neurol. Neurosurg. Psychiatry 74, 29.

Tajima, Y., Mito, Y., Owada, Y., et al. 1997. Neurological manifestations of primary Sjogren's syndrome in Japanese patients. Intern. Med. 36, 690.

Takahashi, Y., Takata, T., Hoshino, M., et al. 2003. Benefit of IVIG for long-standing ataxic sensory neuronopathy with Sjogren's syndrome. IV immunoglobulin. Neurology 60, 503.

Tanaka, Y., Tsukada, N., Koh, C.S., Yanagisawa, N. 1989. A case of Sjogren's syndrome with mononeuritis associated with high levels of circulating immune complexes. Rinsho Shinkeigaku 29, 336.

Tesar, J.T., McMillan, V., Molina, R., Armstrong, J. 1992. Optic neuropathy and central nervous system disease associated with primary Sjogren's syndrome. Am. J. Med. 92, 686.

Trojano, M., Paolicelli, D. 2001. The differential diagnosis of multiple sclerosis: classification and clinical features of relapsing and progressive neurological syndromes. Neurol. Sci. 22, S98.

Tumiati, B., Casoli, P., Parmeggiani, A. 1997. Hearing loss in the Sjogren syndrome. Ann. Intern. Med. 126, 450.

Van Dijk, G.W., Wokke, J.H.J. 1998. The diversity of peripheral nervous system disorders in Sjogren's syndrome. Neth. J. Med. 53, 193.

Vrethem, M., Lindvall, B., Holmgren, H., et al. 1990. Neuropathy and myopathy in primary Sjogren's syndrome: neurophysiological, immunological and muscle biopsy results. Acta Neurol. Scand. 82, 126.

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CHAPTER 15

Systemic Sclerosis

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1. Introduction

The importance and frequency of neurological involvement in systemic sclerosis (SSc) has been much debated. Traditional dogma suggests that, compared with other autoimmune rheumatic diseases, there is a relatively low frequency of neurological manifestations and certainly severe peripheral neuropathy is uncommon and patients do not develop florid encephalopathy other than in the context of accelerated phase hypertension, as in a hypertensive scleroderma renal crisis, or in lupus-scleroderma overlap syndromes, and even this is rare (Gordon et al., 1970). Conversely, a number of studies suggest that milder neuropathy, especially affecting autonomic function, are quite frequent and may underlie the development of complications such as gastrointestinal dysmotility at early stages before structural changes or fibrosis occur. Isolated cranial nerve lesions are perhaps the most frequent clinically apparent complication. It has also been reported that the hemiplegic limb is less likely to develop the cutaneous features of SSc, as observed in other rheumatic diseases (Sethi et al., 1990). A case of localized SSc was described by Kinger (1922) after cranial nerve injury. This has emphasized the importance of the nervous system in the pathogenesis and disease manifestations of SSc. Recent publications have highlighted the interest in this fascinating aspect of complication of SSc (Nadeau, 2002; Cerinic et al., 1996; Herrick et al., 1996).

Neurological events may also occur as a result of treatment of complications of SSc in particular potent immunosuppressives. Schneider (1991) described a case of progressive multifocal leukencephalopathy (PML) in a patient with undifferentiated connective tissue disorder with sclerodermatous involvement. This patient presented with spastic hemiplegia, ophthalmoplegia, speech disturbances and bladder dysfunction after a 12 year treatment with corticosteroid and 4 year of treatment with azathioprine. Myasthenia gravis (MG) has been reported in less than 1% of patients treated with penicillamine. They may harbor increased titers of acetylcholine receptor antibodies in their sera. The clinical presentation of penicillamine-induced MG seems similar to idiopathic MG. Penicillamine-related MG is relatively benign and typically resolves several months after the drug is discontinued although it sometimes can cause life-threatening muscle weakness requiring aggressive therapy (Steen et al., 1986).

2. Prevalence

Studies have shown that clinical peripheral nervous system (PNS) disease is relatively uncommon in SSc. When 125 patients with SSc were screened prospectively for neurological complications over a period allowing more than 300 patient-years of follow-up, clinically evident peripheral neuropathies were found in 4 cases with carpal tunnel syndrome and 1 case each of distal axonal sensory neuropathy,

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mononeuritis multiplex and trigeminal sensory neuropathy (Lee et al., 1984). Rigorous screening of 32 patients with SSc for clinical neuropathy found 2 cases of trigeminal sensory neuropathy; 1 case each of distal axonal neuropathy, brachial plexopathy and lumbosacral plexopathy; and 6 cases of asymptomatic nerve conduction abnormalities; 3 with distal axonal polyneuropathy, 1 with probable myopathy and superimposed polyneuropathy, 1 with trigeminal neuropathy (TN), and 1 with focal ulnar neuropathy (Hietaharju et al., 1993a–c).

Conversely, recent reports have suggested that peripheral neuropathy is seen in 10–20% patients with scleroderma. In addition, studies, which have included subclinical muscle involvement have shown a higher incidence of neurological involvement (up to 40%). In another study by Averbuch-Heller et al. (1992), neurological abnormalities were detected in 40% of 50 SSc patients, with a total of 28 neurological manifestations. All levels of the central nervous system (CNS) and PNS were affected: muscle (22%), peripheral nerve (18%), spinal cord (8%), and brain (6%). Of note were the presence of myelopathy in four patients and inclusion-body myositis in two.

In addition, it has been shown that there is no significant difference in the occurrence of neurological events in patients with SSc and other CTDs. Hietaharju et al. (1993a–c) studied 122 patients with a connective tissue disease (42 with systemic lupus erythematosus (SLE), 48 with Sjogren's syndrome and 32 with scleroderma) and noted that neurological complications were evenly distributed among the groups in 69% of SLE patients, in 71% of Sjogren's syndrome patients and in 66% of scleroderma patients. Several reports with small sample size have suggested that patients with anti-U1RNP antibodies, and possibly those with anti-Scl70 antibodies, may have a higher risk of developing neurological complications. Hierarinta et al. (1994) showed that, among the 11 patients with SSc and neurological involvement with TN, polyneuropathy and myopathy, either anti-U1RNP antibodies or anti-Scl70 antibodies were detected in the sera of 8 patients. Significant neurological involvement is uncommon in patients with anti-PM-Scl antibody.

In another study by Farrell and Medsger (1982), serum antibodies to ribonucleoprotein were identified in 9 (45%) of 20 SSc patients with TN as compared to 25 (8%) of 329 patients without TN. Contraction amplitudes in the smooth muscle as well as the striated muscle esophagus and lower esophageal sphincter pressures were demonstrated by Stacher et al. (2000) to be significantly lower and autonomic dysfunction more frequent in patients with than in those without anti-Sc170 (6 of 9 vs. 6 of 16 patients) but there was no difference in the upper esophageal sphincter pressures.

Overall, neurological complications are reported to occur between 1 and 19% of SSc cases in different series. Straub et al. (1997) compared the prevalence of autonomic neuropathy (ANP) in patients with different chronic diseases and found that there was a high prevalence rate of papillary ANP of 16% in SSc compared to 19, 29 and 66% in Crohn's disease, SLE and diabetes. They suggested that this may be due to alterations of structures of the CNS in these patients. In this study, sensorimotor dysfunction was also noted to occur in 32% of patients with SSc compared to 29 and 10% of patients with insulin-dependent diabetes mellitus and SLE. The authors postulated that this may be related to focal fibrotic lesions.

3. Etiology/Pathogenesis

Vasculopathy may be an important contributory to the pathogenesis of neuropathy in SSc as there is a close network of the microvascular abnormalities in SSc and the distribution of vasa nervorum. The nervous system is dependent on the vascular network for its nutrition, oxygenation and disposal of toxic metabolites. Therefore, any microvascular alterations may result in nerve dysfunction. Endothelial damage as a primary event in SSc may involve the epi-, peri- and endoneurial leading to microangiopathy. Vasculitis with inflammatory involvement of affected vessels, surrounding fibrinoid necrosis and perivascular inflammatory infiltrate may result in ischemic infarction of nerves. Like other rheumatic diseases, these pathological changes have been described in SSc with associated mononeuritis multiplex and localized SSc. The presence of specific antibodies in SSc suggests a possible autoimmune mechanism in which the nervous system is targeted. Howe et al. (1994)

showed that antimyenteric neuronal antibodies was observed in SSc patients and this was associated with gastrointestinal dysmotility and Raynaud's phenomenon.

This was supported by recent study in which passive immunization of purified immunoglobulin G from serum samples of patients with SSc injected intraperitoneally into a rat model resulted in prolongation in the myoelectric activity (Eaker et al., 1999). Zeballos et al. (1994) measured serum antibodies directed against sulfatides, which are frequently associated with motor or sensorimotor neuropathies, in 34 patients with SSc (28 of which has peripheral neuropathy) to establish the prevalence of such anti-glycosphingolipid autoantibodies in SSc. They found lower levels of sulfatide antibodies in SSc compared to healthy individuals but the presence of sulfatide antibodies did not correlate with the development of peripheral neuropathy in these patients. The authors suggested that relatively low-titer glycosphingolipid antibodies may arise as part of a non-specific polyclonal gammopathy in rheumatological disorders but generally without clinical manifestation (Zeballos et al., 1994). In contrast, immunoglobulin G from patients with SSc was shown to inhibit M3-muscarinic receptor-mediated murine intestinal contractions. These contractions appear to be mediated via L-type voltage-gated calcium channels. This suggests that defects in cholinergic excitatory neurotransmission may underlie the gastrointestinal dysmotility in SSc (Goldblatt et al., 2002).

Multiple case-control studies in the literature have demonstrated modest associations of certain HLA alleles or haplotypes with SSc (Tan et al., 2000). Kuwana et al. (1999) and Gilchrist et al. (2001) have shown consistent correlation between specific HLA genes and autoantibody status. Hietarinta et al. (1994) compared 30 patients with SSc and 188 controls for class I and class II MHC antigens and found that there were higher frequencies of HLA antigens B8 and DR3 in patients with neurological complications than those without.

Altered neurotransmitter levels have been suggested to be involved in autonomic manifestations of SSc. Danese et al. (2000) demonstrated a statistically significant reduction in vasoactive intestinal peptide levels in 11 patients compared to controls and this was associated with a decreased inferior esophageal pressure as measured on manometry.

Local compressive nerve damage may occur in SSc. It has been reported by the Pittsburg group that carpal tunnel syndrome occurs more commonly in the edematous phase of early diffuse SSc than in the later stages of the disease. However, in the later stage of disease, the excessive amounts of collagen deposit may result in progressive compression and retraction of the adjacent nerve. Extrinsic compression from adjacent tissues may cause similar nerve dysfunction. An example is the development of painful TN caused by resorption of the angle and inferior alveolar border of the mandible with pressure ischemia from tight sclerotic skin resulting in compression neuropathy of the inferior alveolar nerve (Fischoff and Sirois, 2000).

An autopsy of a patient with SSc and neuropathy showed severe sclerosis of the spinal peripheral nerves with extensive degeneration of nerve fibers. The blood vessels in and around nerves had thickened walls without any inflammation. The lack of inflammation may reflect the chronicity of the clinical neuropathy in this case (Richter, 1954). A sural nerve biopsy in a case of mixed sensorimotor peripheral neuropathy with neurotrophic ulceration in SSc showed a reduction in myelinated nerve fibers of all diameters with moderate endoneurial fibrosis, intimal hyperplasia of the epineurial vessels but no inflammation or necrosis. These limited data appear to discount the role of inflammation or vasculitis in neuropathy. In contrast, Dyck et al. (1997) reported mononeuropathy multiplex in six patients in a retrospective study of patients with limited SSc and sural nerve biopsy specimens demonstrated multifocal fiber loss and perivascular inflammation; one was diagnostic for necrotizing vasculitis and two others were highly suggestive for necrotizing vasculitis. Significant axonal degeneration was significantly increased in these patients. This has also been shown by Oddis et al. (1987) in six patients with overlap scleroderma and Sjogren's syndrome, demonstrating necrotizing vasculitis on sural nerve biopsy in association with mononeuritis multiplex.

Clinicopathological studies have shown axonal degeneration with increased endoneurial connective tissue in sural nerve biopsies from SSc patients with peripheral neuropathy with clusters of myelinated

fibers indicating axonal regeneration. Only mild microangiopathic changes were evident in the endo, peri and epineurial vessels. Abnormal production of collagen tissue and presence of microvascular disease may play a role in this form of neuropathy (Corbo et al., 1993).

Neuropathology in localized SSc has been described in several cases of en coup de sabre with a spectrum of pathological features including sclerotic meningeal and cortical blood vessels, intraparenchymal calcification, inflammatory changes with perivascular infiltrates and gliosis, band-like sclerosis and vessel fibrosis without evidence of inflammation, the latter being viewed as an end-stage pathology by Stone et al. (2001). Several reports have described the radiological findings in patients with localized SSc and these included both ipsilateral and contralateral white and gray matter lesions. Stone et al. (2001) suggested that the inflammatory process observed in cerebral biopsies is consistent with the intense inflammation of the dermis and subcutaneous tissue in the early stages of localized SSc. High frequencies of serological findings of positive ANA and rheumatoid factor with presence of oligoclonal bands in the CSF would suggest that there is an inflammatory or immune-mediated mechanism underlying the associated cerebral process in localized SSc. It is not surprising that some of the neuroradiological and pathological features in Parry–Romberg syndrome are similar to that of localized SSc as both of these diseases are often thought of overlapping conditions and may coexist.

Rapid development of neurological complication in a case report of a lady with plaque morphoea associated with localized SSc in the 33rd week of pregnancy is reminiscent of the effect of pregnancy on the course of autoimmune diseases. It is probably that pregnancy-related hormonal changes may trigger progression of the disease with cerebral involvement (Unterberger et al., 2003).

4. Clinical manifestations

Myopathy is frequently observed in scleroderma. Follansbee et al. (1993) reported 17% of 1095 patients with SSc to have skeletal myopathy and a quarter of these patients also have evidence of myocardial involvement. In 80% of those affected, this is a relatively indolent disorder marked by muscle fibrosis without inflammation, minimal proximal weakness and serum muscle enzyme elevations up to twice normal levels. In 20% of patients, the myopathy meets the criteria for polymyositis. Clements et al. (1978) reported three patients out of 24 patients demonstrated inflammatory muscle disease indistinguishable from polymyositis while a fourth patient developed marked weakness associated with a generalized neuropathic process. In these patients, there is concurrent myocardial involvement and a substantial risk of congestive heart failure, symptomatic arrhythmias and sudden death.

4.1. Central nervous system

There is increasing evidence of SSc patients suffering from CNS involvement, most often in the form of ischemic cerebrovascular disease and cognitive impairment. Hemiplegia and transient ischemic attacks have been reported to occur in 2–6% of cases (Gordon et al., 1970; Averbuch-Heller et al., 1992). These events are not clearly related to common vascular risk factors or to the failure of other organs or systems and it has been postulated that autoimmune-mediated narrowing cerebral blood vessels may underlie the pathogenesis of cerebrovascular events in SSc (Veale et al., 1995; Lee and Haynes, 1987; Estey et al., 1979; Pathak and Gabor, 1991; Leinwand et al., 1954; Piper and Helwig, 1950). CNS or psychiatric symptoms were present in five patients (16%), including encephalopathy, psychosis, anxiety disorder, grand mal seizures and transient ischemic attack as shown by Hietaharju et al. (1993a–c). Dengler et al. (1989) reported observed brainstem dysfunction with vertigo, diplopia and nystagmus and one case of cerebral venous thrombosis in four patients with active SSc at the time of cerebrovascular disease.

Transient global amnesia has been described in a lady with SSc with headaches when Raynaud's symptoms occurred in her hands, suggesting an ischemic event secondary to a vasospastic mechanism like Raynaud's phenomenon (Nishida et al., 1990). Seijo Martinez et al. (2000) describe a middle-aged

male with limited SSc presenting with insidious onset of choreic movements affecting the right-sided limbs. Brain single photon emission computed tomography (SPECT) showed bilateral hypoperfusion bilaterally, predominantly on the left side and MR imaging confirmed an infarct in the left caudate and adjacent internal capsule, suggesting a direct primary cerebrovascular damage in SSc (Seijo Martinez et al., 2000). Presumed CNS vasculitis in SSc was described in an angiographic study with segmental symmetrical arterial narrowing and the patient responded to aggressive immunosuppressive therapy (Pathak and Gabor, 1991).

Histopathological evidence of CNS involvement was supported by foci of ischemic neuronal necrosis and calcification of the small deep cerebral arteries without glial or inflammatory reaction detected at autopsy in two cases of limited SSc, presenting with severe dementia or focal cerebral infarct. Vascular abnormalities were found in the basal ganglia, hippocampus and dentate nuclei, but also in the walls of the small arteries of cortical areas, especially the frontal lobes, the cerebellar cortex and the mammillary bodies (Heron et al., 1998). Unlike structural brain examinations using CT and MRI, SPECT with perfusion tracers can disclose regional hypoperfusion in neurologically asymptomatic patients with SSc (Nobili et al., 2002). In an earlier study, Cutolo et al. (2000) detected no significant difference regarding the presence of common vascular risk factors and the involvement of other organs between SSc patients with and without cerebral hypoperfusion. Therefore, when the possible influences of all these confounding variables on cerebral perfusion are excluded or minimized, the hypoperfusion detected on SPECT would suggest microangiopathic damage of brain vessels. It is believed that complex endothelial cell dysfunction leading to typical non-inflammatory microangiopathy, characterized by vascular tissue proliferation and obliterative microvascular lesions, might alter the function of the nervous system during SSc, although the mechanism causing endothelial damage is poorly explained.

Internal organ calcification is rare in SSc in contrast to calcification of soft tissue. Isolated cases of paraspinal and spinal calcinosis have been reported recently (Van de Perre et al., 2003; Schweitzer et al., 1991; Walden et al., 1990; Pinstein et al., 1989; Haverbush et al., 1974). Patients may present themselves with focal pain with reduced range of movement, weakness and radiculopathy. Ward et al. (1997) described two cases of established diffuse SSc involving the cervical and lumbar region who presented themselves with spinal pain associated with weakness of affected muscles. CT imaging of the former revealed tumoral calcinosis at the lumbar facet joints with spinal stenosis. CT-guided aspiration of the intraspinal calcification yielded calcium hydroxyapatite. She improved following lumbar laminotomy, hemilaminectomy and diskectomy. The second patient had reduced cervical movement and CT revealed prevertebral calcific masses between the level of foramen magnum and C3. Although standard radiograph is usually sufficient to confirm the diagnosis, MRI is useful to evaluate the precise location and extension of the lesions and in this case, it revealed that the masses produced anterior displacement of the airway and left internal carotid artery anterolaterally. Brain calcifications involving the basal ganglia and gyrus have been reported. In the setting of coexisting ischemic stroke, extensive wall calcification of the small arteries and arterioles may be present and these areas of calcification may be markers for more severe vascular involvement in the brain (Seijo Martinez et al., 2000; Grassi et al., 2001; Blanco et al., 1999; Kanzato et al., 1999). Intracranial calcification including vascular calcification is reported in association with scleroderma en coup de sabre, the linear variant of localized SSc on the face and skull may be complicated by both ocular and CNS manifestations. They may present as ptosis, uveitis, pseudo-oculomotor palsy, retrobulbar pain, headache, focal neurological deficits or seizures of the complex partial type or by clinically silent abnormalities. In contrast to other forms of linear SSc, the intracerebral lesions are not always confined to adjacent sites of skin disease.

4.2. Peripheral nervous system

The PNS is also targeted by SSc: a distal mononeuropathy of the median nerve is a frequent and early feature. This probably reflects the peripheral musculoskeletal inflammation that occurs at early stages of

diffuse cutaneous SSc that impinges on the median nerve in the carpal tunnel. Many cases of peripheral neuropathy has been reported in SSc with a case of polyneuropathy observed by Richter (1954). Early case series reported a frequency of less than 5%. Retrospective studies have found peripheral neuropathy in 0.01–14% of patients (Lee et al., 1984; Averbuch-Heller et al., 1992). Mononeuritis multiplex, TN and entrapment neuropathies such as carpal tunnel syndrome are most commonly reported. This may occur alone or in association with other neurological symptoms and signs such as TN and other cranial nerve lesions. Poncelet and Connolly (2003) examined 14 patients with neurological examination, nerve conduction studies and quantitative sensory testing. Sensory symptoms, especially loss of sensation or neuropathic pain (burning or lancinating), were the most common complaints. Unlike other axonal sensory neuropathies, this study demonstrated asymmetrical onset of neuropathy with involvement of proximal limbs with relative sparing distally. The neuropathy also appear to have an upper limb predominance. Although in majority of the cases the symptoms coincided with the diagnosis of SSc, in some cases, the symptoms preceded the systemic disease by several years. This has been shown in several studies. Neurological examination revealed reduced vibration in 50% or pinprick sensation in 28% in the upper or lower extremities, focal atrophy or proximal weakness and decreased deep tendon reflexes in 14% of patients. Nerve conduction studies showed reduced sensory nerve action potentials and carpal tunnel syndrome in one patient. Quantitative sensory testing of the upper and lower extremity revealed increased cold or vibration detection thresholds in eight patients. A number of patients develop paresthesia and neuropathic pain in their hands.

Schady et al. (1991) prospectively studied 29 patients with SSc using clinical examination, quantitative sensory testing (thermal, heat:pain and vibration), nerve conduction studies and sympathetic skin response. The most common abnormality was an increase in thermal thresholds in the hands (four) and feet (five). Only one patient had abnormal vibration sense. No increase in heat:pain threshold was found in this study. Two-point discrimination was abnormal in 10 patients. Sympathetic skin response was abnormal in four patients. Four patients had electrophysiological evidence of a sensory axonopathy. Sensory fibers has been reported to be reduced in SSc (Hietaharju et al., 1993a–c).

Entrapment neuropathy including median nerve compression has been reported in SSc. Machet et al. (1992) found clinical or EMG evidence of carpal tunnel syndrome in 4 of 16 patients. It may be the presenting feature in patients with early diffuse SSc and may precede the onset of Raynaud's phenomenon or definite skin thickening. The Pittsburg group reported 17% and 1% cases of carpal tunnel syndrome in a cohort of 186 patients with early(>3 years) and late (>6 years) disease, respectively. This may suggest that patients in their early edematous phase of disease are likely to develop entrapment neuropathy secondary to edema and inflammation (Medsger, 2003).

In a recent study of 32 SSc patients, 14 (43.7%) patients developed a decrement of the median nerve terminal latency index and 7 (21.8%) of either the median or the ulnar nerve. Four (12.5%) patients had a distal neuropathy of the upper limbs (one with unilateral and two with bilateral involvement of the median nerve and one bilateral involvement of the ulnar nerve). The amplitude and area of the compound muscular action potential (distal and proximal), sensory action potential and of the median nerve terminal latency index were significantly decreased in patients with respect to controls (Lori et al., 1996). Apart from three cases of carpal tunnel syndrome, Mondelli et al. (1995) reported one case of tarsal tunnel syndrome and one Guyon's canal syndrome. He also demonstrated subclinical distal peripheral neuropathy in 17 patients with SSc. Electrophysiological studies showed that the mean distal sensory and motor conduction findings of the median, ulnar, sural and tibial nerves were significantly lower than those of a control group.

Subclinical peripheral nerve abnormalities in SSc is well recognized with asymptomatic deficits of tactile sensation, detectable by examining two-point discrimination or sensitivity to von Frey hairs and altered tactile thresholds occurring more commonly distally in the feet than in the hands (Schady et al., 1991; Serup, 1984). These abnormalities are more common distally, in feet more than hands, and finger

tips more than palms, and occur over skin that is not clinically sclerodermatous.

In summary, there is a strong evidence that a peripheral sensory motor neuropathy occurs frequently in SSc. It has also been reported that sensorimotor polyneuropathy may occur before the onset of systemic disease (Lopez Dominguez et al., 1995). The affected area of the PNS is variable and may lie anywhere between the cranial and distal mononeuropathy and mononeuropathy multiplex. Although there is good evidence to show that entrapment syndrome occurs in the early phase of the disease, neurophysiological alterations at the wrist level may also suggest microvascular involvement.

4.3. Cranial nerves

Facial sensory TN is common in connective tissue diseases. It occurs in 5–9% of patients with SSc (Brick and Brick, 1989). It may account for 47% of the neurological involvement in undifferentiated connective tissue diseases and 19% in SSc. It is characteristic of SSc alone or in association with Sjogren's syndrome. A retrospective study showed 16 TN cases in 442 patients with a higher proportion in these cases of overlap syndrome, myositis and WCC less than 4000 ml^{-1} was reported in 1968 by Beighton et al. (1968). Since then, numerous case reports and series have been reported (Fischoff and Sirois, 2000; Jimenez-Moreno et al., 1998; Vicente et al., 1991; Heald, 1989). In addition, a recent Italian study reported early involvement of trigeminal sensory neuropathy in four patients characterized by the slow and gradual numbness of the face muscles, which developed into pain and paresthesia, weakening or disappearance of the sense of taste and in one case loss of sensitivity at the oro-pharynx and this progression of symptoms preceded by 3 years the onset of systemic manifestations, and consequently diagnosis of SSc (Scardina et al., 2002).

It may be bilateral and affects all sensory modalities but rarely the muscles of mastication. It typically involves the V2 and V3 distributions and occasionally affects all three divisions of the nerve. It is frequently associated with numbness and pain, which may be throbbing, aching, scalding, burning or lancinating. The inside of the mouth is frequently involved. The sensory abnormalities evolve slowly and may spread contralaterally in an asymmetrical fashion. The corneal reflex is more likely to be impaired if the numbness has involved the upper trigeminal division. Blink reflex latencies may reveal an 'afferent' defect with modest prolongation of latency. Trigeminal sensory evoked responses may show prolongation of latencies. They have normal jaw jerks, suggesting that the lesion in this type of TN is in the trigeminal ganglion or in the proximal part of the main trigeminal divisions. It has been reported that TN may precede the onset of systemic disease by several years and this was illustrated by Scardina et al. (2002) who noted that in 12% of patients with orofacial manifestations of SSc had a history of trigeminal sensory neuropathy before the onset of systemic skin involvement. Gadolinium-enhanced T1-weighted MRI brain may show enhancement and some enlargement of the pre-ganglionic segment of the affected nerve and this may resolve when the symptoms abate.

The differential diagnosis for trigeminal is wide and may include bone disease, tumor, infection and vascular abnormalities. Less often the 7^{th}, 9^{th}, 8^{th}, 4^{th} and rarely the 6^{th}, 10^{th} and 12^{th} cranial nerves may be involved.

Unilateral or bilateral optic neuropathy has been reported (Das et al., 2002; Boschi et al., 1993). Hietaharju et al. (1993a–c) detected among 32 patients that abnormal visual evoked potentials were recorded from 5/32 patients (16%), suggesting optic neuropathy as a primary complication of SSc although none of them were symptomatic.

4.4. Autonomic nervous system

Autonomic nerve dysfunction (parasympathetic impairment and marked sympathetic overactivity) seems to be a fundamental etiological factor linked to the development of microvascular, cardiac and gastrointestinal alterations. It is now recognized that autonomic dysfunction is the earliest structure targeted by the disease in the gastrointestinal tract. Its role in the pathophysiology of some SSc disease manifestations is well defined. In this regard, parasympathetic dysfunction is known to characterize the early stage of gut wall involvement in SSc. Using

esophageal manometry and autonomic function tests for cardiovascular and papillary autonomic dysfunction, Lock et al. (1998) reported in 36 patients significant esophageal dysfunction in all patients. Patients with autonomic dysfunction had significantly reduced mean distal esophageal contraction amplitudes compared to patients without autonomic nervous dysfunction. The association of autonomic dysfunction and esophageal dysfunction was significant. Although previous reports have implicated that ANP in patients with established SSc, it is important to appreciate that ANP may be a very early feature in SSc patients (Sjogren, 1994; Ferri et al., 1997; Straub et al., 1996). Cozzolino et al. (2002) have reported two cases with cardiac autonomic dysfunction in which there was no clinical evidence of cutaneous fibrosis, suggesting that sympathetic derangement may occur before SSc is manifest. Malandrini et al. (2000) also found early involvement of the autonomic nervous system and to a lesser extent of smooth muscle cells in nerve and smooth muscle structures of the anorectal wall underlying gastrointestinal dysfunction in three patients with SSc. Deep rectal biopsy from affected areas showed axonal degeneration and cytoskeletal abnormalities in the bundles of unmyelinated fibers. There was also focal degeneration of smooth muscle cells, often in association with the presence of partially degranulated mast cells.

In SSc, both sympathetic and parasympathetic irideal impairment have been demonstrated. Using automated standardized infrared pupillometry, Bertinotti et al. (2002) studied the pupillary response to substance P, a sensory neuropeptide which induces myosis via specific receptors on the iris sphincter muscle. They demonstrated a higher basal and substance P-stimulated myosis was found in localized SSc versus both diffuse SSc and controls, whereas no differences existed between dSSc and controls. This is in contrast to other inflammatory rheumatic diseases such as SLE in which the pupillary parasympathetic nervous system seems to be more affected than the sympathetic branch of autonomic nervous system. However, in this study, they demonstrated that in SSc both sympathetic and parasympathetic pupil control to be equally impaired and that pupillary nervous control is differently affected in the two subsets of SSc.

Straub et al. (1996) assessed in 19 patients, pupillary ANP using pupillometry and cardiovascular ANP using a standardized test battery. He reported a prevalence of pupillary and cardiovascular ANP was 21.2 and 15.7% in SSc, respectively, and this was similar to patients with SLE. He also showed that renal involvement was associated with more severe ANP in patients with SSc.

Dessein et al. (1992) reported that autonomic dysfunction occurred in all 34 patients. Mean resting plasma adrenaline levels were significantly higher than matched controls. Plasma catecholamine (adrenaline, noradrenaline, and dopamine) concentrations and mean arterial blood pressures fluctuated inappropriately during standing and sustained handgrip in 28 (82%) of the patients. Mean resting plasma adrenaline levels were noted to be higher than matched controls and these levels appear to have an inverse correlation with disease duration suggesting that autonomic dysfunction may be more prominent in early disease. The latter was not supported in other study by Straub et al. (1996).

5. Therapy

Management of neurological manifestations is targeted according to its severity and the level of affected nervous system. It is equally important to take into account the involvement of other organ manifestations as CNS involvement per se is unusual in SSc. In the presence of significant inflammation or associated inflammatory involvement of other organs, systemic steroids and aggressive immunosuppressive therapy are warranted.

Specific therapy may be required for isolated cranial neuropathy. First line therapy remains carbamazepine or oxcarbazepine beginning at 100 or 200 mg two to three times daily depending on the size of the patient and their tolerance to the medications with a gradual dose increase over time. If these are ineffective or poorly tolerated, Baclofen at 5–10 mg twice daily, titrated up to 20 mg four times daily may be used. Gabapentin at 300 mg at bedtime may also be an option. Peripheral neuropathy with continuous burning dysaesthesia and hypersensitivity may benefit from tricyclic antidepressant such as amitriptyline and most will improve at 25–75 mg before bedtime. Adjunctive pain control can be

achieved with use of a mild narcotic. Percutaneous radiofrequency thermocoagulation of the affected nerve is a less invasive surgical approach to reduce the neuropathic pain. Surgical repositioning of the nerve is another option.

Mild compressive neuropathy would respond to conservative therapy. A neutral wrist splint during sleep is often used for carpal tunnel syndrome. Anti-inflammatory agents may help to reduce the symptoms. If these measures do not relieve the symptoms, steroid injections are useful as a temporizing measure as the edema and inflammatory phase may improve with time. Surgical decompression with sectioning of the transverse carpal ligament is indicated in those patients with severe wasting and weakness of the thumb abductors, persistent numbness or paresthesia, or in those who have failed conservative measures or have ongoing denervation in the abductor pollicis brevis on EMG studies.

Autonomic dysfunction is generally not severe enough to lead to symptomatic orthostatic hypotension and, therefore, rarely require specific therapy. Similarly, arrhythmias and conductive disturbances although are relatively common, they are frequently asymptomatic and require no therapy. Proton pump inhibitors and prokinetic agents including metocloperamide, domperidone and erythromycin are widely used to treat the gastrointestinal dysmotility. This has led to significant improvement in the morbidity associated with gastrointestinal manifestations. Supplemental nutrition support, enteral or parenteral, may be necessary in difficult cases.

6. Conclusion

Neurological manifestations of SSc are diverse and of differing clinical significance. Entrapment neuropathy and isolated cranial neuropathy are common clinical problems that require appropriate intervention. True CNS involvement is unusual as a primary disease event and generally reflects an overlap disorder or complications of events such as severe hypertension, intercurrent infection or medication. It seems likely, however, that subclinical peripheral nerve involvement and especially autonomic neuropathy is likely to occur quite frequently and may influence the features and severity of other manifestations including peripheral vascular insufficiency, cardiac disease or gastrointestinal tract involvement.

Key points

- Recent literature has reported a higher incidence of neurological complications of SSc than previously suggested.
- Precise mechanisms underlying this aspect of disease remain speculative and may involve microangiopathy, autoimmune-mediated neuronal damage, genetic predisposition and local factors such as compression.
- Few pathological evidence are available and a spectrum of neuropathological features have been described ranging from perivascular inflammation and vasculitis to end-stage gliosis.
- All levels of the nervous system may be affected. Myopathy is common, unlike frank inflammatory myositis which is mainly restricted to patients with overlap syndrome with a risk of myocardial involvement.
- CNS involvement may present as cerebrovascular disease (ischemic or hemorrhagic), seizures, cognitive impairment and psychiatric symptomatology. Intracranial and intraspinal calcification may also manifest as local or CNS symptoms.
- Distal axonal mono- or polyneuropathy is a major feature and typically affects the median nerve. Isolated cranial nerve lesions have been reported with facial sensory TN as a characteristic feature of this complication.
- Autoimmune dysfunction is characterized by parasympathetic impairment or marked sympathetic overactivity and have been implicated in the manifestation of gastrointestinal, cardiac and peripheral vascular insufficiency.
- The importance of neurological dysfunction in SSc also lies in the fact that some of these complications are increasingly recognized early or may even precede the onset of the systemic disease.

References

Averbuch-Heller, L., Steiner, I., Abramsky, O. 1992. Neurologic manifestations of progressive systemic sclerosis. Arch. Neurol. 49 (12), 1292–1295.

Beighton, P., Gumpel, J.M., Cornes, N.G. 1968. Prodromal trigeminal sensory neuropathy in progressive systemic sclerosis. Ann. Rheum. Dis. 27 (4), 367–369.

Bertinotti, L., Pietrini, U., Del Rosso, A., Casale, R., Colangelo, N., Zoppi, M., Matucci-Cerinic, M. 2002. The use of pupillometry in joint and connective tissue diseases. Ann. N. Y. Acad. Sci. 966, 446–455. Review.

Blanco, P., Viallard, J.F., Ellie, E., Faure, I., Mercie, P., Pellegrin, J.L., Leng, B. 1999. Extensive brain calcifications in systemic sclerosis: two cases. J. Neurol. Neurosurg. Psychiatry 67 (5), 697–698.

Boschi, A., Snyers, B., Lambert, M. 1993. Bilateral optic neuropathy associated with the crest variant of scleroderma. Eur. J. Ophthalmol. 3 (4), 219–222.

Brick, J.E., Brick, J.F. 1989. Neurologic manifestations of rheumatologic disease. Neurol. Clin. 7 (3), 629–639.

Cerinic, M.M., Generini, S., Pignone, A., Casale, R. 1996. The nervous system in systemic sclerosis (scleroderma). Clinical features and pathogenetic mechanisms. Rheum. Dis. Clin. North Am. 22 (4), 879–892.

Clements, P.J., Furst, D.E., Campion, D.S., Bohan, A., Harris, R., Levy, J., Paulus, H.E. 1978. Muscle disease in progressive systemic sclerosis: diagnostic and therapeutic considerations. Arthritis Rheum. 21 (1), 62–71.

Corbo, M., Nemni, R., Iannaccone, S., Quattrini, A., Lodi, M., Praderio, L., Comola, M., Lorenzetti, I., Comi, G., Canal, N. 1993. Peripheral neuropathy in scleroderma. Clin. Neuropathol. 12 (2), 63–67.

Cozzolino, D., Naclerio, C., Iengo, R., D'Angelo, S., Cuomo, G., Valentini, G. 2002. Cardiac autonomic dysfunction precedes the development of fibrosis in patients with systemic sclerosis. Rheumatology (Oxford) 41 (5), 586–588.

Cutolo, M., Nobili, F., Sulli, A., Pizzorni, C., Briata, M., Faelli, F., Vitali, P., Mariani, G., Copello, F., Seriolo, B., Barone, C., Rodriguez, G. 2000. Evidence of cerebral hypoperfusion in scleroderma patients. Rheumatology (Oxford) 39 (12), 1366–1373.

Danese, C., Caiola, S., Lucia, P., Cedrone, L., Colotto, M., Arceri, D., Angrisani, L. 2000. Relationship among VIP plasma levels, esophageal dysfunction and microcirculation in systemic sclerosis. Minerva Med. 91 (9), 185–189.

Das, C.P., Prabhakar, S., Lal, V., Kharbanda, P.S. 2002. Scleroderma, stroke, optic neuropathy: a rare association. Neurol. India 50 (4), 504–507.

Dengler, J.M., Levine, S.R., Tietjen, G., Washington, J.M. 1989. Clinical and radiologic features of cerebrovascular disease in scleroderma. Ann. Neurol. 26, 128–129.

Dessein, P.H., Joffe, B.I., Metz, R.M., Millar, D.L., Lawson, M., Stanwix, A.E. 1992. Autonomic dysfunction in systemic sclerosis: sympathetic overactivity and instability. Am. J. Med. 93 (2), 143–150.

Dyck, P.J., Hunder, G.G., Dyck, P.J. 1997. A case-control and nerve biopsy study of CREST multiple mononeuropathy. Neurology 49 (6), 1641–1645.

Eaker, E.Y., Kuldau, J.G., Verne, G.N., Ross, S.O., Sallustio, J.E. 1999. Myenteric neuronal antibodies in scleroderma: passive transfer evokes alterations in intestinal myoelectric activity in a rat model. J. Lab. Clin. Med. 133 (6), 551–556.

Estey, E., Lieberman, A., Pinto, R., Meltzer, M., Ransohoff, J. 1979. Cerebral arteritis in scleroderma. Stroke 10, 595–597.

Farrell, D.A., Medsger, T.A. Jr. 1982. Trigeminal neuropathy in progressive systemic sclerosis. Am. J. Med. 73 (1), 57–62.

Ferri, C., Emdin, M., Giuggioli, D., Carpeggiani, C., Maielli, M., Varga, A., Michelassi, C., Pasero, G., L'Abbate, A. 1997. Autonomic dysfunction in systemic sclerosis: time and frequency domain 24 hour heart rate variability analysis. Br. J. Rheumatol. 36 (6), 669–676.

Fischoff, D.K., Sirois, D. 2000. Painful trigeminal neuropathy caused by severe mandibular resorption and nerve compression in a patient with systemic sclerosis: case report and literature review. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 90 (4), 456–459.

Follansbee, W.P., Zerbe, T.R., Medsger, T.A. Jr. 1993. Cardiac and skeletal muscle disease in systemic sclerosis (scleroderma): a high risk association. Am. Heart J. 125 (1), 194–203.

Gilchrist, F.C., Bunn, C., Foley, P.J., Lympany, P.A., Black, C.M., Welsh, K.I., du Bois, R.M. 2001. Class II HLA associations with autoantibodies in scleroderma: a highly significant role for HLA-DP. Genes Immun. 2 (2), 76–81.

Goldblatt, F., Gordon, T.P., Waterman, S.A. 2002. Antibody-mediated gastrointestinal dysmotility in scleroderma. Gastroenterology. 123 (4), 1144–1150.

Gordon, R.M., Silverstein, A. 1970. Neurologic manifestations in progressive systemic sclerosis. Arch. Neurol. 22 (2), 126–134.

Grassi, W., Medico, P.D., Izzo, F., Cervini, C. 2001. Microvascular involvement in systemic sclerosis: capillaroscopic findings. Semin. Arthritis Rheum. 30 (6), 397–402.

Haverbush, T.J., Wilde, A.H., Hawk, W.A. Jr., Scherbel, A.L. 1974. Osteolysis of the ribs and cervical spine in progressive systemic sclerosis (scleroderma). A case report. J. Bone Joint Surg. Am. 56 (3), 637–640.

Heald, A. 1989. Progressive systemic sclerosis presenting as a case of trigeminal neuropathy. J. Neurol. Neurosurg. Psychiatry 52 (7), 918–920.

Heron, E., Fornes, P., Rance, A., Emmerich, J., Bayle, O., Fiessinger, J.-N. 1998. Brain involvement in scleroderma. Two autopsy cases. Stroke 29, 719–721.

Herrick, A.L., Jayson, M.I.V. 1996. Organ involvement: nervous system. Syst. Scler., 441–452.

Hietaharju, A., Jaaskelainen, S., Hietarinta, M., Frey, H. 1993a. Central nervous system involvement and psychiatric manifestations in systemic sclerosis (scleroderma): clinical and neurophysiological evaluation. Acta Neurol. Scand. 87 (5), 382–387.

Hietaharju, A., Jaaskelainen, S., Kalimo, H., Hietarinta, M. 1993b. Peripheral neuromuscular manifestations in systemic sclerosis (scleroderma). Muscle Nerve 16 (11), 1204–1212.

Hietaharju, A., Jantti, V., Korpela, M., Frey, H. 1993c. Nervous system involvement in systemic lupus erythematosus. Sjogren syndrome and scleroderma. Acta Neurol. Scand. 88 (4), 299–308.

Hietarinta, M., Ilonen, J., Lassila, O., Hietaharju, A. 1994a. Association of HLA antigens with anti-Scl-70-antibodies and clinical manifestations of systemic sclerosis (scleroderma). Br. J. Rheumatol. 33 (4), 323–326.

Hietarinta, M., Lassila, O., Hietaharju, A. 1994b. Association of anti-U1RNP- and anti-Scl-70-antibodies with neurological manifestations in systemic sclerosis (scleroderma). Scand. J. Rheumatol. 23 (2), 64–67.

Howe, S., Eaker, E.Y., Sallustio, J.E., Peebles, C., Tan, E.M., Williams, R.C. Jr. 1994. Antimyenteric neuronal antibodies in scleroderma. J. Clin. Invest. 94 (2), 761–770.

Jimenez-Moreno, J., Selva-O'Callaghan, A., Rovira-Canellas, A., Solans-Laque, R., Len, O., Olias, M., Fonollosa-Pla, V., Vilardell-Tarres, M. 1998. Trigeminal sensory neuropathy in systemic sclerosis. Br. J. Rheumatol. 37 (5), 587–589.

Kanzato, N., Matsuzaki, T., Komine, Y., Saito, M., Saito, A., Yoshio, T., Suehara, M. 1999. Localized scleroderma associated with progressing ischemic stroke. J. Neurol. Sci. 163 (1), 86–89.

Kinger, L.B. 1922. Scleroderma following nerve injury. Arch. Dermatol. Syphilol. 5, 579.

Kuwana, M., Inoko, H., Kameda, H., Nojima, T., Sato, S., Nakamura, K., Ogasawara, T., Hirakata, M., Ohosone, Y., Kaburaki, J., Okano, Y., Mimori, T. 1999. Association of human leukocyte antigen class II genes with autoantibody profiles, but not with disease susceptibility in Japanese patients with systemic sclerosis. Intern. Med. 38 (4), 336–344.

Lee, J.L., Haynes, J.M. 1987. Carotid arteritis and cerebral infarction due to scleroderma. Neurology 17, 18–22.

Lee, P., Bruni, J., Sukenik, S. 1984. Neurological manifestations in systemic sclerosis (scleroderma). J. Rheumatol. 11 (4), 480–483.

Leinwand, I., Duryee, A.W., Richter, M.N. 1954. Scleroderma (based on a study of over 150 cases). Ann. Intern. Med. 41, 1003–1041.

Lock, G., Straub, R.H., Zeuner, M., Antoniou, E., Holstege, A., Scholmerich, J., Lang, B. 1998. Association of autonomic nervous dysfunction and esophageal dysmotility in systemic sclerosis. J. Rheumatol. 25 (7), 1330–1335.

Lopez Dominguez, J.M., Blanco Ollero, A., Salaberri Maestrojuan, J., Casado Chocan, J.L., Chinchon Lara, I., Robledo Strauss, A., Diaz Espejo, C. 1995. Peripheral neuropathy in progressive systemic sclerosis. Neurologia 10 (4), 178–180.

Lori, S., Matucci-Cerinic, M., Casale, R., Generini, S., Lombardi, A., Pignone, A., Scaletti, C., Gangemi, P.F., Cagnoni, M. 1996. Peripheral nervous system involvement in systemic sclerosis: the median nerve as target structure. Clin. Exp. Rheumatol. 14 (6), 601–605.

Machet, L., Vaillant, L., Machet, M.C., Esteve, E., Muller, C., Khallouf, R., Lorette, G. 1992. Carpal tunnel syndrome and systemic sclerosis. Dermatology. 185 (2), 101–103.

Malandrini, A., Selvi, E., Villanova, M., Berti, G., Sabadini, L., Salvadori, C., Gambelli, S., De Stefano, R., Vernillo, R., Marcolongo, R., Guazzi, G. 2000. Autonomic nervous system and smooth muscle cell involvement in systemic sclerosis: ultrastructural study of 3 cases. J. Rheumatol. 27 (5), 1203–1206.

Medsger, T.A. Jr. 2003. Natural history of systemic sclerosis and the assessment of disease activity, severity, functional status, and psychologic well-being. Rheum. Dis. Clin. North Am. 29 (2), 255–273.

A recent review on systemic sclerosis.

Mondelli, M., Romano, C., Della Porta, P.D., Rossi, A. 1995. Electrophysiological evidence of 'nerve entrapment syndromes' and subclinical peripheral neuropathy in progressive systemic sclerosis (scleroderma). J. Neurol. 242 (4), 185–194.

Nadeau, S.E. 2002. Neurologic manifestations of connective tissue disease. Neurol. Clin. 20 (1), 151–178.

Nishida, A., Kaiya, H., Uematsu, M., Maeda, M., Mori, S., Wakabayashi, S. 1990. Transient global amnesia and Raynaud's phenomenon in scleroderma. Acta Neurol. Scand. 81 (6), 550–552.

Nobili, F., Cutolo, M., Sulli, A., Vitali, P., Vignola, S., Rodriguez, G. 2002. Brain functional involvement by perfusion SPECT in systemic sclerosis and Behcet's disease. Ann. N. Y. Acad. Sci. 966, 409–414.

Oddis, C.V., Eisenbeis, C.H. Jr., Reidbord, H.E., Steen, V.D., Medsger, T.A. Jr. 1987. Vasculitis in systemic sclerosis: association with Sjogren's syndrome and the CREST syndrome variant. J. Rheumatol. 14 (5), 942–948.

Pathak, R., Gabor, A.J. 1991. Scleroderma and central nervous system vasculitis. Stroke 22, 410–413.

Pinstein, M.L., Sebes, J.I., Leventhal, M., Robertson, J.T. 1989. Case report 579: progressive systemic sclerosis (PSS) with cervical cord compression syndrome, osteolysis and bilateral facet arthropathy. Skeletal Radiol. 18 (8), 603–605.

Piper, W.N., Helwig, E.B. 1950. Progressive systemic sclerosis. Arch. Dermatol. 72, 535–546.

Poncelet, A.N., Connolly, M.K. 2003. Peripheral neuropathy in scleroderma. Muscle Nerve. 28 (3), 330–335.

Richter, R.B. 1954. Peripheral neuropathy and connective tissue disease. J. Neuropathol. Exp. Neurol. 13 (1), 168–180.

Scardina, G.A., Mazzullo, M., Messina, P. 2002. Early diagnosis of progressive systemic sclerosis: the role of oro-facial phenomena. Minerva Stomatol. 51 (7–8), 311–317.

Schady, W., Sheard, A., Hassell, A., Holt, L., Jayson, M.I., Klimiuk, P. 1991. Peripheral nerve dysfunction in scleroderma. Q. J. Med. 80 (292), 661–675.

Schneider, F. 1991. Progressive multifocal leukoencephalopathy as a cause of neurologic symptoms in Sharp syndrome. Z. Rheumatol. 50 (4), 222–224.

Schweitzer, M.E., Cervilla, V., Manaster, B.J., Gerharter, J., Dalinka, M., Peck, W.W., Resnick, D. 1991. Cervical paraspinal calcification in collagen vascular diseases. Am. J. Roentgenol. 157 (3), 523–525.

Seijo Martinez, M., Castro del Rio, M., Losada Campa, A., Varela Freijanes, A., Rodriguez, M. 2000. Chorea as the presenting form of progressive systemic sclerosis. Neurologia 15 (7), 304–306.

Serup, J. 1984. Tactile sensitivity in systemic sclerosis. Assessment of two-point and circle discriminations of the digit. Dermatologica 168 (6), 279–282.

Sethi, S., Sequeira, W. 1990. Sparing effect of hemiplegia on scleroderma. Ann. Rheum. Dis. 49 (12), 999–1000.

Sjogren, R.W. 1994. Gastrointestinal motility disorders in scleroderma. Arthritis Rheum. 37 (9), 1265–1282.

Stacher, G., Merio, R., Budka, C., Schneider, C., Smolen, J., Tappeiner, G. 2000. Cardiovascular autonomic function, autoantibodies, and esophageal motor activity in patients with systemic sclerosis and mixed connective tissue disease. J. Rheumatol. 27 (3), 692–697.

Steen, V.D., Blair, S., Medsger, T.A. Jr. 1986. The toxicity of D-penicillamine in systemic sclerosis. Ann. Intern. Med. 104 (5), 699–705.

Stone, J., Franks, A.J., Guthrie, J.A., Johnson, M.H. 2001. Scleroderma 'en coup de sabre': pathological evidence of intracerebral inflammation. J. Neurol. Neurosurg. Psychiatry 70 (3), 382–385.

Straub, R.H., Zeuner, M., Lock, G., Rath, H., Hein, R., Scholmerich, J., Lang, B. 1996. Autonomic and sensorimotor neuropathy in patients with systemic lupus erythematosus and systemic sclerosis. J. Rheumatol. 23 (1), 87–92.

Straub, R.H., Andus, T., Lock, G., Zeuner, M., Palitzsch, K.D., Gross, V., Lang, B., Scholmerich, J. 1997. Cardiovascular and pupillary autonomic and somatosensory neuropathy in chronic diseases with autoimmune phenomena. A comparative study of patients with Crohn disease, ulcerative colitis, systemic lupus erythematosus, progressive systemic sclerosis and type I diabetes mellitus. Med. Klin. 92 (11), 647–653.

Tan, F.K., Arnett, F.C. 2000. Genetic factors in the etiology of systemic sclerosis and Raynaud phenomenon. Curr. Opin. Rheumatol. 12 (6), 511–519.

Unterberger, I., Trinka, E., Engelhardt, K., Muigg, A., Eller, P., Wagner, M., Sepp, N., Bauer, G. 2003. Linear scleroderma 'en coup de sabre' coexisting with plaque-morphea: neuroradiological manifestation and response to corticosteroids. J. Neurol. Neurosurg. Psychiatry 74 (5), 661–664.

Van de Perre, S., Vanhoenacker, F.M., Op de Beeck, B., Gielen, J.L., De Schepper, A.M. 2003. Paraspinal cervical calcifications associated with scleroderma. JBR-BTR 86 (2), 80–82.

Veale, D.J., Collidge, T.A., Belch, J.J. 1995. Increased prevalence of symptomatic macrovascular disease in systemic sclerosis. Ann. Rheum. Dis. 54 (10), 853–855.

Vicente, A., Herrero, C., Martin, E., Valls, J., Graus, F., Mascaro, J.M. 1991. Trigeminal sensory-neuropathy in systemic sclerosis. Clin. Exp. Dermatol. 16 (5), 403.

Walden, C.A., Gilbert, P., Rogers, L.F., Hendrix, R.W. 1990. Case report 620. Progressive systemic sclerosis (PSS) with paraspinous and intraspinous calcifications. Skeletal Radiol. 19 (5), 377–378.

Ward, M., Cure, J., Schabel, S., Smith, E.A., Schumacher, H.R. Jr., Silver, R.M. 1997. Symptomatic spinal calcinosis in systemic sclerosis (scleroderma). Arthritis Rheum. 40 (10), 1892–1895.

Zeballos, R.S., Fox, R.I., Cheresh, D.A., McPherson, R.A. 1994. Anti-glycosphingolipid autoantibodies in rheumatologic disorders. J. Clin. Lab. Anal. 8 (6), 378–384.

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CHAPTER 16

Paraneoplastic Syndromes

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1. Introduction

The term 'paraneoplastic syndrome' refers to a heterogeneous group of disorders that arise as non-metastatic complications of a malignancy. First recognized by Trousseu in 1865, as an association between venous thrombosis and gastric carcinoma (Siegelman and Needleman, 1992), many of these disorders alter the function of various organ systems via release of soluble molecules. Hypercalcemia developing due to ectopic expression of parathyroid hormone-related proteins, most commonly by squamous cell carcinoma of the lung or renal cell carcinoma, is the most classic example of a paraneoplastic syndrome.

A report by Denny-Brown (1948) described two patients with sensory neuropathy and bronchogenic carcinoma and subsequent autopsy showed complete destruction of the dorsal root ganglia with perivascular lymphocytes infiltration and no evidence of tumor metastasis. By the 1950s, it was recognized that perivascular aggregation of leukocytes could involve all areas of the neuraxis. For example, Brain et al. (1951) described three patients with cerebellar degeneration and cancer, in whom pathologic examination revealed Purkinje neuronal cell loss with lymphocytic infiltration. Wilkinson (1964) showed that serum of a patient with small-cell lung cancer (SCLC)-associated peripheral neuropathy contained low titer complement-fixing antibodies that bound antigens expressed within the central nervous system (CNS) and the dorsal root ganglia. A number of clinical syndromes describing remote effects of cancers were described by Brain and Norris (1965), but the pathophysiology of the disorders remained obscure. The prevailing view at the time was that the inflammation evident in the brains of these patients were likely due to an opportunistic viral infection associated with the cancer, which in fact did turn out to be correct in the case of progressive multifocal leukoencephalopathy (Henson and Urich, 1982).

During the past 30 years, paraneoplastic neurologic syndromes have been recognized as immune-mediated nervous system disorders that can affect any part of the nervous system, ranging from the neuromuscular junction and muscle in patients with solid or hematologic malignancies, to the peripheral nerves in SCLC, to the CNS. This notion was first suggested by Trotter et al. (1976), and established by Posner and colleagues in the 1980s (Anderson et al., 1987), who documented high titer antibodies reactive with clinically affected areas of the nervous system. These antibodies were found to be present in the serum and cerebrospinal fluid of PND patients, and, ultimately, to also react with tumors obtained from these patients. More recently, it has been recognized that patients with paraneoplastic disorders harbor both antibodies and T cells that target specific neural antigens expressed by various tumors (Table 1).

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Table 1
Paraneoplastic autoantibodies and their associations with neurologic symptoms (Darnell and Posner 2003)

Antibody	Cloned antigen genes	Tumor	Neurological symptoms	References
Anti-voltage-gated calcium channel (VGCC)	P/Q type VGCC MysB	Small-cell lung cancer	Lambert–Eaton myasthenic syndrome	Sanders (2003)
Anti-acetylcholine receptor (AChR)	AChR	Thymoma	Myasthenia gravis	Patrick and Lindstorm (1973)
Anti-voltage-gated potassium channels (VGPC)	Potassium channel	Thymoma, small-cell lung cancer	Neuromyotonia	Vernino and Lennon (2002)
Anti-myelin-associated glycoprotein (MAG)	MAG	Waldenstrom's macroglobulinemia	Peripheral neuropathy	Vital (2001)
Anti-Yo	CDR 34, CDR 62	Ovarian, breast and lung cancers	Paraneoplastic cerebellar degeneration (PCD)	Fathallah-Shaykh et al. (1991)
Anti-mGluR1	Glutamate receptor	Hodgkin's lymphoma	Paraneoplastic cerebellar degeneration	Smitt et al. (2000)
Anti-Tr	MAZ (?)	Hodgkin's lymphoma	Cerebellar degeneration	Bataller et al. (2002)
Anti-PCA-2	280 kD protein	Small-cell lung cancer	Encephalomyelitis, cerebellar degeneration, LEMS	Bataller et al. (2001)
Anti-Hu	HuD, HuC	Small-cell lung cancer, neuroblastoma, prostate cancer	Encephalomyelitis, sensory neuropathy, autonomic dysfunction, cerebellar degeneration	Graus et al. (2001); Dalmau et al. (1992); Szabo et al. (1991)
Anti-amphiphysin	Amphiphysin	Breast cancer, small-cell lung cancer	Stiff-person syndrome, paraneoplastic encephalomyelitis	Folli et al. (1993)
Anti-CV-2	POP 66	Thymoma, small-cell lung cancer	Encephalomyelitis, cerebellar degeneration, chorea, sensory neuropathy	Antoine et al. (2001)
Anti-Ma1	Ma1	Lung cancer, other cancers	Brain stem encephalitis, cerebellar degeneration	Rosenfeld et al. (2001)
Anti-Ma2	Ma2	Testicular cancer	Limbic brain stem encephalitis	Rosenfeld et al. (2001)
ANNA-3	?	Lung cancer	Sensory neuropathy, encephalomyelitis	Chan et al. (2001)
Anti-Ri	Nova	Gynecologic, lung and bladder	Ataxia with or without opsoclonus-myoclonus	Luque et al. (1991); Buckenovich et al. (1996); Ule et al. (2003)

This chapter will discuss paraneoplastic neurologic syndromes, which are thought to be immune-mediated, and will focus on the neurologic complications of these challenging syndromes.

2. Prevalence/Epidemiology

Paraneoplastic neurologic syndromes are usually rare and only affect less than 0.01% patients with malignancies. However, exceptions exist and include: Lambert–Eaton myasthenic syndrome (LEMS) which is recognized in 3% of patients with SCLC (Elrinton et al., 1991; Meddison et al., 2001); myasthenia gravis (MG) which is recognized in 15% of patients with thymoma; and demyelinating peripheral neuropathy which affects 50% of patients with POEMS (Darnell and Posner, 2003b).

Most of the paraneoplastic syndromes are associated with certain malignancies. Classic examples are: patients with paraneoplastic encephalomyelitis/subacute peripheral neuropathy (PEM/SSN), more than

75% have SCLC (Dalmau et al., 1992); patients with paraneoplastic cerebellar degeneration associated with the anti-Yo antibody, more than 95% of whom have breast or ovarian cancer (Peterson et al., 1992); and adult patients with opsoclonus-myoclonus ataxia, over half of whom have gynecologic tumors (Luque et al., 1991; Pranzatelli, 1992).

3. Etiology/pathogenesis

The pathogenesis of paraneoplastic neurological syndromes is poorly understood partially due to the inconsistent pathological features. For example, in paraneoplastic cerebellar degeneration associated with anti-Yo antibody, there is selective deletion of Purkinje neurons within the cerebellum with little or no evidence of inflammation (Peterson et al., 1992). On the other hand, in PEM/SSN associated with the anti-Hu antibody, there is widespread neuronal degeneration and inflammatory infiltrates within the CNS parenchyma (Graus et al., 2001). Despite inconsistent pathological features, an abundance of evidence suggests that these disorders are immune-mediated and the immune response is directed against antigen(s) expressed by cells at immunologically privileged sites such as brain or by tumors [also called onconeural antigens (Darnell, 1996)]. Under normal physiologic conditions, onconeural antigens are not subjected to immune surveillance due to their exclusive expression at immunologically privileged sites. The expression of the onconeural antigens by tumor cells at the periphery may trigger immune response with activation of B and T cells leading to the destruction of tumor and neural tissue (Darnell et al., 2003b).

Several lines of evidence support the above hypothesis. First, most patients with these disorders express antibodies that target antigens expressed exclusively by neurons or specific tumors. Secondly, some patients harbor cytotoxic CD8 + lymphocytes that target cells that express similar antigens (Albert et al., 1998). Cerebrospinal fluid analysis of these patients with active disease reveals pleocytosis with lymphocyte predominance (Albert et al., 2000). Molecular analysis of CD8 + T cell receptors isolated from CNS tissue of patients demonstrates clonal expansion of specific T cell clones (Voltz et al., 1998). There is also evidence suggesting effective anti-tumor immunity in some patients with these disorders (Albert and Darnell, 2004; Darnell and Posner, 2003a,b). For example, most patients present with occult tumor and limited stage disease, and, in rare cases, with radiological evidence of tumor regression.

Some of the antibodies that play a role in various paraneoplastic syndromes are shown in Table 1. In some paraneoplastic syndromes the pathogenic role of antibodies that target membrane-bound or extra-cellular antigens is well established. For example, antibodies against the P/Q type VGCC that are expressed in patients with LEMS have been shown to disrupt normal activity of P/Q type VGCC and passive transfer of these antibodies to rodents reproduced the syndrome. In other syndromes the role of the paraneoplastic antibodies in disease pathogenesis is not that well established. For example, anti-Hu antibodies in PEM/SSN bind to the Hu antigen, which is an RNA-binding protein and expressed within the nucleus and the cytoplasm. Passive transfer of this antibody to animals failed to reproduce the neurologic syndrome.

Furthermore, some studies suggested that the Hu antibodies can penetrate into cells in vivo; anti-Hu antibodies have been shown to be present within the CNS neuronal nuclei of a patient who died of PEM/SSN (Dalmau et al., 1991). The possibility that antibodies can penetrate into the cytoplasm or the nucleus of living cells and possibly disrupt cellular activity have also been suggested by Alarcon-Sagovia et al. (1996) who demonstrated the presence of anti-DNA antibodies within the nuclei of cells in patient with systemic lupus erythematosus.

In addition, there is evidence that patients with paraneoplastic cerebellar degeneration, which is associated with anti-Yo antibodies, harbor cytotoxic CD8 + T cells that express the Yo antigen (Albert et al., 2000). However, despite recent reports suggesting that neurons express components of the major histocompatibility class (MHC) I and class II molecules (Corriveau et al., 1998), the role of cellular immunity in disease pathogenesis is yet to be established.

One hurdle that has to be overcome in the effort to understand disease pathogenesis is the development of an animal model that replicates the neurologic

disease. In one report, animals immunized with DNA corresponding to the Hu antigen showed some protection against subsequent inoculation with tumor cells that express Hu. However, no neurologic symptoms were observed and the relevance of this model to paraneoplastic neurologic syndrome is not clear (Carpentier et al., 1998).

4. Clinical manifestations and diagnostic considerations

The clinical presentations of paraneoplastic syndromes may involve any part of the peripheral or CNS and the neurologic disease usually appears first and progresses rapidly. The identification of antibodies and their target neural antigens has substantially improved our ability to make an early diagnosis of specific neurologic syndromes and to identify the presence of tumors (Table 1). For example, the presence of the anti-Hu antibody in patients with progressive neuropathy and history of heavy smoking is highly suggestive of the diagnosis of PEM/SSN and SCLC.

4.1. Paraneoplastic syndromes associated with muscle weakness

LEMS is associated with anti-P/Q VGCC antibodies and disruption of neuromuscular junction function. Patients usually present with a gradual onset hip-girdle and to a lesser extent shoulder-girdle weakness, often complain about inability to get up from a chair, and symptoms improve during the day and with exercise. Patients also frequently present themselves with erectile dysfuction and other signs of autonomic dysfunction such as dry mouth. Less commonly, patients may present themselves with general weakness, fatigue myalgias and muscle stiffness. Oculobulbal involvement is rare except ptosis. It is important to note that neurological symptoms usually precede the detection of neoplasm (Sanders, 2003). Electrophysiological features of the disease include the facilitation of compound muscle action potentials following repetitive stimulation at high rates or maximal voluntary contractions for 10–20 s (Tim et al., 2000). Majority of the patients (>90%) test positive for the anti-P/Q VGCC antibody, which interferes with the normal calcium flux required for release of acetylcholine from the pre-synaptic neuromuscular or autonomic junctions. In addition 30% of patients test positive for other autoantibodies (Lennon et al., 1995; O'Neill et al., 1988). Of those patients with LEMS, 40–50% have SCLC (Tim et al., 2000) and other tumors are not commonly associated with this disorder.

MG is characterized by antibodies against acetylcholine receptors and it is most commonly associated with thymic hyperplasia (90%) or thymic epithelial tumor (10%). Patients with MG tend to have progressive muscle weakness that worsens during the day with marked involvement of the oculobulbar musculature (Drachman, 1994).

Other immune disorders associated with muscle weakness and malignancy include: inflammatory myopathies (especially dermatomyositis); paraneoplastic neuromyotonia (mostly in patients with SCLC, thymoma, and Hodgkin's lymphoma associated with antibodies against voltage-gated potassium channels); paraneoplastic myelitis (lymphoma); subacute motor neuropathy (lymphoma); and syndromes resembling amyotrophic lateral sclerosis (lymphoma).

Stiff-person (man) syndrome characterized with progressive muscle axial muscle stiffness is also associated with a number of tumor types, including multiple myeloma, lung, breast cancer, and antibodies against glutamic acid decarboxylase (GAD; Schiff et al., 2003) or amphiphysin (Folli et al., 1993). Detailed review of paraneoplastic conditions that interfere with muscle functions can be found by others authors (Dalmau and Rosenfeld, 2003).

4.2. Paraneoplastic syndromes associated with sensory or sensory motor neuropathy

Subacute sensory neuropathies are most commonly associated with SCLC and the presence of anti-Hu antibodies (Dalmau et al., 1992). Neurologic syndromes often precede the diagnosis of malignancies and patients report a history of heavy smoking. Patients with subacute sensory 'pins and needles' neuropathy initially report loss of vibratory sensation and joint position loss followed by the loss of pain and temperature sensation. Sensory deficit often results in

sensory ataxia, loss of dexterity with pseudoathatoid movement of the fingers and extremities, loss of deep tendon reflexes, sensorineural hearing loss, and loss of taste (Dalmau et al., 1992). Some patients also present with SICCA symptoms. Neurologic symptoms may start in one extremity but over time may spread and involve the entire body. In small number of patients motor weakness may also be present. Neurophysiologic profile reveals reduced or absent sensory potentials with normal motor nerve conduction velocities and histologic analysis reveals complete degeneration of the dorsal root ganglia. Ventral nerve root degeneration and secondary demyelination have also been described. In other patients, memory loss (limbic encephalopathy), autonomic dysfunction, cerebellar dysfunction, or blindness may be present (see below). Early in the course, cerebrospinal fluid analysis may show pleocytosis, increase protein and oligoclonal bands.

Patients with monoclonal gamopathies such as primary amyloidosis, multiple myeloma, monoclonal gamopathy of undetermined significance (MGUS), and Waldenstrom's macroglobulinemia may also present with sensory motor neuropathies. The presentation of the neuropathy varies on the type of malignancy (Ropper and Gorson, 1998) and some patients have high titers of anti-myelin-associated glycoprotein (MAG) antibodies (Manschot et al., 2000).

Paraneoplastic vasculitis that presents as mononeuritis multiplex or proximal weakness have been reported in lung, prostate, and endometrium cancers, and lymphomas (Oh, 1997); usually vasculitis precede the diagnosis of cancer and resembles small vessel vasculitis.

4.3. Paraneoplastic autonomic neuropathy

Patients with malignancies may present with signs of autonomic dysfunction such as hypothermia, orthostatic hypotension, or intestinal pseudo-obstruction. This presentation may also be accompanied by sensory neuropathy, cerebellar dysfunction or encephelopathy. Autonomic dysfunction is common in, what is perhaps the most common paraneoplastic syndrome, LEMS (affecting ~3% of SCLCa patients) (Newsom-Davis, 1999). These patients harbor antibodies to pre-synaptic calcium channels. Most patients with paraneoplastic autonomic neuropathy have SCLC and anti-Hu antibodies (Dalmau et al., 1992). Associations with other solid tumors or Hodgkin's disease have also been reported. Some patients with autonomic dysfunction also express anti-nicotinic acetylcholine receptor antibodies (Vernino et al., 1998). Furthermore, immunization of animals with nicotinic acetylcholine receptors induces autonomic dysfunction in animals (Lennon et al., 2003).

4.4. Paraneoplastic syndromes associated with central nervous system dysfunction

4.4.1. Paraneoplastic cerebellar degeneration

Patients with paraneoplastic cerebellar degeneration initially present with nausea, vomiting, and dizziness, and within several days develop gait difficulties, appendicular ataxia, dysarthria, dysphasia, and diplopia. This presentation may be isolated or be part of more generalized nervous system dysfunction such as peripheral neuropathy or encephalopathy.

Isolated paraneoplastic cerebellar dysfunction is commonly associated with gynecologic tumors (breast, ovarian, endometrial) and the expression of the anti-Yo antibodies. The Yo antigen that is expressed in these tumors (also called cdr2 (Darnell et al., 2000)) is a myc-binding protein that is normally expressed in brain and testes but is also widely expressed by ovarian and breast tumors (Okano et al., 1999). On pathological examination of the tumor, there is selective deletion of the Purkinje cell layer, usually without inflammatory infiltrates (Peterson et al., 1992). Cerebrospinal fluid analysis may be normal or show mild pleocytosis with T cell dominance (Albert et al., 2000). Most patients are females with a median age of 59 years (range 29–72 years; Peterson et al., 1992) and gynecologic cancer. In 63% of the cases neurological symptoms precede the diagnosis of cancer and few patients develop symptoms prior to tumor recurrence (Rojas et al., 2000). The progression of cerebellar dysfunction may be rapid as 59% of the patients are chair bound when the diagnosis is established. During the course of the disease, 94% of the patients become non-ambulatory (Rojas et al., 2000).

Patients with clinical signs of cerebellar dysfunction who test positive for the anti-Yo antibody should be evaluated carefully for the presence of cancer. Cases of occult tumors have been reported and any suspicious breast nodule or lymph node should be examined to rule out cancer. In recent series the median survival of 34 patients was 22 months (range 3–164 months). It is believed that patients harboring the Yo antibody have evidence of effective tumor immunity (e.g. patients typically harbor non-metastatic tumors (Albert and Darnell, 2004)); however, the overall prognosis is poor, as half the patients ultimately succumb to either tumor progression or neurologic disease (12/34 and 9/34 patients, respectively, in one series) (Rojas et al., 2000). Rare cases of cerebellar dysfunction associated with anti-Yo antibodies have also been described in patients with adenocarcinoma of the lung (Peterson et al., 1992). In addition, some patients with Hodgkin's lymphoma and isolated cerebellar degeneration express anti-Tr antibodies that bind the *myc*-associated zinc finger protein (MAZ) (Bataller et al., 2002).

Paraneoplastic cerebellar degeneration has also been described in the setting of paraneoplastic peripheral neuropathy and encephalomyelitis. The underlying tumor is SCLC in 80% of patients as part of PEM/SSN syndrome associated with the anti-Hu antibodies (Mason et al., 1997). On pathological examination there is evidence of inflammatory infiltrates and widespread neuronal destruction extending to the deep cerebellar nuclei (Mason et al., 1997). Cases of LEMS associated with cerebellar degeneration as well as patients with anti-P/Q VGCC antibodies without neuromuscular disease have also been reported (Clouston et al., 1992; Elrinton et al., 1991).

Other paraneoplastic cerebellar syndromes include: (a) patients with lung cancer, thymoma or uterine carcinoma may present with encephelopathy, peripheral neuropathy, optic neuritis, and cerebellar degeneration associated with anti-CV-2 antibodies that bind cytoplasmic antigen in a subset of glial cells (Antoine et al., 2001); (b) patients with breast, colon and parotid tumors that express anti-Ma-1 antibodies may also present with brain stem and cerebellar dysfunction (Dalmau et al., 1999).

4.4.2. Paraneoplastic encephalomyelitis

The symptoms of PEM are diverse and reflect the extent of CNS damage. Symptoms may arise from injury to the dorsal root ganglia, autonomic nervous system, spinal cord, cerebellum, brain stem, or temporal-limbic regions. On pathologic examination the extent of CNS damage may be wide spread with characteristic perivascular and interstitial infiltrates, gliosis and loss of neurons. Patients with paraneoplastic brain stem encephalitis present with various symptoms including nystagmus, dysphasia, dysarthria, sensorineural deafness, trigeminal sensory loss, or vertigo (Dalmau et al., 1992). Patients with paraneoplastic limbic encephalitis present with progressive behavioral changes and memory loss, seizures, or dementia (Gultekin et al., 2000).

The vast majority of patients with PEM have SCLC and anti-Hu antibodies. Young males who present with encephalomyelitis are more likely to have testicular cancer and abnormal titer of anti-Ma2 (also called anti-Ta) antibody. The Ma2 antigen is expressed in the neuronal nucleoli within the CNS and in germ-cell tumors and it shares homology with the Ma1 antigen that is associated with cerebellar and brain stem dysfunction (Voltz et al., 1999).

Other case reports of paraneoplastic encephalitis associated with other solid or hematological tumors have been described (Dalmau and Rosenfeld, 2003). The diagnosis of paraneoplastic limbic encephalitis is established based on clinical history, neurologic examination, proximity between the development of the neurologic disease and the diagnosis of tumor, and exclusion of other causes of encephalomyelitis (Gultekin et al., 2000). The presence of anti-onconeural antibody, typically either the Hu antibody or the Ma2 antibody in the serum or the CSF supports the diagnosis. In addition, in 70% of the patients, MRI shows some alteration in temporal-limbic regions. CSF analysis most often shows increased protein with no evidence of malignant cells. CSF pleocytosis with lymphocyte predominance is seen occasionally. Electrophysiologic testing is used to assess patients with peripheral neuropathies or seizures (Gultekin et al., 2000).

4.4.3. Paraneoplastic opsoclonus-myoclonus ataxia

Patient with paraneoplastic opsoclonus-myoclonus ataxia present with rapid, irregular, non-rhythmic movements of the eye in horizontal and vertical directions and twitching or spasm of a muscle or a group of muscles as well as ataxia (the association with ataxia is termed POMA). The disorder affects 2% of children with neuroblastoma and has been associated with other pediatric tumors (Posner, 1995). Adults are more likely to have ataxia. The most frequent tumor in adult male patients with POMA syndrome is SCLC while female patients are more likely to have gynecologic tumor (Posner, 1995). About half of the patients with the disorder express anti-Ri antibodies (also called anti-neural nuclear autoantibody type 2 or ANNA 2) which bind the NOVA-1 antigen, a neuron-specific RNA-binding protein (Luque et al., 1991; Buckenovich et al., 1996). Recent research provides evidence that NOVA plays important role in the regulation of alternative splicing in neurons and may help regulate protein expression in the inhibitory synapse (Ule et al., 2003).

4.4.4. Paraneoplastic visual syndrome

Several paraneoplastic visual syndromes have been described: cancer-associated retinopathy that affects patients with SCLC and gynecological tumors (in association with the expression of anti-recovering antibodies); melanoma-associated retinopathy; and paraneoplastic optic neuropathy (Ling and Pavesio, 2003).

5. Differential diagnosis

Paraneoplastic neurologic syndromes represent diverse group of disorders and patients who present with signs and symptoms consistent with these syndromes should be evaluated thoroughly.

It is important not to be swayed by various diagnostic tests that may confuse the clinician. For example, some patients have 14-3-3 protein associated with Creuzfeldt–Jakob disease but it is likely that these findings are due to extensive CNS damage and represent false positive results for this test (Saiz et al., 1999). In this respect, the presence of a specific onco-neural antibody strongly supports the diagnosis. However, the absence of onconeural antibodies does not exclude the possibility of paraneoplastic syndrome and cases of paraneoplastic neurological syndromes without identifiable tumor have been described (Darnell and De Angelis, 1993; Albert and Darnell, 2004). The diagnosis of tumor may be difficult as the tumor appears months to years after the neurologic disease is established (Gultekin et al., 2000). Sensitive imaging studies for the detection of tumor such as whole-body positron emission tomography are often used.

Differential diagnosis of neuropathies is broad and includes diabetes, nutritional deficiency (i.e. B12), drug toxicity (i.e. cisplatin), or high tumor burden (Gomm et al., 1990). In addition, other causes of neurologic disorders that are associated with cancer must be first excluded. For example, chronic sensory motor neuropathy is found in 10–15% of all cancer patients. The pathogenesis of this disorder is not immune-mediated as no antibodies against nerve or tumors are found and the neuropathy develops in patients with advanced metastatic disease.

Differential diagnosis of paraneoplastic autonomic neuropathy includes other medical causes of autonomic dysfunction such as drug toxicity (β-blockers), diabetics, nutritional deficiency (B12 deficiency) or amyloidosis. Infectious diseases (Chaga's disease or HIV) should also be excluded. Signs of sympathetic nervous system hyperactivity such as cardiac arrhythmias or excessive sweating may be associated with direct tumor invasion into sympathetic nerves rather than paraneoplastic syndrome.

Differential diagnosis of PEM include other immune disorders (i.e. systemic lupus erythematosus), nutritional deficiencies (i.e. Wernicke-Korsakoff encephalopathy), drug toxicity (i.e. doxifluradine), or infectious (i.e. herpes simplex encephalitis).

Differential diagnosis of paraneoplastic opsoclonus-myoclonus ataxia includes infectious or metabolic disorders, intracranial hemorrhage or metastatic cancer.

A complete discussion of PND differential diagnosis has been published elsewhere (Darnell, 1994).

6. Treatment

The goal of the treatment is to eradicate the tumor and slow the progression of the neurologic disease. Paraneoplastic disorders are rare and the neurological course is often variable, which hinders the design of a well-designed clinical trial to establish the best immunosuppressive therapy. In some disorders treatment of the tumor stabilizes the neurologic symptoms. In one study of 200 patients with PEM/SSN and anti-Hu antibodies, tumor treatment was associated with better neurologic outcome and lower mortality rate (Graus et al., 2001). Similarly, a study of 50 patients with limbic encephalitis, mostly with anti-Hu, or -Ma2 antibodies, have suggested that treatment of the tumor is associated with better neurological outcome than immune therapy (Gultekin et al., 2000). Patients with limbic encephalitis associated with anti-Hu antibodies have improved outcomes following a course of corticosteroids (Kaniecki and Morris, 1993) but the response to this therapy was highly variable and thus the evidence is anecdotal. There is also some anectodal evidence that intravenous immunoglobulin (IVIG), cyclophosphamide, and methylprednisolone halt the disease progression in patients with peripheral neuropathies associated with anti-Hu antibodies (Keime-Guibert et al., 2000). Most authorities justify early treatment with immunosuppressive agent to prevent potentially destructive immune response against neuronal antigen (Darnell et al., 2003).

Anecdotal evidence also suggests that treatment with IVIG, cyclophosphamide, and methylprednisolone improves neurologic outcome in patients with paraneoplastic cerebellar dysfunction (Keime-Guibert et al., 2000). However, usually patients with paraneoplastic cerebellar dysfunction associated with anti-Yo antibodies exhibit no neurologic response to treatment of the tumor or immunosuppression therapy (Rojas et al., 2000). Some authors used tacrolimus which target T cells and decrease number of activated T cells in the CSF of patients with PCD but there was no evidence of clinical efficacy of this approach (Albert et al., 2000).

By contrast, patients with LEMS benefit from effective treatment of the tumor with most patients reporting a significant improvement in muscle strength by treatment of the tumor alone (Chalk et al., 1990; Sanders, 2003). However, immunotherapy without effective treatment of the tumor usually results in poor to moderate improvement in muscle strength (Sanders, 2003). Nevertheless, 50–60% of LEMS patients are not diagnosed with cancer. In this population more aggressive immunotherapy is justified. Patients with severe muscle weakness exhibit a transient, short-term improvement in muscle strength following IVIG and plasmapheresis (Bain et al., 1996). Successive treatment with IVIG results in incremental improvement in muscle strength. Some patients require maintenance immunosuppressive treatment with prednisone or azathioprine to produce a more sustained improvement in muscle strength.

Other therapeutic modalities are also used to enhance neurotransmitter levels at the neuromuscular junction or central synapse. In stiff-man syndrome, benzodiazepenes (GABA-agonists) effectively treat the disorder (Levy et al., 1999). Other specific pharmacologic agents that have been used in LEMS include 3,4-diaminopyridine (DAP), which enhance neurotransmitter release by blocking potassium conductance and 85% of patients have a significant clinical improvement (Newsom-Davis, 2003). Side effects of DAP include paresthesias, seizure, asthma and possibly arrhythmia and this drug should be used with caution (McEvoy et al., 1989).

Guanine hydrochloride inhibits mitochondrial calcium uptake and increase intracellular calcium concentrations leading to enhancement of acetylcholine release at the neuromuscular junction. Patients with LEMS are reported to exhibit improvement in muscle strength following treatment with guanine hydrochloride (Sanders, 2003). Side effects of guanine hydrochloride are significant and include renal, hepatic, psychiatric and neurologic abnormalities. Treatment with cholinesterase inhibitor such as pyridostigmine is not effective as a monotherapy for LEMS. Several agents such as neuromuscular blocking agents used in anesthesia, aminoglycoside antibiotics, antiarrhythmic, β-adrenergic and calcium channel blocking agents may exacerbate LEMS and should be used with caution (Sanders, 2003).

Patients under 45 years with paraneoplastic MG who have positive titer of anti-acetylcholine receptor antibodies and thymoma, benefit from thymectomy

(Gronseth and Barohn, 2000). Older patients or patients who fail thymomectomy may benefit from prednisone alone or combined with azathioprine (Palace et al., 1998). Mycophenolate mofetil can be used to treat patients who cannot tolerate azathioprine (Chaudry et al., 2001). In addition, cyclosporine, or cyclophosphamide may also be used (Newsom-Davis, 2003). Plasmapheresis and IVIG are effective short-term interventions in cases of severe muscle weakness (Gajdos et al., 1997).

Key points

- The term 'paraneoplastic syndrome' refers to a heterogeneous group of disorders that arise as non-metastatic complications of a malignancy.
- Paraneoplastic neurologic syndromes have been recognized as disorders that can affect any part of the nervous system in patients with malignancies.
- The possibility of anti-tumor immunity and immune-mediated nervous system damage has been suggested in the pathogenesis of paraneoplastic syndromes.
- The identification of antibodies and their target neural antigens has substantially improved our ability to make an early diagnosis of specific paraneoplastic neurologic syndromes and to identify the presence of tumors.

References

Alarcon-Sagovia, D., Ruiz-Arguelles, A., Llorente, L. 1996. Broken dogma: penetration of autoantibodies into living cells. Immun. Today 17, 163–164.

Albert, M.L., Austin, L.M., Darnell, R.B. 2000. Detection and treatment of activated T cells in the cerebrospinal; fluid of patients with paraneoplastic cerebellar degeneration. Ann. Neurol. 47, 9–17.

Albert, M.L., Darnell, J.C., Bender, A., Francisco, L.M., Bhardwaj, N., Darnell, R.B. 1998. Tumor-specific killer cells in paraneoplastic cerebellar degeneration. Nat. Med. 4, 1321–1324.

Albert, M.L., Darnell, R.B. 2004. Paraneoplastic neurological degenerations: keys to tumour immunity. Nat. Rev. Cancer 4, 36–44.

Anderson, N.E., Cunningham, J.M., Posner, J.B. 1987. Autoimmune pathogenesis of paraneoplastic neurological syndromes. Crit. Rev. Neurobiol. 3, 245–299.

Antoine, J.C., Honnorat, J., Camdessanche, J.P., et al. 2001. Paraneoplastic anti-CV-2 antibody react with peripheral nerve and are associated with mixed axonal and demyelinating peripheral neuropathy. Ann. Neurol. 49, 214–222.

Bain, P.G., Motomura, M., Newsom-Davis, J., Misbah, S.A., Chapel, H.M., Lee, M.L., Vincent, A. 1996. Effects of intervenous gammaglobulins on muscle weakness and calcium channel antibodies in the Lambert–Eaton myasthenic syndrome. Neurology 47, 678–683.

Bataller, L., Graus, F., Saiz, A., Vilchez, J.J. 2001. Clinical outcome in adult idiopathic or paraneoplastic opsoclonus-myoclonus. Brain 124, 437–443.

Bataller, L., Deborly, F., Wade, B.S., Graus, F., Rosenfeld, M.R., Dalmau, J. 2002. The MAZ protein is an autoantigen of Hodgkin's disease and paraneoplastic cerebellar dysfunction. Ann. Neurol. 53, 123–127.

Brain, L., Norris, F.J. 1965. The Remote Effects of Cancer on the Nervous System. Grune and Stratton, New York.

Brain, W.R., Daniel, P.M., Greenfield, J.G. 1951. Subacute cortical cerebellar degeneration and its relation to carcinoma. J. Neurol. Neurosurg. Psychiatry 14, 59–75.

Buckenovich, R.J., Yang, Y.Y., Darnell, R.B. 1996. The onconeural antigen, NOVA-1 is a neuron-specific RNA-binding protein, the activity of which is inhibited by paraneoplastic antibodies. J. Neurosci. 16, 1114–1123.

Carpentier, A.F., Rosenfeld, M.R., Delattre, J.-Y., Whalen, R.G., Posner, J.B., Damau, J. 1998. DNA vaccination with HuD inhibits the growth of neuroblastoma in mice. Clin. Cancer Res. 4, 2819–2824.

Chalk, C.H., Murray, N.M., Newsom-Davis, J., O'Neill, J.H., Spiro, S.G. 1990. Response of the Lambert–Eaton myasthenic syndrome to treatment of associated small-cell lung carcinoma. Neurology 40, 1543–1552.

Chan, K.H., Vernino, S., Lennon, V.A. 2001. ANNA-3 anti-neural nuclear antibody: marker of lung cancer-related autoimmunity. Ann. Neurol. 50, 301–311.

Chaudry, V., Cornblath, D.R., Griffin, J.W., O'brien, R., Drachman, D.B. 2001. Mycophenolate mofetil: a safe and promising immunosuppressant in neuromuscular disease. Neurology 56, 94–96.

Clouston, P.D., Saper, C.B., Arbizu, T., Johnston, I., Lang, B., Newsom-Davis, J., Posner, J.B. 1992. Paraneoplastic cerebellar degeneration. III. Cerebellar degeneration, cancer, and the Lambert–Eaton myasthenic syndrome. Neurology 42, 1944–1950.

Corriveau, R.A., Huh, G.S., Shatz, C.J. 1998. Regulation of class I MHC gene expression in the developing and mature CNS by neural activation. Neuron 21, 505–520.

Dalmau, J., Furaneaux, H.M., Rosenblum, M.K., Graus, F., Posner, J.B. 1991. Detection of the anti-Hu antibody in specific regions of the nervous system and tumor from patients with paraneoplastic encephalomyelitis/sensory neuropathy. Neurology 41, 17564–17570.

Dalmau, J., Gultekin, S.H., Voltz, R., Hoard, R., Deschamps, T., Balmaceda, C., Batchelor, T., Gerstner, E., Eichen, J., Frennier, J., Posner, J.B., Rosenfeld, M.R. 1999. Ma-1, a novel neuron- and

testis-specific protein, is recognized by the serum of patients with paraneoplastic neurologic disorder. Brain 122, 27.

Dalmau, J., Graus, F., Rosenbaum, M.K., Posner, J.B. 1992. Anti-Hu-associated paraneoplastic encephalomyelitis/sensory neuropathy. A clinical study of 71 patients. Medicine 71, 59–72.

Dalmau, J., Rosenfeld, M.R. 2003. Paraneoplastic syndromes of the nervous system, up to date, version 11.3, on line publication.

Darnell, J.C., Albert, M.L., Darnell, R.B. 2000. Cdr2, a target antigen of naturally occurring human tumor immunity, is widely expressed in gynecological tumors. Cancer Res. 60, 2136–2139.

Darnell, R.B., De Angelis, L.M. 1993. Regression of small cell lung carcinoma in patients with paraneoplastic neuronal antibodies. Lancet 341, 21–23.

Darnell, R.B. 1994. Paraneoplastic syndromes. In: E. Feldmann (Ed.), Current Diagnosis in Neurology. Mosby Year Book, Inc., Philadelphia, pp. 137–141.

Darnell, R.B. 1996. Onconeural antigens and the paraneoplastic neurologic disorders: at the intersection of cancer, immunity and the brain. Proc. Natl Acad. Sci. USA 93, 4529–4536.

Darnell, R.B., Posner, J.B. 2003a. Observing the invisible: successful tumor immunity in humans. Nat. Immunol. 4, 201.

Darnell, R.B., Posner, J.B. 2003b. Paraneoplastic syndromes of the nervous system. N. Engl. J. Med. 349, 1543–1554.
A recent review article on the paraneoplastic syndromes of the nervous system.

Denny-Brown, D. 1948. Primary sensory neuropathy with muscle changes associated with carcinoma. J. Neurol. Neurosurg. Psychiatry 11, 73–87.

Drachman, D.B. 1994. Myasthenia gravis. N. Engl. J. Med. 330, 1797–1803.

Elrinton, G.M., Murray, N.M., Spiro, S.G., Newsom-Davis, J. 1991. Neurological paraneoplastic syndromes in patients with small cell lung cancer. J. Neurol. Neurosurg. Psychiatry 54, 764–767.

Fathallah-Shaykh, H., Wolf, S., Wong, E., Posner, J.B., Furneaux, H.M. 1991. Cloning of a leucine-zipper protein recognized by the sera of patients with antibody-associated paraneoplastic cerebellar degeneration. Proc. Natl Acad. Sci. 88, 3451–3454.

Folli, F., Solimena, M., Cofiell, R., Austoni, M., Tallini, G., Fassetta, G., Bates, D., Cartlidge, N., Bottazzo, G., Piccolo, G., DeCamilli, P. 1993. Autoantibodies to a 128-kD synaptic protein in three women with stiff-man syndrome and breast cancer. N. Engl. J. Med. 328, 546–551.

Gajdos, P., Chevret, S., Clair, B., Tranchant, C., Chastang, C. 1997. Clinical trial of plasma exchange and high-dose intervenous immunoglobulins in myasthenia gravis: Myasthenia Gravis Clinical Study Group. Ann. Neurol. 41, 789–796.

Gomm, S.A., Thatcher, N., Barber, P.V., Cumming, W.J. 1990. A clinicopathologic of the paraneoplastic neuromuscular syndromes associated with lung cancer. Q. J. Med. 75, 577–582.

Graus, F., Keime-Guibert, F., Rene, R., Benyahia, B., Ribalta, T., Ascaso, C., Escaramis, G., Delattre, J.Y. 2001. Anti-Hu-associated paraneoplastic encephalomyelitis: analysis of 200 patients. Brain 124, 1138–1148.

Gronseth, G.S., Barohn, R.J. 2000. Practice parameter: thymomectomy for autoimmune myasthenia gravis (an evidence based review): report of the Quality Standard Subcommittee of the American Academy of Neurology. Neurology 55, 7–15.

Gultekin, S.H., Rosenfeld, M.R., Voltz, R., Eichen, J., Posner, J.B., Dalmau, J. 2000. Paraneoplastic limbic encephelitis: neurological symptoms, immunological findings and tumor associations in 50 patients. Brain 123, 1481–1494.

Henson, R.A., Urich, H. 1982. Cancer and the Nervous System: the Neurologic Manifestations of the Systemic Malignant Disease, 1 ed., Blackwell Scientific, London.

Kaniecki, R., Morris, J.C. 1993. Reversible paraneoplastic limbic encephelitis. Neurology 43, 2418–2421.

Keime-Guibert, F., Graus, F., Fleury, A., Rene, R., Honnorat, J., Broet, P., Delattre, J.Y. 2000. Treatment of paraneoplastic neurologic syndromes with anti-neural antibodies (anti-HU, and -Yo) with combinations of immunoglobulins, cyclophosphamide and methylprednisolone. J. Neurol. Neurosurg. Psychiatry 68, 479.

Lennon, V.A., Ermilov, L.G., Szurszewski, J.H., Vernino, S. 2003. Immunization with neuronal acetylcholine receptor induces neurological auto-immune disease. J. Clin. Invest. 111, 907–1006.

Lennon, V.A., Kryzer, T.J., Greismann, G.E., et al. 1995. Calcium-channel antibodies in the Lambert–Eaton myasthenic syndrome and other paraneoplastic syndromes. N. Engl. J. Med. 332, 1472–1476.

Levy, L.M., Dalakas, M.C., Floeter, M.K. 1999. The stiff-person syndrome: an autoimmune disorder affecting neurotransmission of gamma-aminobutyric acid. Ann. Intern. Med. 131, 522–530.

Ling, C.P., Pavesio, C. 2003. Paraneoplastic syndromes associate with visual loss. Curr. Opin. Opthalmol. 14, 426–432.

Luque, F.A., Furneaux, H.M., Ferzinger, R., Rosenblum, M., Wray, S., Schold, S., Glantz, M., Jaeckle, K., Biran, H., Lesser, M., et al. 1991. Anti-Ri: antibody associated with paraneoplastic opsoclonus myoclonus and breast cancer. Ann. Neurol. 29, 241–251.

Manschot, S.M., Notermans, N.C., Van den Berg, L.H., Verschuuren, J.J., Lokhorst, H.M. 2000. Three families with polyneuropathy associated with monoclonal gammopathy. Arch. Neurol. 57, 740–746.

Mason, W.P., Graus, F., Lang, B., Honnorat, J., Delattre, J.Y., Valideoriola, F., Antoine, J.C., Rosenblum, M.K., Rosenfield, M.R., Newsom-Davis, J., Posner, J.B., Dalmau, J. 1997. Small-cell lung cancer, paraneoplastic cerebellar degeneration and the Lambert–Eaton myasthenic syndrome. Brain 120, 1279–1300.

McEvoy, K.M., Windebank, A.J., Daube, J.R., Low, P.A. 1989. 3, 4,-Diaminopyridine in Lambert-Eaton myasthenic syndrome and myasthenia gravis. N. Engl. J. Med. 321, 1567–1571.

Meddison, P., Lang, B., Mills, K., Newsom-Davis, J. 2001. Long term outcome in Lambert–Eaton myasthenic syndrome without lung cancer. J. Neurol. Neurosurg. Psychiatry 70, 212–217.

Newsom-Davis, J. 1999. Paraneoplastic neurological disorders. J. R. Coll. Physicians Lond. 33, 225–227.

Newsom-Davis, J. 2003. Therapy for myasthenia gravis and Lambert–Eaton myasthenic syndrome. Semin. Neurol. 23, 191–198.

Oh, S.J. 1997. Paraneoplastic vasculitis of the peripheral nervous system. Neurol. Clin. 15, 849–853.

Okano, H.J., Park, W.Y., Corradi, J.P., Darnell, R.B. 1999. The cytoplasmic Purkinje antigen cdr2 down regulates Myc function: implications for neuronal and tumor cell survival. Genes Dev. 13, 2987–3098.

Okano, H.J., Park, W.Y., Corradi, J.P., Darnell, R.B. 1999. The cytoplasmic Purkinje antigen cdr2 downregulates Mye function: implications for neuronal and tumor cell survival. Genes. Dev. 13, 2987–3098.

Palace, J., Newsom-Davis, J., Lecky, B. 1998. A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. Myasthenia Gravis Study Group. Ann. Neurol. 41, 789–796.

Patrick, J., Lindstorm, J. 1973. Auto immune response to acetylcholine receptor. 180, 871–872.

Peterson, K., Rosenblum, M.K., Kotanides, H., Posner, J.B. 1992. Paraneoplastic cerebellar degeneration. I. A clinical analysis of 55 anti-Yo antibody positive patients. Neurology 42, 1931–1937.

Posner, J.B. 1995. Neurologic Complications of Cancer. Davis, Philadelphia.

Pranzatelli, M.R. 1992. The neurobiology of the opsoclonus-myoclonus syndrome. Clin. Neuropharmacol. 15, 186–228.

Rojas, I., Graus, F., Keime-Guibert, F., Rene, R., Delattre, J.Y., Ramon, J.M., Dalmau, J., Posner, J.B. 2000. Long-term clinical outcome of paraneoplastic cerebellar degeneration and anti-Yo antibody. Neurology 55, 713–715.

Ropper, A.H., Gorson, K.C. 1998. Neuropathies associated with paraproteinemia. N. Engl. J. Med. 338, 1601–1609.

Rosenfeld, M.R., Eichen, J.G., Wade, D.F., Posner, J.B., Dalmau, J. 2001. Molecular and clinical diversity in paraneoplastic immunity to Ma proteins. Ann. Neurol. 50, 339–348.

Saiz, A., Graus, F., Dalmau, J., Pifarré, A., Marin, C., Tolosa, E. 1999. Detection of the 14-3-3 brain protein in the cerebral spinal fluid of patients with paraneoplastic neurologic disorder. Ann. Neurol. 46, 774–777.

Sanders, D.B. 2003. Lambert–Eaton myasthenic syndrome: diagnosis and treatment. Ann. NY Acad. Sci. 998, 500–508.

Schiff, D., Dalmau, J., Myers, D.J. 2003. Anti-GAD antibody positive stiff-limb syndrome in multiple myeloma. J. Neurooncol. 65, 173–175.

Siegelman, E.S., Needleman, L. 1992. Venous thrombosis and cancer (letter). N. Engl. J. Med. 328, 885.

Sillevis Smitt, P., Kinoshita, A., De Leeuw, B., Moll, W., Coesmans, M., Jaarsma, D., Henzen-Logmans, S. Vecht, C., De Zeeuw, C., Sekiyama, N., Nakanishi, S., Shigemoto, R., 2000. Paraneoplastic cerebellar ataxia due to antibodies against glutamate receptors. N. Engl. J. Med. 342, 21–27.

Szabo, A., Dalmau, J., Manley, G., Rosenfeld, M., Wong, E., Henson, J., Posner, J.B., Furneaux, H.M. 1991. HuD, a paraneoplastic encephalomyelitis antigen, contains RNA binding domains and is homologous to Elav and self-lethal. Cell 67, 325–333.

Tim, R.W., Massey, J.M., Sanders, D.B. 2000. Lambert Eaton myasthenic syndrome: electrodiagnostic findings and response to treatment. Neurology 54, 2176.

Trotter, J., Hendin, B., Osterland, C. 1976. Cerebellar degeneration with Hodgkin's disease: an immunological study. Arch. Neurol. 33, 660–661.

Ule, J., Jensen, K.B., Ruggio, M., Mele, A., Ule, A., Darnell, R.B. 2003. CLIP identifies Nova-regulated RNA networks in the brain. Science 302, 1212–1215.

Vernino, S., Adamski, J., Kryzer, T.J., Kryzer, T.J., Fealey, R.D., Lennon, V.A. 1998. Neuronal nicotinic Ach receptor antibody in subacute autonomic neuropathy and cancer-related syndromes. Neurology 50, 1806–1812.

Vernino, S., Lennon, V.A. 2002. Ion channel and striational antibodies define continuum of autoimmune neuromuscular hyperexcitability. Muscle Nerve 26, 702–707.

Vital, A. 2001. Paraproteinemic neuropathies. Brain Pathol. 11, 399–407.

Voltz, R., Dalmau, J., Posner, J.B., Rosenfeld, M.R. 1998. T-cell receptor analysis in anti-Hu associated paraneoplastic encephalomyelitis. Neurology 51, 1146–1150.

Voltz, R., Gultekin, S.H., Rosenfeld, M.R., Gerstner, E., Eichen, J., Posner, J.B., Dalmau, J. 1999. A serologic marker of paraneoplastic limbic and brain stem encephelitis in patients with testicular cancer. N. Engl. J. Med. 340, 1788.

Wilkinson, P.C. 1964. Serological findings in carcinomatous neuropathy. Lancet I, 1301–1303.

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