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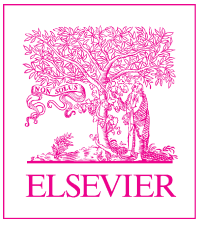

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Foreword

This is the first volume in the *Handbook of Clinical Neurology* series devoted entirely to neuro-otology, a relatively young branch of clinical medicine that studies and treats neurologic disorders of the ear, eighth cranial nerve, and associated central pathways, leading to symptoms such as vertigo, dizziness, and hearing disorders.

Herman Kingma and Raymond van de Berg start their chapter on the anatomy, physiology, and physics of the peripheral vestibular system by quoting Wilson and Melvill-Jones' preface to the famous book, *Mammalian Vestibular Physiology* (1979): "It is easy to underrate the importance of a sensory system whose receptor is buried deep within the skull and of whose performance we are usually not aware". After reading this neuro-otology volume, it is no longer possible to deny the importance of this complex system for our normal daily activities and the great impact of uni- or bilateral vestibular loss.

We were very fortunate to have as volume editors two distinguished scholars, Joseph M. Furman from the Department of Otolaryngology, University of Pittsburgh, Pittsburgh, PA, USA and Thomas Lempert from the Department of Neurology, Schlosspark-Klinik and Vestibular Research Group, Berlin, Germany. They have assembled an excellent, international, and multidisciplinary group of experts and guided them firmly to create this comprehensive book. We are grateful to them and to all the contributors.

This volume will not only be of interest to clinical neurologists. Parts of it will appeal also to psychiatrists (e.g., the chapter on functional and psychiatric vestibular disorders) and pediatricians (e.g., the chapter on vertigo and dizziness in children). Moreover, the first part of this volume, which discusses the anatomy, physiology, neurotransmitters, pharmacology, integration of information, and physics of the peripheral and central vestibular systems, will appeal to both neuro-otologists and basic neuroscientists working in the field.

In addition to the printed version, the volume will be available electronically on Elsevier's Science Direct website, which is becoming increasingly popular with readers and will facilitate the book's accessibility. Indeed, all of the volumes in the present series of the *Handbook* are available electronically on this website.

As always, it is a pleasure to thank Elsevier, our publisher – and in particular Michael Parkinson in Scotland and Kristi Anderson and Mara E. Conner in San Diego – for their assistance in the development and production of this volume.

Michael J. Aminoff
François Boller
Dick F. Swaab

Preface

Vertigo and dizziness rank among the most common symptoms in primary care, otolaryngology, and neurology. Causes vary from harmless but bothersome conditions such as benign paroxysmal positional vertigo to life-threatening emergencies such as posterior fossa strokes. Our understanding of diagnosis, pathophysiologic mechanisms, and effective treatments has increased considerably in the last two decades. New developments include algorithms for bedside detection of vestibular strokes, the delineation of vestibular migraine as one of the most frequent causes of recurrent vertigo, description of variants of benign paroxysmal positional vertigo, devices for testing individual semicircular canals and otolith organs, and the advancement of vestibular rehabilitation as the most important therapeutic tool in neuro-otology.

This volume of the *Handbook of Clinical Neurology* assembles contributions from leading international authors to communicate the current clinical knowledge of neuro-otology and a comprehensive list of references. Chapters 1–14 deal with basic knowledge and general principles of neuro-otology, such as anatomy, physiology, epidemiology, history taking, examination, and vestibular rehabilitation. This is followed by the disease-specific Chapters 15–28, covering all common causes of vertigo and dizziness. The numerous tables and figures in this book make the field of vestibular science and medicine even more accessible.

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Thomas Lempert

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Chapter 1

Anatomy, physiology, and physics of the peripheral vestibular system

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Abstract

Many medical doctors consider vertigo and dizziness as the major, almost obligatory complaints in patients with vestibular disorders. In this chapter, we will explain that vestibular disorders result in much more diverse and complex complaints. Many of these other complaints are unfortunately often misinterpreted and incorrectly classified as psychogenic. When we really understand the function of the vestibular system, it becomes quite obvious why patients with vestibular disorders complain about a loss of visual acuity, imbalance, fear of falling, cognitive and attentional problems, fatigue that persists even when the vertigo attacks and dizziness decreases or even disappears. Another interesting new aspect in this chapter is that we explain why the function of the otolith system is so important, and that it is a mistake to focus on the function of the semicircular canals only, especially when we want to understand why some patients seem to suffer more than others from the loss of canal function as objectified by reduced caloric responses.

INTRODUCTION

In their preface to the book, *Mammalian Vestibular Physiology*, published in 1979, the famous vestibular scientists Wilson and Melvill Jones made a perceptive statement: "It is easy to underrate the importance of a sensory system whose receptor is buried deep within the skull and of whose performance we are usually not aware" (Wilson and Melvill Jones, 1979). This statement is still up to date, as many doctors are unaware of the relevance of the vestibular system in daily life and also think that central compensation and sensory substitution almost completely deal with vestibular loss and reduce complaints to a minimum. Also, in unilateral loss, it is often stated that the healthy labyrinth will take over. How absurd such a statement is, becomes clear if we claim that losing one ear or one eye is of no importance as we can still hear with one ear and see with one eye. Losing one vestibular organ, like losing one ear or eye, results in a disturbing asymmetry. Bilateral vestibular areflexia (there is not even a common word for it in lay language) is a major handicap like deafness or blindness. But apparently, symptoms associated with bilateral vestibular areflexia are often not recognized, leading to a delay of many years before a correct diagnosis is made (van de Berg et al., 2011; Guinand et al., 2015a; Guyot, 2015). The major reason is that the function of the vestibular system is poorly understood by both doctors and patients. This unawareness also led to problems in obtaining permission to develop a vestibular implant for humans, very different from the development of cochlear implants several decades ago. Only after publication of a number of scientific articles showing the impact and incidence of severe bilateral vestibular loss was a Swiss–Dutch research team allowed to execute the first human vestibular implantation in August 2012 (Pelizzone et al., 2014; Perez Fornos et al., 2014; Guinand et al., 2015b).

This all illustrates how poorly the function and relevance of the vestibular system is understood in clinical practice, and this is what has motivated us to write this

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chapter in the hope that the real value of this complex vestibular system in human life will become obvious for everyone and that this awareness can lead to an earlier diagnosis and better patient management.

A major misperception is that vertigo is the major vestibular symptom of a peripheral vestibular function disturbance, which only holds for abrupt asymmetries of vestibular function. A slowly decreasing or relatively stable but permanent function loss is more frequent (e.g., aging) and – despite central compensation and sensory substitution – leads to a diversity of other complaints due to the impaired ability of the normally extremely sensitive labyrinthine sensors to detect head motion and head orientation relative to gravity (Kingma and Janssen, 2013). These persisting complaints are: a loss of visual (dynamic) acuity, imbalance, fear of falling and actual falls, visual vertigo, chronically enhanced cognitive load, and fatigue reflecting the various functions of the labyrinth.

To serve all disciplines, we choose a multidisciplinary approach, including clinical sciences, physiology, and physics.

GENERAL INTRODUCTION TO THE LABYRINTH

The two balance organs located in the left and right temporal bone of the skull, the vestibular nerves, the vestibular nuclei, the vestibulocerebellum, and the vestibular cortex are not the only but the major structures that together form the vestibular system. In this chapter we will focus on the balance organs providing sensory input to the central vestibular system.

The vestibular system contributes to optimize visual acuity during head motion, enhances balance control, and allows detection of self-motion and orientation relative to gravity. As these tasks are quite complicated in many conditions of daily life, we also use vision, proprioception (including gravity receptors along the large blood vessels), and learning processes. In fact, the brain seems to neglect vestibular input under several conditions when no other sensory input is available to verify the interpretation of motion or spatial orientation (divers in deep, dark water and skiers covered by snow in an avalanche). Only very fast vestibulo-ocular and vestibulospinal reflexes seem to be an exception to this rule. The vestibular system makes use of specialized sensors located in the head to monitor angular accelerations (rotations in three dimensions (3D)) and linear accelerations (translations in 3D and tilt relative to the gravity vector) of the head in space. During head movements, many forces act upon these sensors and often all sensors are stimulated simultaneously. On earth, head movements always occur within the gravitational field and are often composed of both rotations and translations. Physical principles teach us that the position and orientation of the sensors in the head are irrelevant for a precise detection of rotations but crucial for detection of additional translational components and centrifugal forces (Kingma and Janssen, 2013). If we rotate around any axis, both labyrinths will always sense the same rotational acceleration (Fig. 1.1) and translational acceleration. In contrast, centrifugal forces during rotation increase with eccentricity (Fig. 1.2).

The function of the labyrinth can be illustrated by the following example. Imagine that you hold a glass of water filled to the brim. Any movement (translation or rotation) with small accelerations or small tilts will make the water move and lead to spillage. Only very smooth movements and extremely small tilts avoid the water being spilled. Basically, the human labyrinth acts like such a glass of water fixed in the head: it detects extremely small accelerations or tilts. It is hard avoiding stimulation of this very sensitive head motion sensor system, similar to avoiding water spillage when moving the glass.

The anatomy of the labyrinth in the head is of course much more complex than a glass of water. In each temporal bone, on either side (Fig. 1.3), we find a bony labyrinth, composed of cavities and tubes. Inside the bony labyrinth lies the membranous labyrinth (Fig. 1.4) surrounded by perilymph that is supplied from the subarachnoid space via the ductus perilymphaticus. The membranous labyrinth is filled with endolymph. The endolymph is a secretion product of the dark cells in the vestibular part of the labyrinth and the stria vascularis in the cochlear part of the labyrinth. Resorption of the endolymph takes place in the saccus endolymphaticus. The membranous labyrinth is kept in position within the bony labyrinth by a fine network of connective fibers.

Within the membranous labyrinth we can distinguish three functional entities: the semicircular canals, the vestibule, and the cochlea (Fig. 1.4). The semicircular canals and vestibule form the vestibular part of the labyrinth. The vestibule hosts the otolith organs, the utriculus and sacculus. Together, the canals and otolith organs are most sensitive for relatively low-frequency head movements and head tilt. The auditory part, the cochlea, can be considered as a phylogenetically later developed extension of the vestibule allowing the perception of high-frequency movements and vibrations (sound). The otolith organs are the most fundamental motion sensors in the head. In invertebrates, the so-called statocyst (Fig. 1.5) can be considered as a precursor of the human statolith system. It is a sphere composed of ciliated hair cells, mechanoreceptors, on the bottom of which lie relatively heavy calcium carbonate crystals, the statoconia. With tilts relative to gravity or movements with substantial acceleration (rotational or translational), these crystals will move and activate the hair cells, leading to

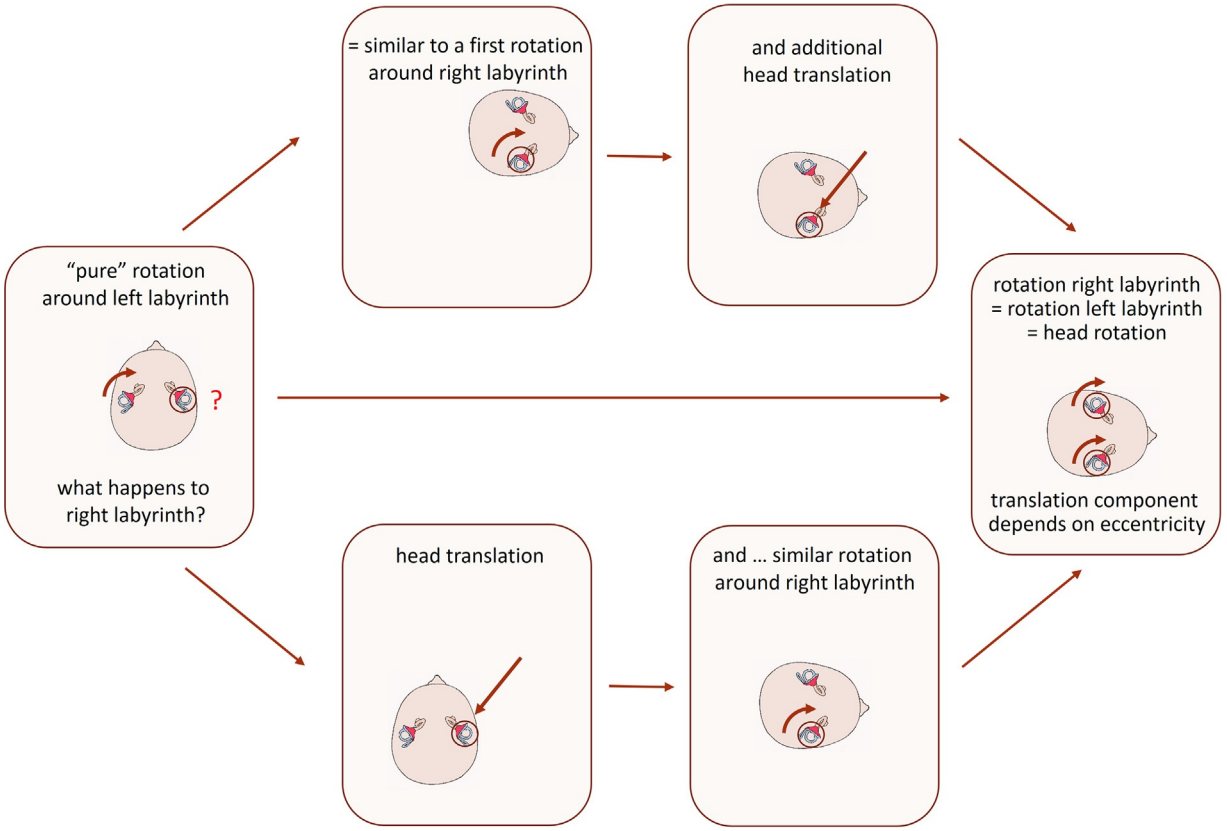


Fig. 1.1. A movement of an object is generally the sum of rotations and translations. Any movement can be divided into a rotation around a freely chosen rotation axis combined with an appropriate translation. So, the rotation component of the labyrinth is always the same irrespective the position of the rotation axis relative to the labyrinth and always similar for both labyrinths: only the additional translation component depends on the eccentricity.

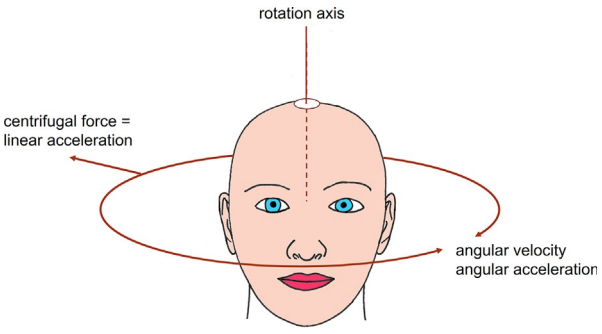


Fig. 1.2. Rotation induces always additional radial (centrifugal) and tangential forces of any structure not on the rotation axis. So during rotation the centrifugal forces acting on the labyrinths will always be different for the left and right labyrinth (different stimulation of the left and right utriculus and sacculus) unless rotating around an axis EXACTLY between two perfectly identical labyrinths.

perception of motion or tilt. The same holds for the human statolith system in the labyrinth, the utriculus and sacculus: this system detects any motion with accelerations, tilts, and due to centrifugal forces, also rotations. However, the statolith system cannot supply unambiguous information about the type of movement: no sensitive distinction is possible between tilt, rotation, and translation. Therefore the labyrinth was provided with an extension that has a specific sensitivity for rotations, i.e., angular accelerations: the three semicircular canals (Fig. 1.6). Thanks to these canals the brain is often, but not always, able to distinguish between rotations, translations, and tilt.

The primary motion sensors in the labyrinth, the so-called hair cells, are mechanoreceptor cells that transform a mechanic displacement into electric energy. In line with this phylogenetic aspect they are to some extent quite similar in the vestibular and the auditory organs. The sensitivity of the three functional entities in the labyrinth for translations, rotations, tilts, and sounds does not depend so much on the type of hair cell, but much more on the specific place and way the hair cells are built in dedicated structures: the cupula in the canals, the macula in the vestibule, and the organ of Corti in the cochlea (Wilson and Melvill Jones, 1979; Kingma and Janssen, 2013).

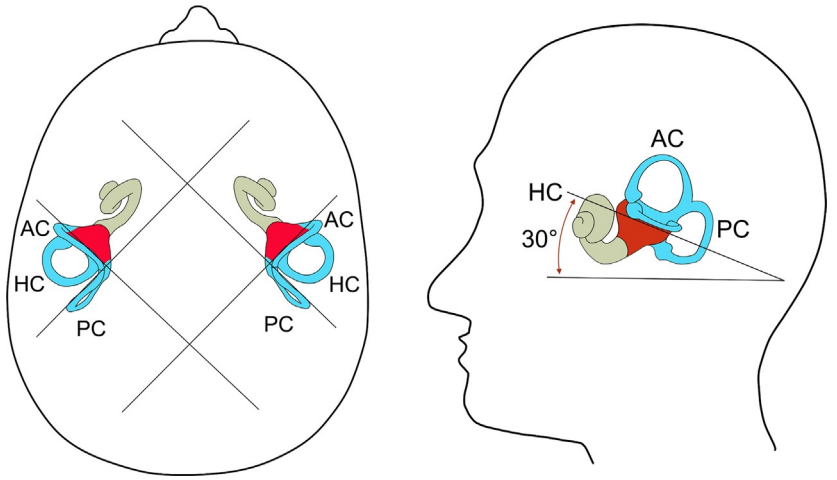


Fig. 1.3. Schematic drawing of the orientation of the two labyrinths in the skull. HC, horizontal (or lateral) canal; PC, posterior canal; AC, anterior (or superior) canal.

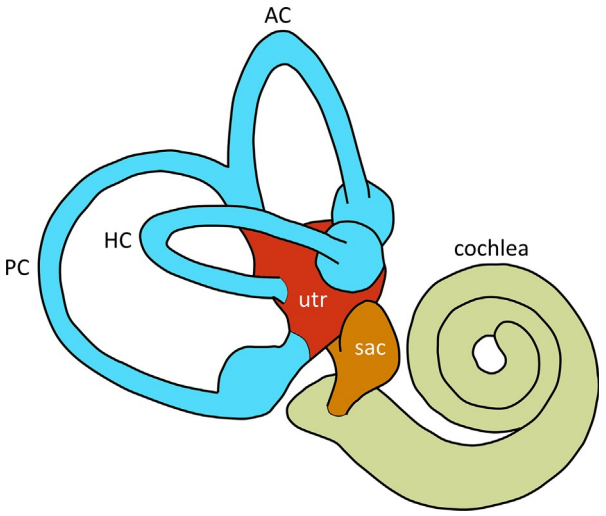
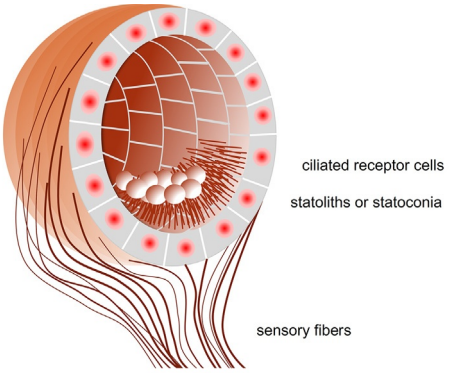


Fig. 1.4. Schematic drawing of the *right* membranous labyrinth: HC, horizontal (or lateral) canal; PC, posterior canal; AC, anterior (or superior) canal; Utr, utriculus; Sac, sacculus.



statocyst: sensitive for any movement, gravity and sound
(translations, rotations (centrifugation), tilt)

Fig. 1.5. Schematic drawing of the statocyst: the statolith organ in invertebrates. The statocyst is a mechanoreceptor system that is sensitive for any movement, tilt and sound.

The vestibular hair cells (Fig. 1.7) are composed of a cell body and a bundle of cilia on top of them, on average about 50 stereocilia and one kinocilium (Hudspeth and Corey, 1977; frog's sacculus). The stereocilia form a bundle of cilia that increase in length the closer they are to the kinocilium. On their top, the cilia are mechanically interconnected by elastic tip links. The tip links make the cilia of one hair cell move together upon accelerations and are also thought to mechanically open and close ion channels positioned on top of the stereocilia. The kinocilium is the longest cilium, that is deflected the most by small movements of the cupula in the canals and of the macula in the vestibule; but thanks to the tip links, all cilia will move in synchrony with it and thereby enhance total sensitivity.

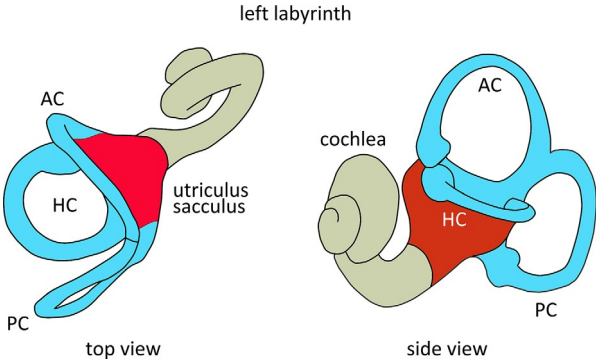


Fig. 1.6. Top and side view of the left labyrinth. HC, horizontal (or lateral) canal; PC, posterior canal; AC, anterior (or superior) canal. The vestibular labyrinth reaches its mature size between 17 and 19 weeks of gestational age. A detailed quantitative description of the dimensions of the human labyrinth is given by Jeffery and Spoor (2004).

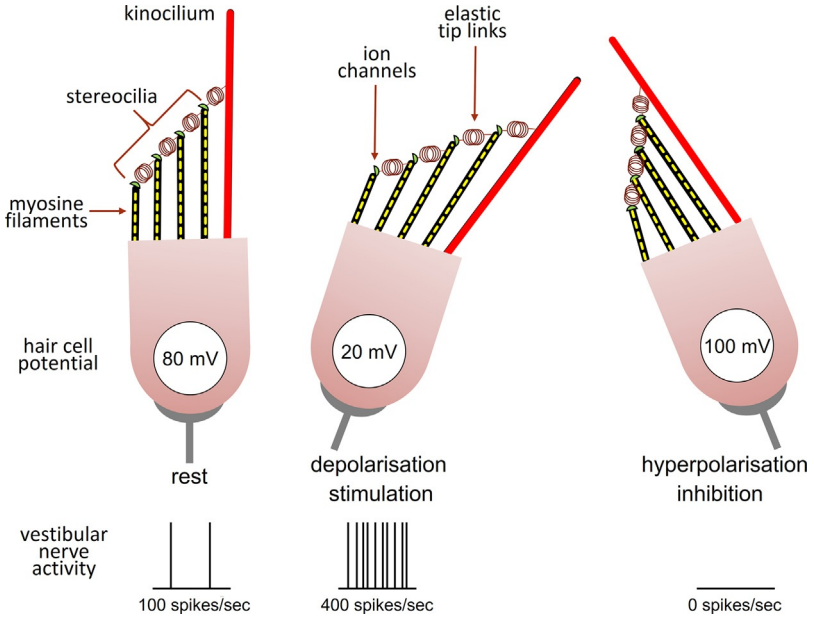


Fig. 1.7. Schematic drawing of the hair cell. From left to right: the hair cell in rest, hair cell in response to a deflection toward the kinocilium and the hair cell in response to a deflection away from the kinioocilium. Note that the hair cell is a mechano-receptor with asymmetric sensitivity.

The hair cell receptor potential at rest is about 80 mV and changes about 20 mV per micron lateral shift of the cilia (Fig. 1.7). Afferent nerve fibers of the hair cells show a spontaneous firing rate in the range of about 100 spikes per second (Hudspeth and Corey, 1977; van de Berg et al., 2011). The receptor potential decreases and nerve fiber spike rate increases when the stereocilia move towards the kinocilium, and vice versa. The maximum change in receptor potential due to a deflection of cilia in the direction of the kinocilia is substantially larger than in the case of a cilia deflection away from the kinocilia, making the hair cell an asymmetric sensitive mechanoreceptor cell (second law of Ewald); in the hair cell of the frog's sacculus the maximum differs by a factor of about 4: a change of –1.8 mV versus + 7.0 mV (Hudspeth and Corey, 1977).

Each of the two balance organs that make use of hair cells as mechanoreceptors hosts five primary sensors to detect movements and orientation of the head in space. Three semicircular canals detect angular acceleration in 3D (rotations). Two otolith organs, the utriculus and sacculus, detect accelerations in 3D (translations and rotations) and head orientation (tilt) relative to the gravity vector. During rotation the head is subject to centrifugal forces directed away from the rotation axis; these forces are also detected by the utriculus and sacculus. The canals are able to detect angular accelerations exceeding $0.5°/s^2$. The otolith organs detect linear accelerations exceeding $2\ cm/s^2$, angular accelerations exceeding $3.0°/s^2$, and head tilt with an accuracy of about 0.5°.

The specific difference in sensitivity for rotations, translations, and tilt of the vestibule is explained solely by the specific anatomic shape and structure of the canals and statolith organs, and basically not due to any differences in hair cell structure.

THE OTOLITH ORGANS

There are two otolith (synonym: statolith) organs in each labyrinth: the utriculus and sacculus that are located in the membranous labyrinth, in the vestibule. Both organs contain a sensory epithelium, the macula of the utriculus, and the macula of the sacculus. When we keep our head upright, the surface of the macula of the utriculus is oriented in the horizontal plane and curves slightly towards the anterior and upwards by about 20–30°. The macula of the sacculus is oriented against the medial wall of the sacculus, parallel to the sagittal plane, orthogonal to the macula of the utriculus. The stereocilia of the hair cells expand into a gelatinous, deformable, elastic mass (Fig. 1.10). Relatively heavy calcium carbonate crystals or otoconia are attached on the top of this gelatinous mass by fine collagen connective fibers. These mostly hexagonally shaped crystals have a specific mass of $2.95\ g/cm^3$ and a diameter varying from 3 to 30 μm. The hair cells in the utriculus are oriented with their polarization direction towards an imaginary line, the striola, in the middle of the surface (Figs. 1.8 and 1.9). At the level of the utricular striola, the membrane is very thin and the hair cells have short cilia. The hair cells in the sacculus are oriented with

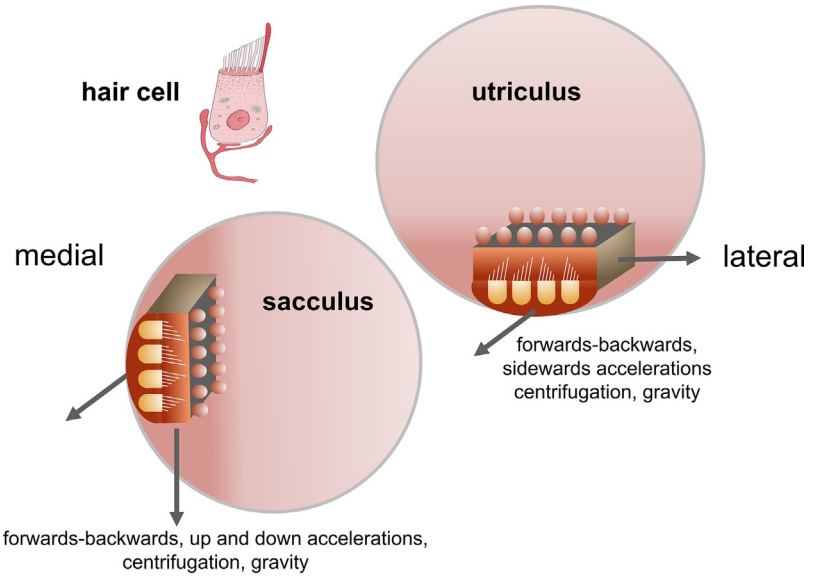


Fig. 1.8. Orientation of the sacculus and utriculus in the labyrinth.

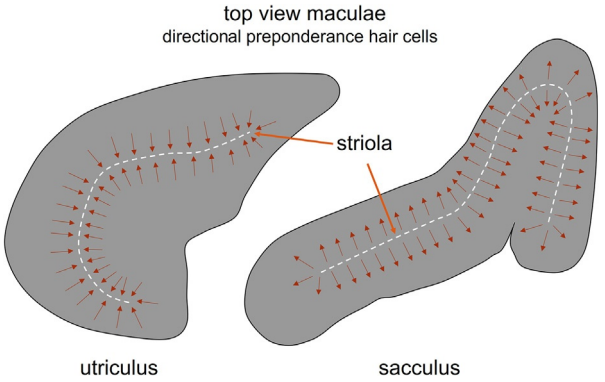


Fig. 1.9. Directional sensitivity of the hair cells in the utriculus and sacculus.

their polarization direction away from the striola. At the level of the saccular striola, the membrane is relatively thick and the hair cells have long cilia.

PHYSICS OF THE OTOLITH SYSTEM

An analog of the otoconial membrane is a car with an antenna on which an orange is pierced (air friction is neglected). Due to the inertia of mass, the orange will bend backwards as soon as the car accelerates. The antenna will bend backwards and remain deflected over an angle proportional to the car acceleration. Due to its elasticity, the antenna will start to return to its vertical orientation as soon as the car reaches constant velocity.

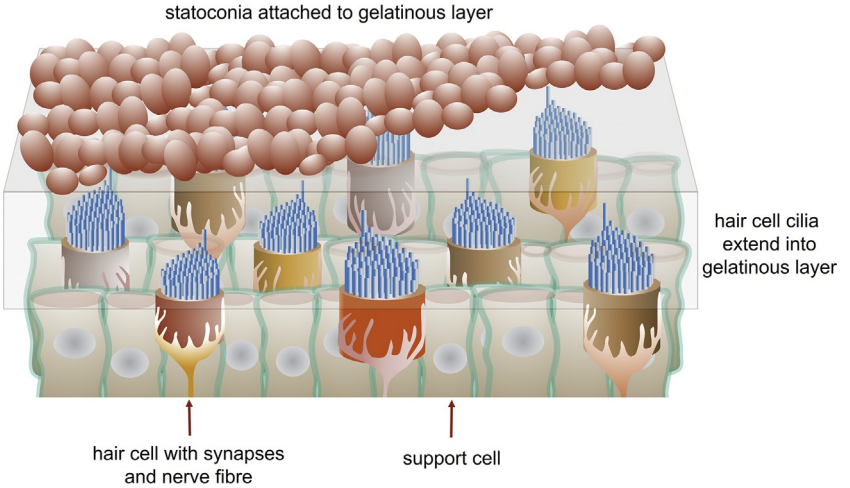


Fig. 1.10. Schematic representation of the otolith membrane, with the macula as sensory epithelium. Like the statocyst, the utriculus and saculus are mechanoreceptor systems that are sensitive for any movement and to a limited extent to sound. They are the most rudimentary sensors of head motion and tilt. Compared to the statocyst, the utriculus and sacculus have a more specific 3D orientation and the hair cells are oriented in different direction and amplitude sensitivities.

Now the erect position of the antenna indicates constant velocity or standstill. Upon deceleration of the car, due to the inertia of the orange, the antenna will bend forwards. Now the inclination of the antenna is proportional to the deceleration. Due to its elasticity, the antenna will return to its vertical orientation as soon as the car stops. When we tilt the car, the antenna will deflect in the direction of tilt over an angle proportional to the tilt angle relative to the gravity vector. No distinction is possible between tilt and translation (compare with Figs. 1.11 and 1.12). Also, when we start to rotate and hold the antenna upright, the antenna will start to bend outwards due to centrifugal force.

The otolith system is sensitive to linear accelerations, rotations/centrifugation and tilt thanks to the principle of inertia of mass. Assume that the head undergoes linear acceleration (Fig. 1.11). The lower part of the utricular membrane immediately follows the head movement, but the otoconia on the top of the membrane will lag behind, resulting in a deflection of the cilia. This bending causes depolarization or hyperpolarization of the hair cells depending on the direction of deflection of the cilia (Fig. 1.7). The hair cells of the macula are polarized in all directions, in contrast to the semicircular canals. A tilt relative to the gravity vector or centrifugation also induces a shear force in the plane of the otoconial membrane and a deflection of the cilia. The otolith organs cannot distinguish between head tilt, rotation, and head translation (for example, an acceleration forwards leads to a similar deflection of the cilia as a backward tilt of the head: Fig. 1.11). The only exception to this may be that the eccentricity of the otolith membranes can be different relative to the rotation axis. This may result in a difference in direction and/or strength of the centrifugal forces acting upon the otolith membranes. Whether this provides a physiologically relevant and sufficient sensitivity to discriminate between rotations versus tilt or translation is still the subject of study. At constant rotational head velocity, the canals are not stimulated. However, during both constant and changing rotational head velocity the otolith system is still stimulated due to centrifugal force, probably having a supporting and regulatory function for the canals (see below).

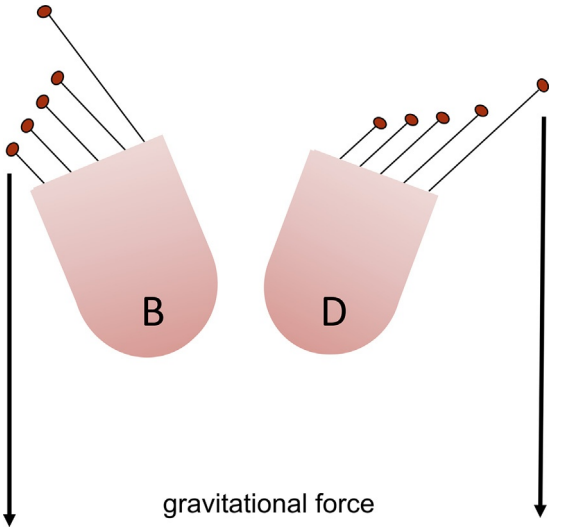


Fig. 1.12. Schematic deflection pattern of the cilia of the hair cells in the utriculus and sacculus upon tilt.

THEORETIC MODEL

During linear head acceleration, centrifugation, or head tilt, the otoconia mass shifts relative to the macula due to otoconial mass inertia, causing opposing viscous friction and an elastic force. Therefore the otolith organ semicircular canals can be modeled similarly to the semicircular canals with a simple mechanic analog, using inertia (I), viscosity (B), and elasticity (K) as physical quantities (Fig. 1.13). The moment of inertia is given

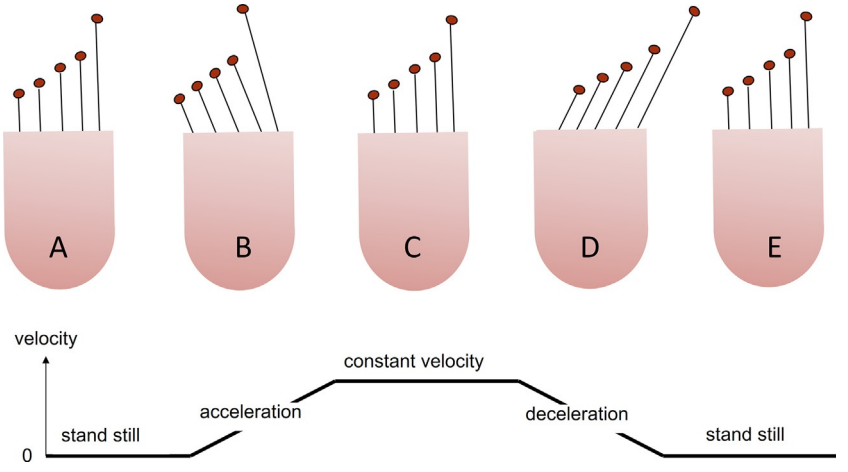


Fig. 1.11. Schematic deflection pattern of the cilia of the hair cells in the utriculus and sacculus upon translation.

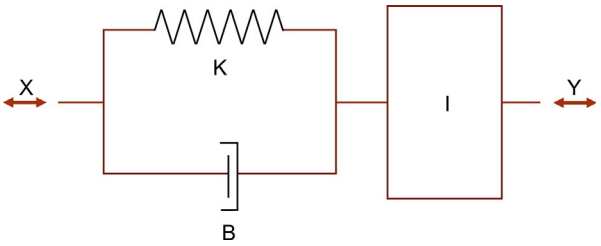


Fig. 1.13. Mechanical analog of the statolith organ: I, otoconia mass inertia; B, viscous friction; K, elastic restoring force; x, position of the head; y, position of the otoconia; □, $x-y$, relative displacement of the otolith membrane.

by $I \cdot \ddot{y}$, the moment of viscous friction by $B \cdot \dot{\delta}$, and the moment of elasticity by $K \cdot \delta$, which would lead to a second-order differential equation similar to the semicircular canals. In the case of the otolith organ, however, since the otoconial mass is immersed in endolymph fluid of density ρ_e, any linear acceleration will generate a buoyancy force acting according to Archimedes' principle in the direction of imposed acceleration and equal to $(\rho_e/\rho_o) \cdot I \cdot \ddot{x}$, with ρ_o the density of the otoconial mass. Therefore, the second-order differential equation of the otolith organ is:

$$\left(1-\frac{\rho_e}{\rho_o}\right) I \cdot \ddot{x} = I \cdot \ddot{\delta} + B \cdot \dot{\delta} + K \cdot \delta$$

with $\ddot{x}$ linear head acceleration, $\ddot{y}$ linear otoconia acceleration, and δ relative displacement of the otolithic membrane, using $\delta = x - y$ (Melvill Jones, 1979; Kingma and Janssen, 2013). The transfer function can be written as:

$$\frac{\delta}{\ddot{x}}(s) = \left(1-\frac{\rho_e}{\rho_o}\right) \cdot \frac{I}{I \cdot s^2 + B \cdot s + K}$$

with linear head acceleration $\ddot{x}$ as input and relative otolithic membrane displacement δ as output. The form of this transfer function is shown in Figure 1.14A, using the fact that I/B ($T_1 \approx 0.1$ s) is smaller than B/K ($T_2 \approx 1$ s).

The otolith organ is sensitive for constant (0 Hz) and low-frequency linear accelerations. Because a gravitational acceleration and a corresponding linear acceleration of the system are physically equivalent (Einstein's equivalence principle), the otolith organs cannot distinguish between pure head translations, head tilts, and rotations, unless they make use of a specific arrangement of the direction-sensitive hair cells in the sensory epithelium. The relative otolith membrane displacement δ in response to constant linear acceleration is similar to the cupula displacement in response to angular acceleration, as shown in Figure 1.12. Agrawal et al. (2012) found a decrease in amplitude of the cervical and ocular vestibular-evoked myogenic potentials with age, suggesting an age-related decline of the statolith system (Fig. 1.14B).

SEMICIRCULAR CANALS

As shown in Figure 1.4, three semicircular canals can be identified in the vestibular labyrinth: the lateral, posterior, and anterior canal that slightly differ in size: the lateral canal has a diameter of about 2.3 mm (SD 0.21), the posterior canal 3.1 mm (SD 0.30), and the anterior canal 3.2 mm (SD 0.24). The canals are oriented more or less orthogonally to each other (Fig. 1.4); the orientation of all canals varies among healthy subjects (SD between 4.1° and 5.4°). The inner diameter of the canals is estimated to vary between 0.2 and 0.3 mm (see Melvill Jones, 1979).

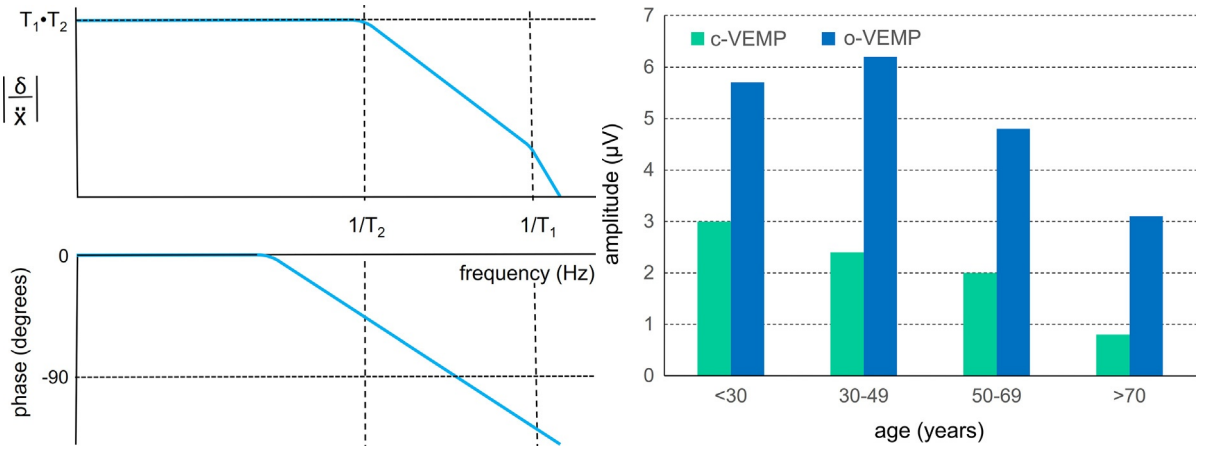


Fig. 1.14. (**A**) Bode plot of the frequency response of the transfer function equation 4, representing the dynamic response of the mechanical analog of the otolith organ. Upper trace: amplitude spectrum (gain = sensitivity). Lower trace: phase as a function of frequency. (**B**) Response amplitudes of c-VEMP (asummed to reflect saccular function) and o-VEMP (assumed to reflect utricular function) as a function of age (after Agrawal et al.).

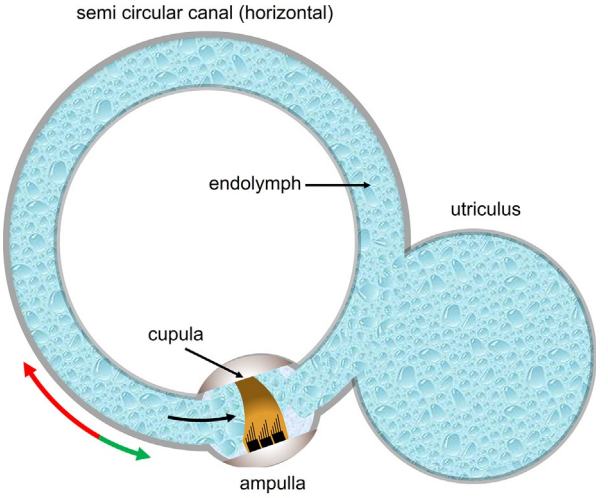


Fig. 1.15. Schematic presentation of the semicircular canals with the cupula holding the hair cells. Due to the similar orientation of all hair cells in the cupula, the asymmetric sensitivity of the hair cells results in an asymmetric sensitivity of the semicircular canals.

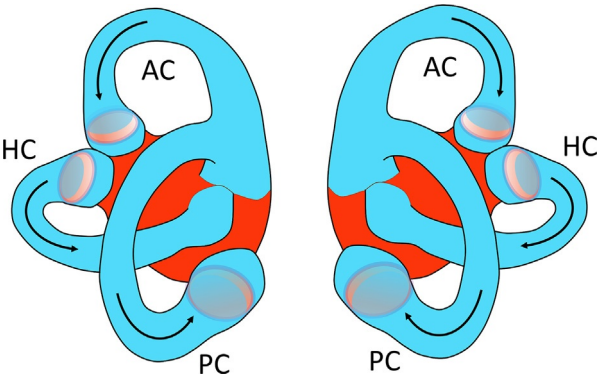


Fig. 1.16. Back view of the two vestibular labyrinths. The arrows indicate the preferred (maximum sensitivity) rotation direction in each canal. HC, horizontal canal; PC, posterior canal; AC, anterior canal. Note that the direction of the sensitivity of the canals is opposite for the HC compared to that of the AC and PC (opposite orientation of the hair cells in the cupulae).

The hair cells of the canals are located in the basal part of a gelatinous mass, the cupula, that extends through the ampulla of each canal and forms a flap that closes the semicircular canal, preventing endolymph from passing the ampulla (Fig. 1.15). The cilia extend into the cupula.

As indicated above, the hair cells have the highest sensitivity for deflections to the kinocilium: the polarization direction. In the cupula all hair cells are arranged with the same direction of polarization. As a consequence, the receptor potential of all hair cells in a cupula decreases or increases in synchrony upon a cupula deflection. But again, as the maximum sensitivity is in the polarization direction, there is also a preferred direction of a cupula deflection, explaining the asymmetric sensitivity of each semicircular canal: actually, each canal is most sensitive for rotations in the direction of that specific canal (Fig. 1.16).

The polarization direction of the hair cells in the cupula of the horizontal canal is such that the canal is more sensitive for a cupula deflection towards the ampulla (ampullopetal), which corresponds to a head rotation in the opposite direction (arrow; see explanation below related to the physics of cupula deflection). The polarization direction of the hair cells in the cupula of the vertical canals is such that the canal is more sensitive for a cupula deflection away from the ampulla (ampullofugal), which again corresponds to a head rotation in the opposite direction (arrow). As a rule of thumb, each canal is maximally sensitive for rotations in the direction of that canal about an axis orthogonal to the plane of that canal.

Through this orientation we are supplied with three pairs of canals with a complementary and opposing optimal sensitivity (Fig. 1.16): (1) the left and right horizontal canal; (2) the left anterior and right posterior canal;

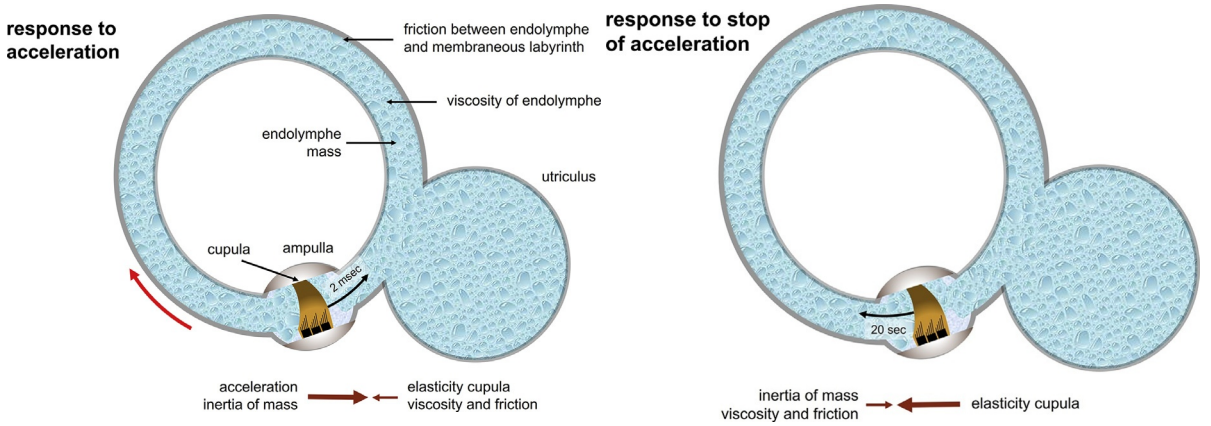


Fig. 1.17. (**A**) Clockwise angular acceleration of the canals leads to a ampullopetal endolymphatic flow and a deflection of the cupula and hair cells that all have the same polarisation. Clockwise angular acceleration leads to cupula deflection in the opposite direction. (**B**) When rotation velocity becomes constant, the cupula starts to move back to the original (resting) position, which takes about 20 seconds on average (time constant about 6 seconds). This implies that it is not possible to distinghuish on the basis of canal input to the brain between standstill and constant rotation.

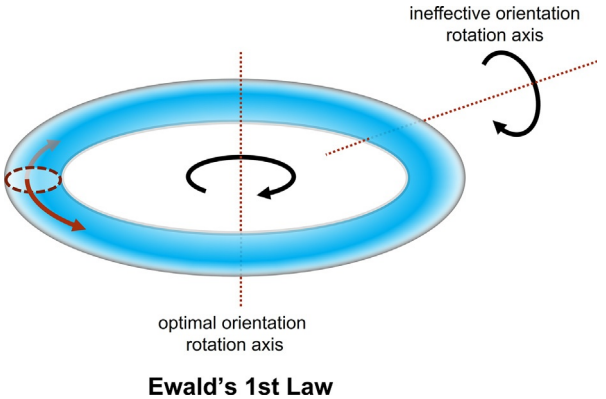


Fig. 1.18. First law of Ewald: cupula deflection will be maximal for rotations around an axis orthogonal to the plane in which the canal is situated; cupula deflection will be minimal for rotations around an axis in the plane in which the canal is situated.

and (3) the right anterior and left posterior canal. The sensitivity (gain) of the semicircular canal is such that it generates close to 1 spike/s per °/s at 0.5 Hz in the afferent nerve fibers (Yang and Hullar, 2007).

When the head is rotated, the endolymph fluid lags behind due to mass inertia and exerts a force against the cupula (Fig. 1.17A), causing the cupula to bend. When constant rotation is reached (Fig. 1.17B) and acceleration becomes nil, the driving inertial force will become nil too (Newton's law: force = mass × acceleration). Now the cupula will bend back to its original position, driven by the cupula elasticity against the viscosity of the endolymph and the friction between endolymph and membranous labyrinth. The endolymph will move maximally when the rotation axis is orthogonal to the plane in which the canal is oriented (Fig. 1.18; the endolymph and cupula will not move when the rotation axis is in the plane of the canal: Ewald's first law). As mentioned already (Fig. 1.1), the impact of rotation on an individual canal does not depend on the distance between the axis of rotation and the center of the canal – parallel axis theorem (Feynman, 2011). In contrast, the centrifugal component related to rotation depends on the location of the labyrinth relative to the rotation axis.

The brain receives opposite signals from the two labyrinths and detects the difference between both of them, which in engineering terms is considered as working as a differential amplifier. The redundancy in a system with two labyrinths (similar to hearing and vision) makes it less vulnerable for unilateral loss of function. But, also, detecting the difference between the two oppositely sensitive labyrinths enhances the sensitivity twofold, whereas a common disturbance from outside is subtracted (common-mode rejection).

PHYSICS OF THE CANALS

An analog of a canal without cupula is a closed bottle completely filled with water (without any air on top) fixed on a turntable. As soon as the turntable starts to rotate, the bottle will follow the rotation immediately. However, due to the inertia of mass, the water will lag behind and only after a while – due to the adhesion of the water to the bottle wall and the internal cohesion of the water molecules – will the water start to rotate and then rotate with the same angular velocity as the bottle and turntable. Without this friction (adhesion) and viscosity (cohesion), the water would not move at all; with more friction and viscosity the water will follow the bottle movement faster. Besides friction and viscosity, the

total mass and specific mass of the fluid or inertia play a crucial role: the greater the fluid mass, the more force (acceleration) is needed in order to move the water. Friction, viscosity, mass, and acceleration all determine how much the water lags behind the bottle movement and over which angle it will be displaced until the water has reached the same angular velocity as the bottle. As long as the turntable, bottle, and water rotate at a constant velocity, no further change will occur. The angle over which the water is rotated compared to the bottle is proportional to the applied angular acceleration of the bottle. As soon as the turntable stops, the bottle will stop as well, but the water will still rotate inside the bottle. The velocity of the water will decrease over time due to the friction between bottle and water and ultimately the water will come to a complete standstill. If the deceleration is the same as the acceleration, the same time will be needed for the water to come to a standstill and the water will have rotated to exactly the same position as in the beginning of the experiment: no net relative angular displacement is left. In fact, deceleration and acceleration need not be the same: the same position is always reached when the steps in velocity during acceleration and deceleration are opposite but have the same magnitude. For example, the velocity step is the same but opposite (120°/s and –120°/s) when we accelerate in 12 seconds with $10°/s^2$ to 120°/s, and the bottle stops when we decelerate in 2 seconds by $60°/s^2$ from 120°/s to standstill. So the relative displacement is proportional to the velocity step: = acceleration $\times T_{acceleration}$. This has a direct clinical application: velocity steps are used widely in vestibular diagnostics using rotatory chairs.

When we put a very light fluid or gas (low specific mass) in the bottle (decreasing the mass inertia) or a very viscous fluid that has a strong adherence (high friction) to the bottle wall, the displacement of the content relative to the bottle will be almost negligible.

So, the relative displacement increases with mass, decreases with friction (adhesion and cohesion), and increases with the magnitude of the step in velocity. Any translation of the turntable and bottle on top will not lead to any movement of the water as the water cannot be compressed. The water will only start to move by rotation.

The situation is slightly more complex in the semicircular canal: here the cupula prevents the endolymph from rotating freely in the canal (Fig. 1.15). The cupula can be considered as an elastic membrane that can slightly bend in both directions. As soon as the canal starts rotating, the endolymph lags behind due to its inertia of mass. Again, the less friction and the more endolymph mass are in the canal, the more the fluid will tend to lag behind and the stronger will be the force acting upon the cupula. The stiffness of the cupula will, however, prevent a large deflection: within milliseconds an equilibrium will be reached between the inertial force acting upon the cupula and the elastic force from the cupula. As long as the acceleration continues, this equilibrium will remain, resulting in a persistent deflection that stimulates the hair cells in the cupula. The stronger the acceleration, the more the cupula will bend: the constant deflection of the cupula will be proportional to the acceleration. Low cupula stiffness (high elasticity), high endolymph mass, and low friction will all result in a larger cupula deflection (higher sensitivity). When constant angular velocity is reached, the cupula will start to bend back to its neutral position as there is no driving force (acceleration) any more to maintain the cupula deflection. However, the return lasts quite long, as now the elastic force of the cupula alone will have to move the endolymph mass against friction. A low cupula stiffness (high elasticity = small elastic force), a high endolymph mass, and strong friction will result in a slower return of the cupula to its neutral position. In pathology and aging, endolymph viscosity (friction) and cupula stiffness can change; in benign paroxysmal positional vertigo (BPPV) the specific mass of the endolymph can be assumed to increase. In summary:

1. increase of cupula stiffness or increase of endolymph viscosity: lower canal sensitivity and shorter postrotatory sensations
2. increase of absolute endolymph mass: higher canal sensitivity and longer postrotatory sensations
3. change of endolymph specific mass compared to that of the cupula: sensitivity of the canals for gravity and linear accelerations is induced.

A canal is physiologically insensitive to (coincidental) linear accelerations (Melvill Jones, 1979) because the cupula and endolymph have the same density. If differences in densities occur, the canal dynamics will be more complex, and would lead to a dependency on the orientation of both the gravity vector relative to the canal plane and the axis of rotation, as well as on the distance between the axis of rotation and the center of the semicircular canal (Kondrachuk et al., 2008). This effect is a familiar experience after alcohol intake, resulting in the sensation of rotation when lying in bed, and can even induce eye movements known as positional alcohol nystagmus (Goldberg, 1966). This is also the effect experienced in the common vestibular disorder BPPV. In BPPV, otoconia are present in the semicircular canals. These particles make the semicircular canal system sensitive to the orientation of gravity and can adhere to the cupula – cupulolithiasis (Schuknecht, 1962) – or remain free-floating, which is called canalithiasis (Rajguru et al., 2004, 2005).

THEORETIC MODEL OF THE SEMICIRCULAR CANALS

Many years ago physicists and physiologists like Melvill Jones and Groen presented a second-order model to explain the precise working of the semicircular canal. We refer to this excellent paper for a detailed description.

During head rotation the endolymph lags behind the movement of the semicircular canals due to mass inertia, causing viscous friction. Additionally, the deflected cupula has elastic properties. Therefore the semicircular canals can be modeled with a mechanic analog, using inertia (I), viscosity (B), and elasticity/stiffness (K) as physical quantities (Fig. 1.19). The following assumptions are made. The fluid flow in the semicircular canal is assumed to be laminar as the Reynolds number is below 1. The density of the endolymph is very close to 1 and considered similar to the density of the cupula. This similarity makes the canals insensitive for linear accelerations. The endolymph dynamic viscosity is estimated to be 0.001 Pa/s, the inner radius of the membranous tube 0.163 mm (e.g., Melvill Jones, 1979), and Young's elasticity modulus of the cupula is estimated to be 5.4 Pa (Selva et al., 2009).

The moment of inertia is given by $I \cdot \ddot{p}$, the moment of viscous friction by $B \cdot \dot{\vartheta}$, and the moment of elasticity by $K \cdot \vartheta$, which leads to a second-order differential equation:

$$I \cdot \ddot{p} = B \cdot \dot{\vartheta} + K \cdot \vartheta$$

with $\ddot{p}$ angular endolymph acceleration, $\dot{q}$ angular head velocity and ϑ cupula angle. Using $\vartheta = q - p$ and the fact that I/B ($T_1 \approx 3$ ms) is much smaller than B/K ($T_2 \approx 10$ s) (Melvill Jones, 1979), the transfer function can be written as:

$$\frac{\vartheta}{\dot{q}}(s) = T_1 \cdot T_2 \cdot \frac{s}{(T_1 \cdot s + 1) \cdot (T_2 \cdot s + 1)}$$

with angular head velocity $\dot{q}$ as input and cupula angle ϑ as output. The shape of this transfer function is shown in Figure 1.20A.

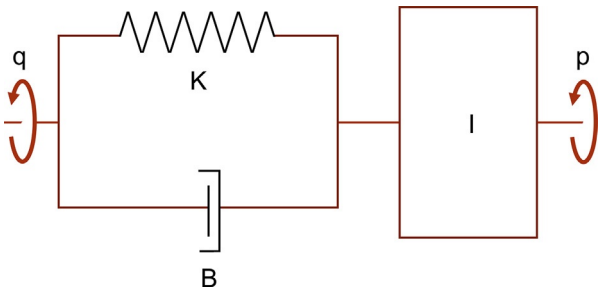


Fig. 1.19. Mechanical analog of the semicircular canal, I, endolymph mass inertia; B, viscous friction; K, cupula restoring force; q, angular position of the head; p, angular position of the endolymph; $q - p$, deflection angle of the cupula.

The model predicts a maximum endolymph movement in the order of magnitude of 1° at velocities of 500°/s. As the perception threshold for angular velocity steps is about 2°/s, this implies that the mechanoreceptors are stimulated by an endolymph displacement of about 0.004°.

The semicircular canals sense angular acceleration because the endolymph mass inertia is the driving force, but at physiologic frequencies of head movements (about 0.5–5 Hz) the semicircular canals work as integrating angular accelerometers (Goldberg and Fernandez, 1971): the cupula afferent signals are proportional to angular head velocity, as indicated by the flat response of the transfer function (Fig. 1.20B).

Agrawal et al. (2012) showed that the dynamic visual acuity decreases for all three canals as a function of age, so suggesting that not only the statolith system (Fig. 1.14B) but also the canal system (Fig. 1.20C) is subject of aging – presbyovestibulopathy as an equivalent of presbyacusis in the auditory system.

CLINICAL INTERPRETATION OF THE THEORETIC MODEL

In Figure 1.20B, the cupula deflection is plotted as a function of head acceleration (left two graphs) and head velocity (right two graphs). For all frequencies below 0.1 Hz, the cupula deflection is clearly proportional and in phase with the head acceleration (left two graphs); the curves are flat up to about 0.1 Hz. However, at higher frequencies the sensitivity (gain) rapidly decreases and the response starts to lag behind (phase).

When we plot the cupula deflection as a function of head velocity (right two graphs), the curves become flat between the middle and higher frequencies (0.1 and 10 Hz): the cupula deflection is proportional and in phase with the head velocity.

The frequency dependence of the canal is not so easily objectified and quantified in clinical practice (Fig. 1.20A). The caloric test can be considered as a low-frequency test, evaluating the low-frequency responses of the horizontal canal. Sinusoidal rotatory tests (torsion swing, sinusoidal harmonic acceleration tests) evaluate the low- and middle-frequency range (0.01–1 Hz) of the canal function. The velocity step test (= acceleration impulse response test) allows in theory a direct quantification of the gain and time constant T_2 of the canals via measurement of the vestibulo-ocular reflex; however, due to the bilateral stimulus it remains often difficult to find out which canal is affected. Also central processing and cognitive processes modify both gain and time constant considerably. This limits a direct interpretation of the function at the peripheral canal level.

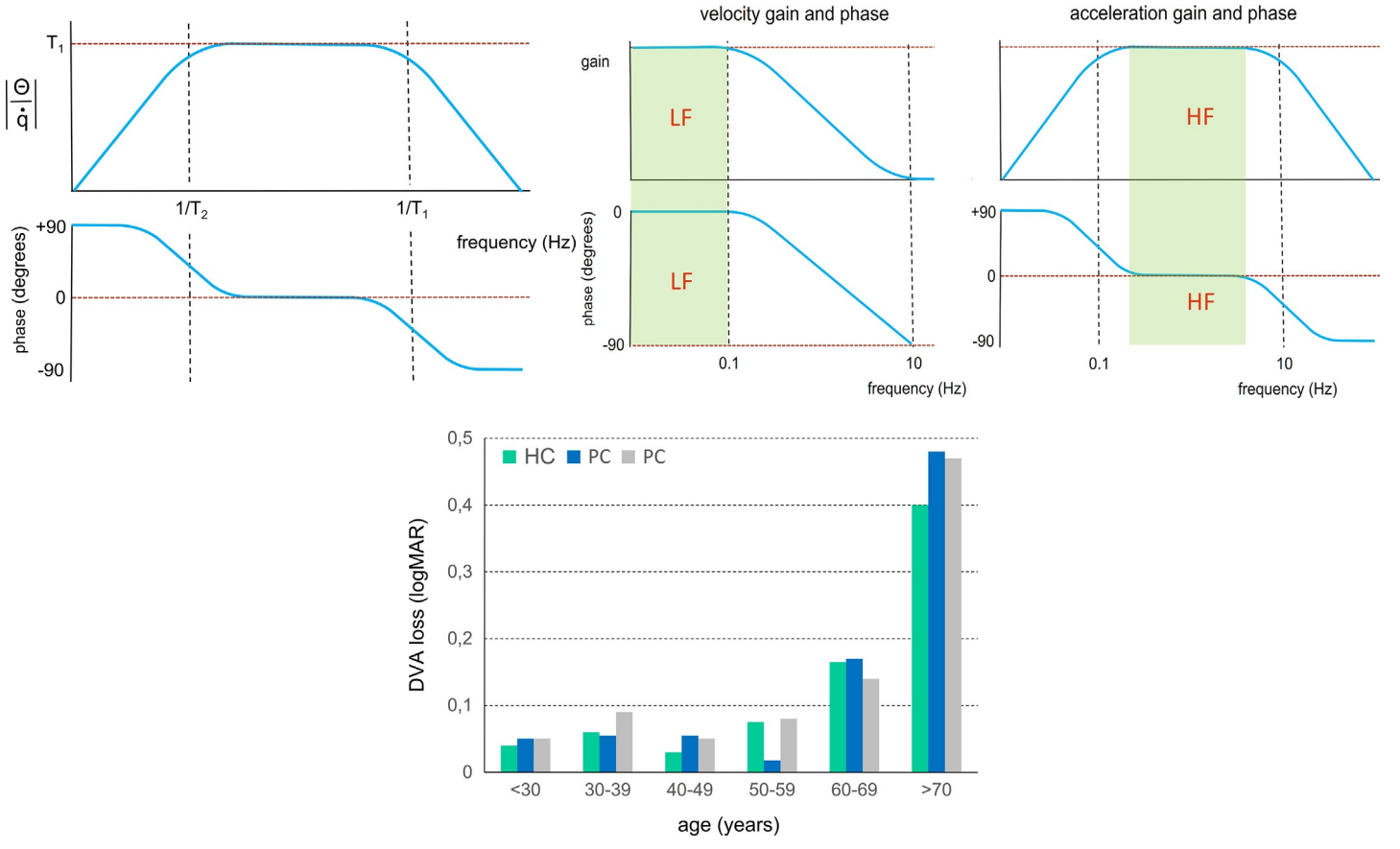


Fig. 1.20. (**A**) Bode plot of the frequency response of the transfer function equation 2, representing the dynamic response of the mechanical analog of the semicircular canals. Upper trace: amplitude spectrum (gain = sensitivity). Lower trace: phase as a function of frequency. (**B**) Gain (sensitivity) and phase (timing) of the canals as a function of the frequency of head rotations. Based upon the second order model, depicted above, and the various known or estimated constants of the canals, the canals behave differently for low versus high rotational frequencies. For low frequencies the cupula deflection is proportional to head acceleration; for high frequencies the cupula deflection is proportional to head velocity. (**C**) The dynamic visual acuity decreases for stimulation in the plane of all three canals with age pointing to the existence of presbyo-vestibulopathy (after Agrawal et al., 2012).

Many attempts have been made to develop high-frequency tests (vestibular autorotation test, head shakers, high-frequency (hydraulic) torsion swing chair tests). None of these obtained a widespread application comparable to the caloric test due to many practical limitations, and limited sensitivity and reproducibility. Passive head impulse tests, fast small-amplitude high-velocity head rotations, can be considered as evaluating the high-frequency function of the canals, allowing quantification of the gain, but not both time constants. Thanks to the development of video eye-tracking devices that allow quantification of head and eye velocity during these head impulses, head impulse testing has become the first choice for quantification of canal function at high frequencies. The caloric test still remains a valuable tool to quantify the low-frequency part of canal function. As can be easily understood from the physics of the canals, low-, middle-, and high-frequency loss can occur, both in isolation and in different combinations.

MULTISENSORY ASPECTS

Canals, maculae, vision, and proprioception all contribute to motion and tilt perception. Both the visual and somatosensory system can only process relatively slow body movements, and can be modeled with a low-pass transfer function, with a cutoff frequency of about 0.2 Hz. The otolith organs detect low-frequency linear accelerations (translations and tilt) up to about 1 Hz, whereas the semicircular canals (semicircular canals) detect angular velocity between 0.1 and 10 Hz. Based on the physics described above we can estimate the frequency dependence of human canals and statolith organs as depicted in Figure 1.21, but the reader should realize that this is speculation rather than estimation. At present

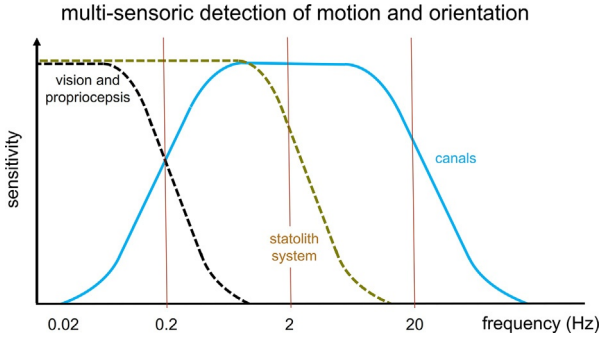


Fig. 1.21. Graphic presentation of the frequency dependence of canal and statolith function, in combination with proprioception and vision. Motion sickness is known to occur often at movement frequencies around 0.2 Hz, where the transition occurs from dominance of visual-proprioceptive input versus that of canal input.

it is not possible to verify these curves in detail due to limits of the diagnostic tests, especially because it is still not possible to stimulate any one of the five vestibular sensors per labyrinth separately. Also, the magnitude of the vestibular responses depends on many factors, including cognitive factors (alertness, instruction) and the precise stimulus conditions (in darkness versus in the light). The visual and somatosensory systems support the otolith organs in the detection of constant linear accelerations (Vaugoyeau et al., 2008) and tilt perception at low frequencies, whereas the semicircular canals support the otolith organs to distinguish true body tilt from translations at frequencies above 0.1 Hz (Green et al., 2005; Merfeld et al., 2005). If different sensory systems give conflicting or insufficient information, hindering the determination of the direction of gravity or distinguishing correctly between environmental and self-motion, motion sickness is quite common (Bles et al., 1998), especially in individuals with an easily activated autonomic nervous system (neurovegetative sensitivity). We also added the hypothetic frequency sensitivity of proprioception and vision, which contribute to motion perception and orientation in the low-frequency range.

PATHOLOGY

Losing sensors for motion and tilt detection unavoidably leads to a loss of functionality and cannot be compensated for by other sensory systems that do not have sufficient sensitivity for the higher frequencies (Fig. 1.15). Indeed, a permanent unilateral or bilateral peripheral loss leads to a permanent reduction of automatic image stabilization during head movement (oscillopsia, reduction of dynamic visual acuity), a permanent loss of automatic balance (“no more talking while walking”) and a permanent loss of automation of spatial orientation (feeling insecure in situations with strong optokinetic stimuli, like busy traffic and supermarkets). The continuous and intense extra cognitive load needed for vision, balance, and orientation leads to fast fatigue, which is a major problem in patients with permanent vestibular deficits.

A decrease in vestibular sensitivity with aging, presbyovestibulopathy, similar to perceptive hearing loss (presbyacusis) is a major cause of a decrease of dynamic visual acuity, reduced balance, and high incidence of falls in the elderly. Besides hair cell degeneration, aging might also affect tissue stiffness and hydration, and thus also affects the vestibular physical quantities of both the semicircular canals and otolith organs:

1. an increasing stiffness K increases the lower cutoff frequency (K/B) and decreases the gain (I/K) below this cutoff frequency

2. an increasing viscosity B decreases the higher cutoff frequency (B/I) and decreases the gain (I/B) below this cutoff frequency.

These effects are schematically shown in Figures 1.16 and 1.17. The vestibular system as a whole is thus affected as well, reducing the distinction between tilt and translation, because the optimal range of the semicircular canals shifts to higher frequencies. This is particularly unfortunate because with age body movements become slower due to stiffer body mechanics.

CONSIDERATIONS CLINICALLY RELEVANT TO THE IMPACT OF LABYRINTHINE FUNCTION LOSS

The vestibular labyrinths act as very sensitive sensors of head acceleration and tilt. As explained above, the utriculus and sacculus can be considered as very rudimentary sensors, sensitive for all motions and tilts, but not able to discriminate between the different types of motion. Depending on the precise motion pattern, additional information from canals allows discrimination between translations, centrifugations, and tilts.

When we lose canal function, as monitored by the caloric test, rotational test, and head impulse tests, we can still detect all motion with the statolith system, although with a lower sensitivity, especially at higher frequencies. When we lose statolith function, the fast intuitive detection of gravity and the sensitivity for translations will be impaired, but rotational sensitivity will be preserved. Often a distinction is much easier when additional visual and proprioceptive information is available. A distinction between slow tilts and translations explicitly requires foreknowledge about the type of movement or additional information from vision and/or proprioception. For example, divers in dark water and people covered by an avalanche are unable to sense their orientation towards gravity: this suggests that the brain is unable to detect the orientation relative to gravity when completely deprived of visual or proprioceptive input, which may be due to this ambiguity in the statolith system.

Motion sickness is considered to occur especially in conditions where we experience conflicts between the motion-sensitive input signals to the brain and/or when the perceived vertical differs from the expected vertical. Subjects without labyrinthine function do not suffer from motion sickness. Interestingly, motion sickness can be caused by stimuli that do not activate the labyrinth, such as visual illusion of motion. This can be explained by the fact that the central vestibular system is always involved in the perception of self-motion and the detection of gravity, even if the information is supplied by the visual system.

To summarize, the major functions of the vestibular system in relation to clinical symptoms are:

- Maintaining visual acuity during head motions: dynamic visual acuity by means of the vestibulo-ocular reflex. Vestibular function loss may lead to a permanent loss of visual acuity and oscillopsia during walking and head motion (oscillopsia is the perception that the image is unstable on the retina). Especially during walking, vertical head movements require compensatory eye movements. It is as yet unclear what the precise contribution of the statolith and canal systems is for image stabilization as the head movements are composed of translational, rotational, and tilt components. This suggests that the correlation between a loss of dynamic visual acuity depends on many factors. The overall impact of a (frequency-dependent) labyrinthine loss for image stabilization needs more research: patients might compensate for the loss of image stabilization (the vestibulo-ocular reflex) partly by small saccades, so-called covert saccades, or by improving the ability of the visual system to analyze the information present in moving images on the retina, similar to what has been suggested in congenital nystagmus.
- Allowing fast balance and postural corrections by an intuitive perception of the gravity vector and fast vestibulospinal reflexes. So the specific contribution of the labyrinth to balance control seems to be speed. Severe labyrinthine loss may therefore lead to permanent imbalance (walking like a drunken sailor), fear of falling, and falls. The impact of a function loss of the statolith system may be of greater relevance than loss of canal function. However, we should still be aware that the brain needs the canal or other sensory input in addition to the inherently ambiguous otolith input to allow a reliable detection of the gravity vector.
- Spatial orientation: discrimination between self-motion and environmental motion and orientation relative to the gravity vector. The loss of labyrinthine function may therefore lead to uncertainty. The trivial sensory substitution that is observed in many patients, particularly with regard to vision, can have adverse consequences as it may lead to visual dependence and sometimes intolerance to moving visual stimuli or repetitive patterns with high contrasts (optokinetic stimuli): one of the presentations of so-called visual vertigo.

A secondary impact of vestibular loss is a loss of automatic image stabilization, balance control, and spatial

orientation, which often leads to fear and the need for permanent cognitive control of gaze and posture, leading to fatigue.

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Chapter 2

Physiology of central pathways

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Abstract

The relative simplicity of the neural circuits that mediate vestibular reflexes is well suited for linking systems and cellular levels of analyses. Notably, a distinctive feature of the vestibular system is that neurons at the first central stage of sensory processing in the vestibular nuclei are premotor neurons; the same neurons that receive vestibular-nerve input also send direct projections to motor pathways. For example, the simplicity of the three-neuron pathway that mediates the vestibulo-ocular reflex leads to the generation of compensatory eye movements within ~5 ms of a head movement. Similarly, relatively direct pathways between the labyrinth and spinal cord control vestibulospinal reflexes. A second distinctive feature of the vestibular system is that the first stage of central processing is strongly multimodal. This is because the vestibular nuclei receive inputs from a wide range of cortical, cerebellar, and other brainstem structures in addition to direct inputs from the vestibular nerve. Recent studies in alert animals have established how extravestibular signals shape these "simple" reflexes to meet the needs of current behavioral goal. Moreover, multimodal interactions at higher levels, such as the vestibular cerebellum, thalamus, and cortex, play a vital role in ensuring accurate self-motion and spatial orientation perception.

INTRODUCTION

Electrophysiologic studies have provided fundamental insights into the functional circuitry of central vestibular pathways. Notably, the vestibular system differs from other sensory systems in that the same neurons that receive direct (i.e., monosynaptic) afferent input can also send direct projections to motoneurons. For example, the most direct pathway mediating the vestibulo-ocular reflex (VOR) pathway is mediated by a three-neuron pathway linking the vestibular afferents and eye muscle motoneurons through the vestibular nuclei. Likewise, a three-neuron pathway connecting vestibular afferents and spinal motoneurons contributes to vestibulospinal reflexes (VSRs). A second distinctive feature of the vestibular system is that the first stage of central processing is remarkably multimodal, as a result of the input it receives from numerous areas within the brainstem, as well as from the cerebellum and cortex (Fig. 2.1). These extravestibular signal inputs relay both sensory (i.e., cutaneous somatosensory, proprioceptive, and visual) and motor-related information to the vestibular nuclei. As a result, vestibular reflex pathways are modulated in a behaviorally dependent manner in everyday life. In addition, this integration of vestibular and extravestibular cues is vital for cognitive functions such as perception of self-movement and spatial orientation. Recent single-unit studies in nonhuman primates have provided further insight into how the computations performed by the cerebellum and cortex shape the higher-level processing required for perception of self-movement and spatial orientation. The findings from these basic neurophysiologic studies have important implications for understanding the deficits observed clinically in patients.

THE VESTIBULAR NUCLEI: NEURAL CODING OF EXTERNALLY APPLIED MOTION

At the first stage of central processing, the vestibular complex comprises four main subdivisions: the medial, superior, lateral, and inferior (or descending) vestibular

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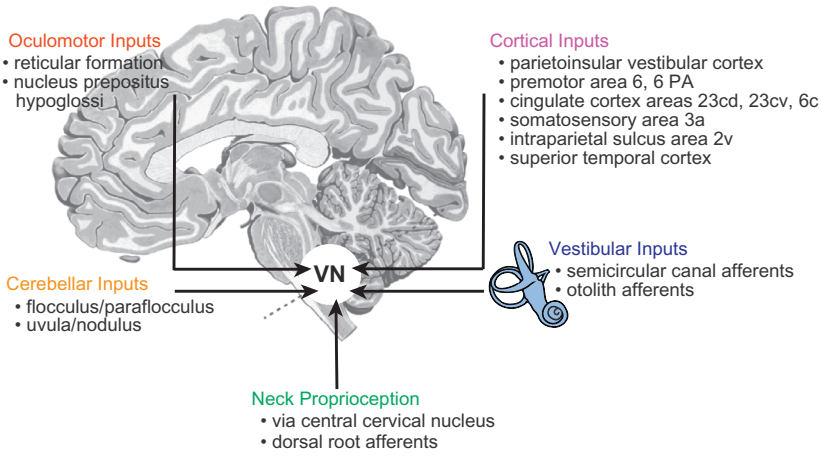

Fig. 2.1. The vestibular nuclei (VN) receive inputs from multiple brain areas, in addition to direct projections from the vestibular afferents of the VIIIth nerve. The midline is denoted by the diagonal dashed line.

nuclei, as well as other minor subgroups including the y and e groups. Although there is no strict segregation of afferent input within the subdivisions of the vestibular nuclei, each subdivision differs in the relative densities of its afferent inputs. For example, the medial and superior nuclei receive mostly horizontal and vertical semicircular canal input, respectively. In contrast, utricular and saccular afferents terminate mainly in the inferior and lateral vestibular nuclei.

General classification of cell types and linear systems analysis

Single-unit recording experiments in behaving monkeys have established how neurons in the vestibular nuclei encode applied rotations and translations. Neurons that respond to horizontal (yaw-axis) rotations are predominantly localized in the rostral medial vestibular nuclei and the ventrolateral vestibular nuclei (Fuchs and Kimm, 1975; Keller and Daniels, 1975; Chubb et al., 1984; Scudder and Fuchs, 1992; Cullen and McCrea, 1993). In contrast, neurons that respond to vertical (pitch- or roll-axis) rotations are primarily located in the superior and medial vestibular nuclei, as well as y-group (Tomlinson and Robinson, 1984; Partsalis et al., 1995; Dickman and Angelaki, 2004). Moreover, neurons that are sensitive to rotations can be further divided into three main classes based on their responses to passive whole-body rotations, translations, and voluntary eye movements. These include: (1) position-vestibular-pause (PVP) neurons; (2) vestibular-only (VO) neurons; and (3) eye-head (EH) neurons, which are each described in further detail below.

Neurons that respond to rotational head motion

To date, most studies of vestibular processing have focused on characterizing neuronal responses to horizontal (yaw-axis) rotations, because they are logistically easier to apply in comparison to either pitch/roll rotations or translations. Vestibular nuclei neurons that respond to horizontal rotations are classified as type I or II neurons (Duensing and Schaefer, 1958), based on whether they are excited by ipsilaterally or contralaterally directed rotations, respectively. Prior studies in head-restrained alert monkeys have well described the responses of individual vestibular nuclei neurons that receive direct horizontal canal afferent input (reviewed in Cullen and Roy, 2004; Cullen, 2012). Notably, a significant percentage of type I PVP, VO, and EH can be activated at monosynaptic latencies by electric stimulation of the ipsilateral vestibular nerve (McCrea et al., 1987; Scudder and Fuchs, 1992). These type I neurons, which comprise the first stage of central processing in the vestibular system, are considered below in relation to their distinctive functional roles, specifically: (1) VOR neurons (i.e., PVP and EH neurons) and (2) posture/self-motion neurons (VO neurons).

VOR neurons

The angular VOR effectively stabilizes gaze during our daily activities by moving the eye in the opposite direction to the ongoing head rotation (Fig. 2.2A). The most direct pathway mediating this vital reflex comprises a three-neuron arc in which the semicircular canal afferents project to central neurons in the vestibular nuclei

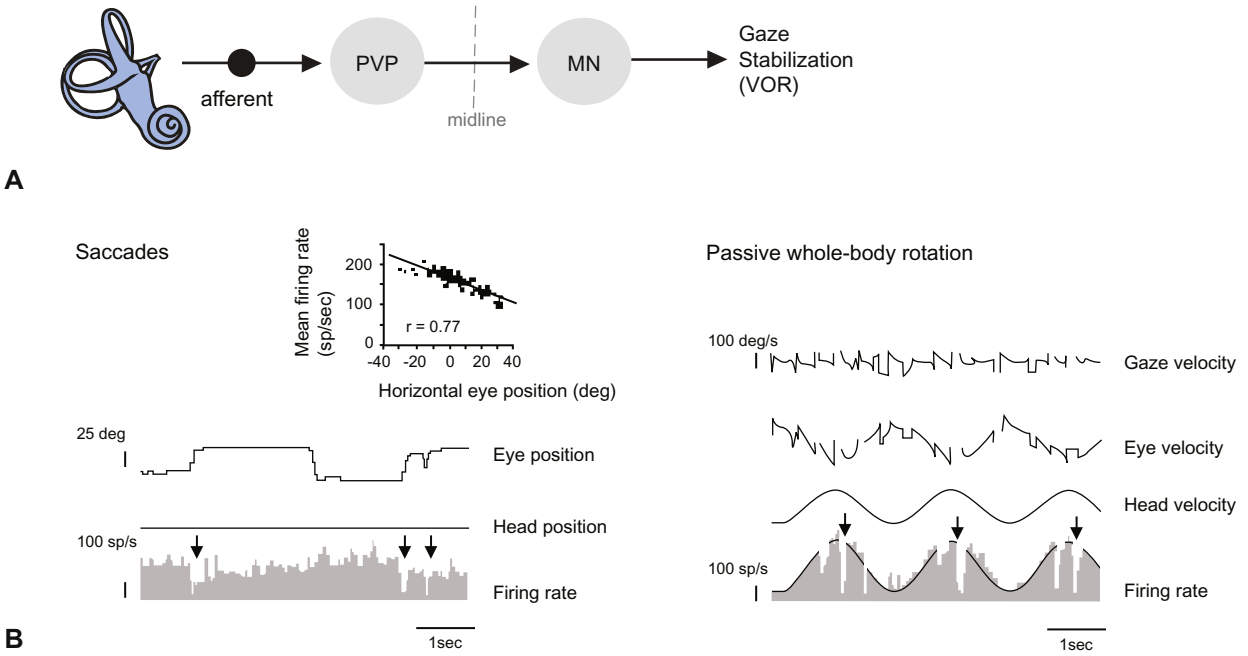

Fig. 2.2. Vestibular nuclei neurons mediate the vestibulo-ocular reflex (VOR). (**A**) Schematic diagram of the direct VOR pathway (top). Position-vestibular-pause (PVP) neurons constitute the middle link of this reflex; they receive direct afferent input and send strong inhibitory projections to ipsilateral abducens motoneurons (MN) to generate compensatory eye movements. (**B**) PVP neurons encode eye position during ocular fixation, head motion during whole-body rotation, and pause during saccades (arrows).

(i.e., VOR neurons), that in turn project to the extraocular motoneurons (Lorente de No, 1933). The majority of the neurons in the vestibular nuclei that comprise the middle link of the direct VOR pathway are type I PVP neurons (Fig. 2.2B). Note that the designation PVP is well established in the vestibular literature, and arose because these neurons carry specific signals during passive head rotations and eye movements. Specifically, the type I PVPs that comprise the direct VOR pathway: (1) carry signals related to contralateral eye position signals during visual fixation; (2) respond to vestibular input caused by ipsilateral head rotations; and (3) pause for saccadic eye movements. Additionally, indirect pathways through the vestibular cerebellum make important contributions to the VOR. In particular, there is a second class of neuron in the vestibular nuclei that receives direct projections from the floccular complex of the cerebellum as well as from the vestibular nerve (McFarland and Fuchs, 1992; Scudder and Fuchs, 1992; Cullen et al., 1993; Roy and Cullen, 2003; Lisberger et al., 1994a, b). These floccular target neurons generally respond to smooth-pursuit and visual cancellation of the VOR, in the same direction. Accordingly, they are also often called EH cells in the literature. EH neurons play a critical role in gaze stability by ensuring the VOR remains calibrated. This is because, as discussed below, EH neurons change their sensitivity to account for the effects of aging or changes in environmental requirements (e.g., a new corrective lens prescription to correct myopia) to appropriately regulate the VOR response so that it remains accurate (for review, see Cullen, 2008).

Posture/self-motion neurons

The second category of vestibular nuclei neurons that receive direct afferent input are called VO neurons (Fig. 2.3A). Notably, VO neurons send projections to the spinal cord and are thought to contribute to the pathways that produce vestibular spinal reflexes (see review by Goldberg and Cullen, 2011). VO neurons are also reciprocally interconnected with the nodulus/uvula of the cerebellum (Reisine and Raphan, 1992), and this anatomic organization is an important component of the velocity storage mechanism that lengthens the time constant of the VOR beyond that provided by the afferent input. Finally, VO neurons provide vestibular input to vestibular-sensitive neurons in thalamus and cortex (Lang et al., 1979; Grusser et al., 1990). VO neurons respond to vestibular stimulation but not eye movements (Fig. 2.3B), and, unlike either PVP and EH neurons, do not project directly to eye motoneurons. Consequently, whereas PVPs and EHs mediate and calibrate the VOR to stabilize gaze and ensure clear vision in everyday life, VO neurons comprise the first stage of central processing

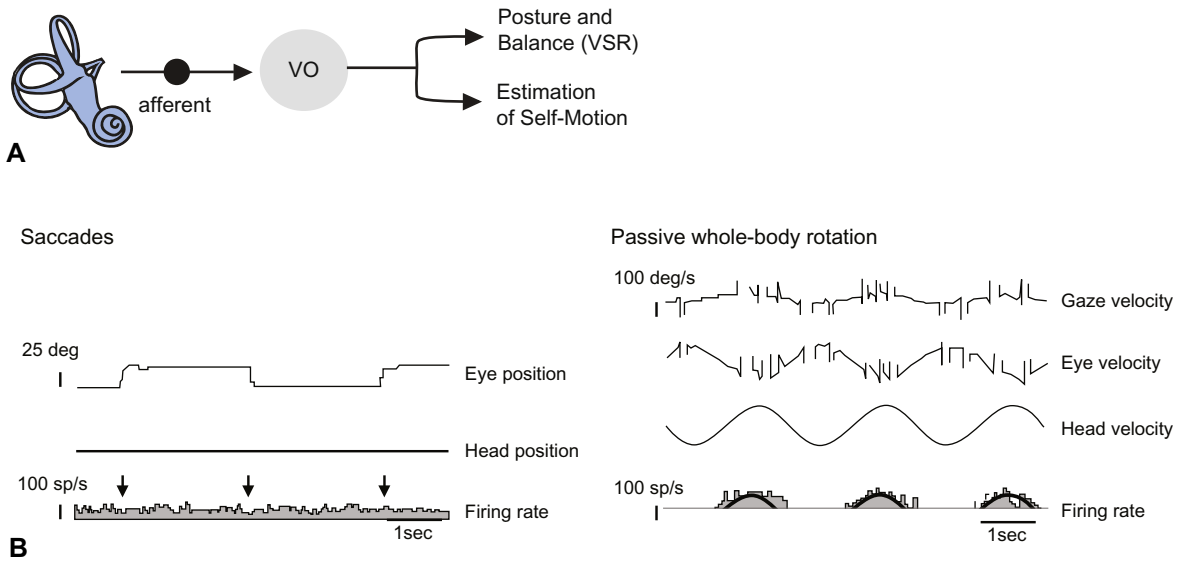

Fig. 2.3. Vestibular nuclei neurons mediate vestibulospinal reflexes and enable the accurate perception of self-motion and spatial orientation. (**A**) Schematic diagram of the contributions of vestibular-only (VO) neurons to vestibulospinal reflexes (VSR) and ascending pathways. VO neurons receive direct afferent input and send projections to spinal cord, cerebellum, and thalamus. (**B**) VO neurons are insensitive to eye position during ocular fixation or saccades, and robustly encode head motion during whole-body rotation (with comparable sensitivity in the dark and light).

in the vestibular pathways responsible for the reflexes underlying posture and balance, as well as the higher-order vestibular processing of head motion required for perception.

Traditionally, vestibular nuclei neuronal responses to sensory input have been characterized by estimating response gain and phase over several cycles of sinusoidal head rotation (reviewed in Cullen, 2012). This approach, termed linear systems analysis, has been applied to the vestibular system to understand how neurons encode head motion because it is commonly assumed that early vestibular processing is fundamentally linear. There are two main lines of evidence to provide support for this idea. First, numerous studies have shown that both afferents and their target neurons in the vestibular nuclei accurately encode the detailed time course of horizontal rotational head motion through linear changes in firing rate over a wide range of frequencies (reviewed in Goldberg, 2000; Cullen and Roy, 2004; Massot et al., 2011). In addition, *in vitro* studies have shown that central vestibular neurons linearly transduce synaptic inputs into changes in firing rate output (Bagnall et al., 2008; McElvain et al., 2015).

Indeed, in the last decade, the linear systems analysis approach has provided key insights into how early vestibular pathways encode rotational head motion over the physiologically relevant frequency range (Dickman and Angelaki, 2004; Sadeghi et al., 2007; Ramachandran and Lisberger, 2008; Massot et al., 2011). In particular, the analysis of natural head motion has revealed significant power up to ~20 Hz (Huterer and Cullen, 2002; Carriot et al., 2014; Schneider et al., 2015). Accordingly, recent studies have characterized the responses of individual vestibular afferents and vestibular nuclei neurons by applying sinusoidal head rotations throughout this frequency range and computing response sensitivities and phases. Experiments using this approach have established that, in primates, both PVP neurons (Roy et al., 2003; Ramachandran and Lisberger, 2008) and VO neurons (Massot et al., 2011) respond with high-pass dynamics that are comparable to those of vestibular afferents. However, EH neurons show distinctive dynamics characterized by strikingly flat gain (and phase) tuning as a function of frequency (Ramachandran and Lisberger, 2008). To date, the functional implications of these differences are not yet fully understood; however, VOs show an increased phase lead relative to PVP neurons that is likely related to the higher inertia of the body versus head (Fernandez and Goldberg, 1971; Bilotto et al., 1982; Boyle et al., 1992).

Neurons that respond to linear head motion: translations and tilt

In addition to receiving direct semicircular canal afferent input, the vestibular nuclei receive direct projections from otolith afferents. In fact, single neurons often receive convergent input such that they respond to

translational as well as rotational motion. Translation-sensitive neurons are categorized using the same nomenclature detailed above for rotationally sensitive neurons (i.e., PVP, EH, and VO neurons). In response to linear head motion, PVP and EH neurons in the vestibular nuclei mediate the translational VOR to produce compensatory eye movements that stabilize gaze. A direct disynaptic pathway exists between the otolith afferents and extraocular motoneurons (Uchino et al., 1994, 1996). However, the translational VOR, unlike the rotational VOR, is largely mediated by more complex polysynaptic pathways (Chen-Huang and McCrea, 1999; Meng et al., 2005; Meng and Angelaki, 2006). As a result, the latency of the translational VOR is relatively longer than that of the rotational VOR; compensatory eye movement generally lags head movement by more than 10 ms (Angelaki and McHenry, 1999) versus the short 5 ms delay of the rotational VOR (Huterer and Cullen, 2002).

VO neurons can also respond to both linear and rotational motion. The application of linear systems analysis has shown that, while the otolith afferent responses generally lead head linear acceleration, the responses of vestibular nuclei neuron fall into three categories: (1) "high-pass" neurons characterized by response modulation and phase leads that increase with frequency; (2) "flat" neurons characterized by constant response modulation and phase leads across frequency; and (3) "low-pass" neurons characterized by response modulation and phase leads that decrease with frequency (Angelaki and Dickman, 2000). In addition, individual vestibular nuclei neurons typically display broader directional tuning for linear motion than their otolith afferent input (Angelaki et al., 1992; Schor and Angelaki, 1992; Angelaki, 1993). Notably, the tuning of an individual otolith afferent is well described by a single preferred direction vector, and its sensitivity approaches zero for linear motion that is orthogonal to this preferred direction. This type of tuning in afferents is commonly referred to as one-dimensional tuning. In contrast, vestibular nuclei neurons display more complex tuning consistent with the fact that they typically receive converging otolith inputs that differ in preferred direction vector. As a result of this convergence, vestibular nuclei neurons typically respond to motion directed in either one or even two directions orthogonal to their preferred direction (Baker et al., 1984; Angelaki, 1992a, b; Yakushin et al., 1999, 2006; Chen-Huang and Peterson, 2006). This type of tuning is commonly referred to as two-dimensional or three-dimensional tuning, respectively (Angelaki and Dickman, 2000; Chen-Huang and Peterson, 2006). Thus, as a result of their convergence inputs, the dynamics of central otolith neuron responses are also more complex than those of peripheral otolith afferents.

Information transmission and detection thresholds in early vestibular pathways

A limitation of the linear system analyses approach traditionally applied to characterize vestibular afferent and central neuron responses is that it does not take into account the important role that neural variability can play in determining how the brain encodes sensory stimuli. Recently a series of studies have shown that semicircular canal afferents with more regular resting spike rates have lower sensitivities but transmit information (i.e., quantified in bits per second) about head rotations with higher fidelity as compared to afferents with more irregular resting spike rates (Sadeghi et al., 2007; Cullen, 2011, 2012; Massot et al., 2011; Neiman et al., 2011; Metzen et al., 2015). This then raises the question: how is information encoded by these two streams of afferent input combined at the next stage of processing?

To date, the available evidence suggests that inputs from both afferent classes are combined at the first stage of central processing in the vestibular nuclei – in VOR pathways (PVP and EH cells) as well as in vestibulospinal pathways (VO cells) (Highstein et al., 1987; Boyle et al., 1992). Recent experiments in the vestibular nuclei of monkeys have specifically provided insights about how neural variability constrains the information encoded by VO neurons (Massot et al., 2011). Somewhat surprisingly, although VO neurons typically have larger response gains than either regular or irregular afferents, they transmit less information over the physiologically relevant frequency range. Correspondingly, due to their high variability, VO neurons also demonstrate significantly higher rotation detection thresholds than even the relatively "noisy" irregular afferents. Overall, the lowest measured thresholds (8°/s) are more than an order of magnitude larger than the perceptual thresholds measured in human studies (0.5°/s). Indeed, it is only by combining the responses of many VO neurons (i.e., >20) that neuronal detection thresholds approach values measured during behavioral experiments ($\sim$2.5 vs. 0.5–1°/s: Clark, 1967; Guedry, 1974; Grabherr et al., 2008; Valko et al., 2012). It has been proposed that the activities of multiple VO neuron are combined at higher stages of processing to obtain the velocity detection thresholds measured in psychophysical experiments (Massot et al., 2011). In order to understand how vestibular pathways encode self-motion, it is necessary to not only characterize individual neurons, but also determine how information from individual neurons is combined. In particular, if fluctuations in neuronal responses are independent, neural noise will be averaged away when inputs are combined downstream (Averbeck and Lee, 2006) to compute the estimates of self-motion required for stable perception and accurate behavior in everyday life.

It is also interesting to note that the markedly higher variability displayed by vestibular central neurons could potentially serve to prevent phase locking or entrainment (Stein et al., 2005; Schneider et al., 2011). This approach may be common across sensory systems. For example, neurons in early visual pathways can transmit detailed information in their spike trains (Meister et al., 1995; Berry et al., 1997; Reich et al., 1997; Desbordes et al., 2008). In contrast, the spike trains of neurons in visual cortex appear to be characterized by relatively large variability (e.g., London et al., 2010). A point worth emphasizing is that a critical assumption of these prior analyses of vestibular processing is that a neuron's ability to reconstruct the stimulus (i.e., coding fraction) can be measured by computing the coding fraction (Gabbiani et al., 1996; Rieke et al., 1996). However, it has been recently shown that central vestibular neurons nonlinearly integrate their afferent input in a way that effectively both extends their coding range for head motion and preferentially encodes the high-frequency features of self-motion (Massot et al., 2012). This finding invalidates the commonly held assumption that the vestibular system uses a linear rate code to transmit information. Accordingly, experiments directed toward understanding the implication of nonlinear behaviors including phase locking and other spike timing codes will likely provide new insights into how self-motion information is encoded by these vestibular nuclei neurons for the subsequent computation of self-motion as well as gaze and posture control.

Vestibular nuclei: integration of canal and otolith afferent inputs

The activities that we engage in during our everyday lives (walking, running, riding in a vehicle) are characterized by complex multidimensional motion patterns that simultaneously stimulate the semicircular canal and otolith organs (Carriot et al., 2013; Schneider et al., 2015). For this reason, understanding how single neurons integrate the incoming information from both types of end organs is fundamental to furthering our knowledge of how the vestibular system encodes self-motion in everyday life. Projections from semicircular canal and otolith organ afferents show considerable overlap in the vestibular nuclei (Gacek, 1969; Dickman and Fang, 1996; Birinyi et al., 2001). However, individual vestibular nuclei neurons generally only receive input from a single semicircular canal and/or otolith organ (Straka and Dieringer, 2004). Interestingly, rotational and linear motion inputs combine in a spatially specific manner, either combining horizontal semicircular canal and utricular signals or vertical semicircular canal and saccular otolith signals (Straka et al., 2002).

Single-unit recording studies in the vestibular nuclei of primates have provided insight into the specific computations that are performed in early vestibular processing to integrate canal and otolith afferent inputs (Tomlinson et al., 1996; Siebold et al., 1999, 2001; Angelaki et al., 2004; Yakushin et al., 2006; Carriot et al., 2015). The majority of vestibular neurons receive convergent inputs, and numerous studies have focused on understanding how the brain integrates these inputs to discriminate tilt from translation. Specifically, while tilt activates both otolith and semicircular canal organs, translation activates only the otolith end organs. Thus, by integrating canal and otolith signals it is theoretically possible to discriminate tilt from translation. Indeed, many neurons in the vestibular nuclei preferentially encode translational motion such that they are relatively insensitive to changes in head orientation relative to gravity (reviewed in Angelaki and Cullen, 2008; Angelaki and Yakusheva, 2009). It has further been shown that inactivation of the semicircular canals can completely eliminate the presence of translation-coding cells (Shaikh et al., 2005; Yakusheva et al., 2007). Thus, interactions between otolith and canal signals allow neurons to selectively encode translational motion and remain relatively insensitive to changes in head orientation relative to gravity. Taken together, these results provide insight into how subjects discriminate tilt from translation (Glasauer and Merfeld, 1997; Angelaki et al., 1999; Merfeld et al., 1999; Bos and Bles, 2002; Zupan et al., 2002; Green and Angelaki, 2003, 2004; Laurens and Angelaki, 2011).

During common everyday activities, the otoliths and semicircular canals are both simultaneously and dynamically stimulated. However, in most prior studies the responses of vestibular nuclei neurons were independently characterized during pure rotations and pure translations. The few studies that have characterized neurons during more complex combined movement found that semicircular canal and otolith inputs are not summed linearly (Dickman and Angelaki, 2002; McArthur et al., 2011; Carriot et al., 2015). Instead vestibular nuclei neurons subadditively integrate semicircular canal and otolith inputs (Carriot et al., 2015), such that they show less modulation than that predicted by the addition of their responses to translation and rotations when each is applied alone. A potential benefit of this subadditive integration is that it effectively expands the dynamic linear range of vestibular neurons to prevent firing-rate saturation or cutoff (i.e., the cessation of firing) in response to high-amplitude natural head movements (Carriot et al., 2014; Schneider et al., 2015). Moreover, on average, the weighting of rotational sensitivities decreases with increasing frequency, whereas the translational weights increases with increasing frequency. This

frequency dependency provides a neural correlate for the finding in human psychophysical experiments that subjects more accurately perceive angular than linear displacement at lower frequencies (Ivanenko et al., 1997; MacNeilage et al., 2010).

Vestibular nuclei: multimodal integration

In everyday life, our sense of self-motion involves the integration of vestibular and extravestibular cues, including visual and proprioceptive sensory signals as well as information derived from our own motor commands. For example, when walking down the street, the visual system provides retinal-image motion (optic flow) cues, whereas the proprioceptive sensors of our muscles, tendons, and joints sense the relative position of neighboring parts of the body. In addition, information related to the motor commands that control our walking can theoretically contribute to the brain's estimate of self-motion. Recent single-unit recording experiments have revealed how single neurons in the vestibular nuclei integrate vestibular and extravestibular cues.

The integration of vestibular and visual cues

As we move through our environment, patterns in the apparent motion of objects, surfaces, and edges in a visual scene are produced by the relative motion between us and the world. The visual cues provided by this large-field visual motion induce reflexive eye movements to maintain stable gaze relative to visual space (Waespe and Henn, 1977a, b, 1979; Boyle et al., 1985). These compensatory eye movements are termed the optokinetic reflex (OKR). The OKR works synergistically with the VOR to maintain gaze stability, and is characterized by an initial rapid rise in eye velocity within ~100 ms of the start of visual motion followed by a slower build-up of eye velocity in primates. The initial rise is controlled by cortical inputs to OKR pathways, while the slower build-up is largely produced by a subcortical pathway that includes the nucleus of the optic tract (NOT) and the accessory optic system (AOS). Interestingly, the relative importance of brainstem and cortical inputs to the OKN pathways is species-dependent. Animals such as mice, gerbils, and rabbits show significant temporal-nasal asymmetries in their OKN responses (Collewijn, 1981; Kaufman, 2002; Stahl et al., 2006), while responses are symmetric in humans and monkeys. It has been proposed that cortical inputs to NOT neurons provide symmetric OKR responses of each eye, thereby ensuring stable binocular vision in primates (see discussion in Leigh and Zee, 2004). There is evidence to support this view. For example, OKN responses are asymmetric in human infants, whose pathways to cortical visual areas are not fully developed (Atkinson et al., 1974; Schor, 1983) and in monkeys with lesions of the occipital cortex.

Neurons within the vestibular nuclei can simultaneously process visual and vestibular inputs – a finding that helps to explain why full-field motion on the retina not only provides an observer with an indication of how fast, and in what direction, the visual world is moving, but also leads to the sensation of self-rotation. Specifically, single-unit recording studies in the vestibular nuclei have indicated that eye movement-sensitive neurons (e.g., PVP neurons) show robust modulation during OKR (reviewed in Cullen, 2011, 2012). Thus, the same neurons play a major role in the premotor control of OKR eye movements as well as the VOR. It is also noteworthy that early studies concluded that all vestibular nuclei neuron classes are driven by optokinetic as well as vestibular stimulation (Waespe and Henn, 1977a, b; Büttner and Büttner, 1979; Boyle et al., 1985; Reisine and Raphan, 1992). However, the more complete quantitative analysis performed in recent studies has established that this is not the case. Specifically, VO neurons, unlike eye movement-sensitive neurons, do not show robust modulation during large-field visual stimulation either in mouse or primates (Beraneck and Cullen, 2007; Bryan and Angelaki, 2009). The same vestibular nuclei neurons that command OKR eye movements likely also contribute to an integrated "velocity storage" network that uses visual information to supplement the decaying signal from vestibular afferents during sustained head movements to encode self-motion (Cohen et al., 1983; Angelaki and Hess, 1995; Wearne et al., 1998).

The integration of vestibular and proprioceptive cues

There are marked differences in how vestibular and proprioceptive information is integrated across species. For example, both eye-sensitive and VO vestibular nuclei neurons can robustly respond to both proprioceptive as well as vestibular stimulation in mice, rats, cats, and alert squirrel monkeys (Boyle and Pompeiano, 1981; Anastasopoulos and Mergner, 1982; Wilson et al., 1990; Gdowski et al., 2001; Barresi et al., 2013; Medrea and Cullen, 2013). In these species, a given neuron's responses to combined stimulation are well approximated by the linear sum of its responses to vestibular and proprioceptive stimulation when each modality is activated in isolation. In contrast, proprioceptive responses are less pronounced in cynomolgus monkeys (Sadeghi et al., 2009) and are actually absent in rhesus monkeys (Roy and Cullen, 2001, 2004). It has been proposed, that these differences evolved as a result of variations in species-specific adaptations in gaze strategies during exploratory behavior. For example, cynomolgus and

rhesus monkeys commonly explore their environment with voluntary head-on-body movements termed gaze shifts (Freedman and Sparks, 1997, 2000; Goossens and van Opstal, 1997; McCluskey and Cullen, 2007). In contrast, head and body motion is more closely linked in rodents to enhance the efficacy of mechanisms that support the stabilization of the head relative to the body (e.g., Baker, 2005; Takemura and King, 2005). Thus, strong convergence with proprioceptive inputs in early vestibular pathways could be disadvantageous in monkeys (and presumably humans), which more commonly exercise voluntary control over the neck musculature.

The integration of vestibular and motor-related information

As mentioned above, information related to the motor commands that produce active self-motion can also theoretically contribute to the brain's estimate of self-motion. Consistent with this idea, recent single-unit recording studies in alert-behaving primates have established that the efficacy of the pathways that mediate VOR as well as VSR is modulated in a behaviorally dependent manner during voluntary movements (Cullen, 2011, 2012). Notably, the head motion sensitivity of the vestibular nuclei neurons that mediate the VOR (i.e., PVP neurons) is substantially attenuated when the goal of the ongoing motor behavior is to voluntarily redirect (rather than stabilize) gaze. Likewise, the head motion sensitivity of the vestibular nuclei neurons that mediate VSR (i.e., VO neurons) is substantially attenuated when the goal of the ongoing motor behavior is to generate voluntary motion of the head through space, rather than to stabilize head motion. In both of these situations, the attenuation is behaviorally advantageous since intact vestibular reflexes would likely be counterproductive, eliciting reflex responses that would oppose intended voluntary behaviors. The mechanisms underlying these two examples of behaviorally dependent processing of vestibular information at the first central stage of processing as well as the implications for behavior and higher-order vestibular processing are explicitly discussed in relation to the VOR and VSR below.

THE ROTATIONAL VESTIBULO-OCULAR REFLEX AND GAZE STABILIZATION

The VOR effectively stabilizes gaze during our everyday activities by moving the eye in the opposite direction to the ongoing head rotation. Numerous studies performed over many decades have well characterized the morpho-physiologic organization of the circuitry underlying the VOR (reviewed in Straka and Dieringer, 2004).

Neural circuitry meditating the vestibulo-ocular reflex

In 1933, Lorente de No first described the most direct pathway between the vestibular end organs and eye muscles, which is mediated by a three-neuron arc in which vestibular afferents project to neurons in the vestibular nuclei, that in turn project to extraocular motoneurons (Fig. 2.4). Subsequent studies have further demonstrated that the fundamental structure of VOR circuitry is well conserved following its establishment in early vertebrates (reviewed in Straka and Baker, 2013). Because of its relative simplicity in comparison to other sensorimotor circuits, the VOR has proven to be an excellent model system for bridging the gap between neuronal circuits and behavior.

Three properties of the VOR make it particularly well suited for stabilizing gaze. First, consistent with the synaptic and axonal delays of the three-neuron arc, the compensatory eye movements produced by the VOR lag head movements by only approximately 5 ms in the primate (Minor et al., 1999; Huterer and Cullen, 2002). Second, the VOR shows remarkably compensatory dynamics over physiologic relevant range of head movements (Armand and Minor, 2001; Huterer and Cullen, 2002) such that its gain (i.e., eye velocity/head velocity) is close to unity, and it shows minimal phase lag. Finally, not only does the VOR remain compensatory for high-frequency head rotations, but it does so for head velocities approaching 500°/s (Paige, 1983; Tomlinson, 1990).

The results of single-unit recordings in monkeys have provided insight into how the circuitry underlying the VOR effectively stabilizes gaze across the wide range of head frequencies and velocities experienced in everyday life (Cullen, 2012). Compensation for the small but finite 5-ms reflex pathway delay is provided by a frequency-dependent increase in neuronal response phase. Specifically, the responses of type I PVP neurons lead rotational head velocity and this lead increases from 10 to 60° for head motion at 0.5 Hz versus 15 Hz (Roy et al., 2003; Ramachandran and Lisberger, 2008). In contrast, compensation for high-velocity head rotations provides the match that exists between the nonlinear dynamics of direct VOR pathways and the complementary dynamics of the oculomotor plant itself. Notably, the responses of PVP neurons show a soft saturation for ipsilateral velocities >200°/s and are silenced for contralateral head velocities of 100–200°/s. These values are less than those that are generated during daily activities, raising the question of how the VOR remains compensatory for head rotations of up to 500°/s. Quantification of extraocular motoneurons during such high-velocity motion has revealed that these nonlinear properties of PVP neurons are effectively offset by the

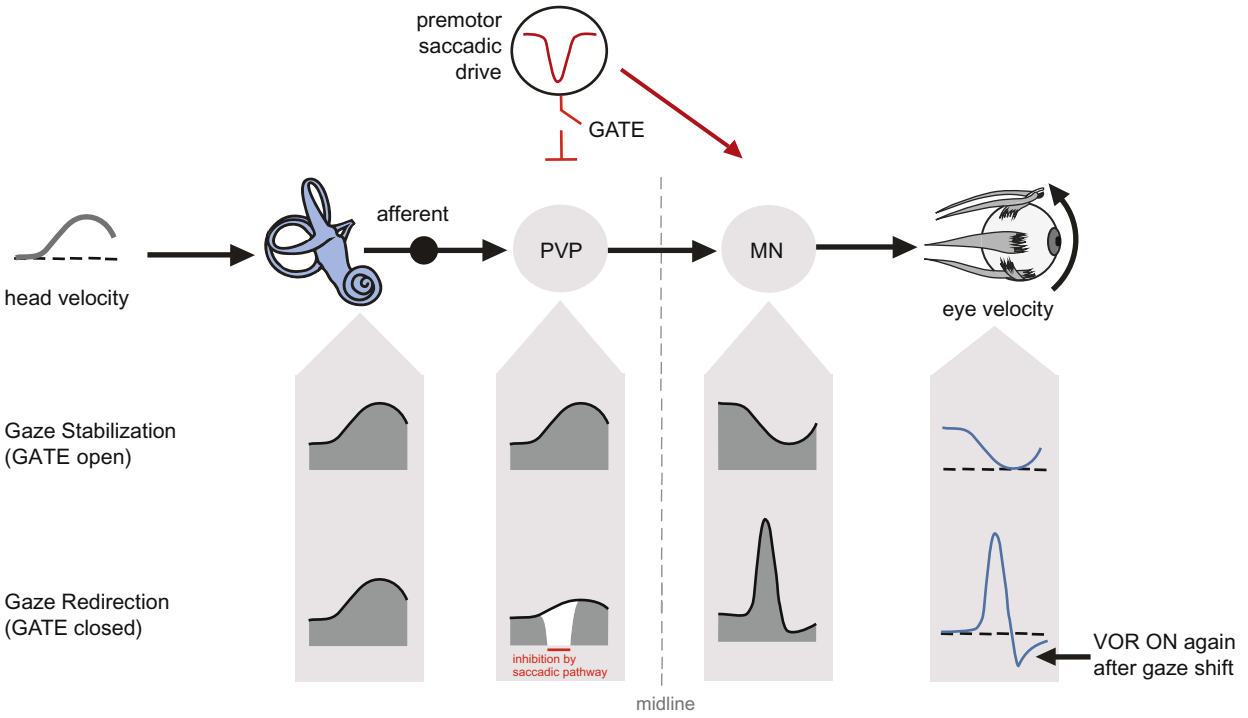

Fig. 2.4. Vestibulo-ocular reflex (VOR) pathway and the mechanism underlying VOR suppression during gaze redirection (i.e., gaze shifts). While the VOR is compensatory over a wide frequency range when the goal is to stabilize gaze, its efficacy is reduced during gaze shifts. Vestibular afferents encode head movements regardless of the behavioral goal. However, experiments in monkeys have shown that, at the next stage of processing, the responses of type I position-vestibular-pauses (PVPs) are suppressed during gaze shifts. The mechanism mediating this suppression is well understood. Specifically, the premotor saccadic pathway that drives gaze shifts via its direct projections to the extraocular motoneurons (MN: red arrow), also strongly inhibits the direct VOR pathway (i.e., closing the "gate" to send a suppression signal). This behaviorally dependent modulation of the VOR is depicted by the shaded panels below the circuit: (1) during gaze stabilization the "gate" remains open and the VOR pathway produces a compensatory eye movement, while (2) during gaze redirection, the "gaze" is closed and the VOR pathway is attenuated by the inhibitory command from the saccadic pathway.

complementary dynamics of the oculomotor plant (Sylvestre and Cullen, 1999).

The efficacy of the vestibulo-ocular reflex is suppressed during voluntary gaze behaviors

The efficacy of the VOR is not constant, but instead depends on the behavioral context. Specifically, the VOR is modulated as a function of the current behavioral gaze goal. When the goal is to maintain stable gaze, the VOR is compensatory (Fig. 2.4). However, the efficacy of the VOR is altered during voluntary gaze behaviors. Behavioral studies in humans and primates have shown that the VOR is attenuated or even suppressed when humans and monkeys voluntarily redirect their gaze (eye/head and or body movements) towards a target of interest (Laurutis and Robinson, 1986; Pelisson and Prablanc, 1986; Tomlinson and Bahra, 1986; Guitton and Volle, 1987; Pelisson et al., 1988; Tomlinson, 1990; Tabak et al., 1996). During gaze shifts, VOR suppression is maximal early in the gaze shift and progressively recovers to reach normal values by gaze-shift end (Cullen et al., 2004). In addition, the gain of the VOR varies as a function of vergence angle (Viirre et al., 1986; Crane and Demer, 1998).

The results of single-unit recordings in monkeys have provided insight into the mechanisms that modulate the efficacy of the direct VOR pathways during voluntary gaze behaviors. Specifically, the head movement-related modulation of PVP neurons is markedly reduced while monkeys redirect their visual axis of gaze using combined eye–head-orienting gaze shifts or pursuit (Roy and Cullen, 1998, 2002; McCrea and Gdowski, 2003). The mechanism mediating this attenuated response is an inhibitory projection to the vestibular nuclei from brainstem premotor saccadic and pursuit pathways (reviewed in Cullen, 2012). Specifically, when gaze is purposefully redirected using either the saccadic or smooth-pursuit pathways, a copy of the premotor motor command that drives the redirection of gaze is sent to the vestibular nuclei to suppress the head movement-related modulation of PVP neurons (Fig. 2.4, gate closed versus

open). Indeed, inhibiting the direct VOR pathways with a copy of the motor command to voluntarily redirect gaze is advantageous in this situation, since an intact VOR movement would function to drive the eye in the opposite direction to the intended change in gaze.

As noted above, the efficacy of the direct VOR pathway is also modulated as a function of viewing distance, as gaze is used to orient the visual axis on a near or far target. This is because the eyes translate as well as rotate relative to space since they cannot both be perfectly aligned with the axis of rotation (Viirre et al., 1986). Consequently, for the same amplitude of head rotation, a larger VOR gain is necessary to stabilize a near than a far earth-fixed target. Differences in the responses of the PVP neurons that mediate the direct VOR pathways are consistent with these distance-related changes in VOR gain (Chen-Huang and McCrea, 1999).

Vestibular compensation and motor learning

The VOR is capable of remarkable compensation following peripheral vestibular loss (human: Gonshor and Melvill Jones, 1976; Allum et al., 1988; Curthoys and Halmagyi, 1995; macaque monkey: Sadeghi et al., 2006). This compensation is critical to maintain accurate perception and motor performance with the loss of vestibular hair cells that occurs as a result of normal aging, as well as to recover from disorders that affect hair cells or afferents (e.g., vestibular nerve neuromas, vestibular neuritis, or trauma). In addition, the vestibular system is capable of impressive adaptation to environmental requirements. This adaptability of the VOR circuitry is vital in the first years of life to compensate for significant changes in head circumference (~30% in the first year), as well as in later life to compensate for common conditions such as the need to wear corrective lenses for visual conditions such as myopia (i.e., nearsightedness). Vestibular scientists have long appreciated the impressive adaptive capabilities in the VOR. For example, in 1976 Gonshor and Melvill Jones asked subjects to view the world through reversing prisms continually for 3–4 weeks. Theoretically the direction of the VOR would need to be reversed to stabilize the world on the retina during head movements with this new "environmental requirement." Indeed, subjects showed adaptive changes in their VOR changes that were consistent with the imposed (and exceptionally challenging) requirements of retinal image stabilization during head movement, indicating extensive and retained learning within the reflex pathway.

Vestibular compensation

Within a month of peripheral vestibular loss, VOR compensation is nearly complete for rotations toward the contralesional side, as well as for less challenging (i.e., lower-frequency and velocity) rotations toward the ipsilesional side (Smith and Curthoys, 1989; Cullen et al., 2009). Compensation processes, however, are not able to fully restore the VOR for more challenging ipsilesional rotations (Halmagyi et al., 1990; Gilchrist et al., 1998; Sadeghi et al., 2006). Our understanding of the basic mechanisms mediating vestibular compensation following peripheral loss has greatly advanced over the past several decades. Single-unit recording experiments in monkeys revealed a small but significant increase in the irregularity of vestibular afferents in the remaining intact contralesional nerve (Sadeghi et al., 2006). This effect might be mediated by compensatory mechanisms involving the vestibular efferent system, which originates from a group of cells near the abducens nucleus in the brainstem and projects back to the vestibular periphery (reviewed in Goldberg, 2000). Furthermore, long-term changes in the strength of the commissural connections between the vestibular nuclei play an important role in compensation (Dieringer and Precht, 1979a, b). Specifically, GABAergic inhibition is reduced on the impaired side, producing a change in the strength of cerebellar input to the vestibular nuclei (reviewed in Straka et al., 2005). *In vitro* experiments have further shown that compensation is accompanied by changes in intrinsic properties of cells on both the contra- and ipsilesional sides (Beraneck et al., 2003, 2004).

In vivo studies in cats and monkeys have provided insight into the time course of the functional changes occurring at the level of specific neurons within the VOR pathways to drive compensation. Immediately following a unilateral peripheral lesion, there is a decrease in the resting discharge of vestibular cells on the ipsilesional side and an increase on the contralesional side (Ris et al., 1995; Ris and Godaux, 1998). This asymmetry underlies the static symptoms that are observed clinically, such as spontaneous nystagmus and head tilt toward the side of the lesion (Curthoys and Halmagyi, 1995; Sadeghi et al., 2006). Recent experiments in behaving monkeys have further shown that the sensitivities of contralateral type I PVP neurons substantially decrease immediately after unilateral vestibular loss, and then recover within a month, reaching values close to those measured before the lesion (Sadeghi et al., 2010). Thus, this improvement in the VOR pathway neurons provides a neural correlate for the dynamic improvement in the VOR performance that is observed over the same timeframe.

Research on basic physiologic mechanisms has further revealed that homeostatic plasticity plays a fundamental role in vestibular compensation. Recent single-unit studies in rhesus monkeys have shown that compensation is mediated by rapid dynamic reweighting of inputs from different modalities (i.e., extravestibular proprioception and motor efference copy signals versus

vestibular signals) at the level of vestibular nuclei neurons (Sadeghi et al., 2010, 2011, 2012; Jamali et al., 2014). In particular, within a day of vestibular loss, type I PVP neurons become responsive to passive stimulation of proprioceptors (note, they are insensitive to such stimulation under normal conditions). In turn, this rapid unmasking of sensitivity to proprioceptive input is linked to faster and more substantial recovery of the neuronal resting rates (Sadeghi et al., 2010). Moreover, in the weeks that follow peripheral vestibular loss, type I PVP neurons also become responsive to motor efference copy input. Thus, multimodal integration is dynamically regulated in the vestibular system in a manner that suggests a causal role for homeostatic plasticity in VOR compensation. It is noteworthy that this strategy is common across different animal species (Dichgans et al., 1973; Newlands and Perachio, 1991; Ris and Godaux, 1998; Vibert et al., 1999; Newlands et al., 2001; Straka et al., 2005), as well as humans (Della Santina et al., 2001, 2002), and likely provides the neural substrate for rehabilitation approaches currently used by clinicians to treat patients. For instance, Cawthorne–Cooksey exercises along with other popular training approaches promote compensation by combining stimulation of vestibular and extravestibular (i.e., proprioceptive and motor efference copy) inputs in patients (Ricci et al., 2010).

Motor learning

Plasticity within vestibular pathways is also essential for fine-tuning the coordination and accuracy of the VOR in response to environmental requirements. Because of its relative simplicity and precise behavioral readout (i.e., eye movements), the VOR circuitry has become a popular model system for investigating how changes in single-neuron responses lead to adaptive modification of circuit function and motor behavior. In particular, to understand the physiologic mechanism of sensorimotor learning, it is necessary to link changes in the patterns of neural activity with specific changes in performance. The cerebellar-based mechanisms mediating VOR motor learning have been extensively characterized (Boyden et al., 2004; Straka and Dieringer, 2004; Cullen, 2008; Medina, 2011). Experiments in alert-behaving animals have shown that initially plasticity within the floccular complex of the cerebellum drives VOR adaptation (Kassardjian et al., 2005; Broussard et al., 2011). These changes then initiate longer-term synaptic changes in target neurons within the vestibular nuclei, specifically in the group of neurons called floccular target cells or EH neurons (Broussard and Lisberger, 1992). *In vivo* and *in vitro* studies further suggest that plasticity occurs within noncerebellar VOR pathways (Beraneck et al., 2008; McElvain et al., 2010; Scarduzio et al., 2012) alongside synaptic changes within the cerebellum to ensure a relatively robust behavioral output. Thus, to ensure accurate motor performance, multiple sites of plasticity shape motor performance even in simple pathways such as the VOR.

VESTIBULOSPINAL AND VESTIBULOCOLIC REFLEXES

In addition to its crucial role in stabilizing the eye relative to space via the VOR, the vestibular system also coordinates postural reflexes. VSRs such as the vestibulocolic reflex (VCR) are critical for maintaining head and body posture during our daily activities. The VCR functions to stabilize the head relative to inertial space by generating a command to move the head in the opposite direction to that of the current head-in-space velocity (Ezure and Sasaki, 1978; Peterson et al., 1981; Baker et al., 1985; Goldberg and Peterson, 1986; Wilson et al., 1990). VO neurons in the VN project to the cervical spinal cord and are thought to mediate the VCR pathway (Fig. 2.5) (Wilson et al., 1990; Boyle, 1993; Boyle et al., 1996; Gdowski and McCrea, 1999). Additionally, projections from vestibulospinal axons to both the cervical and/or lumbar levels of the spinal cord (Abzug et al., 1974; Rapoport et al., 1977; Shinoda et al., 1988) coordinate different parts of the musculature, for example, the neck and axial muscles during head movement to ensure stable posture.

Neural circuitry mediating the vestibulospinal reflex

Similar to the VOR, the most direct pathway connecting the vestibular nerve and spinal cord motoneurons is a three-neuron arc. The summed delays of this direct VSR pathway include the time required for: (1) neural transduction; (2) afferent spike train initiation; (3) synaptic transmission; and (4) conduction times – accounting for a few extra milliseconds required for the longer conduction pathways to the motoneurons of the spinal cord. Indeed, consistent with this direct pathway, vestibular-evoked myogenic potentials first appear ~10 ms following brief clicks played through headphones (i.e., Colebatch et al., 1994). Moreover, these neck muscle-level responses are abolished following vestibular neurectomy, confirming they are driven by vestibular reflexes (Colebatch et al., 1994). However, in response to vestibular stimulation, the latency of the actual compensatory head movement generated by the VSR is >30 ms (VCR: Wilson and Maeda, 1974; Mitchell et al., 2013). There are three key reasons why this latency of movements produced by the VSR is markedly longer than that of the eye movements generated by VOR (~5 ms).

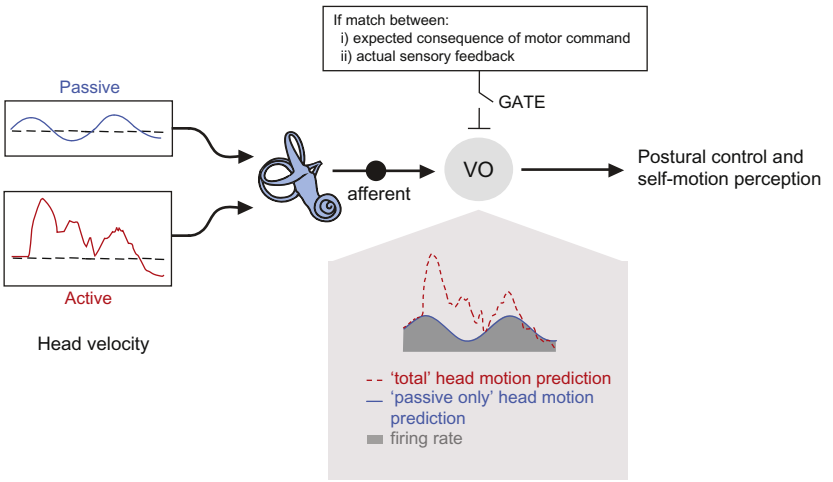

Fig. 2.5. Vestibular-only (VO) neurons and the mechanism underlying their suppression during active head motion. Vestibular afferents encode head movements regardless of whether vestibular stimulation is the result of head motion that is actively generated (vestibular reafference) or passively applied (vestibular exafference). However, during active head movement, VO neurons receive a strong inhibitory input ("gate") that effectively suppresses their responses. In particular, vestibular reafference is canceled when there is a match between the expected sensory consequence of neck motor command and the actual neck proprioceptive feedback.

First, the latency from spinal motoneuron stimulation to head motion onset is ~20 ms (Elsley et al., 2007) – a value significantly longer than the ~3 ms latency between oculomotor neuron stimulation, muscle contraction, and movement (Fuchs and Luschei, 1971). Second, the relatively longer latencies of evoked head motion are consistent with the relatively sluggish dynamics of the neck versus eye plant (Zangemeister et al., 1981; Peng et al., 1996, 1999). Finally, the dominant pathways mediating the VSR are more complex and involve additional structures, including the interstitial nucleus of Cajal, dorsal lateral vestibular nuclei, and medial reticular formation (reviewed in Goldberg and Cullen, 2011).

The efficacy of the vestibulospinal reflex is markedly reduced during active movement

As described above for the VOR, the efficacy of the VSR is not constant but instead depends on the behavioral context. Specifically, VSR pathways are suppressed when the current behavioral goal is to voluntarily move the head relative to the world. The results of single-unit recordings in monkeys have provided insight into the mechanism that is responsible for modulating the efficacy of the direct VSR pathways during voluntary motion.

Vestibular afferents similarly encode self-generated and externally applied head motion (Cullen and Minor, 2002; Sadeghi et al., 2007; Jamali et al., 2009). However, when head movements are self-produced, the head velocity-related responses of VO neurons in the vestibular nuclei are dramatically reduced (McCrea et al., 1999; Roy and Cullen, 2001, 2004; Brooks and Cullen, 2013; Carriot et al., 2014, 2015). Additionally, the head velocity-related responses of these same neurons are similarly attenuated when the head moves in space as a result of voluntary head-on-body motion or body motion (Brooks and Cullen, 2013). The suppression of vestibular input that is the result of head motion produced either by activation of the neck musculature (head-on-body motion) or axial muscles that move the head and body (e.g., orienting body movements; McCluskey and Cullen, 2007; Anastasopoulos et al., 2009) is comparable. Moreover, the level of suppression is striking: in rhesus monkeys vestibular responses are attenuated by ~70% during active rotations and translations (Roy and Cullen, 2001, 2004; Brooks and Cullen, 2013; Carriot et al., 2014, 2015).

Importantly, VO neurons can also selectively respond to passive head motion during combined active and passive motion. For example, when monkeys produce active head-on-body movements while undergoing passive whole-body rotation, VO neurons preferentially respond to the passive component of the vestibular stimulation (Roy and Cullen, 2001; Brooks and Cullen, 2013; Carriot et al., 2014). A series of studies in which the correspondence between intended and actual head movement was experimentally controlled have provided insight into the mechanism that accounts for this striking suppression. Specifically, evidence to date suggests that vestibular input to these neurons is suppressed when there is a match between the predicted and actual proprioceptive sensory feedback during self-motion (i.e., the gate would close in Fig. 2.5: Roy and Cullen, 2004; Brooks and Cullen, 2013, 2014; Carriot et al., 2013).

The differential processing of passive versus active head motion: functional implications

The behaviorally dependent gating of vestibular responses at the level of the vestibular nuclei has significant implications for understanding how the brain ensures accurate posture and motor control during self-motion. In addition, the differentiation of sensory stimulation that arises from passive versus active movement is required for perceptual stability.

First, the reduced sensitivity of these neurons during active head movements is consistent with their functional role in the vestibulospinal pathways that ensure the maintenance of stable posture and balance (reviewed in Cullen, 2011, 2012). In particular, their selective and robust response to unexpected passive vestibular stimulation is behaviorally advantageous, producing the required compensatory reflex responses (e.g., recovery from tripping over an obstacle). Likewise, their attenuated responses to expected active vestibular stimulation are behaviorally advantageous. This is because the same VSRs that are needed to compensate for unexpected motion would actually be counterproductive during self-generated movements (they would oppose the intended motion). Thus, it is vital to reduce the efficacy of the VSR during active movements. Importantly, in addition to their descending projection to the spinal cord, VO neurons have reciprocal connections with regions of the cerebellum that are vital for the control of posture and spatial orientation, including the rostral fastigial nucleus (Shimazu and Smith, 1971; Batton et al., 1977; Carleton and Carpenter, 1984; Homma et al., 1995) and the nodulus/uvula (Walberg and Dietrichs, 1988; Xiong and Matsushita, 2000). Accordingly, the ability of these neurons to preferentially encode unexpected motion also likely contributes to the fine-tuning of motor commands (Brooks et al., 2015).

Second, prior studies have shown that a match between sensory feedback and the causal motor command is required for accurate sensation. Indeed, the differential processing of vestibular sensory input observed in early vestibular processing parallels findings for other voluntary behaviors, for instance, self-produced tactile stimulation (Blakemore et al., 1999, 2000) and perceived force during tapping (Bays et al., 2005) and lifting tasks (Diedrichsen et al., 2003, 2005). This suggests a common strategy across sensory systems regarding the suppression of self-generated sensory inputs. As discussed below, VO neurons provide vestibular information to cortical areas involved in the computation of self-motion perception and orientation (Deecke et al., 1977; Meng et al., 2007; Marlinski and McCrea, 2008; Meng and Angelaki, 2010) through their ascending projections to the thalamus (Wild, 1988; Shiroyama et al., 1999; Zwergal et al., 2009). Thus, the differential coding of passively versus actively generated motion by VO neurons also contributes to perceptual stability during self-motion (i.e., was my motion intended or unexpected?).

HIGHER-ORDER VESTIBULAR PROCESSING

Historically, basic research on the physiology of central vestibular pathways has predominantly focused on the circuitry that mediates reflex pathways such as the VOR and VSR. Studies of patients with vestibular loss have underscored how vital these reflexes are in our everyday lives. In addition, the vestibular system plays fundamental roles in providing our perception of self-movement, spatial orientation, and body representation (reviewed in Mast et al., 2014). Recent neurophysiologic experiments in nonhuman primates have furthered our understanding of the computations performed by the vestibular cerebellum and cortex. These findings are complemented by neuroimaging studies in humans using caloric and galvanic vestibular stimulation that have advanced our knowledge of how these higher-order structures encode and process vestibular stimuli (reviewed in Dieterich and Brandt, 2008, 2010).

Vestibular cerebellum

There are five main regions of the cerebellum (Fig. 2.6) that receive either primary (i.e., from afferents) or secondary (i.e., from vestibular nuclei) vestibular input including the: (1) nodulus and ventral uvula (lobules X and IX); (2) flocculus and ventral paraflocculus; (3) oculomotor vermis of posterior lobe (lobules VI–VII); (4) lobules I–V of the anterior lobe; and (5) deep cerebellar nuclei. As described below, each of these regions makes an important contribution to the processing of vestibular sensory information.

The vestibular nuclei are reciprocally interconnected with the nodulus/uvula of the cerebellum (Wearne et al., 1998). Lesions of both cerebellar structures alter the temporal and three-dimensional spatial processing of vestibular information (reviewed in Goldberg et al., 2012), suggesting it makes significant contributions to the computation of inertial motion (Angelaki and Hess, 1995; Wearne et al., 1998). Recent experiments have provided specific insight into the computations performed within these cerebellar lobules to distinguish head tilt from translation. Einstein's equivalence principle indicates that the otolith organs and, in turn, otolith afferents, will not distinguish linear accelerations that are due to head tilts (relative to gravity) from those that are the result of translational self-motion. However, the activation of the semicircular canals differs in these two conditions, because semicircular canals are stimulated by the

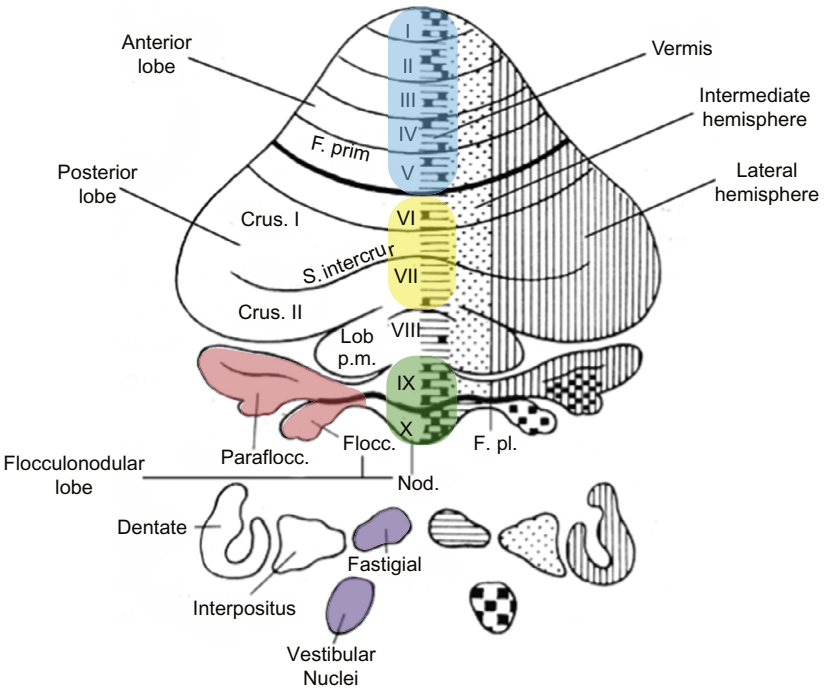

Fig. 2.6. Schematic of the cerebellar cortex with the divisions denoted between the anterior, posterior, and flocculonodular lobes along the rostral–caudal axis. Perpendicular to this, along the medial–lateral axis, the cerebellum can also be divided into three longitudinal zones, including the vermis (I–X), intermediate, and lateral hemispheres, which project to different deep cerebellar nuclei, namely the fastigial, interpositus, and dendate respectively, as well as vestibular nuclei. The main cerebellar regions that receive vestibular input include the nodulus and ventral uvula (green), flocculus and ventral paraflocculus (red), oculomotor vermis of posterior lobe (yellow), lobules I–V of the anterior lobe (blue), and fastigial deep cerebellar nucleus and vestibular nuclei (purple). Flocc., flocculus; Lob p.m., paramedian lobule; Nod., nodulus; Paraflocc., paraflocculus; S. intercrur, intercrural sulcus. (Adapted from Brodal, 1979.)

rotations accompanying head tilt but not by pure translations. Thus, by integrating these two signals, the brain can theoretically distinguish between tilt and translation (Mayne, 1974; Merfeld, 1995; Angelaki et al., 1999; Merfeld et al., 1999, 2001, 2005; Bos and Bles, 2002; Green et al., 2005; Green and Angelaki, 2007; Laurens and Droulez, 2007; Laurens and Angelaki, 2011; Laurens et al., 2011; Zupan et al., 2002). Recent single-unit recording studies in the nodulus and uvula of monkeys suggest the brain explicitly performs such a computation such that some Purkinje cells combine otolith and semicircular canal inputs to encode translation (Yakusheva et al., 2007), while other cells encode tilt (Laurens et al., 2013).

The flocculus and adjoining paraflocculus are involved in the generation and plasticity of compensatory eye movements, including visual ocular following reflexes (i.e., smooth-pursuit and OKR) and the VOR (Lisberger and Fuchs, 1978; Noda and Suzuki, 1979; Miles and Braitman, 1980; Miles et al., 1980; Buttner and Waespe, 1984; Lisberger et al., 1994a, b). As discussed above, this region of the cerebellum plays a vital role in VOR compensation and motor learning (Boyden et al., 2004; Straka and Dieringer, 2004; Cullen, 2008; Medina, 2011), such that during motor compensation and learning, synaptic changes within the floccular complex drive changes in the VOR pathways, which are required to ensure compensatory performance. Lobules VI and VII of the vermis – an area commonly referred to as the oculomotor vermis – are also involved in visual-vestibular processing (Suzuki and Keller, 1982, 1988; Sato and Noda, 1992). In addition to vestibular input, the oculomotor vermis receives eye movement signals from the nucleus preopositus (Belknap and McCrea, 1988) as well as pursuit-related inputs from the dorsolateral pontine nuclei (Brodal, 1979; Yamada and Noda, 1987). This latter region receives input from cortical regions, including the middle temporal and medial superior temporal pursuit areas (Glickstein et al., 1980).

Finally, the vestibular nuclei are reciprocally interconnected with the deep cerebellar nuclei and anterior vermis of the cerebellum (Batton et al., 1977). The anterior region of the cerebellar vermis (lobules I–V) encodes both vestibular and neck proprioceptive-related signals (Manzoni et al., 1998a, b, 1999, 2004) and is involved in the control of VSR. The integration of

vestibular and proprioceptive information ensures that the motor responses produced by these reflexes are appropriate to maintain body stability. The anterior vermis sends strong descending projections to the rostral fastigial nucleus (the most medial of the deep cerebellar nuclei), which also receives proprioceptive input via the central cervical nucleus and the external cuneate nucleus (Voogd et al., 1996). The rostral fastigial nucleus is a critical component of the descending pathway controlling postural reflexes and orienting behaviors; it projects to brainstem structures that control these behaviors, including the vestibular nuclei and medial reticular formation. Many neurons in the rostral fastigial nucleus integrate vestibular and proprioceptive inputs, and in turn encode vestibular signals in a body-centered reference frame (Kleine et al., 2004; Shaikh et al., 2004). In addition, rostral fastigial nucleus neurons encode externally applied head and body-in-space motion in two distinct streams (Brooks and Cullen, 2009). Importantly, these same rostral fastigial nucleus neurons are unresponsive to self-generated head and body motion, suggesting that the cerebellum computes an internal model of the expected sensory consequences of active head motion to selectively cancel responses to active motion (Brooks and Cullen, 2013). This mechanism is likely responsible for the attenuation during active motion observed in early vestibular processing discussed above, and is essential for ensuring accurate spatial orientation and postural control during everyday activities.

Vestibular cortex

The vestibular nuclei and vestibular cerebellum send projections to the regions of the thalamus that are sensitive to vestibular stimulation (reviewed in Lopez and Blanke, 2011). In turn, these regions of the thalamus send ascending projections to areas of cortex. However, unlike visual, auditory, or somatosensory systems, there is no single primary cortical area processing information in the vestibular system. Notably, most neurons in regions of the thalamus and cortex that receive direct and indirect inputs from the vestibular nuclei receive convergent vestibular, visual, and somatosensory inputs (Akbarian et al., 1988, 1992), emphasizing the inherently multimodal nature of vestibular processing.

Neurophysiologic studies have established that vestibular-related activity is found in multiple regions of the cerebral cortex (Fig. 2.7), including: area 2v of the intraparietal sulcus (Buttner and Buettner, 1978), area 3a in the sulcus centralis (Odkvist et al., 1974), ventral intraparietal area (Bremmer et al., 2002), medial superior temporal area (Duffy, 1998) and parietoinsular vestibular cortex (PIVC) (Grusser et al., 1990). Single-unit recording experiments in the ventral intraparietal area in area 7

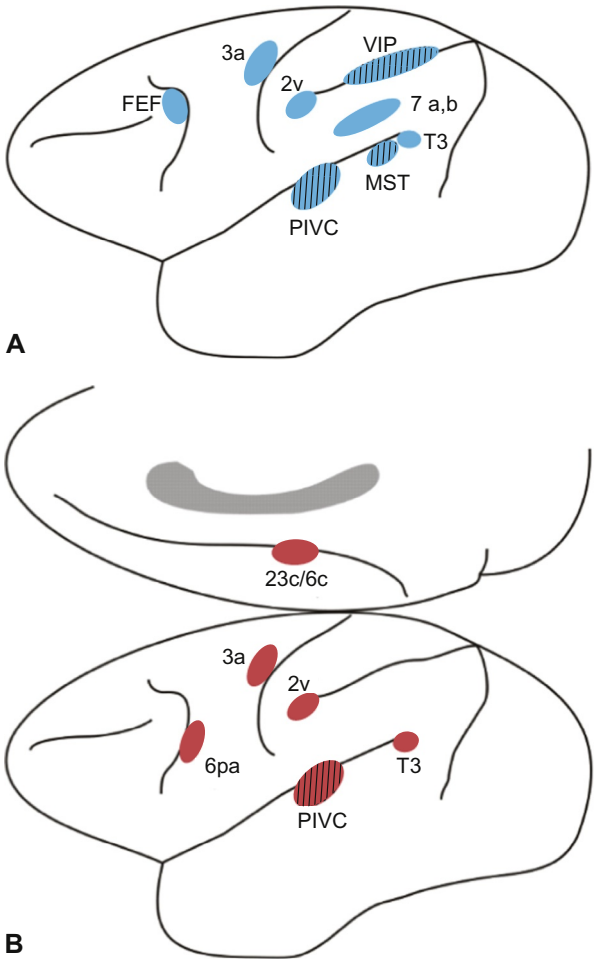

Fig. 2.7. Schematic representation of vestibular cortical areas in monkey. (**A**) Areas of cortex that receive inputs from vestibular nuclei. (**B**) Cortical areas that project back to the vestibular nuclei. FEF, frontal eye field; MST, medial superior temporal; VIP, ventral intraparietal; PIVC, parietoinsular vestibular cortex. Numbers refer to specific Brodmann areas of the cerebral cortex. Striped areas are deep cortical areas, and the gray shaded region in (**B**) denotes the corpus callosum.

found different activity in response to active and passive head movements, including changes in the strength, timing, and direction selectivity of their responses under the two conditions (Bremmer et al., 2002; Klam and Graf, 2003, 2006). This differential encoding of vestibular information is important for shaping appropriate motor responses to guide voluntary movements.

Of all these cortical areas, PIVC is commonly thought to be the most critical for shaping our perception of self-movement, spatial orientation, and body representation. Stimulation of this area has long been known to produce vestibular sensation in humans (Penfield, 1957), and PIVC lesions impair the perception of subjective vertical (Brandt et al., 1994). Additionally, PIVC receives convergent information from many of the other cortical areas

in which vestibular-related activity has been reported (reviewed in Guldin and Grusser, 1998) and cerebral blood flow of PIVC increases during vestibular stimulation (Friberg et al., 1985). Recent electrophysiologic studies have also focused on vestibular processing in the dorsal medial superior temporal cortex (MSTd) (reviewed in Angelaki et al., 2011). Specifically, this cortical area, long known to process optic flow information for visual following and smooth-pursuit eye movements, is also thought to play a role in representing heading direction (Duffy, 1998; Page and Duffy, 2003). Experiments demonstrating a functional link between area MSTd and heading perception based on vestibular signals further suggest that this region plays a role in self-motion perception (Fetsch et al., 2007; Gu et al., 2007). Finally, the transmission of self-motion information from these cortical areas to areas such as entorhinal and perirhinal cortices, and hippocampus likely play a critical role in spatial cognition and navigation (reviewed in Hitier et al., 2014).

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Chapter 3

Neurotransmitters in the vestibular system

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Abstract

Neuronal networks that are linked to the peripheral vestibular system contribute to gravitoinertial sensation, balance control, eye movement control, and autonomic function. Ascending connections to the limbic system and cerebral cortex are also important for motion perception and threat recognition, and play a role in comorbid balance and anxiety disorders. The vestibular system also shows remarkable plasticity, termed vestibular compensation. Activity in these networks is regulated by an interaction between: (1) intrinsic neurotransmitters of the inner ear, vestibular nerve, and vestibular nuclei; (2) neurotransmitters associated with thalamocortical and limbic pathways that receive projections originating in the vestibular nuclei; and (3) locus coeruleus and raphe (serotonergic and nonserotonergic) projections that influence the latter components. Because the ascending vestibular interoceptive and thalamocortical pathways include networks that influence a broad range of stress responses (endocrine and autonomic), memory consolidation, and cognitive functions, common transmitter substrates provide a basis for understanding features of acute and chronic vestibular disorders.

INTRODUCTION

Sensory information from the semicircular canals (SCCs) and otolith organs of the inner ear contribute to gravitoinertial sensation, balance control, and autonomic function. Balance is an "implicit" sense that reflects vestibular, visual motion, and proprioceptive information, and that it is not perceived consciously. Rather, it is perceived indirectly through its influences on normal daily activities (Balaban and Jacob, 2001; Balaban and Thayer, 2001; Staab et al., 2013; Coelho and Balaban, 2015). Vestibular sensory information is interpreted within the context of sensory consequences of efferent/motor effects on vestibular processing, which include eye movements, head movements, and postural adjustments (compensation and sway). These processes are controlled via neurotransmitter interactions between network elements in the inner ear, vestibular nerve, brainstem vestibular nuclei, pathways for vestibulo-ocular, vestibulospinal, and vestibuloautonomic regulation, and ascending thalamocortical and limbic networks. However, the effect of vestibular processing is not limited to the somatic sensorimotor domain. The vestibular system also influences visceral control (Spiegel and Sommer, 1944; Uchino et al., 1970; Zakir et al., 2000; Balaban and Yates, 2004); hence, vestibular "sensations" can include palpitations, nausea, or more vaguely defined visceral feelings such as "queasiness." These features illustrate the integration of vestibular pathways and related neurochemical processes into neural mechanisms for threat assessment and associated responses (Staab et al., 2013).

This review summarizes the neurochemistry of pathways that can influence vestibular system function, from background activity and head motion transduction in the periphery to central pathways. The section on peripheral mechanisms includes a discussion of neurotransmitters associated with trigeminal and autonomic innervation of the inner ear in relation to mechanisms that may impact on vestibular function. Finally, there is a brief discussion of the role of these substrates in vestibular compensation.

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VESTIBULAR PERIPHERY

The inner ear is a complex organ that is encased in the petrous portion of the temporal bone. The apical ends of hair cells of the sensory epithelia project into the endolymph-filled membranous labyrinth, which is surrounded by perilymph that is confluent with the subarachnoid space (cerebrospinal fluid) via the cochlear aqueduct (Sterkers et al., 1988). The membranous labyrinth is enclosed by a connective membrane and lined by endothelial structures, with a basement membrane interposed (Iurato, 1967a, b). The stria vascularis and dark cell regions regulate ionic differences between endolymph and perilymph, maintaining an ionic environment (high K^+, low Na^+) that supports hair cell transduction (Wangemann, 2006; Zbedik et al., 2009). There is a resting endocochlear potential of nearly +80 mV relative to perilymph, but a 0 mV potential relative to the perilymph surrounding the vestibular portion of the labyrinth. The blood–labyrinth barriers (Iurato, 1967a; Jahnke, 1980) have permeability properties that are parallel to properties of the blood–brain and blood–cerebrospinal fluid barriers (Englehardt and Sorokin, 2009), which effectively isolates the inner-ear ionic environment from systemic circulation.

The innervation of the inner ear is derived from the trigeminal nerve, sympathetic innervation that accompanies the vasculature and the vestibulocochlear nerve. The trigeminal and the sympathetic innervation appear to be involved with neural regulation of blood flow, vascular permeability, and endolymph ionic homeostasis. The vestibulocochlear nerve, on the other hand, contains processes of spiral and vestibular ganglion cells and efferents from the brainstem to inner-ear sensory epithelia. Fibers from these sources share a number of markers for neurotransmitter mechanisms, such as excitatory amino acids (EAAs), serotonin, calcitonin gene-related peptide (CGRP), substance P, and catecholamines.

Inner-ear trigeminal ganglion afferents

The vascular supply of the inner ear arises from the labyrinthine artery, which is derived from the cerebral circulation of the basilar artery (Schuknecht, 1974). The trigeminal ganglion sensory innervation to the vertebrobasilar, anterior inferior cerebellar, and labyrinthine arteries appears to include a component that originates from substance P, transient receptor potential cation channel subfamily V member 1 (TrpV1), 5-hydroxytryptamine$_{1B}$ (5-HT_{1B}) and 5-HT_{1D} receptor immunopositive cell bodies in the trigeminal ganglion (Vass et al., 1998, 2004). These trigeminal fibers innervate vessels throughout the inner ear, including the stria vascularis and dark cell region, and can affect cochlear blood flow (Vass et al., 1998, 2001, 2004). The trigeminovascular fibers are also likely to include the trigeminal innervation of blood vessels by C-fibers from ganglion cells that contribute central processes to the spinal trigeminal tract and that coexpress CGRP and 5-$HT_{1B/1D}$ receptors (Smith et al., 2002). The CGRP release from these fibers associated with the middle meningeal artery is inhibited by 5-HT_{1F} receptor agonism, whereas spinal trigeminal nucleus caudalis CGRP release is inhibited by 5-HT_{1D} receptor agonism (Amrutkar et al., 2012); this differential control of CGRP release at central and peripheral sites may be a factor in clinical efficacy of different triptans in vestibular migraine.

Protein extravasation from dural vessels has been regarded as a consequence of trigeminal efferent activation that can produce sensitization of those peripheral trigeminal nociceptors (Moskowitz, 1993, 2007) in vascular-related headaches. Although more recent studies have suggested that neurogenic inflammation may not be a major contributor to migraine pain (Ho et al., 2010), parallel inflammation in the labyrinth may have consequences for auditory and vestibular function. Permeability of the basilar artery, anterior inferior cerebellar artery, and cochlear tissues for protein extravasation increased after either capsaicin application to the cochlear round window or trigeminal ganglion stimulation (Vass et al., 2001). Further, an animal model of serotonin-induced neurogenic inflammation showed significant protein extravasation in both neural (i.e., apical spiral ganglion and intralabyrinthine branches of vestibular nerve), and nonneural (i.e., spiral limbus, stria vascularis, basilar membrane, and tectorial membrane) structures in the inner ear (Koo and Balaban, 2006). The trigeminal modulation of vascular permeability in the labyrinth is significant because disruption of the normal vascular permeability barrier within stria vascularis can impair generation of the endocochlear potential (Cohen-Salmon et al., 2007), which reflects active regulation of ionic differences between endolymph and perilymph by the stria vascularis (Wangemann, 2006; Zbedik et al., 2009). Migraine prophylaxis drugs such as acetazolamide and topirimate have the potential to support nonneurally mediated endolymph homeostasis by inhibiting carbonic anhydrase in the stria vascularis (Lim et al., 1983; Spicer et al., 1990), as well as supporting cells of all vestibular sensory epithelia and the dark cells and transitional cells of the utricle and saccule.

Sympathetic innervation

Sympathetic innervation of the ear includes tyrosine hydroxylase-CGRP-positive fibers on the spiral modiolar artery (Qiu et al., 2001) and the endolymphatic sac (Hozawa and Takasaka, 1993), as well as CGRP,

neuropeptide Y, substance P and vasoactive intestinal peptide-positive fibers on the spiral modiolar and anterior vestibular arteries (Lyon and Payman, 2000). Exogenous CGRP has a strong vasodilatory effect on the spiral modiolar artery (Herzog et al., 2002), to the extent that it can attenuate endothelin-1-mediated vasospasms (Scherer et al., 2002). Although CGRP infusions affect cochlear blood flow (Quirk et al., 1994), they do not appear to alter vestibular blood flow (Burgio et al., 1997).

Vestibular nerve interactions with hair cells

The synaptic organization and neurotransmitters of the sensory epithelia of the cristae ampullaris and maculae are reviewed in detail elsewhere (Lysakowsi and Goldberg, 2004; Eatock and Lysakowski, 2006). Briefly, vestibular afferents have been classified as calyceal, dimorphic, and bouton type on the basis of formation of two specialized types of synaptic complexes with hair cells. Calyceal afferents form calyx-type postsynaptic terminals synapse exclusively on one or more type 1 hair cells in close proximity. Type 1 hair cells are concentrated on the crest of the crista ampullaris and the striola of a macula. Bouton afferents form postsynaptic terminals on widely separated type 2 hair cells. Dimorphic afferents constitute the majority of afferents; they have both calyceal and bouton terminals on different collaterals (Fig. 3.1). The vestibular epithelia also receive direct synaptic input from vestibular efferents, which release transmitters that include acetylcholine, CGRP, adenosine triphosphate (ATP), nitric oxide, and gamma-aminobutyric acid (GABA).

The transmitter mechanism repertoires are the same at both calyx type 1 and bouton type 2 hair cell complexes, and include EAA/glutamate (N-methyl-d-aspartate acid (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and metabotropic Glu receptors), serotonergic (5-HT1B/D/F receptors), cholinergic (nicotinic and muscarinic receptors), CGRP, nitric oxide, purinergic (P2X and P2Y receptors), and GABAergic (GABAA and GABAB receptor) mechanisms (Fig. 3.2). Histamine-mediated responses have been documented for multiple receptor subtypes in vestibular ganglion cells (Bergquist and Dutia, 2006; Desmadryl et al., 2012). Because sources of histaminergic innervation have not been identified in the inner ear, it is logical to suggest that the main histamine actions may be presynaptic at the central terminals in areas with appreciable histaminergic innervation (Tighilet and Lacour, 1996). However, it is possible that histamines associated with neurogenic inflammatory responses could also affect vestibular afferents (Rosa and Famtozzi, 2013). Parallel arguments may be raised for the serotonin receptor mechanisms.

The functional significance of the type 1 hair cell–calyx complex has been the subject of considerable interest and speculation. Empirically, they appear to be specialized for high-frequency, phasic components of responses of calyx-only and dimorphic afferents. However, specialized structural and synaptic relationships at the type 1 and type 2 hair cells require separate consideration.

Type 1 hair cell–calyx complexes

A recent finding by Highstein et al. (2014) raises the novel concept that the synaptic cleft of calyces envelops type 1 hair cells with a sequestered ionic microenvironment that is distinct from the endolymph, perilymph (cerebrospinal fluid) and intracellular environments of hair cells, vestibular afferents, and vestibular efferents. They demonstrated that proton release produces acidification of the synaptic cleft of calyces during hair cell stimulation. The acidification is concurrent with nonquantal excitatory postsynaptic currents (nqEPSCs), carried primarily by Na^+ and K^+ currents, in the calyx

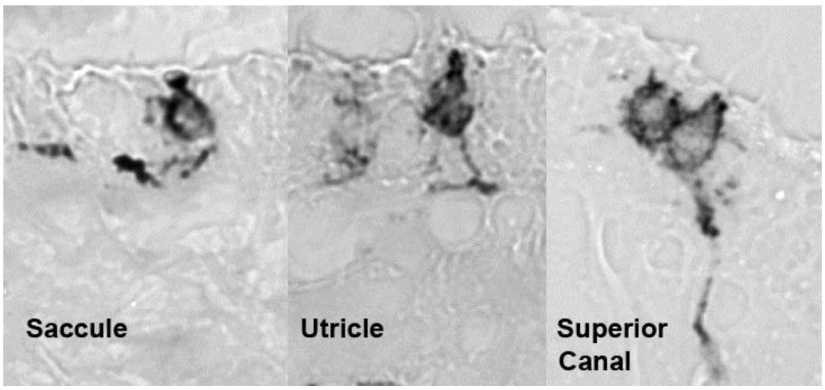

Fig. 3.1. Examples of dimorphic vestibular afferents from the albino rabbit saccular macula, utricular macula, and superior semicircular canal crista. These vestibular afferents were labeled retrogradely with biotinylated dextran amine from an iontophoretic injection site in the superior vestibular nucleus. Note the saccular and utricular examples have a single calyx in addition to boutons on nearby hair cells. The example from the superior semicircular canal crista has a double calyx on adjacent type 1 hair cells.

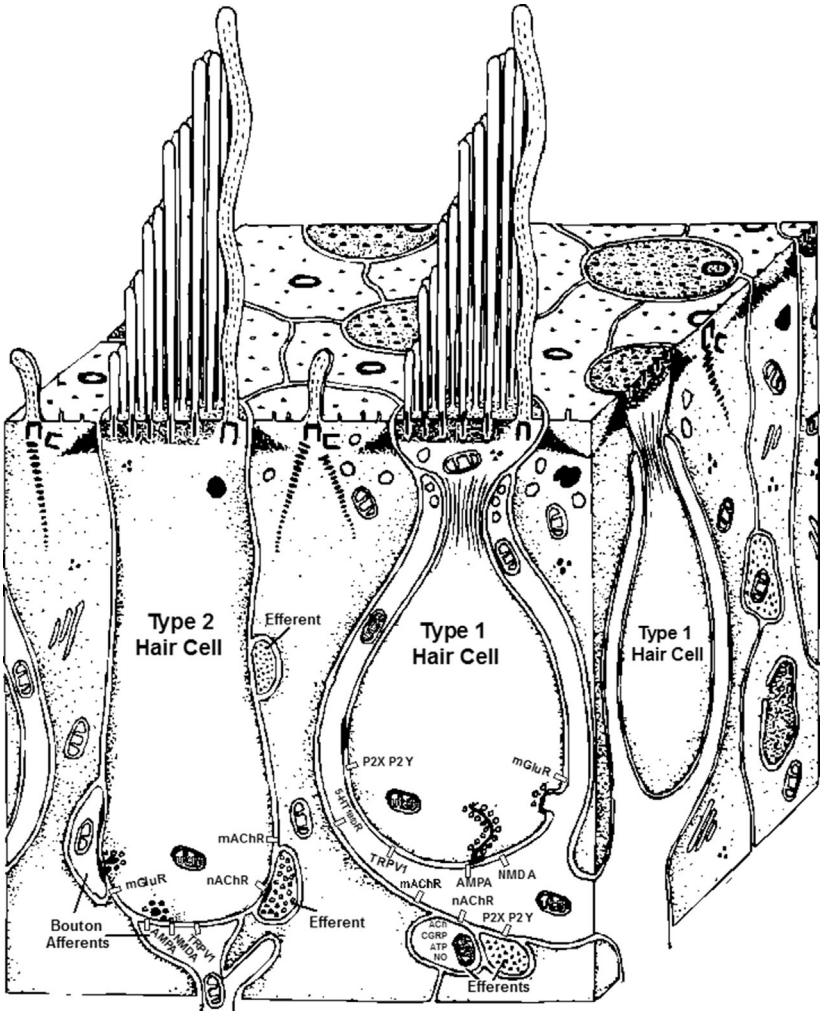

Fig. 3.2. Schematic diagram of neurotransmitter mechanisms associated with type 1 and type 2 hair cell-vestibular afferent-vestibular efferent transmission. Receptor types are indicated by labeled rectangles in the appropriate elements. AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), NMDA (N-methyl-d-aspartate acid), and mGluR (metabotropic glutamate receptor) – glutamate receptor subtypes; mAchR and nAchR, muscarinic and nicotinic cholinergic receptors, respectively; P2X and P2Y, purinergic receptor classes; TrpV1, transient receptor potential cation channel superfamily V type 1; ACh, acetylcholine; CGRP, calcitonin gene-related peptide; NO, nitric oxide. (Modified from Spoendlin, 1966.)

endings. The TrpV receptors, a family of chemically gated nonspecific cation channels that are sensitive to extracellular pH, temperature, and chemical ligands (Caterina et al., 1997; Jordt et al., 2000), are a reasonable candidate for postsynaptic contributions to the calyx nqEPSCs. Vestibular and spiral ganglion cells express TrpV1, TrpV2, TrpV3, and TrpV4 mRNAs and TrpV1 protein (Balaban et al., 2003; Kitahara et al., 2005b; Takumida et al., 2005; Kamamura et al., 2013) and 5-lipooxygenase, an enzyme that produces eicosanoid ligands of the TrpV1 receptor (Hwang et al., 2000). The effects of pH on cation permeability of TrpV1 receptors are well known, and include proton currents through the open channel (Jordt et al., 2000; Ryu et al., 2003; Hellwig et al., 2004; Lee and Zheng, 2015). The TrpV1 sensitivity to pH is also potentiated by protein kinase C activation (Vellani et al., 2001; Crandall et al., 2002). In particular, these calyx-related postsynaptic mechanisms focus attention on the roles of ionic fluxes in synaptic cleft microenvironment on neurotransmission by: (1) quantal EAA transmission via the cleft; (2) nonquantal activity via the cleft; and (3) actions of efferents on the outer face of the calyx.

Type 2 bouton and efferent synaptology

The synaptic organization at type 2 hair cells differs from type 1 hair cells because: (1) the vestibular ganglion cell dendrites are small postsynaptic boutons on the hair cells; and (2) the efferents synapse directly on the hair cells.

As in the calyx terminals, the direct EAA effects on the afferents are mediated by NMDA and AMPA receptors. However, the cholinergic (and peptidergic) efferent effects are directly on to the hair cells. The activity related to signaling by TrpV1 is likely to differ in bouton endings from calyces, due to differences in a proton contribution from the synaptic cleft.

The potential roles of TrpV1 and mitochondrial uncoupling protein (UCP) expression in vestibular ganglion cells were reviewed previously in relation to responses of spiral ganglion cells to oxidative stress (Balaban, 2005); however, the general context is relevant to basic neurotransmission at calyces. Vestibular ganglion cells (and immunostained calyces) strongly express mitochondrial UCPs 1–4 (Kitahara et al., 2004, 2005a; Balaban, 2005). Mitochondrial UCP activation regulates the magnitude of a proton leak across the mitochondrial inner membrane. This leak can uncouple cellular respiration from ATP production (lowering ATP production), lower the mitochondrial potential to decrease production of reactive oxygen species, and produce local thermogenesis via dissipation of oxidation energy as heat (Riquier and Bouillaud, 2000a,b). A basal proton leak, which may approach 25% uncoupling of capacity in muscle, is established by constitutive mitochondrial UCP levels. Superoxide and lipid peroxidation breakdown products activate feedback regulation of UCP2 and UCP3 (Echtay et al., 2002a, b, 2003), which, in turn, reduce mitochondrial superoxide production by lowering the mitochondrial membrane potential (Vidal-Puig et al., 2000; Echtay et al., 2002a). These effects on ATP production, intracellular proton buffering, and possible local thermogenic processes become considerations in hair cell primary afferent transmission.

VESTIBULAR NERVE

The peripheral dendrites of vestibular ganglion cells have been described above in terms of their contributions to synaptology at type 1 and type 2 hair cells. The cell bodies of the ganglion cells lie in the internal auditory canal and central processes terminate in the vestibular nuclei. The neurotransmitter repertoires in the vestibular nuclei raise the possibility that receptors expressed by ganglion cells may mediate different processes centrally rather than peripherally. Endocannabinoid mechanisms are one example of such a mechanism that may act at both TrpV1 and cannabinoid (CB1 and CB2) receptors on central and peripheral processes of vestibular ganglion cells (Ross, 2003; Chávez et al., 2010). Suàrez et al. (2008) reported that CB1 and CB2 receptors are located primarily in axons within the vestibular nuclei, but that cells in the lateral vestibular nucleus also show relatively strong CB1 immunoreactivity. They also reported expression of major synthetic enzymes for endocannabinoids in cells and fibers throughout the vestibular nuclei. Hence, presynaptic effects of endogenous cannabinoids may play a modulatory role on primary vestibular processing. Given the concept that cannabinoid drugs may be used to jointly target neurally mediated (e.g., pain) and inflammatory effects mediated by TrpV1 and cannabinoid receptors in arthritis (Lowin and Straub, 2015), it is worth considering a similar approach for vestibular disorders with an inflammatory component, such as trauma and vestibular neuritis.

VESTIBULAR NUCLEI

The neurotransmitter repertoire that has been reported in the vestibular nuclei is quite diverse (Holstein, 2000; Kevetter et al., 2000; Saxon and Beitz, 2000; Slater et al., 2000): it includes EAA, GABA, glycine, acetylcholine, serotonin, norepinephrine, dopamine, histamine, endocannabinoids, neuropeptides, and melatonin (Ahn et al., 2012). Transmitters associated with major pathways are summarized below.

Vestibulo-ocular reflex pathways

Excitatory and inhibitory reflex components for angular vestibulo-ocular reflexes (VORs) are associated with connections of afferents from each SCC to the vestibular nuclei and group y (Ito et al., 1977; Yamamoto et al., 1978; Ito, 1984). Flocculus and nodulus zones provide GABAergic inhibition to some of these pathways (Ito et al., 1982; Balaban, 1984; Ito, 1984; Voogd et al., 1996; Balaban et al., 2000; Billig and Balaban, 2004, 2005). For example, the flocculus provides inhibition to a subset of neuron reflex pathways to yoked extraocular muscle pairs: (1) excitatory anterior SCC-ipsilateral superior rectus and inhibitory anterior SCC-ipsilateral inferior rectus reflexes; (2) excitatory anterior SCC-contralateral inferior oblique and anterior SCC-contralateral superior oblique reflexes; and (3) excitatory horizontal SCC-ipsilateral medial rectus and inhibitory horizontal SCC-contralateral lateral rectus reflexes (Ito et al., 1977). The related regions of the vestibular nuclei contain cell populations that express EAA/glutamate biomarkers, GABA biomarkers, and glycine markers (Bagnall et al., 2007). The relay neurons for excitatory VOR components to motoneurons for singly and multiply innervated extraocular muscle fibers likely use EAAs as a transmitter (i.e., express vesicular glutamate transporters 1 and 2) (Nguyen and Spencer, 1999; Zeeh et al., 2015), while the inhibitory relay neurons are likely GABAergic (Zeeh et al., 2015) or glycinergic for the horizontal VOR (Spencer et al., 1989). In mice, the GABA-expressing medial vestibular nucleus cells (which include interneurons) can be distinguished from the EAA or

glycinergic cells on the basis of differences in maximum firing rate, input resistance, and rebound firing rate. Subsets of both the glutamatergic and glycinergic cells for excitatory and inhibitory VORs, respectively, receive either dense or sparse flocculus inhibition (Shin et al., 2011). Some glutamatergic cells receive no cerebellar input (Shin et al., 2011) and could include neurons related to excitatory VORs that do not receive flocculus inhibition (e.g., excitatory posterior SCC-ipsilateral superior oblique reflex, excitatory posterior SCC-contralateral inferior rectus reflex and excitatory horizontal SCC-contralateral lateral rectus reflex (Ito et al., 1977)). Cerebellovestibular, vestibular nucleus commissural, and VOR relay cells also display distinct gene expression profiles for some ion channel markers (Kodama et al., 2012).

The circuitry that produces translational and naso-occipital linear VORs (Paige and Tomko, 1991a, b) has not been delineated in the same detail as angular vestibulo-ocular pathways (Suzuki et al., 1969; Baker et al., 1973; Schwindt et al., 1973; Sasaki et al., 1991; Curthoys, 2010). However, it is of interest that direct connections from the vestibular nuclei to choline acetyltransferase-positive Edinger–Westphal and anteromedian neurons (Balaban, 2003) could be a mediator of pupillary and lens accommodation components of vergence (naso-occipital) linear VORs. The utricle-driven reflexes form part of the substrate for ocular vestibular-evoked myogenic potential testing (Curthoys, 2010). These short-latency pathways help to maintain gaze stabilization during motion relative to gravity and locomotion.

Vestibulospinal pathways

There are two direct vestibular nucleus pathways to the spinal cord. The lateral vestibulospinal pathway (LVST) originates primarily in the lateral vestibular nucleus and contributes excitatory direct connections to ipsilateral limb musculature (Wilson and Melvill Jones, 1979; Ito, 1984). It is under inhibitory modulation from Purkinje cells in zone B of the cerebellar lobe. The medial vestibulospinal tract (MVST) provides bilateral excitatory and inhibitory projections to motoneurons for axial (particularly neck) musculature. It is under inhibitory modulation from cerebellar zone A Purkinje cells. Saccular-driven MVST function is a basis for the cervical vestibular-evoked myogenic potential test (Curthoys, 2010). Vesicular glutamate transporter expression is associated with LVST terminals in lumbar spinal cord (Brodal, 1969), which is consistent with the excitatory direct influence on spinal motoneurons.

Vestibuloautonomic connections

Vestibuloautonomic connections include direct projections from the vestibular nuclei to the solitary nucleus, dorsal motor vagal nucleus, ventrolateral medullary reticular formation, lateral medullary tegmentum, ambiguus and parambiguus nuclei and the Edinger–Westphal–anteromedian nucleus complex (Balaban, 2003; Balaban and Yates, 2004). More recent studies have confirmed the medullary projections (Holstein et al., 2011, 2014) and demonstrated contributions from cells expressing markers for either glutamate or GABA in the caudal medial vestibular and inferior vestibular nuclei (Holstein et al., 2016). The GABAergic fibers show some evidence of preference for the caudal ventrolateral medulla; potential glycinergic projections were not explored.

Locus coeruleus and raphe pathways

The locus coeruleus and the dorsal raphe nucleus (DRN) have long been recognized as participants in central migraine circuits (Goadsby et al., 2002; Pietrobon and Striessnig, 2003; Furman et al., 2013), vestibular-related interoceptive circuits (Balaban and Thayer, 2001; Balaban, 2011; Balaban et al., 2011), and vestibular sensorimotor pathways (Schuerger and Balaban, 1999; Halberstadt and Balaban, 2003, 2006a, b; Cuccurazzu and Halberstadt, 2008). The noradrenergic coeruleovestibular pathway originates from cell bodies in the caudal aspect of locus coeruleus and nucleus subcoeruleus (Schuerger and Balaban, 1993, 1999). Many of these fibers travel caudally, then curve laterally and back rostrally toward the acoustic tubercle. Branches of these axons terminate in the vestibular nuclei. The relative density of innervation of these nuclei is summarized from our previous publications (Schuerger and Balaban, 1999) in Table 3.1. These regions of origin in the locus coeruleus and nucleus subcoeruleus are also a source of noradrenergic innervations to the cerebellum, neocortex, hypothalamus, and hippocampus (Loughlin et al., 1986; Schuerger and Balaban, 1999). In addition to noradrenergic transmission markers, a large proportion of locus coeruleus neurons are immunoreactive for CGRP (Tiller-Borcich et al., 1988; de Lacalle and Saper, 2000; Tajti et al., 2001). These cells also express the stress response-related corticotropin-releasing hormone (CRH), glucocorticoid, and mineralocorticoid receptors (Joels and Baram, 2009). Because the firing rate of locus coeruleus neurons increases with exposure to novel or imperative sensory stimuli, they have been suggested as mediators of reorientation of attention in contexts associated with stress or anxiety (Aston-Jones et al., 1991; Foote et al., 1991; Bremner et al., 1996). During the induction of motion sickness by galvanic vestibular stimulation (Balaban et al., 2014), Fos expression by locus coeruleus cells is associated strongly with Fos expression in a network that includes medial, lateral, and inferior vestibular nuclei, lateral nucleus tractus solitarius, medial parabrachial nucleus, Kölliker–Fuse nucleus, and the periaqueductal gray.

Table 3.1

Vestibular nuclear monoaminergic terminal regions

	Locus coeruleus (norepinephrine)	Large-caliber dorsal raphe nucleus (serotonin fibers only via medial longitudinal fasciculus)	Small-caliber dorsal raphe nucleus (serotonin and nonserotonin via ventricular plexus)	Influences on central vestibular pathways
Deiters/dorsal LVN (LVST origin)	Heavy	Dense	Sparse	Lateral vestibulospinal tract
SVN-PBN path origin	Intermediate to heavy	Dense	Sparse	Ascending interoceptive and vestibuloautonomic
Nodulus terminal region in MVN and SVN	Intermediate	Sparse	Heavy medially, lighter laterally	VOR dynamics
Nucleus prepositus hypoglossi	Intermediate to heavy	Sparse	Heavy medially, lighter laterally	VOR dynamics
Flocculus terminal region in MVN and ventral LVN	Low to intermediate	Dense	MVN only	VORs under flocculus inhibition
Caudal MVN-PBN path origin	Minimal to low	Dense	Light	Ascending interoceptive and vestibuloautonomic
IVN-PBN path origin	Minimal to low	Sparse	Sparse	Ascending interoceptive and vestibuloautonomic

LVN, lateral vestibular nucleus; LVST, lateral vestibulospinal tract; SVN, superior vestibular nucleus; PBN, parabrachial nucleus; MVN, medial vestibular nucleus; VOR, vestibulo-ocular reflex; IVN, inferior vestibular nucleus.

The vestibular nuclei receive serotonergic and nonserotonergic afferents from the pallidus/obscurus raphe nuclei and from the DRN. The latter projection is light; the DRN projections to the vestibular nuclei are more substantial and termination regions are summarized in Table 3.1. The nonserotonergic (5-HT transporter-negative or tryptophan hydroxylase-negative) neurons in the DRN include populations that express excitatory amino acids (Clements et al., 1987), dopamine (Yoshida et al., 1989; Stratford and Wirtshafter, 1990), GABA (Stamp and Semba, 1995; Bagdy et al., 2000), and neuropeptides (Lechner et al., 1993; Petit et al., 1995). Dorsal raphe neurons also express CRH and mineralocorticoid receptors highly (Joels and Baram, 2009), in addition to the 5-$HT_{1B/1D}$ receptors (Sari et al., 1999; Sari, 2004) that are expressed by their target regions. Approximately 25% of both serotonergic and nonserotonergic DRN vestibular cells also send collaterals to the central amygdaloid nucleus (Halberstadt and Balaban, 2006b), which receives dense DRN projections (Vertes, 1991) that contain relatively few nonserotonergic fibers (Halberstadt and Balaban, 2008).

During the induction of motion sickness by galvanic vestibular stimulation (Balaban et al., 2014), the serotonergic and nonserotonergic DRN cells show different patterns of Fos activation. The Fos expression in serotoninergic DRN cells is: (1) inversely related to Fos labeling in a network that includes nucleus raphe magnus (serotonergic and nonserotonergic cells), inferior vestibular nucleus, medial and lateral subnuclei of the solitary nucleus, lateral parabrachial nucleus, and Kölliker–Fuse nucleus; and (2) inversely related to Fos labeling in a network that includes the lateral aspect of the superior vestibular nucleus (innervated by serotonergic DRN fibers (Halberstadt and Balaban, 2007; Table 3.1), external cuneate nucleus, subtrigeminal nucleus, medial parabrachial nucleus, and the ventral and lateral periaqueductal gray. By contrast, the Fos labeling of nonserotonergic DRN cells was related most strongly to Fos labeling in the commissural solitary subnucleus, serotonergic raphe magnus neurons and cells in the medial aspect of the superior vestibular nucleus (a region receiving dense nonserotonergic DRN innervation (Halberstadt and Balaban, 2007), Table 3.1).

DRN neuron discharges accompany periods of facilitated motor activity, inhibited sensory information processing, and hormonal and neuroendocrine activation (Jacobs and Fornal, 1993). Dorsal raphe neuron activity is reduced during epochs when sensory processing is disinhibited and motor activity is disfacilitated. Hence, both serotonergic and nonserotonergic DRN transmission appears to participate in implementation of behavioral repertoires to either (1) gather more sensory contextual information or (2) act in response to the current situational context. The Fos data suggest that there are multiple influences on different vestibular sensory and motor networks.

Vestibular-perceptual pathways

Ascending vestibular interoceptive and thalamocortical pathways include networks that influence a broad range of stress responses (endocrine and autonomic), memory consolidation, and cognitive functions (Joels and Baram, 2009; Lupien et al., 2009; Roozendaal et al., 2009; Ulrich-Lai and Herman, 2009). Chemical mediators of these responses include serotonin, norepinephrine, dopamine, vasopressin, CRH, urocortins, glucocorticoids, mineralocorticoids, and dynorphin, which are believed to act simultaneously at multiple sites in these networks. These system-level effects are parallel to the persistent concept that coordinated neuromodulatory effects may influence postural control stability (Balaban et al., 1989; Chew et al., 1994), perception of anxiety, and postural threat (Balaban and Thayer, 2001; Balaban et al., 2011; Staab et al., 2013), and the relationship between symptomatic otic capsule defects and performance on standardized learning and memory tests (Wackym et al., 2015).

Vestibuloparabrachial interoceptive pathway

Networks that maintain subjective awareness of the current status of physiologic functioning have been termed interoceptive (Craig, 2002b). They assess information about current sensory and motor performance and generate feelings of self-awareness that are often termed the "sentient self" (Craig, 2009). Vestibular, visceral sensory, and nociceptive pathways converge in a network involving the parabrachial nucleus, central amygdaloid nucleus, and bed nucleus of the stria terminalis, several posterior thalamic intralaminar nuclei, the hypothalamus, and insular cortex. It has long been of interest as a site that contains prominent and rich plexuses of fibers expressing neuropeptides, such as thyrotropin-releasing hormone, dynorphins, beta-endorphin, leucine encephalin, alpha melanocyte-stimulating hormone, neuropeptide Y, cholecystokinin, and galanin (Fodor et al., 1992).

Because it serves an important role in the formation of conditioned fear and anxiety responses, the parabrachial nucleus has been recognized as a brainstem component in central networks related to panic and anxiety disorders (Charney and Deutsch, 1996; Goddard and Charney, 1997; Gorman et al., 2000; Ressler and Nemeroff, 2000). In this regard, the nociceptive pathways from lamina 1 of the spinal cord to the parabrachial nucleus appear to have a role in mediating the autonomic, affective, and emotional aspects of pain (Bernard et al., 1996a; Craig, 2002a; Gauriau and Bernard, 2002). The vestibuloparabrachial pathway has two sources. The caudal medial vestibular nucleus and the inferior vestibular nucleus are the origin of (1) light descending projections to the nucleus of the solitary tract, dorsal motor vagal nucleus, nucleus ambiguus/parambiguus, the ventrolateral medullary reticular formation, nucleus raphe magnus, and the lateral medullary tegmentum; (2) an ascending projection to preganglionic parasympathetic neurons in the Edinger–Westphal and anteromedian nuclei (Balaban, 2003); and (3) relatively dense ascending projections to the parabrachial nucleus (Balaban, 1996; Porter and Balaban, 1997). On the other hand, the superior vestibular nucleus and the rostral pole of the medial vestibular nucleus contribute dense ascending projections to the caudal aspect of the parabrachial region. Neurons in the caudal parabrachial vestibular nucleus respond to both angular and linear motions of the head in space, in a manner that resembles head-fixed inertial guidance sensors (Balaban et al., 2002; McCandless and Balaban, 2010). Descending connections from the parabrachial nucleus terminate in both rostral and caudal aspects of the vestibular nuclei, covering a territory greater than the sites of origin of the vestibuloparabrachial pathway (Balaban, 2004). The parabrachial nucleus also has reciprocal connections with the central amygdaloid nucleus, infralimbic cortex, and hypothalamus (Fulweiler and Saper, 1984; Herbert et al., 1990; Moga et al., 1990). The potential neurotransmitters associated with these ascending parabrachial connections to the central amygdaloid nucleus include glutamate (Guo et al., 2005; Lopez de Armentia and Sah, 2007), CGRP (D'Hanis et al., 2007), and neurotensin (Yamano et al., 1988). The reciprocal amygdaloparabrachial projection utilizes transmitters that include GABA (Jia et al., 2005) and neuropeptides such as corticotropin-releasing factor, neurotensin, and somatostatin (Moga and Gray, 1985).

The caudal parabrachial nucleus (site of the vestibulorecipient region) also contributes to parabrachiothalamic connections. The parabrachio-recipient thalamic sites include the centromedian nucleus, ventromedial nucleus, and ventroposterior nucleus (Krout and Loewy, 2000). Neuroanatomic studies have shown that related networks

are notable for the presence of CGRP immunoreactive neurons (Kruger et al., 1988a, b; Yasui et al., 1989; de Lacalle and Saper, 2000; Tajti et al., 2001), such as regions related to visceral, vestibular, and nociceptive pathways in the rostrodorsal and caudoventral parabrachial nucleus (Cechetto et al., 1985; Feil and Herbert, 1995; Balaban, 1996, 2004; Bernard et al., 1996b; Porter and Balaban, 1997; Saxon and Hopkins, 1998; Balaban et al., 2002), several posterior thalamic intralaminar nuclei, including the subparafascicular nucleus (Shiroyama et al., 1999; de Lacalle and Saper, 2000), and periventricular regions of the hypothalamus. These cells give rise to dense CGRP-immunopositive terminal fields in the insular cortex, central amygdaloid nucleus, bed nucleus of the stria terminalis, and the amygdalostrial transition region (de Lacalle and Saper, 2000; D'Hanis et al., 2007).

Vestibulothalamocortical pathways

Recent reviews of these vestibular pathways and related multimodal interactions include pathways to areas that include the parietoinsular vestibular cortex, somatomotor cortex (areas 1v and 3av), posterior parietal cortex (area 7), and medial superior temporal cortex (Balaban et al., 2011; Lopez and Blanke, 2011; Wijesinghe et al., 2015), but no exclusively vestibular koniocortex. These vestibulothalamocortical projections have been described extensively in the literature (Lang et al., 1979; Magnin and Kennedy, 1979; Maciewicz et al., 1982; Shiroyama et al., 1995, 1999; Meng et al., 2007). The reader is referred to the extensive literature on thalamocortical transmission, such as McCormick's classic review (1992), regarding neurotransmitters in these circuits.

VESTIBULAR COMPENSATION

The profound capability for balance control compensation after peripheral vestibular injury was well known in the late 19th century. Bechterew's (1883) account of functional recovery after unilateral, serial bilateral, and simultaneous bilateral damage to the vestibular periphery firmly established the phenomenology of what is now termed vestibular compensation (Magnus, 1924 (reprint 1980)). Decades of basic research into cellular and molecular mechanisms of vestibular compensation have implicated changes in multiple transmitter systems at multiple central sites in compensation (Llinas and Walton, 1979; Smith and Curthoys, 1989; Balaban, 2001; Lacour, 2006; Dutia, 2010; Lacour and Tighilet, 2010). There are many temporally overlapping changes in neurotransmitter substrates that mediate functional changes; in fact, nonpharmaceutical vestibular rehabilitation therapy has become a standard focus of intervention to guide these plastic processes to produce improved compensation (Balaban et al., 2012; Lacour and Bernard-Demanze, 2014). This is a confirmation of Llinas and Walton's (1979) assertion that vestibular compensation is a distributed, systems-level phenomenon in vestibular networks. Hence, experience and practice appear to support the concept that one global and overarching function of transmission in these vestibular networks is to support a relatively rapid and efficient functional plasticity in response to gradual (e.g., age-related hair cell loss: Merchant et al., 2000; Rauch et al., 2000), inflammatory (e.g., vestibular neuritis), or catastrophic (e.g., trauma-induced) peripheral vestibular dysfunction.

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Chapter 4

Multisensory integration in balance control

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Abstract

This chapter provides an introduction to the topic of multisensory integration in balance control in, both, health and disease. One of the best-studied examples is that of visuo–vestibular interaction, which is the ability of the visual system to enhance or suppress the vestibulo-ocular reflex (VOR suppression). Of clinical relevance, examination of VOR suppression is clinically useful because only central, not peripheral, lesions impair VOR suppression. Visual, somatosensory (proprioceptive), and vestibular inputs interact strongly and continuously in the control of upright balance. Experiments with visual motion stimuli show that the visual system generates visually-evoked postural responses that, at least initially, can override vestibular and proprioceptive signals. This paradigm has been useful for the study of the syndrome of visual vertigo or vision-induced dizziness, which can appear after vestibular disease. These patients typically report dizziness when exposed to optokinetic stimuli or visually charged environments, such as supermarkets. The principles of the rehabilitation treatment of these patients, which use repeated exposure to visual motion, are presented. Finally, we offer a diagnostic algorithm in approaching the patient reporting oscillopsia – the illusion of oscillation of the visual environment, which should not be confused with the syndrome mentioned earlier of visual vertigo.

A GENERAL INTRODUCTION TO SENSORY INTERACTIONS IN BALANCE CONTROL

The main sensory inputs underpinning spatial orientation and balance control are provided by the visual, the vestibular, and the somatosensory, mostly proprioceptive, systems. The vestibular system is the more frequently discussed in this book because vestibular disorders are the main cause of dizziness and vertigo. However, from the point of view of spatial orientation under normal circumstances the main players are vision for spatial orientation and proprioception for balance. In this section we will use simple intuitive examples, albeit all backed up by experimental evidence, to introduce essential concepts of multisensory organization of the balance and spatial orientation systems. These principles are necessary not only for understanding how balance works but also for grasping the basic principles of balance rehabilitation.

There is a considerable degree of overlap and redundancy in the vestibular, visual, and proprioceptive sensory systems (Peterka, 2002). One can tell if one is upright by the pressure on the sole of the feet, the tension in the ankle muscles, the static gravitational vestibular input (otolith), or by viewing that objects such as buildings or trees in the environment look properly upright. Despite this overlap in the "message" conveyed by the various inputs there are major differences in the functions played by each of these systems. The vestibular apparatus is the only system solely dedicated to the detection of head motion (angular = semicircular canals; linear- = otoliths) and head position with respect to the gravitational vector (otoliths) (Fernandez and Goldberg, 1976). Its mechanical inertial properties, akin to those of engineering accelerometers, guarantee that only during real movements (accelerations) of the head will their sensory epithelium signal motion. These mechanical properties

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of the vestibular system are equally useful to signal absence of head movements, for instance, proprioceptive signals are virtually the same whether the head turns upon the trunk or the trunk turns under the head. It is the absence of dynamic vestibular signals during the latter that allows the brain to establish that the trunk, not the head, has turned. This may partly underlie the enhancement or disinhibition of neck reflexes, like the cervico-ocular reflex, when animals and humans lose vestibular function bilaterally (Bronstein and Hood, 1986; Popov et al., 1999; Yakushin et al., 2011).

In contrast to the vestibular system, the visual system is particularly susceptible to being "tricked" into interpreting that one is moving with respect to the environment whenever large portions of the visual environment move (Kleinschmidt et al., 2002). This visually elicited illusion of self-motion is called vection, as happens during the railway illusion, where we think our train has moved when in fact it is the train next to ours that has pulled out. Hence, from the point of view of spatial orientation, the visual input is said to be ambiguous as it can equally signal self or surroundings motion. In such circumstances of sensory ambiguity the inertially based sensory systems are required to "disambiguate" this situation by informing the central nervous system (CNS) that, despite the visual system signaling body motion, this could not be confirmed by the vestibular or proprioceptive systems. In this regard the CNS is said to have comparators, that is, neural mechanisms that bring together sensory signals from different receptors and examine how well matched these signals are (Wolsley et al., 1996). If these various inputs are not proportional or matched to each other, a "warning" signal is generated alerting the organism of unusual or unexpected sensory conditions, which in turn leads to further action via automatic or voluntary mechanisms, e.g., looking out of the train window at stationary objects to see whether we are moving or not.

This leads to the concept of sensory weighting, namely how much "weight" the CNS places on each individual system at any one time (Asslander and Peterka, 2014). In most natural environments the three sensory inputs are synergistic and congruent. For instance, if you are standing upright and somebody pushes sideways from your right, the CNS will be informed by the visual system that you have moved to the left because you see the world shift to your right by the proprioceptive system, because muscles on the right side of your body have stretched, and by the vestibular system because your head has accelerated towards the left. However if you were standing in total darkness when the push occurs then you can only rely on the inertial systems (vestibulo-proprioceptive) which then become upregulated; that is, they are given more functional weight by the CNS. Similar mechanisms also operate in disease, therefore allowing for central compensation of sensory deficits; for instance, in a patient who suffers bilateral vestibular failure the remaining sensory inputs (vision and proprioception) also become upregulated (e.g., vision: Bronstein et al., 1996; proprioception: Bronstein and Hood, 1986).

Despite the considerable degree of overlap amongst these three sensory systems, their functional specificity remains. This is provided by their intrinsic anatomic structure which in turn determines the optimal operational frequency range of their peripheral receptors. The best examples are the high-frequency preference of the vestibular apparatus and the lower-frequency preference of the visual system (Barnes, 1983) and this will be illustrated yet again with the railway illusion. If you have experienced the sensation that your own train pulled off when in fact it didn't, you will have noticed that this illusion (vection) is only induced when you are exposed to a very gentle visual acceleration provided by the neighboring train. At low frequencies and accelerations levels, that is, when outside its optimal frequency range, the vestibular system is unable to confirm whether there is or there isn't head motion. In such situations, the CNS accepts or "trusts" the visual signals indicating self-motion because they have been collected at the visual system optimal-frequency range. In contrast, we don't experience vection when a fast train passes by because, at such high-frequency/acceleration range, the vestibular system is "trustworthy" and the CNS accepts the absence of vestibular signals as indicative that no self-motion has occurred. Experimental and modeling approaches supported these conclusions (Carver et al., 2006).

The frequency specificity of the visuovestibular systems is further illustrated by this simple experiment. Hold the page that you are reading at arm's length and read it. Then oscillate your head side to side ("no-no") at approximately 1–2 Hz (5–10 cycles in 5 seconds) and continue to read. You will notice that you can still read pretty well. Then keep the head stationary and oscillate the page in front of you at the same rate – now you will notice that you are no longer able to read. This illustrates that the vestibulo-ocular reflex (VOR) is capable of operating at high frequencies of motion but that visual pursuit, like all visually driven systems, is not – it only works well at lower frequencies of target oscillation. Figure 4.1 presents quantitative data of the original experiments proving this.

These differences in the frequency capacity of the visual and vestibular systems are partly due to the longer latency of the visual pathways (many synapses) than the VOR (two synapses), but also to the biophysical characteristics of the peripheral receptors. Think of the canal-endolymph system as a bowl filled up with soup. If you rotate the bowl extremely slowly, the soup and bowl will move together with no differential velocity between

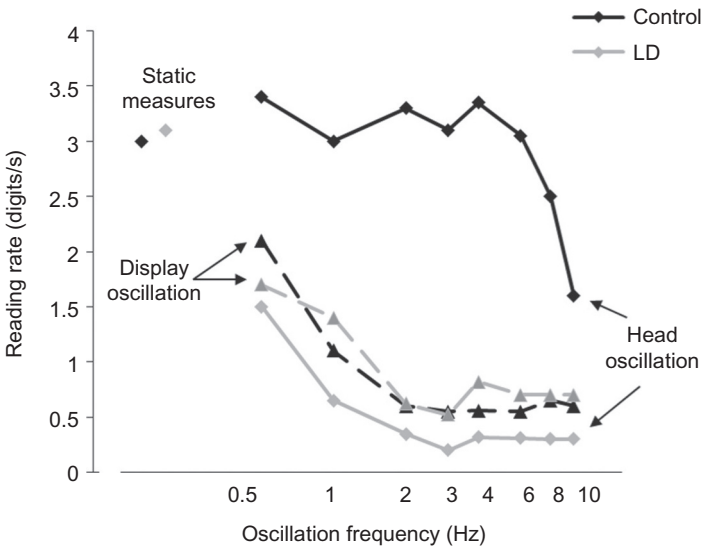

Fig. 4.1. This figure compares reading ability (*y*-axis) as a function of oscillation frequency (*x*-axis) in two experimental conditions: during oscillation of the visual display (eliciting pursuit eye movements) and during head oscillation (eliciting vestibulo-ocular eye movements). Note the considerably higher visual performance during head oscillation except for one labyrinthine-defective subject (LD, illustrated in light gray). In this subject, reading performance during head oscillation and target oscillation are the same because, in the absent of vestibulo-ocular reflex, he can only follow the visual display with pursuit eye movements. In the group of normal subjects, the frequency response of the vestibulo-ocular reflex (head oscillation) is much higher than that of pursuit movements (visual display oscillation). (Courtesy of Graham Barnes, reconstructed from Barnes, 1983.).

the two – cupular deflection would not occur in this case. If you turn the bowl faster you will be able to see the soup rotating slower than the bowl and this differential velocity would induce cupular deflection. In summary, the canal-endolymph system is not very efficient at signaling low-frequency or acceleration motion. More generally, frequency content is partly relevant to a fundamental question of vestibular physiology: how does the brain distinguish linear acceleration, which might require a compensatory eye movement response, from gravity, which usually does not require an eye response (Merfeld et al., 1999; Kingma and Janssen, 2013; Clark et al., 2015).

Finally, we will illustrate the concept of sensory conflict, which was introduced above with the example of the railway illusion. In this example it can be said that the visual input (the train moving on the next track) is in conflict with the vestibular and proprioceptive signals (which signal no real body or train motion). However, the most common example of a specific visuovestibular conflict is illustrated by Figure 4.2, showing two passengers seated on a bus. When the bus is turning, a passenger reading a newspaper will experience sensory conflict as the visual system will not confirm the head-turning input provided by the vestibular system. Such conflict situations, as many of you would have experienced personally, often lead to nausea and motion sickness feelings. If the passenger is however looking outside the bus the visuovestibular conflict is resolved because both sensory inputs are now congruent. Hence the advice given to passengers to prevent or delay motion sickness by seeking view of the horizon looking out of windows or going up on deck if on a ship (Murdin et al., 2011).

So far, most concepts discussed have been kept within the boundaries of the sensory systems. However, even for low-level brainstem reflexes, sensory explanations alone are insufficient to understand the general functional principles of the balance system. The motor system is inextricably linked to balance and postural control and we must remember that descending modulatory inputs from higher levels in the brain are at least as important as local or segmental reflexes. The head–neck system can illustrate this point. Neck and head stability are subserved by two reflexes, the neck-afferent based cervicocolic reflex or CCR, which stabilizes the head upon the trunk, and the vestibulocolic reflex or VCR, which stabilizes the head in space. How do these two reflexes interact during body movements? In certain conditions both these reflexes are synergistic. For instance, if somebody pushes your head forwards, the stretching of the neck extensors will elicit the CCR and the head will realign with the body. In parallel, the head push will also result in head rotation and tilt, eliciting simultaneous semicircular canal- and otolith-mediated vestibulocolic reflexes (VCRs), restoring the head to its upright position. In this example both VCR and CCR work in agreement or synergistically. Think now of a person tripping on the road

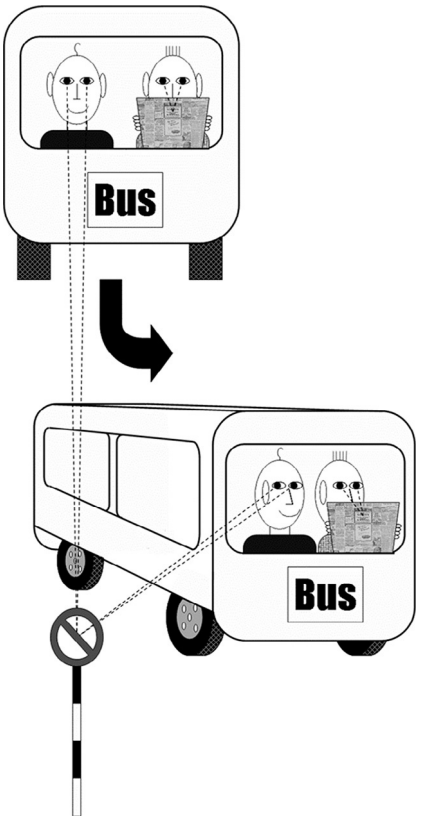

Fig. 4.2. The subject sitting on the right-hand side of the bus is looking outside and thus, as the bus turns, he senses the turn both by the vestibular system and the visual system – these two sensory signals are congruent. The subject sitting on the left of the bus is reading the newspaper which moves with him and so, when the bus turns, his vestibular system indicates a turn but his visual system does not – the visual and vestibular inputs are now said to be in conflict. (Modified from Bronstein and Lempert (2007), with permission from Cambridge University Press.)

and falling forwards. As the trunk tilts forwards, the VCR will tend to realign the head to the gravitational vector, whereas the CCR will tend to work in the opposite direction and realign the head with the trunk. As the net head motion cannot be resolved as a "tug of war" between CCRs and VCRs, central descending inputs will modulate the final pattern of neck muscle contraction according to general context ("what is needed now?") and constraints such as avoiding a head injury. Another example of VCR and CCR top-down modulation takes place during voluntary head movements when descending influences will have to switch off both CCRs and VCRs so that the head can actually turn (Peterson et al., 1985; Peng et al., 1999). Such internal neural actions are thought to be mediated by efference copy mechanisms and, indeed, brainstem neurons coding for such elusive internally generated signals have been found (Cullen, 2014).

Finally, the influence of context in balance control can be linked to cognition and the tuning of a particular movement response to a specific environment, internally represented in our brains on the basis of multiple sensory inputs. In the area of balance, context can modify vestibular reflexes, for instance, otolith-ocular responses operating at short latency which, in order to be functionally powerful, require appropriate visual context and convergence cues (Gianna et al., 1997; Misslisch et al., 2001). Other examples of clinical relevance are the profound modifications, both in simple vestibular reflexes and complex balance tasks, induced by fear and postural threats, where vestibular reflexes become weighted up if a risk of fall is perceived (Horslen et al., 2014). It is easy to see how, through this top-down modulation, high-order, cognitive, and emotional influences are capable of interacting with balance and postural function in health and disease.

We will now apply some of the concepts briefly presented in this introduction to a more specific, clinically relevant example, in order to understand how visual input interacts with balance in health and disease.

VISUAL–VESTIBULAR INTERACTIONS IN HEALTH AND DISEASE

The more studied and clinically useful form of multisensory interaction is the specific modulation of vestibular responses by visual input termed VORs. When we rotate in the dark, or in the light whilst gazing at the surroundings, a strong vestibular nystagmus is induced – the slow phase affords visual stability of the earth-fixed surroundings and the quick phases afford refixation upon different objects in the environment. However, when we focus on an object that rotates with us, the vestibular nystagmus induced by the rotation has to be suppressed to allow effective visual fixation. This is what allows us to read a newspaper on a bus, as shown above in Figure 4.2. VOR is driven by visuomotor structures and mechanisms that are closely related to smooth pursuit, as established by animal and human research. In the clinic, patients with CNS lesions disrupting pursuit usually have commensurate disruption in VOR function (Halmagyi and Gresty, 1979; Waterston et al., 1992). In contrast, patients with peripheral vestibular disease show preserved VORs and this feature is a useful pointer for separating central and peripheral vestibular lesions in the clinic. This is why the nystagmus in a patient with a peripheral vestibular lesion is much larger in amplitude, frequency, and slow-phase velocity in the dark than whilst fixating in the light.

More generally, visual suppression of vestibular imbalance is also the first line of defense against an acute vestibular disorder, and this applies not only to

nystagmus but also to postural stability. It is well known that in patients with an acute vestibular disorder eye closure, as during the Romberg test, can induce significant instability, veering or even falling towards the lesion side. This can be regarded as an initial phase of central vestibular compensation, which is visually mediated and starts to work immediately after the lesion. Gradually, brainstem and cerebellar mechanisms become dominant in vestibular compensation as the degree of asymmetry in the vestibular system is redressed (Dutia, 2010).

This early compensatory phase after vestibular lesions, where visual input is dominant, has been demonstrated in experiments with devices, as shown in Figure 4.3, which allow subjects to be exposed to large or full-field visual stimuli (Bles et al., 1983). Bles et al. found that patients with bilateral vestibular failure show enhanced responses to movements of the visual surround, particularly when tested soon after the lesion. These enhanced visually evoked postural responses gradually normalize as patients improve and adapt to their lack of vestibular input. This indicates that patients progressively attempt to downregulate the visuopostural loop and rely more on proprioception. Indeed, if similar full-field optokinetic stimulation is delivered to patients with profound proprioceptive loss but preserved vestibular function, the effects are devastating, with a consistent tendency to fall in the direction of the visual motion with virtually no adaptation to the moving visual surroundings (Bronstein, 1986).

Visual vertigo (visually induced dizziness)

Techniques using large-field visual motion stimuli have been particularly useful to understand visually related symptoms observed in dizzy patients, in particular the syndrome variably called visual vertigo (VV) (Bronstein, 1995; Guerraz et al., 2001), visuovestibular mismatch (Longridge et al., 2002), space and motion discomfort (Jacob, 1988; Jacob et al., 2009) or, as recently defined by the Bárány society, visually induced dizziness (Bisdorff et al., 2009).

This syndrome refers to those vestibular patients who report worsening or triggering of dizziness and imbalance in specific and challenging visual environments, as encountered in traffic, crowds, disco lights, and car scenes in films. Typically, dizziness and discomfort develop when walking in busy or complex visual surroundings such as supermarket aisles. The triggering or worsening of dizziness by visual stimulation in some patients with vestibular disorders has long been recognized (Hoffman and Brookler, 1978; Hood, 1980), but only in the last 20 years some research has characterized its physiologic basis (see Bronstein, 2002, for review). For a clinically oriented textbook like this one, we should

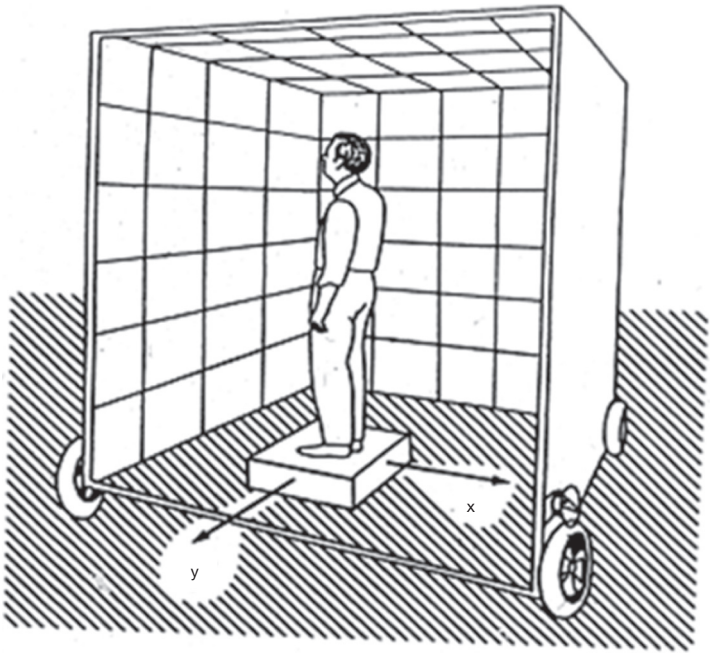

Fig. 4.3. An "optokinetic room" (modified from Bronstein et al., 1991), used for the study of visually evoked postural responses. Large-field visual motion stimulation with devices of this kind, projected images, head-mounted displays, or rotating discs, as shown in Figure 4.4, induce powerful postural sway in patients with the syndrome of visual vertigo. In turn, these devices are useful for desensitization treatment of these patients, as shown in Figure 4.5.

Table 4.1

Oscillopsia diagnostic algorithm

When does the oscillopsia occur?

1. During movements of the head?
   Absent vestibulo-ocular reflex: bilateral loss of vestibular function
   - Postmeningitic
   - Ototoxicity
   - Idiopathic
   - Miscellaneous
2. Triggered by movements of the head
   Positional nystagmus: brainstem-cerebellar disease
3. At rest (not significantly associated to movement)
   Paroxysmal
   - Sound-induced: Tullio phenomenon (superior canal dehiscence)
   - Vestibular paroxysms
     - VIIIth nerve: vestibular paroxysmia
     - Vestibular nuclear lesions
   - Ocular flutter
   - Microflutter
   - Voluntary nystagmus
   - Monocular: superior oblique myokimia

   Continuous
   - Nystagmus (brainstem-cerebellar lesion)
     - Pendular
     - Down/upbeat
     - Torsional
   - Others
   - Pseudonystagmus (head tremor + absent vestibulo-ocular reflex)

Modified from Bronstein (2004).

clarify that VV or visually induced dizziness should not be confused with oscillopsia. Oscillopsia means oscillation of the visual world – the symptom is visual. In VV, the trigger is visual but the symptoms have a vestibular flavor, such as dizziness, vertigo, disorientation, or unsteadiness. Table 4.1 provides a practical algorithm to diagnose oscillopsia at the bedside (Bronstein, 2004).

The symptoms of VV develop after a vestibular insult. A typical patient is a previously asymptomatic person who suffers an acute peripheral disorder (e.g., vestibular neuritis or benign paroxysmal positional vertigo (BPPV)) and, after an initial period of recovery of a few weeks, he/she discovers that the dizzy symptoms do not fully disappear and begin to be aggravated by looking at visually challenging surroundings. Patients may also report anxiety or frustration not only because the symptoms do not go away, but also because medical practitioners tend to disregard the symptoms or tell patients that "they are just in your mind."

The origin and significance of the symptoms of VV in vestibular patients have been the subject of research. We know that tilted or moving visual surroundings have a pronounced influence on these patients' perception of verticality and balance, over and above what can be expected from an underlying vestibular deficit (Bronstein, 1995; Guerraz et al., 2001). For instance, as Figure 4.4 shows, a rotating optokinetic disc induces more unsteadiness in patients with VV than in patients with long-term bilateral absence of vestibular function (Guerraz et al., 2001). The term used to describe an increased responsiveness to orientational or moving visual stimuli is "visual dependency." Of practical interest, patients with central vestibular disorders and patients combining vestibular disorders and congenital squints or squint surgery often report VV, show enhanced visuopostural reactivity (Bronstein, 1995), and respond less well to visuovestibular rehabilitation (Pavlou et al., 2015).

The general interpretation of these findings is that the combination of a vestibular disorder and visual dependence in a given patient is what leads to the VV syndrome. Visual input is inherently ambiguous for balance and spatial orientation because visual motion can be the result of self or surroundings motion. For this reason, relying excessively on vision for balance is never very useful, but the situation will get even worse if the person is both visually dependent and has a vestibular lesion. Ultimately, what makes some patients with vestibular disorders develop excessive visual dependence is not known. Indeed, it is possible that the syndrome

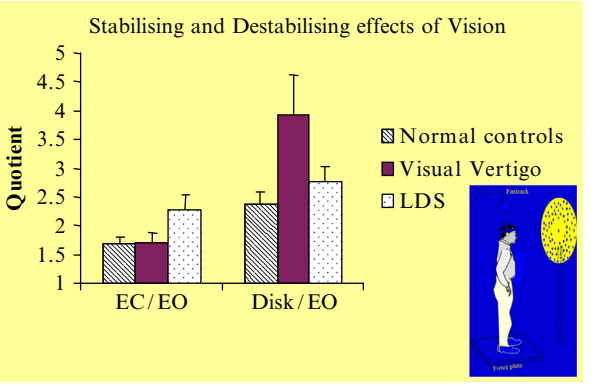

Fig. 4.4. The bars on the left show the amount of body sway induced by closing the eyes (sway with eyes closed/sway with eyes open (EC/EO), or "stabilizing effects of vision," as in the Romberg test) in three group of subjects: normal controls, bilaterally labyrinthine-defective subjects (LDS), and visual vertigo. The bars on the right show the amount of body sway induced by an optokinetic rotating disc, as shown in the inset, expressed as a ratio, sway during disc rotation/sway with eyes open with the stationary disc, disc/EO (or "destabilizing effects of vision"). The data show the disproportionate increase in body sway induced by the rotating disc in the visual vertigo patients. (Modified from Guerraz et al., 2001.)

of VV develops in vestibular patients who were visually dependent beforehand, given that visual dependence is a trait variably expressed in the general population (Witkin and Goodenough, 1981).

Recent data have shown that visual dependence is enhanced even in patients with BPPV (Agarwal et al., 2012). Interestingly, in patients with just a past history of acute vestibular neuritis (i.e., not selected for VV or poor clinical outcome), visual dependence is significantly higher in those with worse clinical outcome (Cousins et al., 2014). Visual dependence, vestibular disorders, and VV is therefore a three-way "chicken and egg"-type problem. Pragmatically, however, simple ways of identifying visual dependency in chronic dizzy patients are available, such as laptop versions of the rod and disc test (Cousins et al., 2014) and questionnaires (Pavlou et al., 2006), and this has clinical value for patient management because, as we will discuss below, specific treatments for visually induced dizziness are available.

The role of the associated anxiety/depression, often observed in patients with chronic dizziness and VV, and whether this is a primary or secondary phenomenon is not fully established either. The evidence so far is somewhat contradictory. As expected, VV is more prevalent in patients attending dizziness clinics than patients attending other clinics (Dannenbaum et al., 2011). Some studies show higher levels of anxiety in VV patients than in vestibulopathy patients without VV (Zur et al., 2015) whereas other studies report that anxiety or depression levels, as measured with established questionnaires, are not higher in unselected VV patients than in other patients seen in dizzy clinics (Guerraz et al., 2001). However, the opposite does not seem to hold true, in that one of the frequent problems reported by patients with psychogenic dizziness is VV (see Chapter 24). It is likely that pre-selection of patients in these studies, some coming from psychiatry clinics but others from neurology and neuro-otology services, is playing a part in these differences. That the psychologic and visuovestibular components in patients with dizziness are intertwined is undeniable, both as witnessed by clinical experience and by recent research from our group. In a prospective study following up patients with vestibular neuritis from the acute to the chronic stages we carried out factor analysis of many psychologic, psychophysical, and vestibular variables. The data have shown that poor clinical outcome is largely dictated by a single statistical factor which combines the results of the rod and disc test (visual dependence) with questionnaires measuring health anxiety and psychosomatic traits.

Another predisposing factor or comorbidity in patients with VV is migraine (Lempert, 2013), and the available evidence suggests that increased visual dependency, as measured with an optokinetic rotating disc, is also a feature of these patients (Furman et al., 2005b; Agarwal et al., 2012). A syndrome bringing together the individual components of migraine, anxiety, and dizziness (migraine anxiety-related dizziness (MARD)) has been described (Furman et al., 2005a), and it is a useful concept when discussing multifactorial, multisensory dizzy symptoms with patients in the clinic.

DIFFERENTIAL DIAGNOSIS

Occasionally, a hyperacute VV syndrome can arise in a patient with an acute brainstem lesion in the vestibular nuclei area, including vomiting in response to visual motion (Khan et al., 1995). However, for the reasons just mentioned above, the more important differential diagnosis in these patients is one of a purely psychologic disorder or panic attacks (Furman and Jacob, 1997). An accepted set of criteria to distinguish between psychologic and vestibular symptoms is, however, not complete at this stage (Brandt, 1996; Bronstein et al., 1997; Furman and Jacob, 1997; Staab et al., 2014). Indeed, it may be argued that such distinctions are academic because, in line with treatment of functional disorders in other areas of neurology (Gelauff et al., 2014), visually aggravated symptoms such as VV need to be treated and rehabilitated in their own right regardless of a "physical or psychologic" origin (Chapter 24; Thompson et al., 2015).

Notwithstanding these general considerations, a patient who has never had a history of vestibular disease, no findings on vestibular examination, and with visual triggers restricted to a single particular environment (e.g., only supermarkets) would be more likely to have a primary psychologic disorder. Reciprocally, a patient with no premorbid psychologic dysfunction who after a vestibular insult develops car-tilting illusions when driving (Page and Gresty, 1985) and dizziness when looking at different moving scenes (traffic, crowds, movies) is more likely to have VV secondary to vestibular disease than a psychiatric disorder. The presence of clearcut abnormalities on vestibular testing can be valuable in understanding the initial trigger that led to the secondary syndrome of VV and, as will be mentioned below, for treatment.

TREATMENT OF VISUAL VERTIGO

There are three aspects in the treatment of patients with the VV syndrome. The first is specific measures for the underlying vestibular disorder, e.g., Menière's disease, BPPV, migraine, and these will be found elsewhere in this book. However, a specific vestibular etiologic diagnosis cannot be confirmed in many patients with chronic dizziness with or without VV as, by definition, this will have to be done retrospectively.

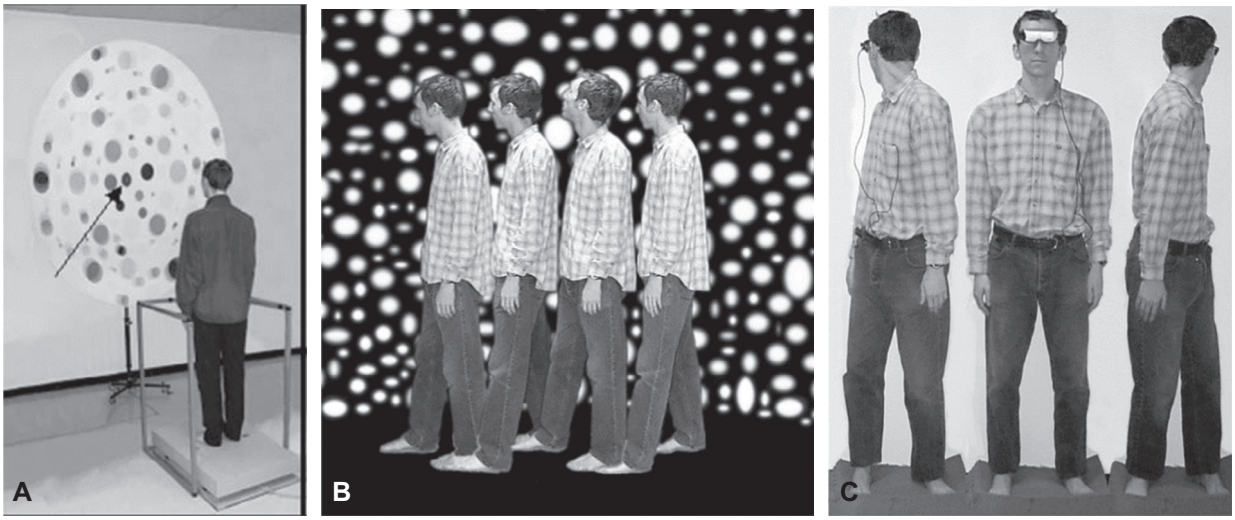

Fig. 4.5. Techniques for promoting visual motion desensitization when treating patients with visual vertigo. Patients may (**A**) fixate the center of rotation (arrow) of the rotating disc, (**B**) walk amidst moving blobs projected by a planetarium, or wear (**C**) goggles projecting moving visual senses. (Modified from Pavlou et al., 2004, with permission from Springer Science and Business Media.)

Second, patients benefit from general reassurance and vestibular rehabilitation with a suitably trained audiologist or physiotherapist. These exercise-based programs can be either generic, like the original Cawthorne–Cooksey approach (Cooksey, 1946) or, preferably, customized to the patient's needs. All regimes involve progressive eye, head, and whole-body movements (bending, turning), as well as walking exercises (Black and Pesznecker, 2003; Pavlou et al., 2004; video-demonstrated in Bronstein and Lempert, 2007).

Critically, specific measures should be introduced in the rehabilitation program in order to reduce the patient's hyperreactivity to visual motion. The aim is to promote desensitization and increase tolerance to visual stimuli and to visuovestibular conflict. Patients are therefore exposed, under the instruction of the balance therapist, to optokinetic stimuli which can be delivered via projection screens, head-mounted virtual reality systems, video monitors, ballroom planetariums, or optokinetic rotating systems (Vitte et al., 1994; Pavlou et al., 2004). The treatment approach is one of progressive difficulty both for the visual stimuli selected and for the more or less challenging postural setting adopted during the visual stimulation. Initially patients watch these stimuli whilst seated, then standing, walking, initially without and then with head movements, in a progressive fashion (Fig. 4.5). Research has shown that these patients benefit from repeated and gradual exposure to such visual motion training programs; both the dizziness and associated psychologic symptoms improve over and above conventional vestibular rehabilitation (Pavlou et al., 2004).

Finally, attention should be paid to the psychologic and psychiatric aspects of these patients. This may involve a variable range of treatments, all the way from simple physician-led reassurance and explanations on the origin of the symptoms up to antidepressant drug treatment and psychotherapy (Chapter 24).

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Chapter 5

The epidemiology of dizziness and vertigo

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Abstract

This chapter gives an overview of the epidemiology of dizziness, vertigo, and imbalance, and of specific vestibular disorders. In the last decade, population-based epidemiologic studies have complemented previous publications from specialized settings and provided evidence for the high burden of dizziness and vertigo in the community. Dizziness (including vertigo) affects about 15% to over 20% of adults yearly in large population-based studies. Vestibular vertigo accounts for about a quarter of dizziness complaints and has a 12-month prevalence of 5% and an annual incidence of 1.4%. Its prevalence rises with age and is about two to three times higher in women than in men. Imbalance has been increasingly studied as a highly prevalent complaint particularly affecting healthy aging. Studies have documented the high prevalence of benign paroxysmal positional vertigo (BPPV) and vestibular migraine (VM), as well as of comorbid anxiety at the population level. BPPV and VM are largely underdiagnosed, while Menière's disease, which is about 10 times less frequent than BPPV, appears to be overdiagnosed. Risk factor research is only at its beginning, but has provided some interesting observations, such as the consistent association of vertigo and migraine, which has greatly contributed to the recognition of VM as a distinct vestibular syndrome.

INTRODUCTION

Well beyond counting cases, epidemiologic data on prevalence, incidence, risk factors, disease burden, and outcomes can help us understand the nature and impact of dizziness and vertigo and can be a valuable resource for evidence-based patient care. In clinical decision making, epidemiologic studies that systematically analyze patterns of disease in defined populations provide clinicians with probabilistic expectations on disease frequency (Lurie and Sox, 1999), as well as on outcome and prognosis. This chapter gives an overview of the epidemiology of dizziness, vertigo, and imbalance, and of specific vestibular disorders, thus updating previous reviews of the epidemiology of dizziness and vertigo (Neuhauser, 2007, 2013).

Compared to cardiovascular or cancer epidemiology, the epidemiology of vertigo and imbalance is still a small and emerging field. However, its potential impact on patient care is rather large. For example, the awareness of vestibular migraine (VM) as a vestibular syndrome causally linked to migraine was promoted by epidemiologic observations indicating a more than chance association of migraine with vertigo and dizziness and not by pathophysiologic hypotheses (Kuritzky et al., 1981; Kayan and Hood, 1984; Neuhauser et al., 2001; Vukovic et al., 2007). Moreover, as robust data on the population-wide high prevalence of dizziness and vertigo and their specific underlying disorders accumulate, a need for improved recognition and therapy of these diseases beyond specialized dizziness clinics and neurotologic training programs becomes evident.

This chapter will focus on the frequency and distribution of dizziness, vertigo, and imbalance, and of selected vestibular disorders and will report recent findings on associated risk factors and personal and healthcare impact. A few definitions and comments on epidemiologic concepts may facilitate the reading. It is essential to bear in mind that the clinical value of most epidemiologic findings reported here is not dictated by their statistical significance, i.e., by their precision, but by

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minimization of bias in the study design, i.e., minimization of systematic error that may affect the validity of the study (the ability to measure the truth), the reliability (the ability to reproduce the results), and the generalizability (does this study result apply to my patient?).

Bias cannot be corrected no matter how statistically sophisticated the analysis. There are two main types of bias, both of which are common in epidemiologic studies on dizziness and vertigo. Selection bias occurs when study participants are systematically different from the group about which the study wants to make an inference. Examples of selection bias are prevalence estimates or prognostic studies from specialized dizziness clinics which may not apply to more unselected patients. For example, the relative frequency of Menière's disease (MD) of 5–11% in the specialized care setting (Neuhauser et al., 2001; Brandt, 2004; Guilemany et al., 2004) is almost certainly due to selection bias and considerably overestimates the prevalence in the community. The least informative are studies with little information on their sampling design, inclusion and exclusion criteria, and proportions of eligible patients who were actually included. Information bias due to misclassification of both symptoms and diagnoses is a particular concern for dizziness studies at two levels: misclassification by study participants, who are given options of describing their subjective symptoms and have to choose among them, and misclassification by investigators, who have to interpret standardized or nonstandardized symptom descriptions and assign medical terms and diagnoses based on insufficiently operationalized diagnostic criteria or criteria that have been modified for study purposes without validation. Patient descriptions may be unclear, inconsistent, and unreliable (Newman-Toker et al., 2007), and there are language-specific linguistic issues. Moreover, patients are more likely to misclassify their symptoms when they are not offered enough options that cover the entire range of specific subcategories and appear to be equally valued by the investigators.

On the other hand, even physicians do not agree on the meaning of the word "vertigo" (Stanton et al., 2007) and investigators tend to diagnose conditions that they know about or are interested in, while ignoring others (Sloane et al., 1989; Maarsingh et al., 2010b). Patients and many physicians tend to use the terms vertigo and dizziness interchangeably, while dizziness experts use vertigo as a vestibular symptom, defined as a sensation of self-motion when no self-motion is occurring (Committee on Hearing and Equilibrium, 1995; Bisdorff et al., 2009). As a general rule, unless the terms dizziness and vertigo and individual diagnoses have been explicitly defined and reported, they may be imprecise and not comparable among studies or even within studies (Maarsingh et al., 2010b).

The recently published classification of vestibular symptoms by the Committee for the Classification of Vestibular Disorders of the Bárány Society (Bisdorff et al., 2009) is a very valuable basis for future studies but has not been applied yet, so most of the findings reported in this chapter do not refer to the exact terms and definitions of this classification. In this chapter, the term vertigo denotes a vestibular symptom but the exact definition varies among studies. Measures of disease frequency in the population are incidence (proportion of newly developed – incident – disease over a specific period of time) and prevalence (proportion of an existing disease, either at one point in time – point prevalence – or during a given period, i.e., period prevalence, e.g., 1-year prevalence). Lifetime prevalence denotes the cumulative lifetime frequency of a disease to the present time, i.e., the proportion of people who have had the event at any time in the past.

DIZZINESS AND VERTIGO IN ADULTS

Dizziness (used as a term that includes vertigo) ranks among the most common complaints in medicine, affecting 15–35% of the general population at some point in their lives (Kroenke and Price, 1993; Yardley et al., 1998; Hannaford et al., 2005; Gopinath et al., 2009; Wiltink et al., 2009; Mendel et al., 2010). Such prevalence estimates may be even higher depending on the wording of the questions inquiring about dizziness, e.g., when no minimal degree of severity is required (Bittar et al., 2013). Of note, when studies recruit participants explicitly for investigating a specific symptom or disorder, the probability of selection bias rises, since those with the particular condition are more motivated to participate than those without. In the 2008 National Health Interview Survey in the USA it was estimated that 11.5% of adult Americans had dizziness in the past 12 months (Lin and Bhattacharyya, 2014) and 14.8% had dizziness or balance problems (Ward et al., 2013). Among elderly persons ($\geq$65 years old), 19.6% had problems with dizziness or balance in the preceding 12 months (Lin and Bhattacharyya, 2012). Balance problems included difficulty with unsteadiness (68%), walking on uneven surfaces (55%), vertigo (30%), and faintness (30%). Elderly women were more often affected than elderly men (21% vs. 18%). Several other studies confirm that about one out of three elderly persons report dizziness (Stevens et al., 2008; Gassmann et al., 2009; Olsson Moller et al., 2013).

Dizziness and vertigo are often recurrent, leading to a much higher annual prevalence than incidence. The incidence of dizziness including vertigo was estimated at 3% per year in unselected adults (Neuhauser et al., 2008). These high prevalence and incidence estimates contrast

with low (or no) estimates of population prevalences of underlying disorders (not frequencies in specialized settings), some of which are largely underdiagnosed, such as benign paroxysmal positional vertigo (BPPV) and VM (von Brevern et al., 2004, 2007; Ekvall Hansson et al., 2005; Neuhauser et al., 2006). Surprisingly, rotatory dizziness, which may be interpreted as vestibular vertigo, has also been reported in up to 20–30% of adults in population-based questionnaire studies (Yardley et al., 1998; Hannaford et al., 2005; Havia et al., 2005; Mendel et al., 2010). Various methodologic factors may lead to this high prevalence, foremost the suggestibility of a rotatory sensation when no or not enough alternative descriptions of symptoms are offered.

An estimate of the proportion of vestibular symptoms among dizziness complaints was achieved by means of a population survey with validated neurotologic interviews carried out in Germany (Neuhauser et al., 2005). This study combined a screening of a representative National Health Survey general population sample (n = 4869) for moderate or severe dizziness or vertigo with detailed validated neurotologic interviews (n = 1003), which included an interactive part similar to a clinical situation and detailed standardized questions. Each participant was classified by at least two raters. Vestibular vertigo was defined as rotational vertigo (illusion of self-motion or object motion), positional vertigo (vertigo or dizziness precipitated by changes of head position, such as lying down or turning in bed), or recurrent dizziness with nausea and oscillopsia or imbalance (Fig. 5.1). The lifetime prevalence of vertigo in adults aged 18–79 was 7.4%, the 1-year prevalence 4.9%, and the 1-year incidence 1.4% (Table 5.1). Vestibular vertigo accounted for almost a quarter (24%) of dizziness/vertigo cases in the community. For the definition of vestibular vertigo, the study emphasized specificity over sensitivity, therefore the prevalence and incidence of vestibular vertigo may actually be even higher in reality.

The study confirmed previous findings of a marked female preponderance among individuals with vertigo (1-year prevalence ratio male to female 1:2.7) and showed that vertigo is almost three times more frequent in the elderly compared to young adults (Fig. 5.2). By design of the study, nonvestibular dizziness was investigated only in participants without vestibular vertigo. More than half of participants with nonvestibular dizziness had orthostatic dizziness with reported provocation by postural changes on standing up from a supine or sitting position and a duration of seconds to 5 minutes. The 12-month population prevalence of orthostatic dizziness was 11% (women 13%, men 8%) (Radtke et al., 2011).

The long-term outcome of dizziness and vertigo is not well studied. For specific diagnoses there are some data on long-term outcome, which is, however, subject to selection bias, since patients with recurrent dizziness are more likely to participate in follow-up examinations. In a general practice community sample from London, UK, 23% of the 18–64-year-old adults invited reported dizziness, of whom only 15% were dizziness-free in the following 18 months (Nazareth et al., 1999). Almost a third reported more handicap from symptoms 18 months later. Similarly, a study on the functional prognosis of dizziness in older adults in primary care in the Netherlands showed persistent dizziness-related impairment at 6-month follow-up in consecutive patients with dizziness (Dros et al., 2012).

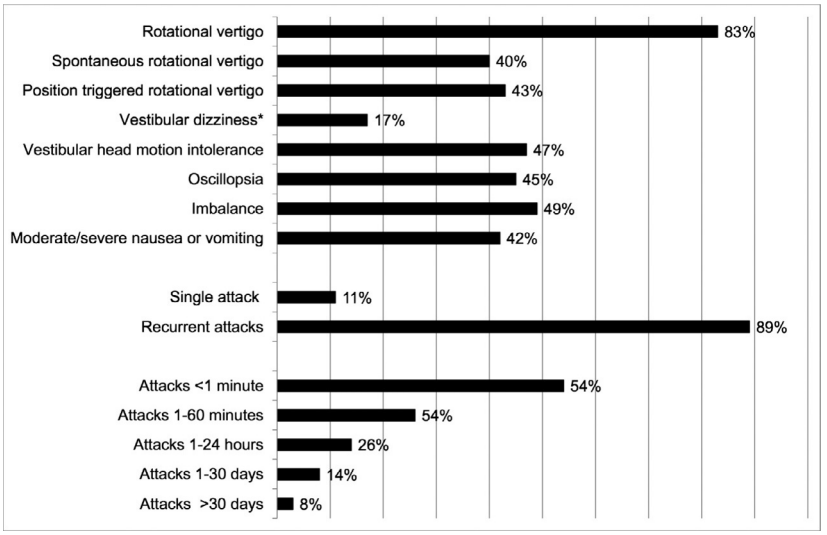

Fig. 5.1. Clinical characteristics of vestibular vertigo in a population-based sample. (Based on data from Neuhauser et al., 2005.)

Table 5.1

Prevalence and incidence of dizziness and vertigo in the general population

	% of the adult population (95% CI)					
	Women	(95% CI)	Men	(95% CI)	Total	(95% CI)
Dizziness* of moderate or severe intensity						
Incidence (1-year)	4.0	(3.2–5.0)	2.3	(1.6–3.1)	3.1	(2.6–3.8)
Prevalence (1-year)	28.9	(26.8–31.1)	16.7	(15.0–18.6)	22.9	(21.5–24.3)
Prevalence (lifetime)	35.9	(33.7–38.3)	22.6	(20.6–24.7)	29.3	(27.8–30.9)
Dizziness* leading to sick leave, medical consultation, or interruption of daily activities						
Incidence (1-year)	2.6	(2.0-3.5)	1.4	(0.9-2.1)	2.0	(1.6–2.5)
Prevalence (lifetime)	24.0	(22.0-26.1)	12.8	(11.3-14.5)	18.5	(17.2–19.8)
Vestibular vertigo						
Incidence (1-year)	1.9	(1.4–2.7)	0.8	(0.4–1.3)	1.4	(1.0–1.8)
Prevalence (1-year)	7.1	(6.0–8.4)	2.6	(1.9–3.5)	4.9	(4.2–5.7)
Prevalence (lifetime)	10.3	(9.0–11.8)	4.3	(3.4–5.4)	7.4	(6.5–8.3)

*Dizziness including vertigo.
Based on data from Neuhauser et al. (2005, 2008).
CI, confidence interval.

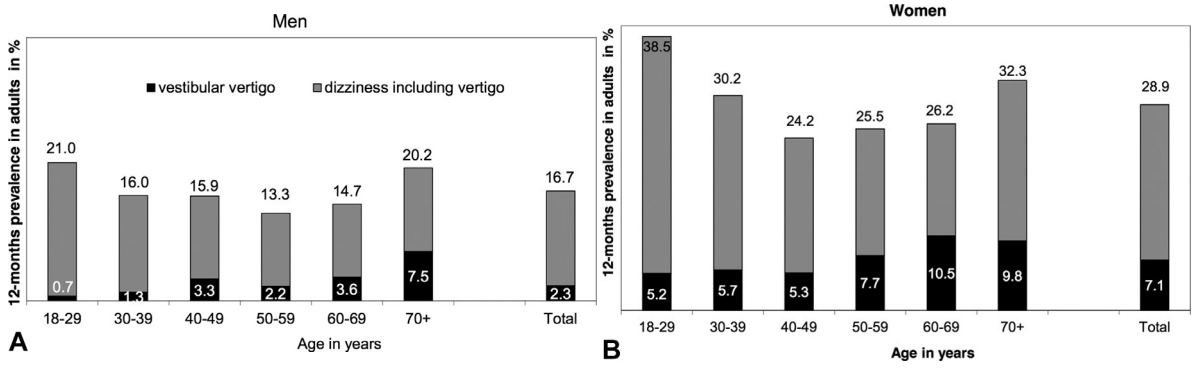

Fig. 5.2. Twelve-month prevalence of dizziness and vestibular vertigo in adults in Germany: (**A**) men and (**B**) women. (Modified from Neuhauser, 2009, with permission from Springer Science and Business Media.)

DIZZINESS AND VERTIGO IN CHILDREN

Data on dizziness and vertigo in children are scarce and often based on unvalidated questionnaires with limited power to exclude provoked physiologic vertigo during playing and to understand and discriminate between terms like "rotational" or "imbalance." Three population-based studies with a number of methodologic differences that hamper comparability report prevalences of 6–18% of dizziness (mostly "rotatory") in children (Abu-Arafeh and Russell, 1995; Niemensivu et al., 2006; Humphriss and Hall, 2011). A rough estimation of the frequency of dizziness in pediatric care is given by a report from a large database of pediatric encounters from the USA, where International Classification of Diseases, 9th edition (ICD-9: World Health Organization, 1975) codes related to vestibular and balance disorders accounted for 0.45% of diagnoses (O'Reilly et al., 2010). This is, as expected, considerably less than the 3.4% and 8.3% reported from adult and geriatric general practice databases (Kruschinski et al., 2008; Maarsingh et al., 2010a).

A recent review of vestibular diagnoses in children compiled over 700 cases, of which benign paroxysmal vertigo of childhood accounted for 19% of diagnoses, VM for 18% (both related to migraine), and head trauma for 14% (Gioacchini et al., 2014). Additionally, motion sickness is frequent in childhood, as shown in a population-based study with over 800 schoolchildren aged 7–12 years; over 40% reported motion sickness when traveling by car or by bus (Henriques et al., 2014). Last but not least, a recent

review on vertigo and dizziness in children (Jahn et al., 2015) underlined that, in children, like in adults, psychiatric comorbidity and somatization are likely to be frequent in patients with vertigo and dizziness (Langhagen et al., 2013; Lee et al., 2014).

IMBALANCE AND UNSTEADINESS

Epidemiologic data on unsteadiness and imbalance have been scarce over decades but recently more studies have been published. In a population-based study from Sweden, the 1-year prevalence of self-reported unsteadiness without a sense of rotation among a sample of 2547 adults was 9.2% (Mendel et al., 2010). As part of a larger population study, only six questions on dizziness/unsteadiness were included, with no definition of unsteadiness given, leading to a potential overestimation of the prevalence of unsteadiness through misclassification of patients who actually suffered from dizziness and vertigo only.

In the 2008 US National Health Interview Survey (Ward et al., 2013), 15% of adult Americans reported dizziness or balance problems in the past 12 months (20% in those aged 65 years and older: Lin and Bhattacharyya, 2012). Nine percent of adult Americans affirmed both dizziness and balance problems in the past 12 months. This prevalence went down to 2.4% when additionally combined with the complaints of having difficulty walking in the dark and difficulty walking on uneven surfaces.

Confusingly, a very high prevalence of 35% of vestibular dysfunction among US adults has been claimed based on data from the National Health and Nutrition Examination Survey (Agrawal et al., 2009). The prevalence refers to the failure to stand unassisted for 30 seconds on a foam-padded surface with eyes closed, a test referred to as the modified Romberg test of standing balance on firm and compliant support surfaces. This is not a purely vestibular test, and a documentation of the test validity and reliability as well as on the rationale for the cutoff is not available.

Various balance tests have been performed in community-dwelling older adults in order to study the risk of imbalance on falls. A meta-analysis reported an overall summary risk ratio of 1.42 (95% confidence interval (CI) 1.08–1.85) and odds ratio 1.98 (1.60–2.46) (Muir et al., 2010) for the association of balance deficits detected on clinical assessment with increased risk of falls in community-dwelling older adults, which was even higher in previous reviews that also included institutionalized populations. Among nine measurement scales used, significant associations for increased fall risk were found for five measures (tandem stand, tandem walk, one-leg stand, performance-oriented mobility assessment, and body sway), and not for the Forward Reach Test, the Berg Balance Scale, or the Timed Up and Go Test. However, the studies did not report prevalences of imbalance.

IMPACT OF DIZZINESS AND VERTIGO

Dizziness and vertigo have a considerable personal impact. In the epidemiologic study from Germany described above, participants with vestibular vertigo and nonvestibular dizziness reported medical consultation (70% and 54%), sick leave (41% and 15%), interruption of daily activities (40% and 12%), and avoidance of leaving the house (19% and 10%). In addition, age- and sex-adjusted health-related quality of life was lower in individuals with dizziness and vertigo compared with dizziness-free control subjects (Neuhauser et al., 2008; Gopinath et al., 2009). Among Americans reporting dizziness/balance problems in the 2008 National Health Interview Survey (Lin and Bhattacharyya, 2014), 34% reported falls, whereas only 9% of nondizzy adults reported a fall. In addition, fall-related injuries were more frequent in individuals with dizziness who reported a fall compared with nondizzy adults reporting a fall (46% vs. 36%).

Vertigo can trigger or exacerbate psychiatric problems, which do not necessarily correlate with deficits on neurotologic testing. In a large population-based study, more than a quarter of participants with dizziness (28%) reported symptoms of an anxiety disorder and had increased healthcare use and impairment (Wiltink et al., 2009). Among current dizziness sufferers, 18% had panic disorder, followed by 13% with generalized anxiety disorder and 9% with social phobia (Wiltink et al., 2009). In a study by Best et al. (2006), patients with vestibular neuritis and persistent vestibular deficits had lower levels of anxiety, depression, and somatization than patients with MD or VM. Development of anxiety or a depressive disorder after the onset of the vestibular disorder is correlated with poor improvement and high persistency of vertigo and dizziness (Best et al., 2009b).

The impact of dizziness and vertigo is particularly high in the elderly and can considerably impair healthy aging (Lin and Bhattacharyya, 2012), including quality of life, physical functioning, social life, and activities of daily living. Self-perceived participation and autonomy were shown to be significantly lower in elderly people with vertigo and dizziness (Mueller et al., 2014a) and dizziness was associated with participation restrictions even after adjustment for age, sex, and chronic conditions. Moreover, dizziness and vertigo accounted for the highest attributable prevalence of disability in an analysis of population-based data of individuals aged 65 years and older (Mueller et al., 2014b). These data underline that dizziness and imbalance in the elderly are relevant public health topics and will become even more important due to the aging of many populations.

Little is known about the occupational impact of vertigo. Sick leave due to vestibular vertigo was reported by 41% of participants with vestibular vertigo working at the time and by 15% of those with nonvestibular

dizziness in a population-based study (Neuhauser et al., 2008). In an 18-month outcome study of a general practice community sample of working-age adults from London, 1 in 20 participants with dizziness gave up work on account of dizziness (Nazareth et al., 1999). In a large series of tertiary care dizziness patients, who can be assumed to have more severe and recurrent or chronic dizziness, all patients reported interference of dizziness with work, 27% reported changing jobs, 21% gave up work, and 50% reported reduced efficiency at work (Bronstein et al., 2010). In employees on long-term sickness leave (more than 8 weeks), dizziness/vertigo was a rather infrequent cause (0.9% of women and 0.7% of men) in a register-based prospective study from Norway (Skoien et al., 2008). This corresponds for women to an annual incidence of long-term sickness leave due to dizziness/vertigo of 7.5/10 000 at risk (vocationally active) and for men 3.2/10 000 at risk. One-quarter of these women and men obtained a disability pension. However, most recurrent vertigo is unlikely to cause such long episodes of sickness leave and the occupational impact of repeated short-term absence or more subtle productivity loss is unknown.

HEALTHCARE USE

Dizziness ranks among the most common reasons for ambulatory care visits (http://www.cdc.gov/nchs/ahcd.htm), despite the fact that in population-based studies up to half of participants reporting dizziness do not consult health professionals (Neuhauser et al., 2008; Lin and Bhattacharyya, 2012; Roberts et al., 2013). The number of those consulting is still large and often several healthcare providers and medical specialties are consulted, resulting in a specific diagnosis that could be reported by the patients only in about 60–70% of cases (Neuhauser et al., 2008; Roberts et al., 2013). For neurologic consultations, vertigo and dizziness are also frequent chief complaints, ranking among the 10 most common reasons for referral both in emergency rooms (Moulin et al., 2003) and in office-based settings (Schappert and Nelson, 1999).

The German neurotologic survey estimated that 1.8% of adults seek medical care annually with the new (first-time) symptom of dizziness or vertigo (0.9% for vestibular vertigo alone) (Neuhauser et al., 2008). Similarly, a Spanish primary care study reported that 7.6 per 1000 inhabitants (i.e., 0.8%) consulted in primary care over 12 months for incident vertigo and 1.8% for combined incident and recurrent vertigo, defined as an illusion of unequivocal rotatory movement (Garrigues et al., 2008). This is in line with reports of 3.4% and 8.3% of patient records with dizziness diagnoses from adult and geriatric general practice databases (Kruschinski et al., 2008; Maarsingh et al., 2010a) or with a prevalence of vertigo diagnoses of 3.1% in a national health insurance database in Taiwan (Lai et al., 2011).

In the German neurotologic study, the proportion with vestibular vertigo increased with age and varied by medical specialty from 35% among those consulting a general practitioner to 59% of those consulting a neurologist. This shows that vestibular vertigo is frequent in all medical settings. More than half of participants with clear-cut vestibular vertigo were diagnosed with a non-vestibular disorder (Neuhauser et al., 2008). At least one medical consultation because of dizziness/vertigo at some point in their life was reported by 17% of this representative sample of adults in Germany, but 42% of participants with dizziness/vertigo of at least moderate severity never consulted a physician.

In the USA, a quarter of ambulatory care visits for dizziness and giddiness were hospital emergency department (ED) consultations (http://www.cdc.gov/nchs/data/ahcd/combined_tables/2009-2010_combined_web_table01.pdf). These visits accounted for 3.6% of all emergency department visits and were associated with high costs (Kerber et al., 2008; Newman-Toker et al., 2008; Saber Tehrani et al., 2013). About 40% of dizzy patients underwent diagnostic imaging by computed tomography (39.4%) or magnetic resonance imaging (2.3%). In primary care, low proportions of specific diagnoses (20% and 60% in studies from Germany and the Netherlands: Kruschinski et al., 2008; Maarsingh et al., 2010a) and very low specialist referral rates are reported (4% in the German primary care data base (Kruschinski et al., 2008) and 3% cited for the Netherlands (Maarsingh et al., 2010b)). Claims that dizziness/vertigo is a nonspecific symptom in a high proportion of patients, especially in old age, have been convincingly contradicted, e.g., by a study showing that, out of 3400 patients over 70 years of age, an accurate diagnosis was possible in more than 75%. In these elderly patients, dizziness often had a multifactorial etiology and caused age-specific impairment, but dizziness caused by age per se was not found (Katsarkas, 2008). In summary, data from primary care and from EDs show that misdiagnosis of vertigo and dizziness is common (von Brevern et al., 2004, 2007; Ekvall Hansson et al., 2005; Neuhauser et al., 2006; Moeller et al., 2008) and suggest that appropriate training for these disorders may benefit patients and save costs.

RISK FACTORS FOR DIZZINESS AND VERTIGO

The benefit of investigating risk factors in series of patients with dizziness or vertigo, i.e., who represent a mix of different etiologies, is limited, and findings must be interpreted cautiously. However, some interesting insights have resulted from such studies, the most

prominent being the consistent association of vertigo and migraine (Kuritzky et al., 1981; Kayan and Hood, 1984; Neuhauser et al., 2001), which has greatly contributed to the recognition of VM as a distinct vestibular syndrome. Migraine is also statistically associated with BPPV (Ishiyama et al., 2000; Lempert et al., 2000; Uneri, 2004) and MD (Radtke et al., 2002). However, the implications of these associations are not clear yet. Since migraine is more common in women, the association of migraine and specific vestibular disorders may partly explain the marked female preponderance among vertigo sufferers (Neuhauser et al., 2005) which has also been consistently reported for specific vestibular disorders, including BPPV (Katsarkas, 1999), MD (Radtke et al., 2002), and VM (Neuhauser et al., 2001). Along that line, case series have suggested that premenstrual or drug-related hormonal changes may increase the risk of vestibular disorders (Andrews et al., 1992; Rybak, 1995), but this was not confirmed by two other large studies (Vessey and Painter, 2001; Neuhauser et al., 2005).

Studies on the factors associated with dizziness and vertigo can help improve clinical practice even if they do not uncover etiologic mechanisms. For example, providing population-based data showing that the number of drugs is associated with vertigo, dizziness, and unsteadiness even after controlling for age (Bisdorff et al., 2013) can draw attention to the relevance of drug-associated dizziness. Moreover, the association of dizziness with mental health problems underlines the importance of an interdisciplinary approach, including psychiatric expertise, when evaluating and treating dizziness patients. In particular, there is increasing evidence of an association of vertigo with depression (Monzani et al., 2001; Grunfeld et al., 2003; Neuhauser et al., 2005; Ketola et al., 2007). A recent study found that a previous psychiatric disorder is a strong predictor for the development of reactive psychiatric disorders in vestibular patients (Best et al., 2009a). The same group reported that a history of mental disorders and stressful life events as well as lower scores of protective factors of subjective well-being, i.e. resilience, sense of coherence, and subjective quality of life, were associated with the development of secondary somatoform dizziness and vertigo 1 year after admission for acute vestibular disease (Tschan et al., 2011).

VERTIGO OF CENTRAL NEUROLOGIC CAUSE

Identification of central or otherwise serious vertigo is a major concern (Eagles et al., 2008; Newman-Toker et al., 2008), in particular since isolated vertigo can occasionally be the only manifestation of vertebrobasilar ischemia (Norrving et al., 1995; Gomez et al., 1996; Lee et al., 2006). However, stroke was found to be a rare cause of dizziness presentations to the ED in a population-based stroke surveillance study: 3.2% of those presenting with any dizziness and only 0.7% of those presenting with isolated dizziness had an acute cerebrovascular cause (Kerber et al., 2006). As a side note, the meaning of the term "isolated" vertigo largely depends on the spectrum of questions asked and clinical examination performed, especially whether or not a neurotologic examination was performed.

It is not straightforward to generalize from ED studies, since the selection of patients presenting to an ED may differ between countries or by level of specialization of the hospital of the ED and since ED diagnoses may include more or less diagnostic work-up and follow-up time. Nevertheless, large ED studies from several countries agree on prevalences of dizziness/vertigo of central neurologic cause of around 5–6% among patients presenting with dizziness/vertigo to the ED (Madlon-Kay, 1985; Cheung et al., 2010), mostly of cerebrovascular origin. At the primary care level and even more at the general population level, the proportion of dizziness/vertigo of central neurologic origin is much lower, since there are selection mechanisms that drive patients with a higher probability of serious conditions to present to the ED. Several studies of patients seen in the ED for dizziness/vertigo investigated their postdischarge risk of stroke (Kim et al., 2011a; Lee et al., 2011; Kerber et al., 2014). This risk was low but not zero, which is not surprising since the risk of stroke is generally not nil in middle-aged and older adults. However, it is noteworthy that a large proportion of this risk occurs in a short period after initial presentation, a finding which was not observed with cardiovascular events (Kim et al., 2011a; Lee et al., 2012). However, good risk stratification rules for identifying dizziness patients at increased risk for a subsequent stroke are lacking. Currently available risk stratification rules that include information readily available outside neurologic or neurotologic settings (e.g., the ABCD2 rule, including age, blood pressure, clinical features, duration of symptoms, diabetes) have only moderate discriminatory power (Navi et al., 2012). Better discrimination of stroke risk can be achieved by adding more specific findings, as included in the HINTS clinical decision rule (head impulse, nystagmus type, test of skew), but these may not be available in primary care settings (Newman-Toker et al., 2013).

EPIDEMIOLOGY OF BENIGN PAROXYSMAL POSITIONAL VERTIGO

The importance of BPPV at the population level is still underestimated due to low recognition rates in primary care (von Brevern et al., 2004; Ekvall Hansson et al., 2005), and scarce epidemiologic data. BPPV is not only

the most frequent cause of recurrent vertigo but also amenable to successful and inexpensive treatment by liberatory maneuvers (Bronstein, 2003). Prevalence and incidence estimates for BPPV have been obtained from the nationally representative neurotologic survey conducted in Germany (von Brevern et al., 2007). Diagnostic criteria for BPPV were at least five attacks of vertigo lasting less than 1 minute without concomitant neurologic symptoms and invariably provoked by typical changes of head position (i.e., lying down, turning over in the supine position, or at least two of the following maneuvers: reclining the head, rising up from supine position, and bending forward). The lifetime prevalence of BPPV was estimated at 2.4%, the 1-year prevalence at 1.6%, and the 1-year incidence at 0.6%. Of note, BPPV diagnoses relied on neurotologic interviews and not on positioning maneuvers, but the prevalence estimates are likely to be rather conservative, since diagnostic criteria emphasized specificity and not sensitivity (the interviews had a specificity of 92% and a sensitivity of 88% in a concurrent validation study).

Two older studies that estimated the incidence of BPPV at 0.01% in Japan (Mizukoshi et al., 1988) and 0.06% in Olmsted County, Minnesota (Froehling et al., 1991) were based on recorded clinical cases and thus likely to considerably underestimate the incidence at the population level. Strikingly higher findings of 9% positive Dix–Hallpike tests in a series of 100 geriatric clinic patients (Oghalai et al., 2000) and of 11% and 39% positive Dix–Hallpike tests in unselected dizziness patients in primary care suggested that BPPV may actually be much more common in the community (Ekvall Hansson et al., 2005; Maarsingh et al., 2010b). In a population-based postal questionnaire study from Stockholm, 5% of 2547 adults reported dizziness provoked by the movement of lying down in the past year (Mendel et al., 2010), a question with considerable predictive capability for diagnosing BPPV (Zhao et al., 2011).

BPPV can manifest from childhood to very old age, with a reported peak age of onset in the sixth decade for idiopathic BPPV and a lower mean age of onset in secondary BPPV (Baloh et al., 1987). The 1-year prevalence of individuals with BPPV attacks (new-onset and recurrent) rises steeply with age: from 0.5% in 18–39-year-olds, to 3.4% in over-60-year-olds (von Brevern et al., 2007). The cumulative (lifetime) incidence of BPPV reaches almost 10% by the age of 80 (von Brevern et al., 2007).

A clinical study reported a mean spontaneous remission time of untreated BPPV episodes of 39 days for posterior-canal BPPV and 16 days for horizontal-canal BPPV (Imai et al., 2005), a difference which is linked to the anatomic orientation of the canals. In the community, however, untreated episodes appear to be shorter, as suggested by a median episode duration of 2 weeks among 80 mostly untreated community-sampled individuals with BPPV (this study did not differentiate the affected canals) (von Brevern et al., 2007). Large case series show that posterior-canal BPPV is the most frequent type, accounting for 60–80% of BPPV cases (Chung et al., 2009; Babac et al., 2014; De Stefano et al., 2014). A large case series of 589 BPPV patients from Korea showed that the frequency of horizontal-canal BPPV may be as high as 40% in patients examined within 24 hours of symptom onset (Chung et al., 2009). Among those presenting after 7 days of onset, the proportion of horizontal-canal BPPV was lower (26%), which is not unexpected considering the high spontaneous remission rate of horizontal-canal BPPV.

At present, the mechanisms of BPPV may be explained by canalolithiasis and cupulolithiasis. However, the underlying causes which lead to detachment of otoconia from the utricle are still poorly understood in the vast majority of patients. Head trauma and inner-ear diseases, such as vestibular neuritis and MD, are probably less frequent causes than previously thought, accounting for 6% of unselected BPPV cases (Karlberg et al., 2000; von Brevern et al., 2007). More women than men are affected by BPPV (female : male ratio 1.5–2.2:1) (Mizukoshi et al., 1988; Katsarkas, 1999; von Brevern et al., 2007), but this seems to be the case only for idiopathic and not for secondary BPPV (Katsarkas, 1999). This female preponderance is still poorly understood pathophysiologically, but may be linked to an equally poorly understood association of BPPV and migraine (Ishiyama et al., 2000; Lempert et al., 2000; Uneri, 2004). Osteoporosis, which is more frequent in middle-aged and elderly women with BPPV compared to controls (Vibert et al., 2003), may also play a role. Studies have found associations of BPPV with diabetes (Cohen et al., 2004), and with hypertension, hyperlipidemia, and stroke (von Brevern et al., 2007), but these observations await replication.

A third to a half of patients have recurrences at 3–years (Nunez et al., 2000; Brandt et al., 2006; Kansu et al., 2010; Perez et al., 2012), with most recurrences occurring in the first year. A higher recurrence rate has been reported in traumatic BPPV compared to idiopathic BPPV (Gordon et al., 2004; Kansu et al., 2010), in women (Brandt et al., 2006; Kansu et al., 2010), in the presence of various chronic diseases like diabetes or osteoporosis (Babac et al., 2014; De Stefano et al., 2014), and for multicanal BPPV (Perez et al., 2012) and anterior-canal BPPV (Perez et al., 2012; Babac et al., 2014). Except for cases secondary to labyrinthitis or neurolabyrinthitis, recurrences affecting the opposite side or a different canal were rather common (Perez et al., 2012).

There is also increasingly more evidence of adverse psychosocial consequences of BPPV, including reduced

health-related quality of life (Lopez-Escamez et al., 2005), severe subjective impairment in affected individuals (von Brevern et al., 2004, 2007), and avoidance behavior in 70% of BPPV sufferers (von Brevern et al., 2007). Medical advice is sought by 80% of BPPV sufferers, but specific diagnostic positioning maneuvers are applied in less than a third of patients seeking medical care (von Brevern et al., 2007). The rate of adequate therapy is even lower, with only 10–20% of BPPV cases seen by a doctor receiving appropriate positioning maneuvers (von Brevern et al., 2004, 2007). Moreover, particle-repositioning maneuvers alone, even if successful, may not be sufficient, as shown in a study with 37 consecutive patients with idiopathic BPPV with unchanged scores of dizziness handicap, anxiety, intolerance of uncertainty, and illness perception despite a successful repositioning treatment (Pollak et al., 2012).

EPIDEMIOLOGY OF VESTIBULAR MIGRAINE

VM is the second most common cause of recurrent vertigo after BPPV (Dieterich and Brandt, 1999; Neuhauser et al., 2001). Various terms, including migrainous vertigo, migraine-associated dizziness, migraine-related vestibulopathy, VM, and benign recurrent vertigo (BRV) all have been applied to roughly the same patient population. VM accounts for 6–7% of patients in neurologic dizziness clinics (Dieterich and Brandt, 1999; Neuhauser et al., 2001) and has been found in 9% of patients in a migraine clinic case series (Neuhauser et al., 2001). In a study in women during the menopausal transition, VM was suspected in 30% of women with migraine or probable migraine (Hsu et al., 2011). The term basilar-type migraine/migraine with brainstem aura is restricted to patients who fulfill the diagnostic criteria of the International Headache Society (Headache Classification Subcommittee of the International Headache Society, 2004; Headache Classification Committee of the International Headache Society (IHS), 2013) for basilar-type migraine, which applies to only about 10% of patients with VM (Cass et al., 1997; Dieterich and Brandt, 1999; Neuhauser et al., 2001).

Dizziness before, during, and after headache was reported by more than half of headache sufferers in a large population-based study (Bisdorff et al., 2010). However, various causes other than VM are possible (Neuhauser and Lempert, 2004). In the general population, migraine headaches and vestibular vertigo concur about three times more often than would be expected by chance. Lifetime prevalences are 14% for migraine (Jensen and Stovner, 2008) and 7% for vestibular vertigo (Neuhauser et al., 2005). Thus, chance concurrence of the two would be 1%, but the German neurotologic survey showed it to be 3.2% (Neuhauser et al., 2006). This survey estimated the prevalence of definite VM in the general adult population based on validated neurotologic interviews (Neuhauser et al., 2005) and previously proposed explicit diagnostic criteria (Neuhauser et al., 2001) that require not only a migraine diagnosis according to the International Headache Society criteria (Headache Classification Subcommittee of the International Headache Society, 2004), but also that migraine symptoms such as migrainous headache, photophobia, phonophobia, or migrainous auras occur concurrently with spontaneous vertigo attacks. The lifetime prevalence of VM was 0.98% (95% CI 0.70–1.37) and the 12-month prevalence 0.89 (95% CI 0.62–1.27) (Neuhauser et al., 2006). This study did not investigate probable VM, which is a more sensitive but less specific diagnostic category than definite VM, requiring spontaneous vertigo attacks not attributable to another cause, and either a history of migraine or concurrence of migraine symptoms during vertigo (Neuhauser et al., 2001).

An even broader term is BRV (Slater, 1979), which describes recurrent spontaneous attacks of vertigo which do not lead to permanent deficits and which cannot be attributed to a specific cause (other than migraine). The population prevalence of probable VM and BRV is not known. A recent large case series of 208 patients with spontaneous episodic vertigo of unknown cause comprised 61% with definite VM, 29% with probable VM, and 10% for which only the broadest term of BRV applied (Cha et al., 2009). These rates confirm expert opinion that VM is a frequent condition both at the population level and in dizziness clinics. Of note, epidemiologic studies of VM are prone to misclassification, in particular to high false-positive rates, due to the difficult differentiation of vestibular vertigo vs. nonvestibular dizziness in questionnaires and structured interviews and to the differential diagnoses that have to be considered. This may explain recently reported very high VM prevalences (Salhofer et al., 2010; Hsu et al., 2011).

VM may occur at any age (Cass et al., 1997; Dieterich and Brandt, 1999). The prevalence of recurrent vertigo probably related to migraine is estimated at 2.8% of children between ages 6 and 12 (Abu-Arafeh and Russell, 1995). Benign paroxysmal vertigo of childhood, an early manifestation of VM, is the most common diagnosis in children presenting with vertigo (Erbek et al., 2006). In adults with VM there is a clear female preponderance, with a reported female-to-male ratio of 1.5–5:1 (Cass et al., 1997; Dieterich and Brandt, 1999; Neuhauser et al., 2001). However, a study reported that, among unselected VM sufferers, there are not significantly more women than among dizziness-free migraineurs (Neuhauser et al., 2006). In most patients, migraine headaches begin earlier in life than VM (Dieterich and Brandt, 1999; Neuhauser et al., 2001, 2006), but little is known

regarding the determinants of VM. A comparison of patients with VM with dizziness-free migraineurs showed an independent association with coronary heart disease but not with sex, age, migrainous aura, education, stroke, hypertension, hyperlipidemia, body mass index, or depression (Neuhauser et al., 2006).

The natural course of VM is not well known, but disease severity has been reported to vary over time (Neuhauser et al., 2003). However, the impact of VM both at the personal and healthcare level may be considerable, as indicated by lower health-related quality-of-life scores in VM patients compared to dizziness-free controls (Neuhauser et al., 2006), higher levels of anxiety and depression in VM patients compared to patients with persistent vestibular deficits (Best et al., 2006), and an overall medical consultation rate of almost 70% among VM sufferers (Neuhauser et al., 2006).

EPIDEMIOLOGY OF VESTIBULAR NEURITIS

Epidemiologic studies on vestibular neuritis, one of the most severely impairing acute vestibular disorders, are scarce, possibly due to the difficulty of diagnosing it by standardized interviews or questionnaires (Zhao et al., 2011). Vestibular neuritis accounts for 3–10% of diagnoses in specialized dizziness clinics (Neuhauser et al., 2001; Brandt, 2004; Guilemany et al., 2004) and was reported to be the second most common dizziness diagnosis after BPPV in a British general practice study (Hanley and O'Dowd, 2002). However, the only published estimation on the frequency of vestibular neuritis in the general population comes from a government report in Japan, stating that vestibular neuritis occurs in 3.5 per 100 000 inhabitants; although this is not further specified, one can assume that this is a 1-year incidence (Sekitani et al., 1993). The methods are not described, but based on the epidemiologic data on other vestibular disorders from this report, considerable underestimation of the frequency of vestibular neuritis in the population is likely. Data from the National Hospital Discharge Registry in Germany document 19 828 cases of vestibular neuronitis (ICD-10 H81.2: World Health Organization, 2010) in 2006, corresponding to 24 per 100 000 inhabitants (personal communication, German National Statistical Office).

Also from Japan originates the single largest published series of about 600 patients aged 3–88 years with a peak of age distribution between 30 and 50. There was no female preponderance as in other vestibular disorders but, on the contrary, a male predominance until the age of 40 (Sekitani et al., 1993). Recurrence rates of 2% and of 11% have been reported from specialized care patients (Huppert et al., 2006; Mandala et al., 2010; Kim et al., 2011b). However, the long-term outcome of vestibular neuritis may not be as favorable as previously thought, since persisting dizziness has been reported in 30–40% of patients (Okinaka et al., 1993; Godemann et al., 2005) and chronic anxiety in 15% (Godemann et al., 2004). In children data are even more scarce, but complete long-term recovery has been reported in a series of 21 children (Taborelli et al., 2000).

EPIDEMIOLOGY OF BILATERAL VESTIBULAR HYPOFUNCTION

Bilateral vestibular hypofunction is a rare condition and, until recently, the only data were from tertiary care case series (Vibert et al., 1995; Rinne et al., 1998; Gillespie and Minor, 1999). By far the largest case series comprised 255 patients seen in a large dizziness unit over a period of 17 years (Zingler et al., 2007, 2008). Sixty-eight percent were men. Diagnosis of bilateral vestibular hypofunction was made at all ages, with a peak in the sixth decade and with the youngest being 12 years old. Previous vertigo attacks had occurred in 36%, indicating a sequential manifestation. The most common causes were ototoxic aminoglycosides (13%), MD (7%), and meningitis (5%), but in about half of the cases the cause remained unclear. A follow-up examination was available in 82 patients 51 ± 6 months after the first examination. Forty-three percent of patients subjectively rated the course of their disease as stable, 28% as worsened, and 29% as improved (Zingler et al., 2008).

A remarkable estimation of the population prevalence of bilateral vestibular hypofunction has been made within the National Health Interview Survey in the 2008 Balance and Dizziness Supplement in the USA (Ward et al., 2013). The case definition was based on a series of questions (presence of visual blurring with head movement; unsteadiness; difficulty walking in darkness or unsteady surfaces and in a straight path; and symptoms being at least "a big problem" and present for at least 1 year), in the absence of other neurologic conditions or eye pathologic conditions affecting vision. In a concurrent validation study this case definition discriminated well between bilateral and unilateral vestibular hypofunction but was not tested against other causes of dizziness or imbalance. Out of almost 22 000 adults interviewed, 12 were identified as having bilateral vestibular hypofunction, corresponding to a prevalence of 28 per 100 000 adults or about 64 000 Americans (both numbers with nonreported but presumably large confidence intervals). Interestingly, only 11% were male, contrasting with the male predominance in the largest clinical case series (Zingler et al., 2007).

EPIDEMIOLOGY OF MENIÈRE'S DISEASE

MD accounts for 3–11% of diagnoses in dizziness clinics (Neuhauser et al., 2001; Brandt, 2004; Guilemany et al.,

2004), but this reflects selection bias in specialized care settings towards severe, recurrent, and difficult-to-treat vestibulopathies. In the general population, MD is a rare disease. Therefore, reliable prevalence and incidence estimates are difficult to obtain. Most studies have been based on patient registers and have various methodologic restrictions (for a summary, see Kotimäki et al., 1999). A thorough re-evaluation of Menière's diagnoses from the Mayo Clinic's centralized diagnostic index in Rochester, Minnesota, according to the previous criteria of the American Academy of Ophthalmology and Otolaryngology (AAOO) Committee on Hearing and Equilibrium, 1995), resulted in an estimated annual incidence rate of 15/100 000 and a point prevalence of 218/100 000 population, which is higher than previous estimates (Wladislavosky-Waserman et al., 1984). Since MD is a rare disease, the prevalence is reported per 100 000 population; however, for comparison, the estimated 218/100 000 correspond to 0.2%. Furthermore, in the Rochester study, only 65% had classic MD, while 26% had vestibular Menière's and 9% had cochlear Menière's, two variants which were included in the 1972 AAOO criteria, but do not fulfill the 1995 diagnostic criteria for MD of the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) (Committee on Hearing and Equilibrium, 1995). Taking this into account, MD appears to be at least 10 times less common than BPPV.

A prevalence of 513/100 000 has been reported from southern Finland, which is considerably higher than figures from previous studies (Havia et al., 2005). The study was based on a questionnaire sent to a sample of the general population inquiring about vertigo, hearing loss, and tinnitus, and a review of available medical records. The 1995 AAO criteria were used, but the published questionnaire suggests that the hearing loss and duration criteria may have been modified. Interestingly, the number of individuals who reported that they suffer from impaired hearing and tinnitus and in addition experienced vertigo at some point in the past was 14 times higher than the number of MD cases. Similarly, a population prevalence of 5% of dizziness in combination with self-reported hearing loss and tinnitus was found in Sweden (Mendel et al., 2010). This illustrates that, when a patient presents with the MD triad of symptoms, i.e., vertigo, hearing loss, and tinnitus, possibly without specific information of the temporal association of these symptoms, the probability of MD is rather low and more specific information is required before suspecting MD. In medical practice, MD was or still is overdiagnosed, as suggested by both the Rochester study and a more recent Finnish study, which applied the AAOO and AAO-HNS criteria respectively and confirmed only 40% of MD diagnoses suspected in primary care (Wladislavosky-Waserman et al., 1984; Kotimäki et al., 1999). An analysis of a very large US health claims database found 195 MD diagnoses per 100 000 adults (Harris and Alexander, 2010).

Generally, MD is regarded as a disease of the middle-aged, which can occasionally occur in children. However, MD is not uncommon after 65 years of age, accounting for 15% of a large case series (Ballester et al., 2002). A female preponderance can be assumed based on the data from Rochester (61% women) (Wladislavosky-Waserman et al., 1984), and is confirmed by the latest data from Finland (Havia et al., 2005). More than 10% bilateral involvement within 6 months of onset was present in a large case series (Vrabec et al., 2007) and a comprehensive review reported up to 35% bilaterality within 10 years and up to 47% within 20 years (Huppert et al., 2010). Hearing loss and reduction of vestibular function appear to take place within 5–10 years, while drop attacks can occur early or late during follow-up.

The debate on the multiple etiologic possibilities of MD is ongoing. An intriguing finding is the increased prevalence of migraine in MD patients (Radtke et al., 2002). In a recent study, MD patients had an earlier onset of symptoms and a greater susceptibility to bilateral hearing loss when they also had migraine (Cha et al., 2007). However, a frequent occurrence of migrainous symptoms during MD attacks has been found, which may reflect some overlap between the diagnostic criteria for MD and for VM (Radtke et al., 2002) or a shared genetic susceptibility (Cha et al., 2008). Inhalant and food allergies have been linked with symptoms of MD (Derebery and Berliner, 2000), but the evidence is not conclusive.

CONCLUSION

Epidemiologic studies have made a substantial contribution in the last decades to bring to attention the burden of disease associated with dizziness, vertigo, and imbalance. Increasingly, studies on specific vestibular disorders improve study design as well as analysis and reporting of results and thus allow generalizability of results to other patient populations. However, it is still a challenge for epidemiologic research to bridge the gap between specialized care settings and its selected patients and the heterogeneous and multidisciplinary settings where most patients with dizziness and vertigo present. Compared to other fields of clinical epidemiology like cardiovascular or cancer epidemiology, the epidemiology of dizziness and vertigo is in an early stage of development of clinical trials, research on risk factors, research on clinical decision rules and healthcare research, all of which have great potential to improve patient care.

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Chapter 6

Vestibular symptoms and history taking

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Abstract

History taking is an essential part in the diagnostic process of vestibular disorders. The approach to focus strongly on the quality of symptoms, like vertigo, dizziness, or unsteadiness, is not that useful as these symptoms often coexist and are all nonspecific, as each of them may arise from vestibular and nonvestibular diseases (like cardiovascular disease) and do not permit to distinguish potentially dangerous from benign causes. Instead, patients should be categorized if they have an acute, episodic, or chronic vestibular syndrome (AVS, EVS, or CVS) to narrow down the spectrum of differential diagnosis. Typical examples of disorders provoking an AVS would be vestibular neuritis or stroke of peripheral or central vestibular structures, of an EVS Menière's disease, benign paroxysmal positional vertigo, or vestibular migraine and of a CVS long-standing uni- or bilateral vestibular failure or cerebellar degeneration. The presence of triggers should be established with a main distinction between positional (change of head orientation with respect to gravity), head motion-induced (time-locked to head motion regardless of direction) and orthostatic position change as the underlying disorders are quite different. Accompanying symptoms also help to orient to the underlying cause, like aural or neurologic symptoms, but also chest pain or dyspnea.

At population level the prevalence of significant vertigo ranges from 3% to 10% and of dizziness from 17% to 30% (Murdin and Schilder, 2015). Vertigo and dizziness rank among the most common reasons for consultation: in primary care 2.6% of patients have it as a chief complaint (Sloane, 1989) and a similar figure of 3.3–4.4% of all emergency department visits are motivated by dizziness (Newman-Toker and Edlow, 2015).

This implies that many physicians in various settings and different specialties will regularly be confronted with patients presenting with these symptoms. Dizziness and vertigo are both nonspecific symptoms. They may arise from disturbances of the vestibular system or have nonvestibular causes. Indeed, in emergency departments about half will not have a primary neuro-otologic cause, but a cardiovascular, metabolic, respiratory, toxic, psychiatric, digestive, or infectious cause (Newman-Toker et al., 2008a). The spectrum of the etiologies may range from benign to dangerous or even life-threatening (Kerber and Newman-Toker, 2015). Vestibular and nonvestibular causes may be benign or dangerous. Benign positional paroxysmal vertigo and Menière's disease are benign vestibular conditions, whereas bacterial labyrinthitis and inner-ear stroke are potentially life-threatening or reflect serious cerebrovascular disease. Vertigo due to orthostatic hypotension may be benign or the expression of a dangerous condition if due to internal hemorrhage.

For the clinician, it is therefore important to have tools at hand that help to triage dangerous from benign causes of vertigo and dizziness and to guide the clinician to the most likely organ system affected.

History taking is crucial in vestibular disease as there are often no biomarkers and the diagnosis relies entirely on history and exclusion of alternative explanations, for example, vestibular migraine. Traditionally, the first question to patients presenting with symptoms suspected to be related to the vestibular system would be to describe in detail what they feel, i.e., to establish the quality of the symptoms.

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This approach, based on the quality of four mutually exclusive symptoms that predict the underlying cause, has been propagated since the 1970s (Drachman and Hart, 1972) and is still widely taught: (1) vertigo is due to vestibular causes; (2) presyncope to cardiovascular causes; (3) disequilibrium to neurologic causes; and (4) nonspecific dizziness to either psychiatric or metabolic causes.

There are at least three potential problems with this approach.

1. The variable use of the terms vertigo and dizziness by professionals and the public (Blakley and Goebel, 2001). In a survey amongst members of two North American scientific societies dealing with neuro-otology, about half agreed on a restricted use of vertigo (limited to the sensation of spinning), whereas the other half advocated an even wider use, encompassing also dizziness, imbalance, and oscillopsia.
2. Patients often find it difficult to describe their symptoms and their descriptions may be inconsistent at different times (Newman-Toker et al., 2007). There is no "normal" vestibular feeling, as there is for vision, hearing, or smell, and the vestibular system remains active in complete unconsciousness. This is probably one of the explanations why the role of the vestibulum was only recognized in the 19th century (Bárány, 1916), as opposed to other senses known since time immemorial. A vestibular feeling that only arises if there is a disturbance in the system may be difficult to describe.
3. Recent research suggests that establishing the exact quality of symptoms is of limited value for guiding the clinician in narrowing down the spectrum of differential diagnoses and in distinguishing dangerous from benign causes of vertigo/dizziness (Kerber and Newman-Toker, 2015). Evidence collected in the last decade, particularly in the emergency setting, has shown that the quality of symptoms approach is flawed and potentially dangerous (Newman-Toker et al., 2008b). A survey amongst emergency department physicians revealed that a large majority of about 90% still adhere to this approach, and 69% agreed not to pursue cardiovascular causes if the patient reported vertigo, or vestibular causes if the patient reported presyncope (Stanton et al., 2007).

VESTIBULAR SYMPTOMS

Regarding the first two aspects, only recently an initiative was taken by the Bárány Society to harmonize the definitions of vestibular symptoms, namely vertigo, dizziness, vestibulovisual symptoms, and postural symptoms (Bisdorff et al., 2009). Great care was taken to phrase these definitions as purely phenomenologically as possible, without implicit or explicit reference to a theory on pathophysiology or a particular disease, as no vestibular symptom has a specific meaning in terms of topology or nosology (Table 6.1).

The aim to create these definitions of vestibular symptoms was not to educate the public or the patients about the "proper" use of these terms but to give a tool to physicians to document patients' descriptions in whatever language or local dialect into a medical language that can be universally understood.

In the proposed nomenclature, vertigo is "a false sense of motion of spinning or nonspinning quality" and dizziness a "disturbed spatial orientation without a false sense of motion." Both symptoms are frequently encountered in patients with vestibular or nonvestibular disorders, whether acute or chronic (Newman-Toker et al., 2007, 2008a) Vertigo and dizziness are each divided into two categories, spontaneous and triggered.

Vestibulovisual symptoms describe a range of visual disturbances that can result from vestibular dysfunction. Because "internal" and "external" vertigo is sometimes dissociated clinically (e.g., in a patient who sees the world spinning or rotating from jerk nystagmus but feels no spinning with eyes closed), the false sensation of motion in the visual surround is named "external vertigo," whereas "internal vertigo" refers to the false sensation of movement of the self. If not otherwise specified, vertigo means "internal vertigo." Oscillopsia describes the impression of a bidirectional, oscillating visual motion that incorporates complaints such as "jumping" or "bouncing" vision as can occur in opsoclonus if the head is still or while moving the head in case of bilateral vestibular failure. Head motion-induced blur and visual lag describe further symptoms related to a dysfunctional vestibulo-ocular reflex, while visual tilt is a usually short-lasting (seconds to hours) impression of 90° or 180° tilt of the visual surround resulting usually, but not exclusively, from central vestibular disorders (Malis and Guyot, 2003; Sierra-Hidalgo et al., 2012).

Unsteadiness describes a balance symptom of postural instability when upright (i.e., sensations of swaying, rocking, or wobbling when sitting, standing, or walking). If the unsteadiness has a particular directional bias, the term directional pulsion is used and the direction specified (e.g., lateropulsion to the right).

VESTIBULAR SYNDROMES

The International Classification of Vestibular Disorders (Bisdorff et al., 2015) proposes a four-layer system, the first layer being the symptoms, the second the syndromes, the third the disorders, and the fourth the mechanisms.

Table 6.1

Definitions of vestibular symptoms according to the Bárány Society

Symptom	Definition	Subtypes
Vertigo	Sensation of motion of self when no motion is present or altered sensation of motion when motion occurs. The motion sensation may be rotary, translational, or tilt. A similar sensation of motion of the environment is a vestibulovisual symptom (external vertigo)	Spontaneous vertigo Triggered vertigo • Positional vertigo • Head-motion vertigo • Visually induced vertigo • Sound-induced vertigo • Valsalva-induced vertigo • Orthostatic vertigo • Other triggered vertigo
Dizziness	A disturbed or altered sensation of spatial orientation without false or altered movement	Spontaneous dizziness Triggered dizziness • Positional dizziness • Head-motion dizziness • Visually induced dizziness • Sound-induced dizziness • Valsalva-induced dizziness • Orthostatic dizziness • Other triggered dizziness
Vestibulovisual symptoms	Visual symptoms that result from vestibular pathology or visual-vestibular interactions. Symptoms arising from ocular pathology are not included	External vertigo Oscillopsia Visual lag Visual tilt Movement-induced blur
Postural symptoms	Balance-related symptoms that occur while in an upright posture. For example, unsteadiness is a sensation of swaying or rocking when sitting, standing, or walking. Symptoms that occur only when changing positions (e.g., standing up from sitting) are classified as orthostatic, not postural	Unsteadiness Directional pulsion Balance-related near fall Balance-related fall

The syndromes represent a bridge between the symptoms and the disorders. Grouping symptoms into vestibular syndromes is useful because in particular disorders the various symptoms are not mutually exclusive but may coexist in variable constellations within an attack or in various attacks (Newman-Toker et al., 2007), allowing clinicians to recognize clinical patterns to narrow down which differential diagnoses to consider. In many areas of medicine, timing and triggers of symptoms reflect underlying pathophysiology or are used to define disease entities, even if underlying mechanisms are still poorly understood. In headaches, for example, timing (like duration and frequency of attacks) is important to distinguish migraine, cluster headaches, or trigeminal neuralgia; explosive onset suggests subarachnoid hemorrhage or thunderclap headaches. Factors that provoke or relieve symptoms are also diagnostically important, like cold wind triggering trigeminal neuralgia or lying down, which makes low-pressure headaches virtually disappear (Headache Classification Committee, 2013).

After establishing the presence of vestibular symptoms, it is useful to fit the patient into one of three syndromes defined by the dimension of time: acute, episodic, and chronic vestibular syndrome (AVS, EVS, and CVS) (Table 6.2).

AVS is a clinical syndrome of acute-onset, continuous vertigo, dizziness, or unsteadiness lasting days to weeks, and generally includes features suggestive of new, ongoing vestibular system dysfunction (e.g., vomiting, nystagmus, severe postural instability). Disorders typically presenting with this syndrome include vestibular neuritis, acute labyrinthitis, traumatic vestibulopathy, demyelinating disease with vestibular involvement, strokes affecting central or peripheral vestibular structures, and intoxications.

EVS is a clinical syndrome of transient vertigo, dizziness, or unsteadiness lasting seconds to hours, occasionally days, and generally including features suggestive of temporary, short-lived vestibular system dysfunction (e.g., nausea, nystagmus, sudden falls) with remissions

Table 6.2

Core definitions for the three primary vestibular syndromes

Syndrome	ICD-11-compatible definition	Examples of disorders
Episodic vestibular syndrome (EVS)	A clinical syndrome of transient vertigo, dizziness, or unsteadiness lasting seconds to hours, occasionally days, and generally including features suggestive of temporary, short-lived vestibular system dysfunction (e.g., nausea, nystagmus, sudden falls). There may also be symptoms or signs suggesting cochlear or central nervous system dysfunction. Episodic vestibular syndrome usually connotes multiple, recurrent attacks caused by an episodic disorder with repeated spells (triggered or spontaneous), but may initially present after the first attack	Vestibular migraine Benign paroxysmal positional vertigo Menière disease Vestibular paroxysmia Transient ischemic attacks affecting vestibular structures Cardiovascular (orthostatic hypotension, vasovagal syncope, myocardial infarction, cardiac arrhythmia) Epilepsy Panic attacks, agoraphobia Motion sickness Medication side-effects
Acute vestibular syndrome (AVS)	A clinical syndrome of acute-onset, continuous vertigo, dizziness, or unsteadiness lasting days to weeks, and generally including features suggestive of new, ongoing vestibular system dysfunction (e.g., vomiting, nystagmus, severe postural instability). There may also be symptoms or signs suggesting cochlear or central nervous system dysfunction. Acute vestibular syndrome usually connotes a single, monophasic attack, often caused by a one-time disorder, but it may instead punctuate a relapsing-and-remitting or stepwise progressive illness course	Vestibular neuritis Labyrinthitis Stroke affecting peripheral or central vestibular structures Traumatic vestibulopathy Demyelinating disease with vestibular involvement Drug intoxication (anticonvulsants, lithium) Antidepressant discontinuation syndrome Carbon monoxide intoxication Thiamine deficiency (Wernicke syndrome)
Chronic vestibular syndrome (CVS)	A clinical syndrome of chronic vertigo, dizziness, or unsteadiness lasting months to years and generally including features suggestive of persistent vestibular system dysfunction (e.g., oscillopsia, nystagmus, gait unsteadiness). There may also be symptoms or signs suggesting cochlear or central nervous system dysfunction. Chronic vestibular syndrome often connotes a progressive, deteriorating course, but sometimes instead reflects a stable, incomplete recovery after an acute vestibular event, or persistent, lingering symptoms between episodic vestibular attacks	Long-standing bilateral and unilateral peripheral lesions Sequelae after stroke Cerebellar degeneration Posterior fossa neoplasms Chronic psychologic or behavioral conditions manifesting prominent vestibular symptoms

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between attacks. Disorders typically presenting this syndrome include benign paroxysmal positional vertigo, Menière's disease, vestibular migraine, panic attacks, hypoglycemia, and transient ischemic attacks affecting central or peripheral vestibular structures. The duration of the episodes also gives important clues. Attack duration in Menière's disease is usually hours, while it varies in vestibular migraine between minutes to hours, sometimes days; positionally triggered vertigo in BPPV lasts usually less than a minute, although patients may experience it as longer. Short spontaneous attacks of less than a minute suggest vestibular paroxysmia supposed to arise from discharges in the vestibular nerve akin to trigeminal neuralgia (Hüfner et al., 2008). Isolated vertigo as an expression of transient ischemic attacks is usually of abrupt onset and lasts minutes (Grad and Baloh, 1989).

CVS is a clinical syndrome of chronic vertigo, dizziness, or unsteadiness lasting months to years and generally including features suggestive of persistent vestibular system dysfunction (e.g., oscillopsia, nystagmus, gait unsteadiness). Disorders typically presenting this syndrome include poorly compensated unilateral vestibulopathy, chronic bilateral vestibulopathy, cerebellar degeneration, posterior cranial fossa neoplasms, and chronic psychologic or behavioral conditions manifesting prominent vestibular symptoms, such as persistent

postural perceptual dizziness (PPPD) (International Classification of Diseases, (ICD-11) beta draft; World Health Organization, 2016).

After categorizing a patient into a vestibular syndrome, to narrow down further the list of differential diagnoses it is useful to distinguish spontaneous from nonspontaneous variants. Spontaneous forms occur without obvious triggers, exposures, or clearly causal events preceding the onset. To qualify as a trigger requires a repetitive and temporally appropriate relationship between the stimulus and the occurrence of the vestibular symptoms. This should be distinguished from an exacerbation of symptoms from an abnormal baseline (e.g., ongoing dizziness made worse by head motion).

Differentiating episodic and chronic vestibular syndromes

To establish if a vestibular syndrome is episodic or chronic is important because the underlying mechanisms and diseases differ, yet this can be difficult in clinical practice. If a patient indicates having vertigo or dizziness with head motion he/she will volunteer that the symptoms will arise on turning the head to the side or on looking up or down, perhaps mainly when moving fast. This obviously is a general hint to a disturbance of the vestibular system, but the potential meaning in terms of diagnosis is quite different if this symptom is present systematically on each head movement or only during limited phases, while exactly the same movement can be executed without any symptom on other occasions. The first scenario would point to a chronic syndrome (e.g., a stable unilateral lesion after a vestibular neuritis or trauma), whereas the second scenario indicates an episodic syndrome (e.g., vestibular migraine with episodic head motion intolerance).

This distinction as to whether symptoms are provoked systematically each time the trigger is active or only during discrete phases has to be carefully established for each trigger. For example, visually induced or positional vertigo/dizziness could occur on each occasion the provoking change of position or exposure to a visual environment is present, or only episodically, e.g., in vestibular migraine. On the other hand, the development of visual dependence after a vestibular lesion of any sort could be the basis of systematically visually triggered vertigo or dizziness in the appropriate environment. It is therefore important to enquire if the patient has asymptomatic phases in the presence of the triggers or not. The duration of the vestibular episode in case the symptom is only present when triggered is defined as the whole period during which the trigger provokes the symptom. This is usually more difficult to establish than a period of time of continuous symptoms that may be exacerbated from an abnormal baseline by activities.

There may also be overlaps among the three syndromes. An AVS may be heralded by an EVS (e.g., several transient ischemic attacks announcing a stroke), AVS recovering to CVS (e.g., a vestibular neuritis merging into a poorly compensated vestibular asymmetry); simultaneous EVS and AVS (head trauma with BPPV and traumatic vestibulopathy); EVS evolving to CVS (e.g., Menière's disease starting off with full recovery between attacks, then evolving to permanent partial vestibular deficit); repeated AVS evolving to CVS (multiple sclerosis with brainstem relapses evolving to chronic ataxia); CVS with superimposed EVS (e.g., PPPD with ongoing vestibular migraine).

Interpreting triggers

For the clinician, the most difficult distinction is between the triggers of head motion, and positionally or orthostatically induced vertigo/dizziness. An intolerance of head movements in any direction and time-locked to the movement points to some kind of faulty measurement or interpretation of the movement by the vestibular system. Peripheral causes like discrete lesions of the vestibulum or the vestibular nerve are possible, but also lesions or dysfunction of the brainstem and cerebellar structures processing vestibular input. Etiologies could be lesions after trauma or infection of the labyrinth or vestibular neuritis or lesion of the brainstem or cerebellum after stroke (Stanton et al., 2007). Head motion intolerance may also be present only during discrete episodes, e.g., in vestibular migraine.

Head motion intolerance needs to be distinguished from vertigo or dizziness induced by change of position, which means that the orientation of the head changes with respect to the gravitational vector and vertigo/dizziness usually occurs after the new position has been reached. Symptoms that are triggered when turning the head from right to left in an upright position would not qualify as positional, but it may be if the provoking movement is bending forward, lying down, looking up, or turning the head from right to left in a lying position. If vertigo/dizziness is only provoked by arising from a lying position, it is more likely to be orthostatic, whereas a positional vertigo/dizziness of BPPV would be triggered also when lying down or turning while lying (von Brevern et al., 2015).

In case of episodic vertigo triggered by a change of position, it is useful to establish the timing pattern. Positional vertigo in vestibular migraine could be present for some hours or a day, and then remit for days and then recur. In patients with BPPV, it is often worse at night and in the morning when getting up over a period of days, weeks, or months. It is, however, difficult to make this distinction on the basis of history alone; only an

examination during a symptomatic episode with observation of the appropriate nystagmus can settle the issue with certainty.

If vertigo/dizziness is only triggered when arising from a lying position to sitting or standing, orthostatic vertigo/dizziness is the most likely cause. Potential etiologies are orthostatic hypotension, postural orthostatic tachycardia syndrome, dysautonomia, presyncope, but also hypovolemia or side-effects of antihypertensive drugs. The reduction of blood flow to the head may produce spinning vertigo with nystagmus of various directions, mostly downbeating, although dizziness is more common than vertigo in this context (Choi et al., 2015). The traditional teaching is that orthostatic hypotension induces by definition dizziness and not vertigo. It is also important to note that the underlying cause may be benign (e.g., postural orthostatic tachycardia syndrome) or dangerous (hypovolemia due to internal bleeding).

Exposure to large-field or complex visual environments may produce visually induced vertigo. In some patients with an identified vestibular disorder and abnormally large perceptual and postural responses to disorienting visual environments, like supermarkets, this may lead to significant levels of handicap (Guerraz et al., 2001) and may contribute to a bad prognosis of recovery from a vestibular neuritis (Cousins et al., 2014). If visually induced vertigo combines with high levels of anxiety, it can lead to agoraphobia as large spaces may be disorienting for visually dependent patients (Staab and Ruckenstein, 2003).

One of the most debilitating chronic vestibular syndromes to recognize is PPPD, formerly known as phobic postural vertigo or chronic subjective dizziness (Staab, 2012). PPPD causes chronic dizziness and unsteadiness, which worsens when exposed to visual motion, self-motion, or when performing precision visual tasks like reading. Usually the worsening of symptoms when exposed is not immediate, but builds up with repeated movements and at rest takes time (hours or more) to return to the usual baseline. This is different from the dizziness in uncomplicated unilateral vestibular loss, where the symptom is time-locked to the movement and stops straight away at rest. PPPD is usually triggered by vestibular symptoms of a primary neurotologic or a nonvestibular cause, such as acute vestibular disorders (25%), vestibular migraine (16.5%), primary panic or generalized anxiety disorders (15% each), postconcussive syndrome (15.1%), or dysautonomia (7%). PPPD may persist after a vestibular event, even if the primary lesion has recovered (e.g., BPPV), or coexist and complicate an episodic vestibular disorder such as vestibular migraine (Staab and Ruckenstein, 2007).

Less common triggers are sounds, which point to an abnormal transmission of sound energy to the vestibulum as in superior canal dehiscence, or Valsalva-type triggers which suggest Chiari malformation, perilymphatic fistula, or situational (pre)syncope.

Exertion can be a trigger of vestibular symptoms; this could obviously be head motion-related and therefore express a vestibular problem, but may also indicate a circulation problem due to anemia, cardiomyopathy, lung disease (e.g., asthma, emphysema), pulmonary hypertension, subclavian steal syndrome or valvular heart disease, or autonomic dysfunction (Staab et al., 2002; Newman-Toker, 2012).

If symptoms of dizziness, perspiration, nausea, and vomiting and generalized malaise do not exist chronically but rather build up gradually if a person is exposed to actual motion or motion of the visual surround, particularly of low frequencies (around 0.4 Hz), it is usually motion sickness (Golding and Gresty, 2015), and not a vestibular disease per se. Susceptibility to motion sickness has a high interindividual variability and is lowest in patients with bilateral vestibular loss and tends to be higher in women and people with migraine (Murdin et al., 2015). If a person with high susceptibility to motion sickness acquires a vestibular disorder, he/she is likely to be relatively sicker.

Accompanying symptoms

Nonvestibular symptoms, which may occur simultaneously or in close temporary connection with the vestibular symptoms, give important clues regarding their topology or etiology. For some common vestibular disorders, such as vestibular migraine and Menière's disease, these nonvestibular symptoms constitute defining criteria (Lempert et al., 2012; Lopez-Escamez et al., 2015).

Some "paravestibular" symptoms commonly associated with vertigo or dizziness, including nausea and vomiting, are more related to the intensity and duration of the vestibular symptoms rather than the underlying origin. They do however hint to a neuro-otologic disorder in a wider sense, as a postural instability due to a peripheral neuropathy in the legs would not be associated with nausea.

As disturbances of the inner ear are a common source of vestibular symptoms, it is important to inquire about cochlear or aural symptoms like deafness, tinnitus, and aural fullness. In Menière's disease fluctuating aural symptoms in close temporal relationship with the vestibular episodes are part of the defining criteria, although in the updated definition, the diagnosis of definite Menière's disease is not based on history alone but requires also proof of hearing loss in middle or low frequencies recorded on an audiogram. Accompanying cochlear symptoms may also occur in potentially serious conditions like mastoiditis, trauma, or inner-ear ischemia.

Vestibular migraine is considered the most common episodic vestibular disorder with spontaneous attacks (Lempert and Neuhauser, 2009). Patients will tend to forward mainly or exclusively their chief complaint of vestibular symptoms. Once it is clear that they have an EVS it is important to establish if they are migraineurs. The migraine headache may regularly occur at the time of presentation of the vestibular symptoms, but may have been more prominent in the past and not so much or not at all at the time the vestibular symptoms started. In vestibular migraine the onset of migraine headaches precedes the onset of vertigo in a vast majority of cases (87%), on average by about 10 years (Cha et al., 2009). It is therefore important to explore a patient's headache history, even if the patient is not bothered by the headaches at that stage and often does not recognize any link between the two symptoms. It is then necessary to establish if headache and nonheadache migraine symptoms (such as photo- and phonophobia or visual aura) are present during at least half of the vestibular episodes.

Accompanying neurologic symptoms that appeared simultaneously with a spontaneous AVS will orient the clinician to consider acute conditions like stroke, multiple sclerosis, or Wernicke's disease. It has been increasingly recognized in the last years that cerebellar stroke may present as isolated vertigo (Choi et al., 2014) and this represents a particular diagnostic challenge in the emergency setting. History alone will not be able to distinguish stroke from vestibular neuritis and has to be complemented with a targeted clinical neuro-otologic assessment (Kattah et al., 2009) focusing on the eye movements (Head Impulse – Nystagmus – Test of Skew: HINTS). Stroke represents a small (3.2%) proportion of all dizziness presentations to the emergency department (Kerber et al., 2006) and approximately 16% of patients with a diagnosis of posterior-circulation stroke report previous transient ischemic attack-like symptoms, and half of those are isolated vertigo (Paul et al., 2013). In this case mainly a new onset of vertigo episodes in a context of vascular risk factors raises suspicion.

Anxiety frequently accompanies vertigo (Pollak et al., 2003) and dizziness. Vice versa, lightheadedness and unsteadiness are second only to cardiopulmonary symptoms (e.g., chest pain, dyspnea) as common manifestations of panic attacks. Vertigo occurs infrequently with panic attacks and is generally less dramatic than the spinning sensations caused by acute peripheral vestibular disorders (Meurer et al., 2015).

EXTERNAL CAUSES

Vestibular symptoms can be caused by exposures or external causes. In case of an AVS some are usually quite obvious, including head trauma, blast injury, vestibular surgery, neck injury with vertebral artery dissection, or intratympanic gentamicin application. Causes that might be less obvious are carbon monoxide intoxication, aminoglycoside toxicity due to systemic application, anticonvulsant or lithium intoxication, decompression syndrome, and high-altitude sickness.

Dizziness and vertigo are estimated to constitute about 5% of all adverse drug reactions (Chimirri et al., 2013), with anticonvulsants, antihypertensives, antibiotics, antidepressants, antipsychotics, and anti-inflammatories being the top substance groups. Potential mechanisms are their actions on the central nervous, autonomic, or cardiovascular systems. Sudden withdrawal may also cause dizziness, vertigo, and ataxia, in particular of selective serotonin uptake inhibitors, serotonin norepinephrine reuptake inhibitors, and tricyclic antidepressants (Haddad, 2001).

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Chapter 7

Bedside examination

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Abstract

In most dizzy patients a limited selection of bedside tests, together with the history, is adequate to establish a differential diagnosis and select the next diagnostic and therapeutic procedures. A set of basic bedside tests that should be applied in every patient with vertigo or imbalance allows identifying: (1) patients who need immediate referral for further assessment and treatment; (2) patients with nonthreatening disorders for which treatment can be started without more detailed testing; (3) patients with benign paroxysmal vertigo, in whom a detailed work-up is not required and who can immediately be treated with an appropriate particle-repositioning maneuver; and (4) patients who need a comprehensive neuro-otologic and neurologic work-up. Additional neuro-otologic bedside tests help to further refine the differential diagnosis.

INTRODUCTION

A full neuro-otologic bedside examination lasts up to 90 minutes, but in most dizzy patients a limited selection of bedside tests, together with the history, is adequate to establish a differential diagnosis and select the next diagnostic and therapeutic procedures. Therefore, this chapter will first describe a set of basic bedside tests that should be applied in every patient with vertigo or imbalance. Since this restricted set of tests serves to filter out patients who require urgent radiologic imaging for possible stroke treatment or who can be potentially cured already during the present consultation, we call it the neuro-otologic triage examination (Fig. 7.1).

After completing the triage examination, the clinician is able to decide: (1) whether the patient is possibly suffering from a stroke and should urgently be evaluated in a stroke unit; (2) whether the patient is affected by a nonthreatening disorder for which treatment can be started without more detailed testing; (3) whether the patient has benign paroxysmal positional vertigo (BPPV) and thus should be treated "on the spot" with a particle-repositioning maneuver; or (4) whether the differential diagnosis is still unclear and an additional neuro-otologic and a complete neurologic bedside examination is required.

After completing the full bedside examination, the clinician is able to determine whether or not, in addition, laboratory tests or imaging studies are needed. Finally, a diagnosis or a differential diagnosis according to the probabilities of candidate disorders is reached and therapies are instituted.

TRIAGE BEDSIDE EXAMINATION

The triage bedside examination aims to:

1. identify patients who need immediate referral for further assessment and treatment, especially patients with suspected cerebrovascular conditions requiring emergency care on a stroke unit
2. identify patients with nonthreatening disorders, such as vestibular migraine and multisensory imbalance, in whom treatment (medication or physical therapy) can be started without more detailed neuro-otologic bedside testing and additional auxiliary testing

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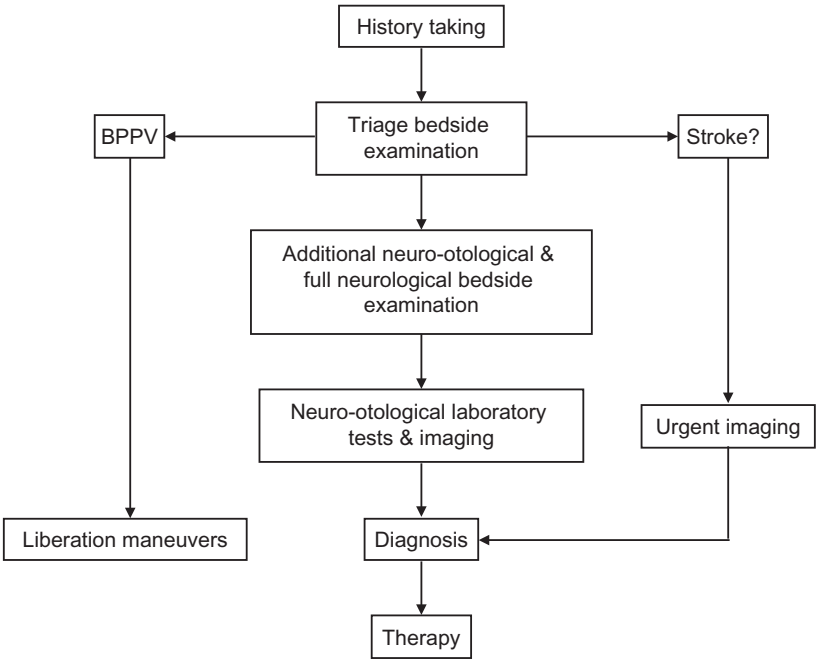

Fig. 7.1. Flow chart depicting the sequence of neuro-otologic evaluation steps. BPPV, benign paroxysmal positional vertigo.

3. identify patients with benign paroxysmal vertigo, in whom a detailed work-up is not required and who can immediately be treated with an appropriate particle-repositioning maneuver
4. identify patients who need a comprehensive neuro-otologic and neurologic work-up, including detailed history taking, bedside examination, auxiliary tests, and imaging.

The triage bedside examination generally suffices to make a reasonable decision on which of the four paths to follow for further evaluation or treatment. The following seven tests can be applied in approximately 10 minutes (in parentheses: main question to be answered by the respective test):

1. ocular stability (spontaneous nystagmus?)
2. head impulse test (catch-up saccades?)
3. alternating cover test (vertical ocular deviation?)
4. dynamic visual acuity (decline by more than two lines?)
5. Romberg test on rubber foam pad (loss of balance?)
6. provocation maneuvers for BPPV (positional nystagmus/vertigo?)
7. malleolar vibration sense (loss of sensation?).

Ocular stability

Normally, with gaze pointing straight ahead, the two eyes remain stable in their neutral position, i.e., in the center of the orbit. Disorders of the labyrinth, the vestibular nerve, and the central structures of the vestibular and ocular motor systems, however, may lead to drifts of the eyes with various horizontal, vertical, and torsional components. These ocular drifts away from the neutral position are typically interrupted by saccadic movements, so-called fast phases, in the opposite direction, which bring the eyes back close to their neutral position, leading to nystagmus.

Properties of this so-called spontaneous nystagmus are important elements in the differential diagnosis of both acute and chronic vertigo. While spontaneous nystagmus with fast and slow phases, so-called jerk nystagmus, can be due to disorders of both the vestibular and ocular motor systems, pendular spontaneous nystagmus is caused by disorders of ocular motor centers and pathways.

Spontaneous nystagmus in patients with acute vertigo

In patients with acute vertigo, the clinician must quickly form an opinion on whether the underlying lesion is neuroanatomically peripheral or central. “Peripheral” includes the vestibular labyrinth and the vestibular nerve, while “central” includes any brain structure that may, if lesioned or irritated, lead to vertigo. The suspicion of acute central vertigo will always lead to emergency procedures, potentially including stroke treatment, while peripheral acute vertigo is usually not due to a life-threatening condition (Tarnutzer et al., 2011).

An expeditious assessment of spontaneous nystagmus in patients with acute vertigo should answer the following questions:

1. Is the main direction of the nystagmus primarily horizontal, vertical or torsional?
   Comment: Spontaneous nystagmus is almost never purely horizontal, vertical, or even torsional. Directional components in addition to the main nystagmus component result from the coordinate system of the neural signal that causes the nystagmus. They also depend on whether the clinician chooses to describe the nystagmus in a head-fixed or eye-fixed reference system. For instance, in an eye-fixed reference system, spontaneous nystagmus resulting from an acute superior vestibular neuritis may appear more horizontal-torsional at gaze directed to the contralesional side and more horizontal-vertical at gaze directed to the ipsilesional side. In contrast, the very same nystagmus, when described in a head-fixed reference system, shows little dependence of its direction on eye position. Most examiners use an eye-fixed reference system.

   Another factor to consider in observing the different directional components of spontaneous nystagmus is the effect of visual fixation suppression. As the horizontal and vertical components of eye movements are more suppressed by visual fixation than the torsional component, the relative magnitude of the torsional component increases when the patient attempts to fix the gaze on a visual target.

   Horizontal spontaneous nystagmus in patients with acute vertigo can be of peripheral-vestibular or of central origin. Only the identification of additional signs allows horizontal spontaneous nystagmus to be attributed to a peripheral or central pathomechanism.

   Vertical spontaneous nystagmus in patients with acute vertigo, however, is practically always of central origin and either downbeat (upward drift) or upbeat (downward drift). In general, downbeat nystagmus is a chronic sign, whereas upbeat nystagmus appears acutely and most often results from a lesion of ocular motor pathways or centers within the brainstem (Pierrot-Deseilligny and Milea, 2005; Kim et al., 2006). Many times, up-beat spontaneous nystagmus disappears over time.

   Torsional spontaneous nystagmus in patients with acute vertigo is frequently associated with a vertical misalignment of the eyes, so-called skew deviation, with the upper poles of the eyes beating in the direction of the hypertropic eye. Additionally, the eyes are statically cyclorotated with their upper poles in the direction of the hypotropic eye (Brandt and Dieterich, 1993). Skew deviation with static binocular cyclorotation, so-called skew torsion, with or without spontaneous torsional nystagmus, may be associated with head tilt in the direction of the hypotropic eye, so-called ocular tilt reaction (Westheimer and Blair, 1975; Halmagyi et al., 1991). Torsional spontaneous nystagmus, skew torsion, or ocular tilt reaction in patients with acute vertigo are usually due to a brainstem lesion.
2. In patients with horizontal spontaneous nystagmus, does the direction of nystagmus reverse when gaze is held in an eccentric position in the direction of the slow phases? In other words, is there a horizontal gaze-evoked nystagmus at right and left gaze, in addition to the underlying horizontal spontaneous nystagmus?
   Comment: For not yet completely understood reasons, the drift velocity of spontaneous nystagmus typically increases at gaze increasingly held in the direction of the fast phases (Robinson et al., 1984; Bockisch and Hegemann, 2008). This pattern is called Alexander's law and in the case of horizontal spontaneous nystagmus points to a peripheral dysfunction that causes acute vertigo (Fig. 7.2). If, however, the

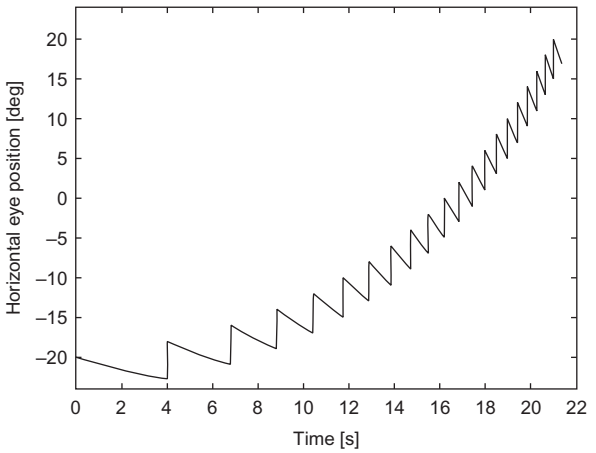

Fig. 7.2. Demonstration of Alexander's law. Simulated horizontal nystagmus caused by an acute vestibular loss on the left side. The patient moves his or her eyes slowly, i.e., within 21 seconds, from the left to the right. The eye drift is always to the side of the deficit, which is the left side (negative direction). As a consequence, the nystagmus always beats to the right. The velocity of the eye drift and consequently the frequency of the nystagmus increase as the the eyes move in the direction of the fast phases.

horizontal nystagmus changes its direction, when the patients holds gaze eccentrically in the horizontal direction of the slow phases, this additional gaze-evoked nystagmus indicates a lesion in the brainstem or cerebellum (Kattah et al., 2009).

3. Does visual fixation suppress or enhance the spontaneous nystagmus?
   Comment: Spontaneous nystagmus caused by an acute peripheral vestibular asymmetry usually can be suppressed by visual fixation. This is best evaluated by comparing the nystagmus during fixation with nystagmus with removed fixation, e.g., by the patient wearing Frenzel goggles, which prevent fixation. Visual fixation only suppresses the horizontal and vertical components of nystagmus; therefore a torsional component becomes more prominent. Lacking visual fixation suppression of spontaneous nystagmus points toward a central lesion (Cnyrim et al., 2008), but the presence of visual fixation suppression does not exclude a central lesion (An et al., 2014). Increasing nystagmus during attempted visual fixation is typical for infantile nystagmus syndromes.

After answering these three questions, the clinician is able to attribute the spontaneous nystagmus in a patient with acute vertigo to a peripheral-vestibular or central dysfunction. An exception is a lesion at the root entry zone of the vestibular nerve, which in absence of central neurologic signs may present like a peripheral vestibulopathy, hence the term vestibular pseudoneuritis (Dieterich, 2002).

Spontaneous nystagmus in patients with chronic vertigo or imbalance

Spontaneous nystagmus in patients with chronic vertigo or imbalance is usually due to a central vestibular or ocular motor dysfunction. The clinician should try to answer the following questions:

1. Is the spontaneous nystagmus jerk or pendular?
2. What is the direction of the spontaneous nystagmus? Does it change over time?
3. Is the spontaneous nystagmus monocular or binocular?
4. Is the spontaneous nystagmus conjugate or disconjugate?
5. Is the spontaneous nystagmus evoked by covering one eye?
6. From the history: is the nystagmus infantile (congenital) or acquired?

Horizontal spontaneous nystagmus due to a peripheral vestibular deficit (e.g., vestibular neuritis) or irritation (e.g., Menière) is usually transient and, after days, can only be seen under Frenzel glasses. Head shaking or mastoid vibration can unmask a peripheral or central asymmetry. This provoked nystagmus, i.e., after head shaking or during vibration, is also best seen under Frenzel glasses (Leigh and Zee, 2015).

Downbeat spontaneous nystagmus is usually due to an impairment of the cerebellar flocculus (Zee et al., 1981). A typical feature of cerebellar downbeat nystagmus is an increase of drift velocity and hence nystagmus intensity with horizontal eccentric gaze. In case of an additional horizontal gaze-evoked nystagmus, the nystagmus direction becomes oblique, i.e., vertical–horizontal, at horizontal gaze eccentricities. Downbeat nystagmus frequently obeys Alexander's law, i.e., upward drift and therefore nystagmus intensity increases with downgaze. In a minority of cases, however, Alexander's law of downbeat nystagmus is reversed (Straumann et al., 2000).

Seesaw nystagmus can be pendular or jerk. While one eye moves upward and incyclorotates (upper pole moving in the contralateral direction), the other eye moves downward and excyclorotates. During the second half of the cycle, this pattern is mirrored between the two eyes.

Acquired pendular nystagmus is horizontal, vertical, oblique, elliptic, or circular. Nystagmus amplitude can be different between the two eyes and there are also monocular forms of pendular nystagmus. If the palate moves in synchrony with the eyes, this combination is called oculopalatal tremor or myoclonus.

Periodic alternating nystagmus is a horizontal spontaneous jerk nystagmus that changes its direction every 90–120 seconds. Typically, the nystagmus becomes weaker before changing its direction.

The nystagmus in infantile nystagmus syndrome, formerly called congenital nystagmus, is almost always horizontal, sometimes with a small torsional component. Eye movements are conjugate and may change direction, amplitude, and morphology, but not frequency, as a function of gaze direction. Usually, there is a gaze direction with minimal nystagmus amplitude, the so-called null zone. Infantile nystagmus syndrome often includes head tremor. Nystagmus and head tremor increase with visual fixation and under emotional stress. A variant of the infantile nystagmus syndrome is latent nystagmus, which is a spontaneous horizontal nystagmus that appears in both eyes when one eye is covered and always beats toward the uncovered eye.

Head impulse test

The patient is asked to fix with the eyes on the tip of the examiner's nose. The examiner, in turn, holds the patient's head patient firmly with both hands, with the

center of each palm approximately over the outer acoustic meatus. The examiner asks the patient to relax the neck muscles as much as possible and rotates the head slowly back and forth in the horizontal plane to get a feeling for the elasticity of the neck muscles. The examiner then informs the patient about upcoming small-amplitude head thrusts to the right and left and repeats the previous instruction to fix with the eyes on the tip of the examiner's nose. The patient is also asked to prevent eye blinks. Head impulses, i.e., thrusts with high acceleration but limited amplitude (<15°), are delivered in the horizontal plane to both sides in pseudo-random order starting from the center position. After each impulse, the head is held in the eccentric position and the eyes are carefully observed for catch-up saccades that bring the eyes back on target (examiner's tip of the nose) in case of a deficient vestibulo-ocular reflex (Halmagyi and Curthoys, 1988). The direction of the head impulse that elicits catch-up saccades indicates the side of a peripheral vestibular deficit, e.g., a head impulse to the right followed by catch-up saccades to the left is compatible with a peripheral vestibular deficit on the right side (Fig. 7.3).

Head impulses should reach peak velocities of 150°/second or more to enable a side-specific assessment of peripheral vestibular function (Weber et al., 2008). The aim is to drive the frequency of the inhibitory vestibular nerve fibers from the contralateral labyrinth down to zero (inhibitory cutoff) in order to isolate the contribution of the excitatory pathways of the high-acceleration vestibulo-ocular reflex along the tested plane (Lasker et al., 2000; Palla and Straumann, 2004).

After each head impulse, the head is slowly rotated back to the center position. Some clinicians, however, prefer to start the head impulse from an eccentric position. While this procedure enables larger amplitudes of head thrusts, the directions become predictable.

Sometimes the catch-up saccades that correct the deficient vestibulo-ocular reflex have a very short latency and therefore occur during the second half of the head impulse. Such covert catch-up saccades cannot be seen clinically, which results in a false-negative head impulse test result (Weber et al., 2008). By applying unpredictable head impulses with larger amplitudes, covert catch-up saccades might become overt in some patients (Tjernström et al., 2012).

Head impulses can also be applied along the vertical semicircular canals, i.e., the left–anterior–right–posterior and right–anterior–left–posterior planes. The neck mechanics in these planes, however, prevent the same high accelerations as the horizontal plane, which makes results less reliable.

A precondition for the correct interpretation of the head impulse test is the absence of central or peripheral ocular motor disorders. Thus, the clinician has to be sure that the efferent portion of the vestibulo-ocular reflex is intact and, as a result, deficits of this reflex can only be due to the afferent portion, i.e., the labyrinth or vestibular nerve. It is therefore advisable to clinically determine that saccadic movements of both eyes are not impaired.

Strabismus, manifest or latent, can also lead to wrong interpretations of the head impulse test, especially in patients in whom eye dominance can switch side, e.g., depending on gaze direction. In these cases, the head impulse test should be performed with one eye patched.

The distance between the patient's eyes and the visual target, i.e., the examiner's nose, should be as wide as possible to minimize the amount of convergence.

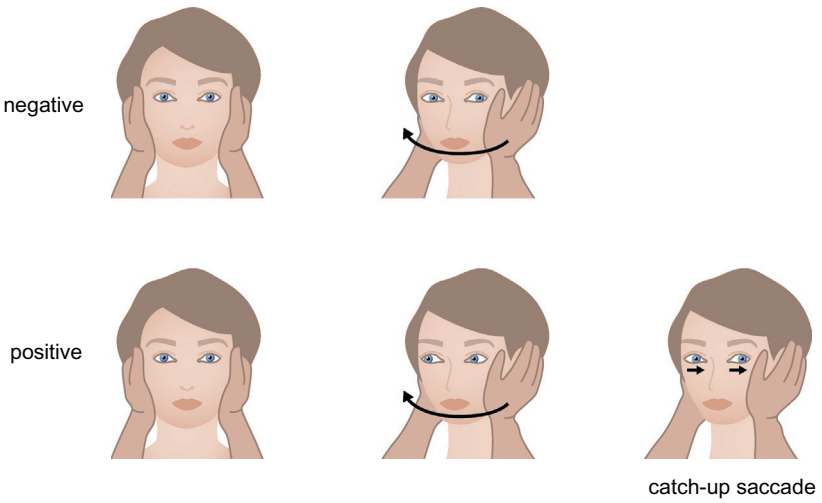

Fig. 7.3. Head impulse test to left. Top row: Negative head impulse test. The eyes remain stable in space. Bottom row: Positive head impulse test in a patient with a left sided peripheral vestibular deficit. The eyes cannot be stabilised during the head impulse; they deviate in the direction of the head rotation. After the head impulse, catch-up saccades bring the lines-of-sight back on target. Reprinted with permission. © Rheuma Schweiz.

Convergence tends to decrease during the head impulse and the subsequent re-convergence might be misinterpreted as a catch-up saccade. Hence, it is advisable to perform the head impulse test with outstretched arms.

A negative head impulse test, i.e., no catch-up saccades after head thrusts, is a normal finding in healthy human subjects. In patients with acute vertigo and spontaneous nystagmus, however, a negative head impulse test is highly suspicious for an acute lesion within the brainstem or cerebellum (Kattah et al., 2009). Conversely, in patients with acute vertigo and spontaneous nystagmus, a positive head impulse test, i.e., catch-up saccades after head thrusts in at least one direction, strongly suggests a recently acquired peripheral vestibular deficit. The only exception is a lesion at the root entry zone of the vestibular nerve within the brainstem, so-called vestibular pseudoneuritis (Thömke and Hopf, 1999; Dieterich, 2002).

Alternating cover test

The patient is asked to fix with the eyes on a small visual target, e.g., the tip of a pen. The tip of the examiner's nose, a blurry flashlight, and similar targets are not adequate since they allow extrafoveal fixation by some degrees. The examiner then alternately covers either eye using the palm or a paddle. The examiner looks for movements of the eye that has just been uncovered. These movements are directed oppositely to the deviation of the eye, when it was still covered. Horizontal eye movements elicited by the alternating cover test are common in healthy subjects, indicating esophoria (eye moves temporally when uncovered) or exophoria (eye moves nasally when uncovered). Vertical eye movements elicited by the alternating cover test, however, are almost always pathological and are due to either a skew deviation or a trochlear nerve palsy.

When a horizontal phoria makes it difficult to recognize the vertical component of eye movements elicited by the alternating cover test, Maddox rods are helpful. With these rods, the examiner can test the vertical and horizontal phorias in isolation. The rods also help to delineate whether the degree of vertical phoria changes with horizontal eye position, which points to paresis of an extraocular muscle.

In a patient with acute vertigo and in the absence of a trochlear nerve palsy, a vertical deviation, either manifest or unmasked with the alternating cover test (or the Maddox rods), indicates a brainstem stroke along the graviceptive pathways until proven otherwise (Kattah et al., 2009).

To distinguish a skew deviation from a trochlear nerve palsy, it is helpful to perform the alternating cover test with the patient in both the sitting and supine position. While in trochlear nerve palsy the vertical deviation of the eyes at gaze straight ahead is independent of the body position, skew deviation decreases when the patient is moved from upright to supine (Wong et al., 2011). This effect is explained by the fact that skew deviation results from asymmetric graviceptive input that leads to a vestigial righting response in the roll plane of the head. In the supine position, in which the roll plane is perpendicular to the gravity vector, the graviceptive pathways in question receive no input and skew deviation becomes minimal.

Skew deviation is usually associated with static binocular cyclorotation. Clinically, static ocular cyclorotation cannot be detected; it can be suspected, however, in cases with additional spontaneous torsional nystagmus. Static ocular cyclorotation can be measured by fundus photography. This technique allows distinguishing skew deviation from trochlear nerve palsy: the hypertropic eye is incyclorated in skew torsion, but excyclorated in trochlear nerve palsy (Fig. 7.4). An additional head tilt is seen in both conditions and is toward the lower eye. The combination of skew torsion and head tilt toward the lower eye as part of the vestigial righting response is called the ocular tilt reaction (Westheimer and Blair, 1975; Halmagyi et al., 1991), while patients with trochlear nerve palsy tilt their head inadvertently toward the unaffected side to reduce vertical diplopia by inducing ocular counterroll to the affected side (anti-Bielschowsky head position).

Dynamic visual acuity

The patient's static visual acuity is determined with both eyes viewing using a standard eye chart, e.g., a Snellen chart. The procedure is then repeated, but under constant horizontal or vertical oscillation of the patient's head, typically with 2 Hz and 10° peak-to-peak amplitude. The head oscillation is passive and applied by the examiner standing behind the patient. The visual acuity with the head oscillating, i.e., dynamic visual acuity, is compared with the static visual acuity. The reduction of visual acuity due to the head oscillation should not exceed two lines on the chart of optotypes. Since the static visual acuity serves as reference, the test can be done with or without eye glasses.

The dynamic visual acuity test relies on an intact vestibulo-ocular reflex (Demer et al., 1994). Therefore, provided ocular motor function is normal, a reduced dynamic visual acuity is highly suggestive of a bilateral vestibular deficit. Effective catch-up saccades can improve dynamic visual acuity over time, despite an unchanged deficit of the vestibulo-ocular reflex. Thus, dynamic visual acuity may also serve as a bedside test to monitor the effects of vestibular rehabilitation.

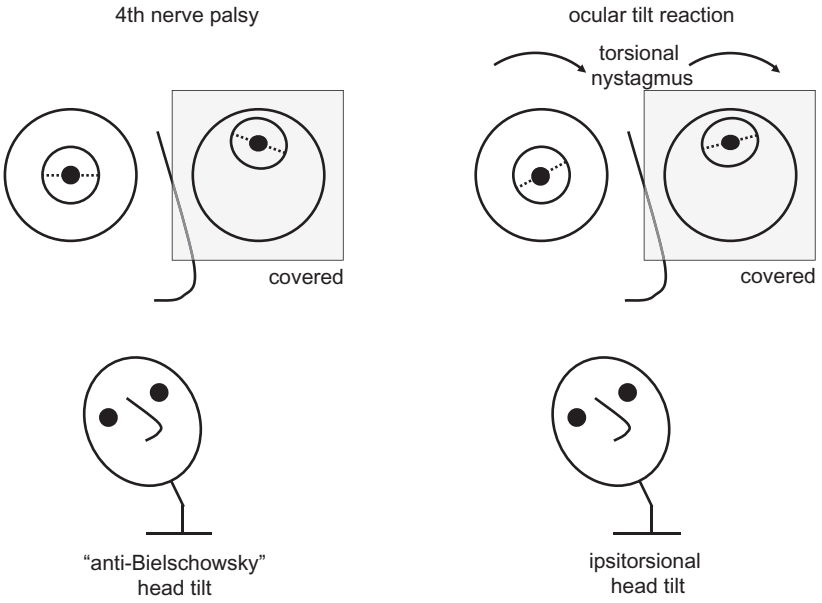

Fig. 7.4. Comparison between fourth-nerve palsy (left panel) and skew deviation (right panel). Fourth-nerve palsy: the affected left eye is excyclorotated and deviates upward when covered, i.e., when the nonaffected eye is viewing. The higher eye is excyclorated (only visible on fundus photography) due to the deficit of the superior oblique muscle, which has downward-intorsional pulling direction. Patients with fourth-nerve palsy spontaneously tilt their head toward the nonaffected (anti-Bielschowsky) side to minimize the contribution of the paretic muscle and hence vertical diplopia. Skew deviation: the higher eye is incyclorated (only visible on fundus photography), which contrasts with the fourth-nerve palsy. Another difference is that the lower eye is excyclorated. Thus, both eyes are cyclorotated to the same side, which is the ipsilesional side for lesions below the crossing of graviceptive pathways in the pons and the contralesional side for lesions above. The binocular torsion can also have a dynamic property, with a torsional nystagmus beating opposite to the static torsional deviation. As in patients with fourth-nerve palsy, the head is tilted in the direction of the lower eye as part of the ocular tilt reaction. In later stages, the head may also be tilted to the other side to compensate for the torsional deviation of both retinas relative to space.

Notice that, in contrast to the head impulse test, dynamic visual acuity does not allow a comparison of the vestibular function between the two sides. Such side-specific diagnostic information can only be obtained with computerized tests that measure visual acuity during head movement in different directions separately (Vital et al., 2010).

Romberg test on rubber foam pad

For the original Romberg test, the patient stands with feet together, hands by the sides, and eyes closed. In this situation with the visual input cancelled, postural control relies on vestibular input and proprioceptive input alone. The test is positive if a patient sways more than normal or falls without being held up by the examiner. A positive Romberg test is nonspecific: vestibular, proprioceptive, or cerebellar deficits as well as combinations thereof may lead to increased sway. The Romberg test is also not very sensitive: patients stand relatively stable even with substantial vestibular or proprioceptive deficits.

The Romberg test on rubber foam, on the other hand, mainly probes the vestibulospinal reflexes, as the foam minimizes the proprioceptive input from the feet (Shumway-Cook and Horak, 1986). Even healthy subjects show increased sway on foam (without falling). As a result, the test is very sensitive to identify patients with unilateral or bilateral vestibular loss. Notice that, in the absence of a vestibular deficit, the Romberg test on foam is also positive in patients with midline cerebellar disorders.

The clinical triad of a pathologic Romberg test on foam, decreased dynamic visual acuity, and catch-up saccades after head impulses to both sides is pathognomonic for a bilateral vestibular loss (Petersen et al., 2013).

Provocation maneuvers for benign paroxysmal positional vertigo

A neuro-otologic work-up decreases the proportion of patients diagnosed with "unclear dizziness" considerably (Geser and Straumann, 2012). This is mainly due to an increase of the number of patients diagnosed with BPPV. Most patients with BPPV can be treated successfully with the appropriate repositioning maneuver for the affected semicircular canal. Therefore, every patient with dizziness or imbalance, even in the absence of typical complaints of BPPV, should be tested with provocation

maneuvers to detect BPPV due to canalolithiasis or cupulolithiasis.

The two maneuvers that should be performed are:

1. The Dix–Hallpike maneuver to detect canalolithiasis of a posterior semicircular canal (Dix and Hallpike, 1952). The patient is moved from the sitting to the head-hanging position with the head rotated about 45° right or left relative to the trunk. Typically, in the presence of posterior canalolithiasis, nystagmus occurs after a few seconds, is upbeat, and shows both a vertical and a torsional component. A positional downbeat nystagmus with or without a torsional component can be central (unmasked cerebellar downbeat nystagmus) or due to an anterior canalolithiasis. Note that upbeat nystagmus in the head-hanging position is geotropic, i.e., directed toward the earth, and downbeat nystagmus is apogeotropic.
2. The supine-roll maneuver to detect a canalolithiasis or cupulolithiasis of the horizontal semicircular canals (McClure, 1985; Pagnini et al., 1989). The patient is asked to lie in the supine position with the head elevated by about 20–30°. Then, the head is quickly rotated to the right-ear-down or left-ear-down position. In the case of horizontal canalolithiasis or cupulolithiasis, horizontal nystagmus with a minor torsional component occurs, whereby the nystagmus beats either geotropically or apogeotropically in both ear-down positions, i.e., the nystagmus changes its direction in the head depending on the head position. Many times, nystagmus appears without latency. An apogeotropic pattern and persistence of nystagmus point to a cupulolithiasis (Baloh et al., 1995).

Malleolar vibration sense

Neuropathy alone or as an element of a syndrome can explain imbalance. While bedside tests for neuropathy can be extensive and time consuming, vibration sense measured at the malleoli is an efficient sign to triage patients for further neuromuscular evaluation. Other clinical signs, such as absent jerk reflexes, reduced positional sense of the toes, or reduced touch sense at the feet, are less reliable and correlate rarely with imbalance.

A bimalleolar vibration sense of 2/8 or below may be compatible with a sensory polyneuropathy as the only cause for imbalance. If the bimalleolar vibration sense is above 2/8, additional factors probably contribute to the imbalance. Notice that a generalized neuropathic process may also involve the vestibular nerve. Thus, such imbalance could be multisensory with a neuropathy that affects two of the three major inputs for balance control, i.e., feet proprioception and vestibular sensation (Palla et al., 2009; Poretti et al., 2013). In the presence of vestibular or visual disorders, an additional sensory polyneuropathy with impaired afferent signals from the feet can be the decisive component that lets the multisensory imbalance become manifest.

There are genetic or idiopathic cerebellar syndromes that include neuropathy with or without additional vestibular areflexia (Wagner et al., 2008; Szmulewicz et al., 2011). Besides identification of syndromic patterns, the recognition of a neuropathy in dizzy patients also has therapeutic importance, e.g., for physical therapy or nutrition.

ADDITIONAL BEDSIDE TESTS

Whether or not additional neuro-otologic bedside tests should be applied depends on the outcome of the triage examination. Results of these additional tests may support, clarify, or refine findings from the triage examination. Rarely, the additional tests will contradict the impression of the triage examination.

The additional bedside tests can be categorized into these groups:

- pupils
- eyelids
- ocular motor system
- vision
- hearing
- gait
- coordination.

In the following, we give an overview of the additional bedside tests without going into details. Most of the tests are elements of a comprehensive neurologic examination.

Pupils

Upon inspection the following question should be answered: are the pupils round and of equal size?

If the direct pupillary light reflexes are equally prompt, there is no afferent or efferent deficit and pupillary testing is complete. But if the direct light reflexes are asymmetric, the consensual light reflex must be tested in addition to determine whether the deficit is afferent or efferent.

The pupillary convergence response is best tested by letting the patient make a vergence saccade from a far target to the patient's own extended index finger held 10 cm in front of the eyes.

Eyelids

Unilateral or bilateral pathologies of the eyelids include ptosis, increased width of the palpebral fissure, lid lag, lid twitch, synkinesis, and infrequent blinking. If myasthenia gravis is suspected, increased fatigability of the upper eyelid can be assessed with the Simpson test.

Ocular motor system

If strabismus is detected, the clinician determines whether the binocular misalignment is: (1) manifest or latent; (2) concomitant, paretic, or internuclear; and (3) horizontal or vertical. (Skew deviation must be distinguished from vertical strabismus, particularly from trochlear nerve palsy.)

The high-acceleration vestibulo-ocular reflex is assessed with the head impulse test along the three pairs of semicircular canals.

With the patient visually fixating on the tip of the nose of the examiner, passive horizontal head oscillations at 0.5–1 Hz evoke redundant activity of the vestibulo-ocular reflex and the smooth-pursuit system; if the patient cannot keep the eyes on the target, both mechanisms are deficient. Other tests that stimulate the vestibular ocular reflex are the provocation maneuvers for canalolithiasis or cupulolithiasis (see triage examination), vibration nystagmus (see below), and head-shaking nystagmus (see below).

Ocular smooth pursuit alone is tested by having the patient follow with the eyes a moving flashlight at about 20°/second, first in the horizontal, then in the vertical direction. Deficient smooth pursuit is compensated by saccadic movements that follow the visual target.

To assess the smooth-pursuit system with the eyes centered and not moving, e.g., when additional gaze-evoked nystagmus interferes with smooth-pursuit eye movements in eccentric positions, visual suppression of the vestibulo-ocular reflex is tested. Provided the vestibulo-ocular reflex is functioning, the inability to suppress nystagmus during head oscillation and simultaneous visual fixation of a head-fixed target demonstrates a deficient smooth-pursuit system.

Saccades are tested in the horizontal, vertical, and occasionally oblique directions. The patient, with the head not moving, changes gaze direction between the examiner's tip of the nose and an eccentric target. Saccades are elicited by verbal command. The examiner assesses the latency, velocity, and accuracy of saccades.

Optokinetic nystagmus is elicited by a visual pattern on a hand-held rotating drum (optokinetic drum). This relatively small stimulus mainly activates the smooth-pursuit system (not the optokinetic system, as the name wrongly suggests). This test allows an efficient assessment of the conjugacy of pursuit eye movements (slow phases of nystagmus) and saccades (fast phases of nystagmus). Patients with visual vertigo standing on foam rubber are sometimes pulled in the direction of the optokinetic drum rotation or show increased body sway in the plane of stimulation.

Spontaneous nystagmus, if not visible during normal viewing, can be exposed by preventing fixation with Frenzel goggles. In cases in which subclinical eye drift originates from a peripheral or central vestibular imbalance in the horizontal plane, the drift or nystagmus can be enhanced and thus made clinically visible by horizontal head shaking (about 2 Hz during 10 seconds) (Leigh and Zee, 2015). If the direction of the drift or nystagmus is vertical or torsional, so-called perverted nystagmus, the underlying pathology is central. Vibrating the mastoid bone, Valsalva maneuver, tragal compression, and hyperventilation are other bedside tests to provoke nystagmus caused by asymmetric vestibular input due to an underlying vestibular pathology (Leigh and Zee, 2015).

Besides spontaneous nystagmus, visual fixation can be interrupted by saccadic intrusions and oscillations. These include square-wave jerks, ocular flutter, and opsoclonus. Myokymia of the superior oblique extraocular muscles manifests as monocular vertical-torsional oscillation.

Nystagmus beating in the direction of gaze at horizontal or vertical gaze eccentricities, so-called gaze-evoked nystagmus, is a sign of impaired eye-velocity-to-position integration in the brainstem and cerebellum. Gaze-evoked nystagmus must be differentiated from spontaneous nystagmus obeying Alexander's law (see triage examination).

Dissociated gaze-evoked nystagmus with smaller and slower fast phases of the adducting eye, typically together with an adduction deficit of the same eye, suggests ipsilateral internuclear ophthalmoplegia. The adduction deficit may disappear or become minimal during convergence.

Vision

Visual acuity for both eyes is determined separately for each eye, preferably with corrective glasses or lenses. Binocular visual acuity with the head stationary serves as the reference for dynamic visual acuity (see triage examination).

The visual field of each eye is tested with the other eye covered. Since the borders of the visual fields are given by the contours of the face, including the nose, an efficient way to test visual fields is to move a visual target, e.g., the examiner's winking index finger, toward the center from different directions. With the patient directing the line of the sight on to the examiner's tip of the

nose, the patient verbally indicates when s/he sees the target. This test allows hemianopsia and quadrantanopsia of one or both eyes to be identified.

Besides assessing the ocular fundus, direct ophthalmoscopy allows the detection of slight ocular motor instabilities. Ophthalmoscopically visible drift of the optic disc due to a peripheral vestibular asymmetry is suppressed when the other eye fixates on a visual target (Zee, 1978). Such visual suppression of the vestibulo-ocular reflex is missing if the drift is due to a central lesion. Direct ophthalmoscopy can also be used to assess the vestibulo-ocular reflex with the patient oscillating the head in the horizontal plane at about 1 Hz and the examiner observing the optic disc through the ophthalmoscope (Zee, 1978). In this configuration, the optic disc remains stable in space only if the vestibulo-ocular reflex is intact.

Hearing

To screen for hypoacusis, a low sound is produced close to the patient's outer acoustic meatus on either side. Acoustic sources can be a vibrating tuning fork, the rubbing of the examiner's thumb over the tip of the index finger, a ticking watch, or a smartphone running a dedicated app.

Lateralized hearing on the Weber test, i.e., with the vibrating tuning fork placed in the middle of the forehead, indicates a conductive hearing deficit on the louder side or a sensorineural hearing deficit on the other side. The Rinne test, in turn, identifies a conductive hearing deficit if the vibrating tuning fork placed on the mastoid process (bone conduction) appears louder than the fork placed near the patient's outer acoustic meatus (air conduction). Thus the combination of the Weber and Rinne tests allows the side of the acoustic deficit and its localization within the ear (middle or inner ear) to be identified.

Otoscopic inspection of the outer acoustic meatus is imperative in these situations: hypoacusis (check for cerumen impaction), local pain, local rash, suspected herpes zoster oticus, and before caloric irrigation (check for intact tympanic membrane).

Gait

Gait testing includes casual gait and tandem gait (walking in a straight line). Observation of disordered gait may assist in differentiating among sensory, cerebellar, basal ganglia-related, hydrocephalic, leukencephalic, and other etiologies.

Patients are then asked to walk straight ahead or step in place (Unterberger or Fukuda stepping test) with the eyes closed. In acute or subacute stages of a one-sided vestibular loss, patients tend to deviate to the side of the lesion.

A locomotor counterpart of the head impulse test is the walk–rotate–walk test. Patients are asked to walk straight ahead and then turn around (180°) with one step and walk back. Typically, patients with a unilateral peripheral vestibular deficit will make a supporting step after they rotate in the direction of the deficit. Of course, this test cannot be performed by patients with movement disorders.

Coordination

Testing the coordination of limb movements in a patient with dizziness or imbalance aims to identify signs of hemispheric cerebellar dysfunction. Limb ataxia may become evident in one of the following tests: finger-to-nose test and heel-to-shin test (eyes closed); finger-to-finger test (eyes open, finger of the patient to finger of the examiner); diadochokinesis of hands (repetitive pronation-supination) and legs (repetitive heel-to-knee movement); rebound phenomenon on arms and legs (the patient presses his or her arm or leg against the examiner's manual resistance; when the resistance is released, the patient's limb moves a short distance and then rebounds to the initial position; the phenomenon is delayed or absent in cerebellar disease).

Truncal coordination is assessed with the Romberg test on firm ground and on foam (see triage examination). Having the patient sit on a soft surface with both arms folded is a Romberg variant that excludes the contribution of the legs.

CONCLUSION

Clinicians who seek to gain more insight in the subspecialty of neuro-otology often assume that they first should learn the functions of the different peripheral and central neuroanatomic structures and then try to relate the signs and symptoms to these structures. Such a meticulous approach, although admirable, may be tedious and potentially frustrating. A more direct road to neuro-otology is based on the phenomenology obtained at the bedside. In a first step, the examiner becomes confident in estimating whether results of clinical tests range within normal limits. Then, with such skill, the examiner is able to identify signs that are clinically relevant. Finally, being familiar with the mechanisms and neuroanatomic structures underlying normal behavior, the examiner makes accurate differential diagnoses and orders appropriate auxiliary tests. With further experience, clinicians will realize that there is a clear hierarchy of neuro-otologic bedside tests. As outlined in this chapter, a set of tests should be applied in every patient with vertigo or imbalance to enable a triage in due time.

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Chapter 8

Eye movements in vestibular disorders

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Abstract

The differential diagnosis of patients with vestibular symptoms usually begins with the question: is the lesion central or is it peripheral? The answer commonly emerges from a careful examination of eye movements, especially when the lesion is located in otherwise clinically silent areas of the brain such as the vestibular portions of the cerebellum (flocculus, paraflocculus which is called the tonsils in humans, nodulus, and uvula) and the vestibular nuclei as well as immediately adjacent areas (the perihypoglossal nuclei and the paramedian nuclei and tracts). The neural circuitry that controls vestibular eye movements is intertwined with a larger network within the brainstem and cerebellum that also controls other types of conjugate eye movements. These include saccades and pursuit as well as the mechanisms that enable steady fixation, both straight ahead and in eccentric gaze positions. Navigating through this complex network requires a thorough knowledge about all classes of eye movements to help localize lesions causing a vestibular disorder. Here we review the different classes of eye movements and how to examine them, and then describe common ocular motor findings associated with central vestibular lesions from both a topographic and functional perspective.

SUBCLASSES OF EYE MOVEMENTS

Different subclasses of eye movements meet the specific requirements of the fovea for optimal visual function. When new information is needed, saccades bring images of objects of interest seen in the periphery to the foveae. Once there, images must be kept relatively still to give the brain time to analyze the new information; pursuit, vestibular movements, and gaze-holding mechanisms perform this function. Vergence mechanisms also bring and keep images of an object on to the foveae by moving the eyes in opposite directions. Vergence contributes to stereoscopic vision, the key component to depth perception; for example, when objects are within arm's length. Failure to move the eyes, or to hold the eyes still when needed, or to maintain proper alignment of the eyes can cause disabling visual symptoms such as the illusion of movement of the world (oscillopsia), double vision (diplopia), and loss of visual acuity. The different subclasses of eye movements are distinguished by their function, physiologic properties, and anatomic substrates.

Saccades

Saccades are the fastest eye movements, with speeds as high as 700°/s and durations usually less than a tenth of a second. Their main function is to bring new images of interest on to the fovea. The peak velocity, accuracy, latency, and conjugacy of the two eyes are characteristics that can be selectively affected by different pathologies. When saccades appear to be slow, but with no limitation in the range of motion, the disturbance is usually in the circuits that specifically generate premotor saccade commands. Selective slowing of horizontal saccades occurs

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with lesions in the pons (pontine paramedian reticular formation or PPRF) and selective slowing of vertical saccades suggests dysfunction within the upper midbrain (rostral interstitial nucleus of the medial longitudinal fasciculus or riMLF). The premotor commands for the quick phases of nystagmus are also generated by the same circuitry in the brainstem. Disconjugate movements can be due to extraocular muscle palsy or, for example, in the case of horizontal saccades, due to internuclear ophthalmoplegia (INO). In INO limited adduction in one eye is due to involvement of the MLF, which connects the abducens and oculomotor nuclei. On eccentric gaze there is often a jerk nystagmus beating outwardly, predominantly in the abducting eye. Impaired accuracy of saccades (dysmetria) is usually appreciated by the subsequent corrective saccades needed to bring the eyes to the visual target. Various patterns of dysmetria with undershooting (hypometria), overshooting (hypermetria), or with inappropriately directed saccades may appear, for example, with cerebellar lesions (see Wallenberg's syndrome, below). These patterns of dysmetria are different from small degrees of dysmetria in normal subjects, who often show a few degrees of hypometria, especially with relatively large, centrifugally directed saccades. Increases in saccade latency usually result from a cerebral cortical disorder, which, when extreme, has been called "ocular motor apraxia." This term, however, is often a misnomer, as the defect is not truly an apraxia but a disturbance of the initiation of saccades.

Normally subjects can largely suppress saccades when steady fixation is desired. Inappropriate saccades, called saccadic intrusions, are involuntary movements that take the eyes off the target. There is usually an interval of 150–200 ms before a corrective movement brings the eyes back to the target. This form of saccadic intrusion and correction is known as a square-wave jerk and, when small, is a common finding in healthy subjects, particularly the elderly. Square-wave jerks can be prominent in cerebellar disorders or degenerative diseases such as progressive supranuclear palsy (Troost and Daroff, 1977; Rascol et al., 1991; Otero-Millan et al., 2011). Saccadic intrusions may also occur as one-upon-the-other, back-to-back saccades, without an intersaccadic interval. When these oscillations are predominantly horizontal, they are called ocular flutter, and if they occur in multiple directions (horizontal, vertical, and torsional), they are called opsoclonus. Diseases associated with ocular flutter and opsoclonus often involve the brainstem and cerebellum and can be immune-mediated (paraneoplastic or parainfectious) or caused by toxins or metabolic derangements.

Smooth pursuit

Smooth-pursuit movements allow clear vision of a moving target by holding the image steady on the fovea. Pursuit performance requires focused attention to track a particular object. Pursuit capabilities decline with age and can be particularly affected by medications. If smooth-pursuit eye movements do not match the movement of the target, corrective saccades are needed to get the eyes back on target. The smooth-pursuit pathways within the brainstem and cerebellum share much circuity with those that generate vestibular movements. For example, the cerebellar output for smooth pursuit relays in part through the medial vestibular nucleus (MVN) and the adjacent nucleus prepositus hypoglossi (NPH), before reaching the ocular motor nuclei. In some patients who have lost vestibular function, smooth pursuit is enhanced in the attempt to stabilize gaze and compensate for the unwanted motion of images during head movement.

When tracking a moving target using both the head and the eyes, one must cancel the vestibulo-ocular reflex (VOR), which, if left unencumbered, would hold gaze steady and prevent smooth tracking of the target. Cancellation of the VOR shares similar mechanisms with smooth pursuit with the head stationary. Patients with vestibular hypofunction who also have a central lesion that impairs smooth pursuit may have normal-appearing VOR cancellation, as the VOR is impaired and does not require cancellation during head movement.

Vestibulo-ocular and optokinetic reflexes

The VOR stabilizes vision during head movements using information about the motion and position of the head from the semicircular canals, which sense angular acceleration, and from the otolith organs, which sense linear acceleration, including the pull of gravity. The rotational VOR produces slow-phase eye movements in response to head rotation in the horizontal (yaw), torsional (roll), or vertical (pitch) planes. The compensatory eye movements are generated in a plane parallel to which the head is rotating (Ewald's first law). When the head tilts in the roll plane (ear to shoulder), torsional eye movements are mainly driven by inputs from the semicircular canals. With a sustained lateral tilt, the eyes counter-roll by a small amount in the direction opposite to the head tilt. This static change in torsion is mediated by inputs from the otoliths (mainly the utricle), which sense the pull of gravity. The translational VOR is also driven by otolith inputs and produces compensatory eye movements in response to head translations from side to side (horizontal), up and down (vertical), or fore and aft (anterior–posterior).

Vestibular responses are characterized by their amplitude (gain), timing (phase), and direction (trajectory) relative to the movement of the head. Loss of vestibular function from either peripheral or central lesions may

cause low gain or short duration of vestibular responses. An unusually high gain, abnormal direction, or excessively long duration of the VOR points to a central lesion (e.g., cerebellar dysfunction). Because of inherent limitations in the ability of labyrinthine sensors to detect sustained head rotations, a central velocity storage mechanism exists, which extends the lower end of the range of frequencies of head motion that can be accurately sensed by the brain. The velocity storage mechanism also allows the brain to differentiate between static head tilt with respect to gravity and head translation, both of which are sensed by the utricles as a linear acceleration (Angelaki et al., 2004). The anatomic substrate for the velocity storage mechanism is within the vestibular nuclei and its connections to the cerebellar nodulus and uvula.

Imbalance of central vestibular tone can cause spontaneous nystagmus just as does a peripheral lesion. Vestibular nystagmus can have mixed horizontal, vertical, and torsional components. Pure torsional or pure vertical nystagmus usually points to a central pathology (Table 8.1). One hallmark of a peripheral nystagmus is that it appears or is accentuated when visual fixation is removed. According to Alexander's law, the nystagmus caused by a peripheral lesion is more intense when gaze is directed toward the side of the fast phase. This may also be the case with central lesions, but, when the opposite occurs, that is, nystagmus intensity increases when the eyes are in the slow-phase direction, a central lesion should be suspected. Lesions involving otolith connections may cause a combination of head tilt, skew deviation (vertical misalignment of the eyes not due to ocular muscle palsy), and ocular counter-roll, which is known as the ocular tilt reaction (OTR). In the OTR, the lower eye is on the side toward which the head is tilted. Also, there is an ocular counter-roll, with the lower eye extorted and the higher eye intorted. There is often an associated deviation of the sense of upright toward the side of the lower eye, as reflected in the subjective visual vertical (Dieterich and Brandt, 1993). Both an OTR and an impaired translational VOR are compensated quickly after injuries affecting peripheral otolith inputs, but they are often enduring after central lesions.

Table 8.1

Clinical features of peripheral vestibular and central nystagmus

Peripheral vestibular nystagmus	Central nystagmus
Mixed, horizontal torsional that beats away from the lesion	Mixed, pure torsional or pure vertical
Jerk movements (fast phase and slow phase)	Jerk or pendular movements
Strongly suppressed by visual fixation	Usually weakly suppressed by visual fixation
Increase with gaze toward the fast phase (Alexander's law)	May increase with gaze away from the fast phase (anti-Alexander's law)
Does not change direction with change in gaze position	May change direction (e.g., rebound, gaze-evoked, or periodic alternating nystagmus)
May be induced by convergence	May be induced or change direction by convergence

Optokinetic nystagmus (OKN) consists of a slow-phase response and resetting quick phases that help the VOR stabilize images on the retina during sustained rotations of the head. OKN supplements and eventually supplants the pure vestibular response from excitation of the labyrinth when the motion of the head is composed of predominantly low frequencies (to which the labyrinth is relatively insensitive), such as during rotation at a constant velocity. OKN abnormalities are best brought out with a full-field stimulus and also by looking at optokinetic after nystagmus (OKAN), which is elicited by putting the subject in darkness immediately after a sustained constant-velocity rotation of the body in light or after sustained stimulation by an optokinetic drum rotating around the stationary subject. OKAN reflects the action of the same velocity storage mechanism that improves the low-frequency performance of the peripheral labyrinthine sensors. OKN abnormalities are associated with peripheral and central vestibular dysfunction and lesions affecting the visual pathways. Acute peripheral vestibular lesions may cause asymmetric OKN with a better slow-phase response when the stimulus is directed toward the side of the lesion (Abel and Barber, 1981). The gain of OKAN is reduced in patients with bilateral loss of vestibular function (Zee et al., 1976).

Vergence

Fixation of a single object requires correct alignment of the visual axes of both eyes by the vergence system. While the premotor commands for vergence are not directly in vestibular pathways, the location of targets relative to the head affects vestibular responses, normally causing an increase in the gain of both the rotational VOR and translational VOR when the target is close. Spontaneous vertical nystagmus is often influenced by the vergence angle. For example, convergence often increases the amplitude of a spontaneous downbeat nystagmus (e.g., from cerebellar lesions) or even changes an upbeat nystagmus to a downbeat nystagmus (e.g., in Wernicke's encephalopathy).

Vergence centers are located within the midbrain and their lesions are associated with impaired vertical gaze and often an increase in convergence tone. Excessive convergence may appear with attempted upward saccades or along with resetting, upward quick phases induced with a downward-moving OKN stimulus (convergence retraction nystagmus). Selective vergence disorders are also reported with pontine lesions; for example, impaired vergence tracking of a target moving slowly but preserved fast vergence responses may occur with caudal pontine lesions. Cerebellar disease may also impair vergence, usually presenting as esotropia (the eyes turn inward) greater at distance (i.e., divergence palsy) (Hüfner et al., 2014).

EYE MOVEMENT FINDINGS WITH LESIONS INVOLVING THE MEDULLA

The medulla houses the bulk of the vestibular nuclei. Other major medullary structures involved in the control of eye movements include the perihypoglossal nuclei, including the NPH, the paramedian nuclei and tracts, the inferior olivary nuclei, and the inferior cerebellar peduncles (restiform bodies) (Fig. 8.1A and Table 8.2). Lesions of the vestibular nuclei can involve these neighboring nuclei or their projections.

Neurons in the NPH and the adjacent MVN have a critical role in generating the commands to hold eccentric positions of gaze, especially horizontal gaze. They also contribute to holding eccentric positions of vertical gaze along with the interstitial nucleus of Cajal (INC) within the midbrain. Lesions involving the NPH–MVN complex can impair horizontal gaze-holding with the eyes rapidly drifting back to center, resulting in a gaze-evoked nystagmus. Asymmetric lesions affecting both the vestibular nucleus and NPH can cause a combination of gaze-evoked and vestibular nystagmus. With large cerebellopontine angle tumors that compress the cerebellum, a Bruns nystagmus may develop, with a low-frequency and large-amplitude nystagmus on looking toward the side of the lesion due to defective gaze-holding, and a high-frequency and small-amplitude nystagmus on looking away from the side of the lesion due to vestibular imbalance (Croxson et al., 1988).

Gaze-evoked nystagmus should be distinguished from physiologic "end-point nystagmus" seen in some normal subjects. End-point nystagmus typically occurs on looking far laterally and, as opposed to gaze-evoked nystagmus, is often poorly sustained after a few beats. It is primarily horizontal and at times more prominent in one eye (usually the abducting eye) and on looking in one direction. End-point nystagmus may have a slight torsional component. A strong down-beating component, however, points to a central vestibulocerebellar dysfunction. Pathologic gaze-evoked nystagmus is usually associated with other ocular motor findings such as impaired smooth-pursuit and rebound nystagmus. Thus, the absence of other ocular motor abnormalities can help one decide if a gaze-evoked nystagmus is "physiologic."

The cell groups of the paramedian tracts also contribute to gaze-holding by relaying information to the networks in the vestibulocerebellum that help improve the function of the gaze-holding mechanisms within the brainstem (see also section on cerebellar lesions, below)

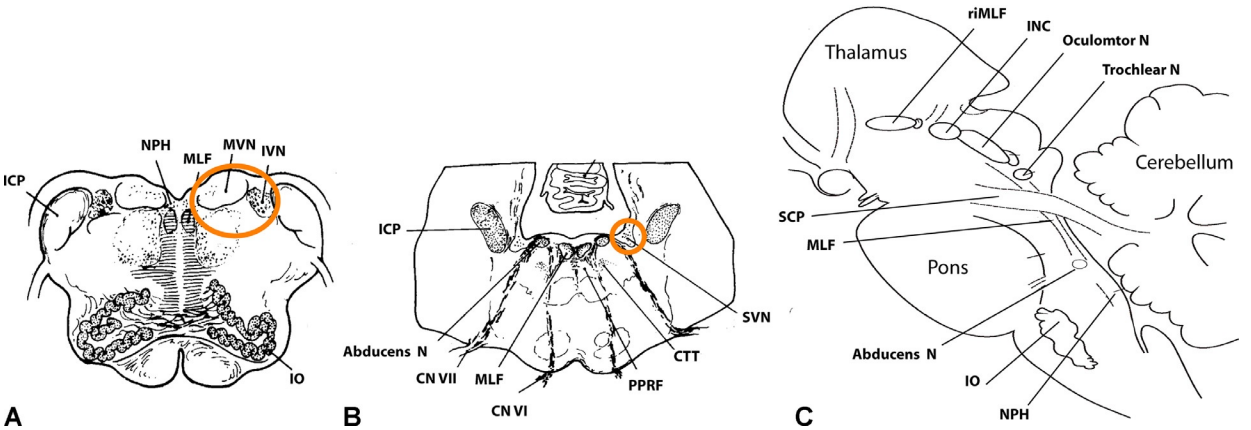

Fig. 8.1. Key structures with ocular motor function within the medulla (**A**: axial section), pons (**B**: axial section), and midbrain (**C**: parasagittal section). MVN, medial vestibular nucleus; IVN, inferior vestibular nucleus; SVN, superior vestibular nucleus (orange circles); ICP, inferior cerebellar peduncle; NPH, nucleus prepositus hypoglossi; MLF, medial longitudinal fasciculus; IO, inferior olive; CN VI, cranial nerve VI; CN VII, cranial nerve VII; PPRF, paramedian pontine reticular formation; CTT; central tegmental tract; SCP, superior cerebellar peduncle; INC, interstitial nucleus of Cajal; riMLF, rostral interstitial nucleus of medial longitudinal fasciculus. (Modified from Leigh and Zee, 2015, with permission from Oxford University Press. **C** is based on a figure from Dr. Anja Horn, Munich.)

Table 8.2

Key medullary structures with ocular motor function and associated clinical findings

Structure	Main ocular motor function	Clinical findings in lesions
Vestibular nucleus (medial and caudal parts)	VOR Gaze-holding	Abnormal head impulse sign Skew deviation or ocular tilt reaction (OTR) Spontaneous nystagmus Gaze-evoked nystagmus
Perihypoglossal nuclei (NPH, Roller, and intercalatus)	Gaze-holding	Gaze-evoked nystagmus (mainly downbeat with lesions of NPH and upbeat with lesions of Roller and intercalatus nuclei)
Cell groups of paramedian tracts	Gaze-holding	Upbeat or downbeat nystagmus
Inferior olivary nuclei	Provide error signals to the cerebellum for adaption	Oculopalatal tremor
Inferior cerebellar peduncles (restiform bodies)	Convey sensory information to the cerebellum	Saccadic overshoot toward the lesion and undershoot away from the lesion (ipsipulsion)

VOR, vestibulo-ocular reflex; NPH, nucleus prepositus hypoglossi.

(Büttner-Ennever and Horn, 1996). Medullary lesions may also cause vertical and often upbeat nystagmus from involvement of the perihypoglossal nuclei, paramedian tract cell groups, or selective disruption in ascending vestibular pathways for upward (versus downward) eye movements (Hirose et al., 1998; Kim et al., 2006; Saito et al., 2010). Both gaze-evoked and upbeat nystagmus are common ocular motor findings in Wernicke's encephalopathy caused by thiamine deficiency, and suggest involvement of the NPH–MVN complex (Abouaf et al., 2011; Kim et al., 2012b). Other eye movement abnormalities in Wernicke's encephalopathy include abducens nerve palsies, horizontal or vertical gaze palsies, selective loss of function of the horizontal VOR and INO (Cogan and Victor, 1954; Kattah et al., 2013).

Lesions affecting the vestibular nucleus can mimic peripheral vestibular lesions with a positive head impulse sign. The head impulse test takes advantage of Ewald's second law (excitation elicits a better response than inhibition); the compensatory slow phase is deficient when the head is rotated toward the side of the lesion at high speed and acceleration. In the setting of an acute vestibular syndrome in which a patient has acute vertigo and a spontaneous nystagmus, a normal head impulse test must raise suspicion for a central lesion in the brainstem or in the posterior medial cerebellum involving the nodulus and uvula (Newman-Toker et al., 2008; Moon et al., 2009). Suspicion of a central lesion becomes even higher if the patient has a bilateral gaze-evoked (direction-changing) nystagmus or skew deviation (Newman-Toker et al., 2008; Kattah et al., 2009). A three-step bedside ocular motor examination, incorporating these three findings (HINTS: head-impulse, nystagmus, test of skew) is a sensitive test to help differentiate central versus peripheral vestibular lesions (Kattah et al., 2009).

The most frequently recognized syndrome involving the vestibular nucleus is dorsolateral medullary infarction, known as Wallenberg's syndrome, due to infarction in the distribution of the posterior inferior cerebellar artery (PICA) (Table 8.3) (Kim, 2003). The ocular motor abnormalities in this syndrome are also associated with involvement of the inferior cerebellar peduncle (Table 8.2) (Straube et al., 1994; Solomon et al., 1995).

Lateropulsion, a conjugate deviation of the eyes toward the side of the lesion, is often a prominent finding in Wallenberg syndrome (Waespe and Wichmann, 1990). This is best seen under closed lids or with blinks, so that when the eyes open, a corrective movement brings them back to fixate again at the center. Lateropulsion also affects saccades, so that horizontal saccades toward the side of the lesion overshoot a visual target and saccades away from the lesion undershoot the target. This is known as "saccade ipsipulsion." Vertical saccades can be affected as well, showing an oblique trajectory directed toward the side of the lesion, followed by a corrective movement back to the target. This is often more prominent for upward vertical saccades (Kaski et al., 2012). Inappropriate torsional saccades or torsipulsion may be superimposed on horizontal or vertical saccades (Helmchen et al., 1997). Smooth pursuit is also commonly impaired while tracking targets away from the side of the lesion (Baloh et al., 1981). Spontaneous nystagmus in Wallenberg's syndrome, similar to the nystagmus from peripheral vestibular lesions, can be

Table 8.3

Ocular motor findings in vascular syndromes involving the brainstem and cerebellum

Vascular territory	Anatomic structure	Main ocular motor findings
Posterior inferior cerebellar artery (PICA)	Lateral medulla Inferior cerebellar peduncle Uvula, nodulus, tonsil	Wallenberg syndrome: Hypermetric saccades toward the side of the lesion and hypometric saccades away from the side of the lesion (ipsipulsion) Conjugate deviation of the eyes toward the side of the lesion (ipsipulsion) Impaired smooth pursuit away from the lesion Spontaneous nystagmus Skew deviation or ocular tilt reaction (OTR): higher eye on the opposite side of the lesion but head tilt and ocular counter-roll toward the side of the lesion Dissociated vertical-torsional nystagmus Gaze-evoked nystagmus
Anterior inferior cerebellar artery (AICA)	Anterior-inferior part of cerebellum (flocculus) Rostral portion of vestibular nucleus Inner ear (through labyrinthine artery)	Positive head impulse sign Spontaneous nystagmus Gaze-evoked nystagmus Hearing loss
Superior cerebellar artery (SCA)	Superior cerebellar peduncle Superior parts of the cerebellar hemisphere	Saccadic overshoot away from the lesion and undershoot toward the lesion (contrapulsion) Vertical nystagmus

horizontal or mixed horizontal-torsional, with the horizontal component usually beating away from the side of the lesion (Morrow and Sharpe, 1988; Rambold and Helmchen, 2005). The torsional component may, however, beat toward the side of the lesion. Lid nystagmus may also occur with lid twitches synchronized with the fast phase of ocular nystagmus (Daroff et al., 1968).

As mentioned earlier, the OTR is the hallmark of lesions affecting otolith-ocular pathways. The central lesions associated with OTR are usually caused by damage to the vestibular nuclei or their projections that mainly ascend to the ocular motor nuclei within the MLF. The OTR is therefore not limited to lesions of the medulla and can be seen at different levels of the brainstem (Fig. 8.2). In patients with Wallenberg's syndrome, when there is involvement of the vestibular nuclei, the head tilt is ipsilateral and the lower eye is on the side of the lesion. In these patients ocular torsion can be unequal between the eyes, with larger torsion in the lower eye, possibly due to additional involvement of the posterior semicircular canal projections (Brodsky et al., 2006). Since projections in the MLF from the vestibular nuclei in the medulla cross the midline before ascending to the ocular motor nuclei and the midbrain, skew deviation with lesions in the pons or midbrain is usually associated with an ipsilateral hypertropia (elevated eye on the side of the lesion) and a contralateral head tilt (Fig. 8.2) (Brandt and Dieterich, 1994).

Lesions affecting the connections of the inferior olivary nucleus may produce pendular ocular oscillations with vertical or torsional components (about 2 cycles per second). This syndrome is known as oculopalatal tremor and usually develops weeks to months after lesions affecting the nuclei and connections within the Guillain–Mollaret triangle (the inferior olive to deep cerebellar nuclei via inferior cerebellar peduncle, and from deep cerebellar nuclei back to inferior olive via superior cerebellar peduncle, through the red nucleus and central tegmental tract) (Yanagisawa et al., 1999; Shaikh et al., 2010; Tilikete et al., 2011). There may be oscillations of the palate, larynx, and diaphragm. The main pathologic finding is hypertrophic degeneration of the inferior olivary nucleus, which leads to an aberrant synchronous discharge from enlarged neurons in contact with each other through electrotonic conduction mediated by gap junctions (De Zeeuw et al., 1998).

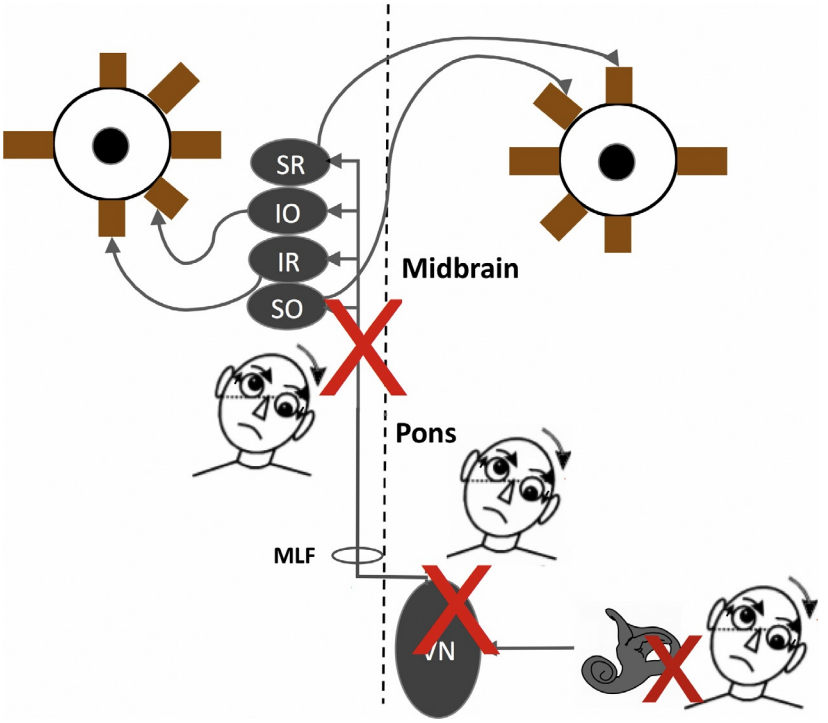

Fig. 8.2. Otolith projections ascend within the medial longitudinal fasciculus (MLF) to reach the ocular muscle nuclei within the midbrain. SR, superior rectus; IO, inferior oblique; IR, inferior rectus; SO, superior oblique. Projections from IR and IO cause depression and extorsion of the contralateral eye. Projections from SR and SO cross again and cause elevation and intorsion of the ipsilateral eye. Lesions affecting the otolith-ocular pathways (red X) result in the ocular tilt reaction characterized by skew (vertical misalignment of the eyes), head tilt, and ocular counter-roll with extorsion in the lower eye and intorsion in the higher eye. Peripheral vestibular lesions or involvement of the vestibular nucleus (VN) may result in ipsilateral head tilt with the lower eye on the side of the lesion. Since MLF projections cross, lesions of the pons or midbrain may result in contralateral head tilt with the elevated eye on the side of the lesion.

EYE MOVEMENT FINDINGS WITH LESIONS INVOLVING THE PONS

The pons houses the most rostral parts of the vestibular nuclei. Other major pontine structures involved in the control of eye movements include the abducens nucleus, the PPRF, and the MLF (Fig. 8.1B and Table 8.4). Diseases affecting the pons often cause disorders of horizontal gaze.

The rostral portion of the vestibular nucleus along with the adjacent dorsolateral brainstem and inferior lateral cerebellum is supplied by the anterior inferior cerebellar artery (AICA). The AICA is also the origin of the labyrinthine artery. Thus, ischemia in the AICA distribution can cause hearing loss and peripheral and central vestibular findings, such as a positive head impulse sign, spontaneous vestibular nystagmus, and gaze-evoked nystagmus (Table 8.3). In addition, there may be impaired smooth pursuit, horizontal head shaking-induced nystagmus (sometimes oppositely directed to the spontaneous nystagmus), or "perverted" head-shaking nystagmus, in which a vertical nystagmus is induced by horizontal head shaking (Huh et al., 2013). These findings point to cerebellar involvement in AICA syndrome. Similar patterns of abnormal head-shaking nystagmus are also reported in the PICA syndrome (Huh and Kim, 2011).

Lesions of the abducens nucleus cause a loss of horizontal gaze toward the same side. Both eyes are affected, because the abducens nucleus – in addition to lateral rectus motoneurons on the same side – contains internuclear neurons with projections through the opposite MLF to the opposite medial rectus subnucleus of the oculomotor nucleus. Vertical and vergence eye movements are spared. Lesions restricted to the abducens nucleus are rare and commonly affect adjacent structures, such as the PPRF, MLF, and the seventh cranial nerve. The PPRF contains neurons that project to the abducens nucleus on the same side and is important for horizontal saccade generation. Lesions of the PPRF cause a saccade palsy to the same side, but may involve all classes of conjugate eye movements when the most caudal portions of the PPRF are affected

Table 8.4

Key pontine structures with ocular motor function and associated clinical findings

Structure	Main ocular motor function	Clinical findings in lesions
Abducens nucleus*	Conjugate horizontal gaze	Ipsilateral conjugate horizontal gaze palsy
PPRF*	Horizontal saccade generation	Selective horizontal saccadic palsy with sparing of vergence and pursuit
MLF	Conjugate gaze and VOR	Internuclear ophthalmoplegia (INO) Convergence can be spared Skew deviation or ocular tilt reaction (OTR) Asymmetric vertical VOR better with upward slow phases Dissociated vertical-torsional nystagmus
CTT	Conveys information from cerebellum to inferior olive	Oculopalatal tremor
Vestibular nucleus (rostral part)	VOR	Spontaneous nystagmus Abnormal head impulse sign Skew deviation

*Isolated lesions not common.
PPRF, paramedian pontine reticular formation; MLF, medial longitudinal fasciculus; VOR, vestibulo-ocular reflex; CTT, central tegmental tract.

(Johnston and Sharpe, 1989). Vergence is spared so that adduction of the eyes with a near stimulus can be intact. Figure 8.3 shows the major connections for different types of horizontal eye movements. Isolated PPRF lesions are uncommon but can be a feature of the syndrome of selective saccadic palsy following cardiac surgery (Eggers et al., 2008). Bilateral pontine lesions may impair vertical eye movements, especially causing slowing of vertical saccades (Hanson et al., 1986).

As noted above, projections in the MLF carry commands for conjugate horizontal movements from abducens internuclear neurons to the medial rectus subnucleus on the opposite side. Lesions of the MLF cause INO with adduction weakness of the eye on the side of lesion and nystagmus of the abducting eye (i.e., dissociated nystagmus). Adduction is impaired with conjugate gaze but may be possible with convergence. The weakness may vary from a total paralysis to a paresis only evident as slowing of adducting saccades but with a full range of motion (adduction lag). Vestibular and smooth-pursuit signals from the vestibular nuclei for vertical eye movement are also carried through the MLF. Thus, INO is often accompanied by skew deviation and other elements of the OTR (Brodsky et al., 2006). The higher eye is usually on the side of the adduction weakness. Posterior-canal projections ascend completely within the MLF but anterior-canal projections have an extra-MLF component (Cremer et al., 1999). Therefore, the vertical VOR can be asymmetric in INO, for example, showing a greater abnormality with vertical head impulses in the plane of the posterior semicircular canal, within the labyrinth opposite to the MLF lesion. A dissociated vertical-torsional nystagmus may also occur, with the torsional component more pronounced in the eye on the side of the lesion and with the top pole beating toward the side of the lesion. The vertical component is usually upbeat and more pronounced in the eye on the side opposite to the lesion (Jeong et al., 2011). In spite of the adduction weakness most patients have normal ocular alignment, presumably due to sparing of convergence.

A lesion of the abducens nucleus or PPRF and adjacent MLF on one side of the brainstem causes a combined horizontal gaze palsy and INO. This is known as the "one-and-a-half syndrome," in which the only preserved conjugate horizontal eye movement is abduction of the eye opposite to the lesion (Frohman et al., 2008). Pontine lesions may also cause saccadic oscillations such as ocular flutter and opsoclonus due to a loss of the normal inhibitory control over inherently excitable saccadic burst neurons (Shaikh et al., 2008). Moreover, oculopalatal tremor may develop after involvement of the central tegmental tract (part of the Guillain–Mollaret triangle) as it traverses the pons.

EYE MOVEMENT FINDINGS WITH LESIONS INVOLVING THE CEREBELLUM

The cerebellum has a central role in the control of eye movements via both immediate "online" control, and long-term adaptive mechanisms that optimize ocular motor performance to meet the needs of the visual system. Distinct regions within the cerebellum are

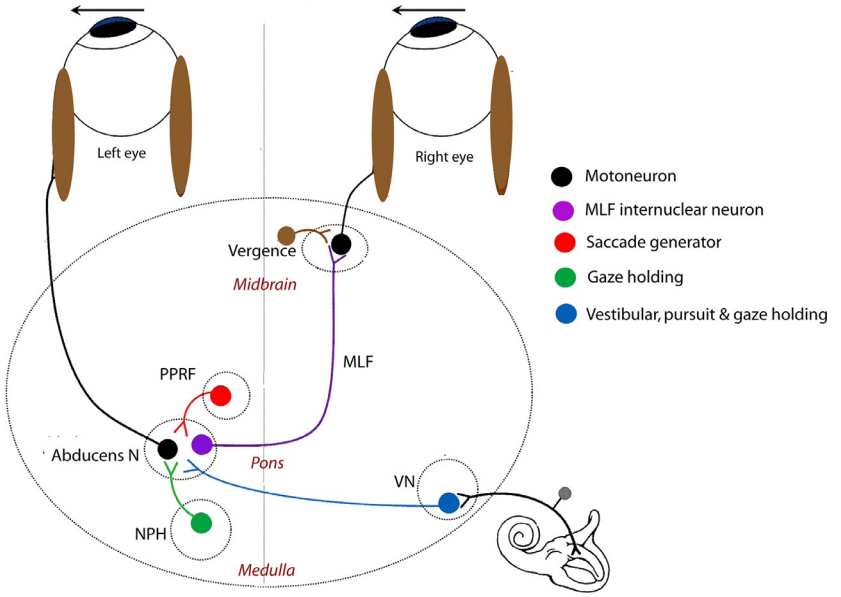

Fig. 8.3. Major connections mediating horizontal gaze. The abducens nucleus contains motoneurons that innervate the ipsilateral lateral rectus muscle, and internuclear neurons with ascending projections via the contralateral medial longitudinal fasciculus (MLF) to the medial rectus motoneurons in the contralateral oculomotor nucleus. Vergence inputs project directly to medial rectus motoneurons within the midbrain. Vestibular inputs project to the contralateral abducens nucleus to drive the horizontal vestibulo-ocular reflex. Saccadic inputs reach the abducens nucleus from the paramedian pontine reticular formation (PPRF). Eye position information reaches the abducens nucleus from neurons in the neural integrator networks within the ipsilateral nucleus prepositus hypoglossi (NPH) and contralateral medial vestibular nucleus (MVN). Pursuit inputs from the cerebellum project to the abducens nucleus via the vestibular nucleus. VN, vestibular nucleus. (Modified from Leigh and Zee, 2015, with permission from Oxford University Press.)

associated with specific aspects of the control of eye movements: (1) the flocculus and paraflocculus (cerebellar tonsil); (2) the nodulus and ventral uvula; and (3) the dorsal vermis (lobules VI and VII) and the underlying caudal fastigial nuclei (Fig. 8.4 and Table 8.5). The flocculus and paraflocculus along with the nodulus and uvula constitute the vestibulocerebellum. The cerebellar hemispheres also have a role in control of eye movements (Dieterich and Brandt, 2008).

Lesions of the vestibulocerebellum may cause gaze-holding deficits, downbeat nystagmus, impaired smooth pursuit with the head still, and defective VOR cancellation when the head and eyes together are tracking a moving object (Zee et al., 1981; Waterston et al., 1992). The flocculus/paraflocculus is critical for improving the function of the gaze-holding networks within the brainstem, and when lesioned, causes a gaze-evoked nystagmus. Lesions of the flocculus can cause an abnormal head impulse response (with head rotation away from the lesioned side) and spontaneous nystagmus (beating toward the side of the lesion), reflecting its close functional link to the vestibular system (Park et al., 2013).

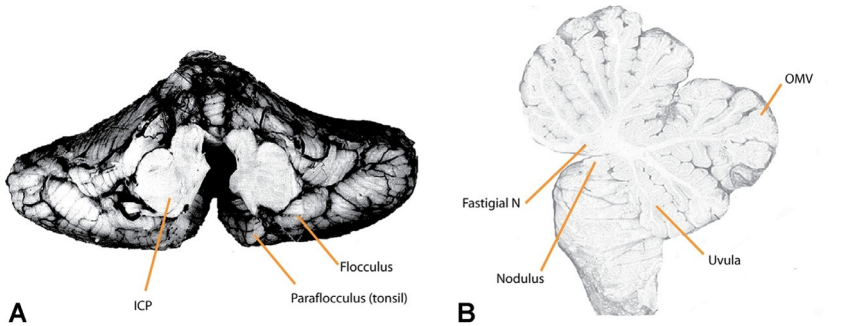

Fig. 8.4. Key structures with ocular motor function within the cerebellum. (**A**), Inferior view. (**B**), Sagittal view of vermis. OMV, ocular motor vermis; ICP, inferior cerebellar peduncle. (Modified Leigh and Zee, 2015, with permission from Oxford University Press.)

Table 8.5

Key regions within the cerebellum with ocular motor function and associated clinical findings

Anatomic region	Ocular motor function	Clinical findings with lesions
Nodulus/uvula and flocculus/paraflocculus (vestibulocerebellum)	r-VOR amplitude and direction r-VOR duration (velocity storage) t-VOR generation Smooth pursuit Gaze-holding	Occasional abnormal head impulse sign Skew deviation, alternating on lateral gaze Downbeat nystagmus Gaze-evoked nystagmus Rebound nystagmus Periodic alternating nystagmus Head shaking-induced nystagmus Impaired smooth pursuit
Dorsal vermis (OMV) Fastigial nucleus (FOR)	Saccade initiation, acceleration accuracy and termination Smooth pursuit initiation and termination	**OMV** Ipsilateral saccade hypometria and contralateral hypermetria of saccades (contrapulsion) Bilateral lesions lead to hypometric saccades Impaired smooth pursuit toward the side of the lesion **FOR*** Hypermetric saccades

*Functional unilateral FOR lesions do not occur, as projections from the FOR on each side immediately cross through the contralateral FOR before they exit the cerebellum.
r-VOR, rotational vestibulo-ocular reflex; t-VOR, translational vestibulo-ocular reflex; OMV, oculomotor vermis; FOR, fastigial region.

Another form of nystagmus typically seen with flocculus/paraflocculus lesions is rebound nystagmus, also tied to dysfunction of the gaze-holding networks (Bondar et al., 1984; Lin and Young, 1999). This form of nystagmus occurs when the eyes return to straight ahead after sustained eccentric gaze, and typically beats in the opposite direction of the gaze-evoked nystagmus. Rebound nystagmus is likely the result of a still intact adaptive mechanism within the brainstem that acts to null the centripetal drift of the gaze-evoked nystagmus. In some patients, a centripetally beating nystagmus develops on eccentric gaze (i.e., fast phases are directed inward), replacing the initial gaze-evoked nystagmus, in which fast phases are directed outward. This is also followed by rebound nystagmus.

Downbeat nystagmus is a distinctive feature of lesions involving the vestibulocerebellum (Kalla et al., 2006; Hüfner et al., 2007). It is more intense on lateral gaze and often increases with convergence (Wagner et al., 2008). Downbeat nystagmus has been linked to a cerebellar bias toward upward slow phases of VOR responses (especially from flocculus/paraflocculus) or to upward vertical smooth pursuit (Marti et al., 2008). Downbeat nystagmus also occurs with nodulus and uvular lesions, but its intensity does not change with vertical gaze position and it can be suppressed with visual fixation (Walker et al., 2009).

Lesions of the nodulus/uvula may also cause a horizontal nystagmus that changes direction every few minutes, known as periodic alternating nystagmus (Waespe et al., 1985). The nystagmus originates from a lack of inhibition by the cerebellum over the velocity storage mechanism within the vestibular nuclei, but the periodic change in direction is driven by the central mechanisms that attempt to null a persistent nystagmus (perhaps similar to the bias developed in rebound nystagmus). Lesions of the vestibulocerebellum may affect both the initiation of pursuit and sustained smooth tracking. Vertical pursuit is often impaired more in the downward direction, producing a marked up–down asymmetry (Marti et al., 2005; Leigh and Zee, 2015). Lesions of the nodulus/uvula especially impair vertical pursuit and the effects on horizontal smooth tracking are not as striking.

The vestibulocerebellum also has a crucial role in modifying long-term VOR performance. This may include adjusting the amplitude of VOR response (gain) or the direction of the slow phase relative to head movement (trajectory). Cerebellar lesions can cause an increase in the amplitude of the slow phase of the VOR that exceeds the size of the movement of the head. This hyperactive response is corrected by “back-up” saccades, as opposed to “catch-up” saccades in vestibular hypofunction (Kheradmand and Zee, 2011). The

response of the VOR to vertical head movements can be asymmetric in patients with cerebellar dysfunction, showing an up–down asymmetry similar to smooth pursuit (lower gain of downward VOR with upward head movement) (Shaikh et al., 2011). An abnormal trajectory of the slow phase of the VOR may be from an inappropriate upward component in response to horizontal head motion, producing a "cross-coupled" VOR. The nodulus/uvula receives otolith inputs both directly from the labyrinth and indirectly via the vestibular nuclei. It plays a role in the VOR response both to head translation and head tilt. Overall cerebellar lesions may profoundly impair the translational VOR, while the rotational VOR is still present, though its amplitude and direction may be wrong (Zee et al., 2002).

Lesions within the vestibulocerebellum generally do not affect saccades except for a brief unwanted postsaccadic drift, but lesions of the dorsal (oculomotor) vermis (OMV) or underlying fastigial (oculomotor) region (FOR) produce saccade dysmetria (Robinson et al., 1993; Takagi et al., 1998; Ye et al., 2010). The OMV plays an important role in controlling the dynamic properties (especially acceleration) and accuracy of eye movement during saccades. The FOR on each side facilitates the generation of saccades toward the opposite side and helps with the termination of saccades toward the same side. For example, the right FOR increases its activity before the beginning of the leftward saccades and toward the end of rightward saccades. Thus, impaired function in one FOR could result in saccade hypermetria toward the same side and hypometria toward the opposite side (i.e., saccade ipsipulsion). A unilateral structural FOR lesion, however, cannot occur, as the efferent projections from the FOR cross immediately and course through the contralateral FOR before leaving the cerebellum through the superior cerebellar peduncle (Voogd et al., 2012). The OMV behaves in a similar but reciprocal way through an inhibitory effect on the FOR. Therefore, the pattern of saccade dysmetria with lesions in the OMV is opposite of that with lesions in the FOR: saccade hypometria toward the same side and hypermetria toward the opposite side (i.e., saccade contrapulsion). More rostral lesions may produce saccade dysmetria by interrupting outputs from the FOR traversing the superior cerebellar peduncle. Because the FOR pathway crosses before entering the superior cerebellar peduncle, contrapulsion of saccades will be the abnormality. On the other hand, more caudal lesions in the medulla may interrupt inputs to the OMV running in the inferior cerebellar peduncle (as part of Wallenberg's syndrome) and cause saccade ipsipulsion equivalent to a unilateral FOR lesion.

The OMV and FOR also participate in the generation of pursuit eye movements (Robinson et al., 1997). They are more involved with the initiation and termination of pursuit, whereas the vestibulocerebellum is more concerned with pursuit during sustained tracking. The OMV and its underlying FOR have a similar functional contribution to control of pursuit as for the saccades. Thus, with experimental lesions of the FOR, pursuit away from the side of the lesion is impaired, while with lesions of the OMV, pursuit is impaired toward the same side.

Other types of eye movement abnormalities also occur with cerebellar dysfunction but are not yet linked to a discrete topography. Patients with cerebellar damage may have a skew deviation that often changes sense with horizontal eye position (alternating skew deviation) (Versino et al., 1996; Zee, 1996; Wong and Sharpe, 2005). The abducting eye is usually higher, producing a pattern of right hyperdeviation in right gaze and left hyperdeviation in left gaze. The source of skew might be an imbalance in otolith-ocular projections to the cerebellum. An esotropia also occurs in cerebellar disease, typically greater at distance and possibly due to impaired divergence (Versino et al., 1996; Wiest et al., 2001; Hüfner et al., 2014). Head shaking-induced nystagmus (sometimes perverted, oppositely directed to the spontaneous nystagmus, or with a quick, large-amplitude reversal) and positional nystagmus also have been reported in cerebellar patients (Kim et al., 2012a; Lee et al., 2014). Other common patterns are downbeat positional nystagmus and direction-changing, horizontal apogeotropic positional nystagmus (i.e., beating to the sky with one ear down). Finally, various forms of saccadic intrusions, such as square-wave jerks, macrosaccadic oscillations, and ocular flutter, may be associated with cerebellar pathologies and often degrade vision in these patients (Leigh and Zee, 2015).

EYE MOVEMENT FINDINGS WITH LESIONS INVOLVING THE MIDBRAIN

Midbrain structures are especially important for the control of vertical eye movements, including saccades and gaze-holding. These structures include the riMLF and the INC (Fig. 8.1C and Table 8.6). The riMLF is involved in generating vertical saccades and quick phases in vertical nystagmus, as well as the quick phases of torsional nystagmus produced during rotation of the head in the roll plane (lateral tilt). The INC plays a key role in holding eccentric vertical gaze. The INC projects to the ocular motoneurons, mainly via the posterior commissure.

Midbrain lesions can impair vertical saccades and produce vertical nystagmus due to impaired vertical gaze-holding. Abnormalities of the eyelids and pupils are also common with midbrain lesions. Vertical smooth pursuit and the vertical VOR may be involved if the MLF projections are affected where they course through the midbrain. Just as with lesions of the MLF in the pons, skew deviation can occur with lesions of the MLF in

Table 8.6

Key midbrain structures with ocular motor function and associated clinical findings

Structure	Main ocular motor function	Clinical findings with lesions
riMLF	Vertical saccade generation	Impaired vertical saccades Tonic cyclodeviation of the eyes toward the side of the lesion Loss of quick phases of the nystagmus during the head roll toward the side of the lesion Torsional nystagmus, top pole beating away from the side of the lesion
INC	Vertical gaze-holding	Vertical gaze-evoked nystagmus Ocular tilt reaction (OTR) Torsional nystagmus, top pole beating toward the side of the lesion
Posterior commissure*	Vertical gaze-holding	Impairment of vertical eye movements (especially upward) Vergence abnormalities (convergence paralysis or spasm) Convergence-retraction nystagmus Pathologic lid retraction Light-near dissociation of pupillary reflex
MLF	Conjugate gaze and VOR	Internuclear ophthalmoplegia (INO) Skew deviation or OTR: higher eye on the side of the lesion, but head tilt and ocular counter-roll away from the side of the lesion Asymmetrical vertical VOR better with upward slow phases Dissociated vertical-torsional nystagmus
Trochlear nucleus	Nucleus of trochlear (IV) cranial nerve	Affected eye higher and extorted (as opposed to skew deviation in which higher eye is intorted)
Oculomotor nucleus	Nucleus of oculomotor (III) cranial nerve	Affected eye lower Limited adduction Ptosis Dilated pupil

*Isolated lesions not common.
riMLF, rostral interstitial nucleus of the medial longitudinal fasciculus; INC, interstitial nucleus of Cajal; MLF, medial longitudinal fasciculus; VOR, vestibulo-ocular reflex.

the midbrain with the higher eye on the side of the lesion (Fig. 8.2). The skew deviation can be distinguished from a vertical deviation due to a trochlear nerve palsy based on the pattern of the torsional deviation of the eyes (Fig. 8.5). In skew deviation, the higher eye is intorted (top pole toward the nose), whereas, in trochlear nerve palsy, the higher eye is extorted (top pole away from the nose). This can be easily appreciated using the bedside bucket test of the subjective visual vertical of each eye alone (Zwergal et al., 2009). Oculomotor nerve palsy can also cause a vertical deviation along with weakness of adduction. In this case, however, the affected eye is usually lower (due to the spared superior oblique muscle), and ptosis or pupillary dilatation is often present.

Each riMLF contributes to both upward and downward saccades, but each generates torsional quick phases in just one direction; for example, the right riMLF is responsible for the quick phases with extorsion of the right eye and intorsion of the left eye. Thus, unilateral midbrain lesions affecting the riMLF on one side abolish ipsitorsional quick phases of the nystagmus during rotation of the head in the roll plane. There may also be a static cyclodeviation of the eyes toward the side of the lesion and a torsional nystagmus beating contralesionally (Leigh et al., 1993; Büttner et al., 2002; Helmchen et al., 2002). Bilateral lesions of the riMLF are more common, which is likely related to the pattern of their blood supply, often from a single perforating vessel (the artery of Percheron) supplying both sides. These lesions may cause loss of downward or all vertical saccades as well as torsional quick phases of nystagmus (Leigh and Zee, 2015). Lesions of the INC produce an OTR and, in contrast to

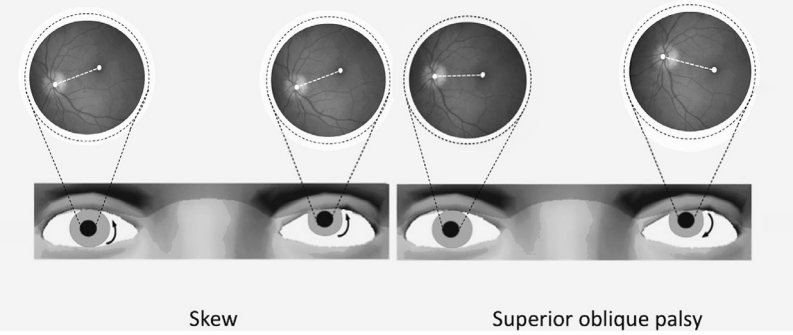

Fig. 8.5. Skew deviation versus trochlear (superior oblique) palsy. With skew deviation the higher eye is intorted (top pole toward the nose) and the lower eye is extorted. With trochlear nerve palsy, the higher eye is extorted (top pole away from the nose) and the lower eye shows no torsional deviation.

the lesions of the riMLF, cause ipsitorsional nystagmus with quick phases moving the top poles of the eyes toward the side of the lesion (Helmchen et al., 1996, 2002).

Lesions of the posterior commissure have the same effects on vertical gaze as INC lesions, but downward movements may be less affected than upward movements. The posterior commissure also carries projections that coordinate vertical eye and lid movements (Büttner-Ennever and Horn, 2014). Lesions of the posterior commissure usually affect all types of eye movements, although the vertical VOR and Bell's phenomenon (upward eye deviation during lid closure) can be spared. Lesions that affect the posterior commissure, such as tumors of the pineal gland or hydrocephalus, are often associated with other findings from involvement of adjacent structures that altogether are known as the dorsal midbrain, pretectal, or Parinaud's syndrome. The findings include downward gaze preference or the "setting sun" sign, a convergence paralysis but sometimes convergence spasm which may present as a pseudo-abducens palsy, and convergence retraction nystagmus (Ochs et al., 1979; Sand et al., 1986; Pullicino et al., 2000). Whipple's disease may also affect the midbrain, producing an unusual pattern of convergence–divergence nystagmus associated with a supranuclear vertical gaze palsy affecting vertical saccades (Leigh and Zee, 2015).

The superior cerebellar peduncle, located at the level of the midbrain, is usually affected by infarctions in the territory of the superior cerebellar artery, which also supplies superior parts of the cerebellar hemisphere (Table 8.3). A characteristic saccade abnormality with lesions of the superior cerebellar peduncle is overshoot of saccades away from the side of the lesion and undershoot toward the side of lesion. This finding is known as saccade contrapulsion, caused by interruption of outputs from the fastigial nucleus within the superior cerebellar peduncle (Voogd et al., 2012). Vertical saccades can be oblique, with a horizontal component away from the side of the lesion.

In conclusion, vestibular ocular function is closely linked to other classes of eye movements, with abnormalities that are often distinctive and can point to a specific pathophysiology or anatomic localization. The neural structures and pathways involved in generating different classes of eye movements or controlling various aspects of ocular motor function stretch out along the brainstem and cerebellum. The knowledge about this intricate network is the key to teasing apart ocular motor findings at the bedside and localizing central lesions from both topographic and functional perspectives.

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Chapter 9

The caloric irrigation test

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Abstract

The test of caloric thermal irrigations is one of the first tests for sensitivity of the peripheral vestibular systems dating to the late 1800s. This chapter reviews the various protocols that have been developed over the years using thermal irrigations to the external auditory canals. The discussion covers the interpretations of the protocols and makes recommendations for those protocols that have the best performance and at the same time are practical to perform. The primary utility of the caloric test has remained the same since its origination – the comparison of the relative sensitivity of the right versus left peripheral vestibular function. This is now known to be applicable to the horizontal canals without any significant influence of the vertical canals. The hypothesized physiology behind the thermal caloric proposed in the early 1900s has now, with the help of experiments in microgravity, been partially verified. Until recently this was the only test that could investigate one peripheral end organ at a time. It is still the one test that emphasizes the low-frequency function of the horizontal canals individually.

INTRODUCTION

The vestibulo-ocular reflex (VOR) is naturally stimulated with head movements of an angular nature in any direction. While rotational stimuli provide the natural means for activating the VOR, it is always exciting one side and inhibiting the other member of the functional pair on the opposite side. Therefore, a means for isolating one periphery at a time was sought. The thermal caloric irrigation test was first described by Robert Bárány (Bárány, 1907; Baloh, 2002). Along with the description of a test that could be used to assess the function of a single vestibular end organ at a time, Bárány also hypothesized as to the physiology behind the reaction obtained with the thermal irrigation. In 1914 he was awarded the Nobel Prize for his studies of the physiology of the vestibular system. While a significant breakthrough in the ability to evaluate clinically the peripheral vestibular system, and a test that has become a mainstay of the clinical assessment of the dizzy patient, it was clearly apparent that it has relevant limitations. Over the years, much work has been done to improve the protocols, to identify the most sensitive outcome parameter(s), and to define more precisely the utility of the test. This chapter provides detail on the protocols that are currently in use and the clinical interpretation of these studies in relationship to other studies of the peripheral and central vestibular/balance systems. We will limit the scope of this chapter to the essential discussions of the caloric test and its basic interpretations. The reader seeking more detailed discussion is referred to Barin (2015a, b).

Utility and limitations of the thermal caloric irrigation test

As indicated above, the primary utility of the thermal caloric test is the ability to isolate one peripheral vestibular apparatus for evaluation at a time. While there are now other studies that also isolate the portions of the peripheral vestibular system for evaluation, such as the ocular and cervical vestibular-evoked myogenic potential (VEMP) for the otolith organs and the video

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head impulse test (vHIT) for the semicircular canals, the caloric test allows for an estimate of the strength of the response that can be used without movement of the head. This allows for bedside evaluations of patients with restricted cervical range of motion. The thermal caloric test is also used for a gross measure of brainstem functioning in comatose patients. From the origination of the test, there have been several limitations to its performance.

The first primary limitation is that, even though the external stimulus that provides for the thermal change (water or air) is controlled as best as possible, there is significant variability in the response from person to person and between ears, occasionally in the same person. The management of this limitation was partially solved by comparing the responses from the left and right ears for a given irrigation and therefore, avoiding the use of the absolute responses from the individual ears (Jongkees equation: Jongkees and Philipszoon, 1964). Even though it has been shown that the Jongkees equation is nonlinear, and, hence, will underestimate the reduction in performance of a single periphery for a given loss of hair cells or afferent nerve fibers, an alternative proposed formula has not be widely accepted (Wexler et al., 1991).

A further issue is the implicit assumption of a normal distribution and unequal variance of the absolute responses to caloric irrigations. This is seen in the fact that the majority of laboratories will use a fixed value of percentage difference (usually 20–30%) as a criterion for an abnormal difference between the responsiveness in the right and left ears on a given patient. By having fixed criteria and using percentage difference, one can achieve the criteria with very little difference between the ears for absolute values when dealing with slow-component velocity responses of $<15°/s$, yet if working with responses that are $>40°/s$, much larger differences in the absolute values would be required to obtain the same percentage difference criteria. To the authors' knowledge, the assumption of the normal distribution with unequal variances has not been demonstrated. Therefore, one needs to use caution in reporting large percentage differences between ears when absolute values are small. The same would be true if the absolute values were large, as the percentage difference may understate the difference.

A second limitation is that the caloric evaluation is a test of principally the horizontal semicircular canal. Because of the anatomic arrangement of the vertical canals and their respective distance from the external auditory canal, there is minimal effect of a thermal stimulus in the external auditory canal on the vertical canals. Therefore, the response to the thermal gradient across the middle ear cleft into the vestibular labyrinth is predominantly from the horizontal canal (Aw et al., 1998).

The frequency range over which thermal caloric stimuli affect the horizontal canal is at the low end of the physiologic range that the semicircular canals can be stimulated. Since the thermal stimulus is a nonphysiologic stimulus, determination of the frequency response of the horizontal canal is estimated by modeling the temporal course of the caloric response as an equivalent sinusoidal rotation. Figure 9.1 shows the time course of eye

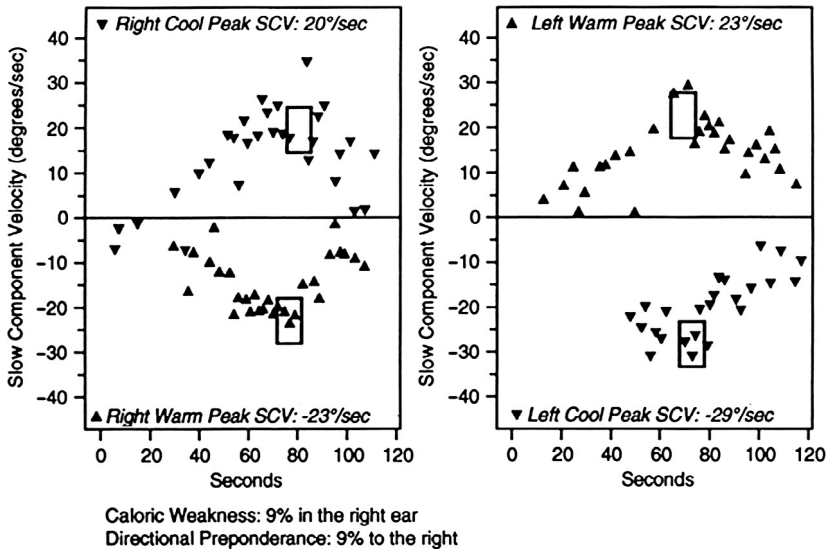

Fig. 9.1. Time course of the response of the slow-component velocities (SCV) for each of the right and left water irrigations. Each triangle represents the slow-phase velocity for a single component of the compensatory eye movement of the nystagmus trace that was generated for the respective irrigations. Individual SCVs for the warm irrigations are represented by the upward-turned triangles, while those for the cool irrigations are shown by the downward-turned triangles. The average maximum SCV is shown listed in each panel. The values for caloric weakness and directional preponderance are shown under the pods.

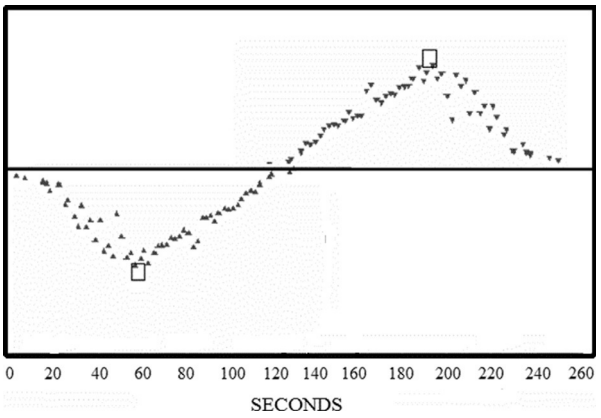

Fig. 9.2. Caloric "pod" as a half-cycle of a sine wave and then the same half-cycle inverted to create one full cycle. The period of the sine wave is ~240 seconds. The reciprocal of 240 seconds is ~0.004 Hz. Thus the caloric stimulus has an effective frequency of about 0.004 Hz.

movement response to four irrigations, warm and cool water on the right and left. The triangles indicate the nystagmus slow-phase eye velocity (SPEV) calculated for each of the repeated VOR responses produced with the respective irrigation. The slow-phase velocity (SPV) profile shows an increase and decrease in the eye velocity over time. If this is taken as the half-cycle of a rotational stimulus, one can calculate the frequency of the rotational stimulus needed to produce the noted SPV profile. This has been reported to be ~0.003 Hz (Fig. 9.2; Hamid et al., 1987). However, secondary to the individual variation in the ability of the thermal gradient to stimulate the horizontal canal, these estimates can vary from 0.003 to 0.008 Hz. The importance of this limitation in the caloric test is that, if the caloric test yields no response for warm, cool, or ice water for a given side, this does not mean that the periphery is completely without function. The test has only evaluated the very-low-frequency region of only the horizontal canal.

CALORIC IRRIGATION METHODS

Water has been the medium of choice to induce temperature change. It has been the preferred stimulus because water delivers more thermal energy secondary to higher specific heat than heated or cooled air. There are two methods that have been used to deliver water to the ear canal, described as open-loop or closed-loop systems. The term open-loop means that the water is infused in the ear canal and dribbles back out into a catch basin. This is the historically oldest form of caloric stimulation. As at the time of writing (March 2015), the closed-loop irrigation system is no longer commercially available and will not be discussed in this chapter.

An alternative to open- and closed-loop water irrigation systems is the use of air as the heat-conducting medium. Although this represents the most popular technique for delivery of heat to the ear canal, it is the least effective medium. Heated or cooled room air returns to ambient room temperature quickly after it leaves the irrigation tip. Over the years, attempts have been made to improve the effectiveness of air as a caloric stimulus by humidifying the air. The concept was that the moisture in humidified air would carry heat more effectively than dry air.

Caloric protocols/techniques

Calibration

The open-loop caloric irrigator consists of two thermostatically controlled "baths" that are heated to 30 °C (cool-water irrigations) and 44 °C (warm-water irrigations), which is roughly 7 °C (11 °F) above and below normal body temperature. The authors recommendthat distilled water be used to reduce the likelihood that debris in tap water, or algae, will foul the pump system. The water is delivered through a single hose that terminates in a disposable 1.5-inch polyethylene tip.

Calibration of the water caloric stimulus is much less complicated, and the required components far less expensive than instrumentation used for calibration of audiometric testing equipment. The critical components of a water caloric irrigation system are a laboratory-grade thermometer, i.e., that shows temperature in centigrade, a container that shows volume in cubic centimeters or milliliters, with a range that includes 250 cc, and a stopwatch. The objective is to deliver to the ear canal 250 mL of water, at 30 °C or 44 °C, over a 25–30-second interval. The stopwatch is used to measure the duration of the water flow. The container is used to measure the total volume of water delivered over the 25–30 seconds. The thermometer is used to ensure the temperature of the water flowing out of the tip of the irrigator is either 30 °C or 44 °C for cool and warm irrigations respectively. It would not make sense to measure water temperature and flow rate unless they could be varied. The electricity delivered to the coils in the caloric baths can be increased and decreased by adjusting a potentiometer on the face of the irrigator. Likewise, the flow rate for each bath can be adjusted with another control. Finally, the flow time can be adjusted to accommodate the specific needs of the protocol. The recommended parameters for open-loop water and air caloric irrigations, as recommended by the British Society of Audiology (BSA, 1999) and American National Standards Institute (ANSI, 1999), are shown in Table 9.1.

Table 9.1

Open- and closed-loop water and air caloric irrigation parameters recommended by the American National Standards Institute (ANSI), and British Standards Association (BSA) to generate equivalent responses

	Most commonly reported in literature			ANSI (1999) recommended			BSA (1999) recommended		
	Open-loop water	Air	Closed-loop water	Open-loop water	Air	Closed-loop water	Open-loop water	Air	Closed-loop water
Volume	250 mL	8 liters	–	200 ± 20 mL	X	350 ± 35 mL	250 ± 10 mL	8 ± 0.4 liters	X
Duration	30 seconds	60 seconds	45 seconds	40 ± 1 seconds	X	40 ± 1 seconds	30 seconds	60 seconds	X
Temperature (warm/cool)	44/30°/C	50/24°/C	46/28°/C	44/30 ± 0.5 °/C	X	44/27°/C	44/30 ± 0.4 °/C	50/24 ± 0.4 °/C	X

Adapted from Barin (2008a).

Initial considerations – medications

A common pretest consideration is how to manage patients who have been prescribed medications that have the potential to affect the caloric test. These common medications include, but are not limited to, vestibular suppressants, antiemetics, anxiolytics, and antidepressants. It is the recommendation of both the BSA and ANSI that these medications be discontinued for at least 48 hours prior to the time of the test. Although the face validity of such a policy is strong, it is often a difficult policy to implement. When given a list of medications or classes of medications, it is common for the lay public to be confused and, for the sake of convenience, often discontinue taking all medications 2 days prior to testing. This means that the potential exists for patients to discontinue abruptly antipsychotic, antiseizure, or cardiac medications. It is noteworthy that the authors are unaware of any systematic investigation of dose-related effects of the most common medications on quantitative measures of vestibular system function. We have conducted tests both with and without adherence to the ANSI recommendations and found no evidence of a trend for bilateral caloric response reductions to occur, i.e., the most common expected effect of suppressant medications.

Bithermal caloric testing

Alternate binaural bithermal caloric test (ABBT)

An otoscopic examination is conducted to ensure the ear canal is free of obstructions that could affect the quality of the irrigation. Additionally, immittance testing and/or acoustic absorbance testing is performed to ensure there is no perforation of the tympanic membrane (TM).

The technique of the ABBT has changed little since it was first described by Fitzgerald and Hallpike (1942). The original test was conducted with an open-loop caloric irrigator and with eyes open and fixated on a distant target, since electro-oculography (EOG) had not yet been developed. The measurement parameters were latency to the onset of nystagmus (measured in seconds), and duration of the response (also measured in seconds). Contemporary techniques employ either EOG or videooculographic (VOG) recording techniques to track eye position, both of which enable the examiner to record eye movements in a "vision-denied" condition, i.e., eye recordings are obtained with the patient in darkness.

Once either electrodes have been placed at the outer canthus of each eye for bitemporal EOG recording and above and below one eye to record vertical eye movements or infrared goggles have been placed over the eyes for VOG recording, the recording system is calibrated using automated routines. The patient's head is elevated to a 30° angle (related to supine) to place the horizontal canal into a vertical plane so that the horizontal canal is positioned optimally for stimulation.

The patient then is advised what to expect and the caloric irrigation begins. The irrigation is 30 seconds. The first beats of nystagmus occur approximately 30 seconds following the onset of the irrigation. The intensity of the nystagmus builds over another 30–45 seconds as the heat diffuses into the horizontal canal and diminishes as the heat leaves the horizontal semicircular canal. Throughout the postirrigation interval the patient is requested to participate in "alerting" exercises, e.g., counting up, out loud, by "serial 7 s" or naming animals that start with different letters of the alphabet, that make it difficult for patients to suppress caloric-induced nystagmus. It is prudent for clinicians to have many alerting exercises of varying difficulty to engage patients with differing educational backgrounds.

The nystagmus measurement variable of choice is average peak SPEV. This measurement variable is associated with the lowest coefficient of variation and greatest sensitivity to the presence of disease (Henriksson, 1956).

The method we employ is to conduct the irrigations in the following order: right warm or left warm, depending on which ear is suspect in unilateral impairment. That is,

the suspect ear is the first to be irrigated. Then, the other warm irrigation is performed followed by cool irrigations using the same order as that used for warm irrigations. If, after the two warm caloric irrigations, the monothermal asymmetry (calculated as ((right warm – left warm)/(right warm + left warm)) × 100) is 10% or less (Murnane et al., 2009), we terminate the caloric test and record a normal result.

Simultaneous binaural bithermal calorics

A variation on the ABBT was described by Brookler (1976, 2002). This modification was referred to as the simultaneous binaural bithermal caloric screening test. As the name suggests, the examiner irrigated both ears simultaneously with cool and then warm water using a closed-loop irrigation system. Since we are not discussing the closed-loop systems in this chapter, the reader is referred to the original articles for information on this technique.

Monothermal warm caloric screening test (MWCT)

General

The availability of a one-temperature caloric test would reduce the time required to complete vestibular function assessment and reduce any discomfort experienced during caloric testing. The time saved could be spent conducting other parts of the assessment, e.g., VEMP tests. Bernstein (1965) and Hart (1965) were the first to suggest that the ABBT might be replaced by a single-temperature caloric test. Barber et al. (1971) suggested that, if certain criteria were fulfilled, it might be possible to substitute a one-temperature, or "monothermal," caloric test for the ABBT. The authors reported a 7% false-negative rate when the interaural SPEV asymmetry was >25% and where each of the irrigations produced a caloric nystagmus SPEV of 11°/s or greater. The authors reported that the monothermal warm percent SPEV asymmetry was calculated as: (left warm SPEV – right warm SPEV)/ (left warm SPEV + right warm SPEV) × 100. There were no subsequent reports of the MWCT until the reports of Jacobson and colleagues (Jacobson and Means, 1985; Jacobson et al., 1995). The investigators reported again that the warm monothermal caloric test best predicted the result of the ABBT. They also reported that performance of the MWCT at identifying an abnormality improved if all electronystagmography/video-nystagmography subtests, including ocular motor system testing and positional and positioning testing, were normal. There followed a series of reports that either supported (Murnane et al., 2009) or failed to support (e.g., Keith et al., 1991) the use of the MWCT.

Becker (1979) reported a 14% false-negative rate and a 22% false-positive rate for the MWCT using the ABBT as the gold standard and the criteria for abnormality reported by Barber et al. There was 77% overall agreement between the percent asymmetry from the ABBT and the MWCT asymmetry. Jacobson and Means (1985) reported a false-negative rate of 5–6% using their own normative data to define a statistically significant monothermal warm caloric asymmetry (i.e., 30%) and failure criteria developed by Barber et al., i.e., maximum SPEV ≥11°/s, and Jacobson and Means, i.e., all tests normal leading up to the caloric test.

Most recently, Murnane and colleagues (2009), in an impressive, large, retrospective investigation reported that, using either 20% or 25% monothermal asymmetry as upper limits, the false-negative rate of the MWCT was 1–3%. What has been lost in the discussion of monothermal testing is the understanding that this is a screening test. The assumption is that there will be false-positive outcomes. However, those patients will simply receive the remaining cool caloric irrigations to complete the bithermal test. The time saved if the MWCT is normal can be used to complete other tests in the battery (e.g., vHIT, VEMP).

To summarize, it appears that the MWCT has a place in the vestibular function test battery. We recommend that caloric testing begin with warm-water irrigations. If the patient is unable or unwilling to complete the ABBT, and if the MWCT is normal, it is possible to predict with high accuracy that the ABBT would have been normal. It is our recommendation to complete the full ABBT whenever it is possible to do so.

Special protocols

Ice-water irrigation

When there is no response to the ABBT stimuli, either unilaterally or bilaterally, it is important for the clinician to attempt to obtain a response using an ice-water stimulus. The test is conducted in the vision-denied condition, with the patient in the semirecumbent position, and with the patient's head turned away from the test ear. The ear canal is filled with ice water (i.e., ~2 cc volume) and the patient maintains the head-turned position for 30 seconds. After 30 seconds the head is returned to the midline position and eye movement recordings commence with the patient performing alerting tasks. The clinician is seeking evidence that there is any residual low-frequency function. Where the impairment is believed to be bilateral and complete, e.g., where ototoxicity is believed to have occurred, in addition to ice-water caloric testing, it is advised to perform sinusoidal harmonic acceleration testing. There is much empiric

evidence to support this recommendation. It is possible to lose low-frequency sensitivity and yet have middle- and high-frequency function remain intact.

Reversal of position – supine / prone

In a sudden, unilateral, peripheral impairment the patient will generate a spontaneous nystagmus with the fast phase of the nystagmus "beating" toward the better-functioning ear. When a spontaneous nystagmus occurs it can be difficult to differentiate an ice-water caloric response from the pre-existing spontaneous nystagmus. The simple, but often awkward, solution is to turn the patient prone on the examination table at the peak of the ice-water response. When the patient's head position is inverted 180°, the direction of the hydrostatic pressure across the cupula on the affected side also reverses, as does the nystagmus direction. If the nystagmus direction does not reverse, then the response is the pre-existing spontaneous nystagmus that is direction-fixed. That is, turning the patient prone during the ice-water caloric will have no effect on the direction of the nystagmus if the response represents only the spontaneous nystagmus.

Vestibulo-ocular reflex suppression

Usually, at the peak of the caloric response, or shortly thereafter, the patient is asked to suppress the caloric-induced nystagmus by staring at a fixed target. The target may be as simple as the examiner's finger, or may be an illuminated LED on the inside surface of the video goggles. If the connections between the vestibulocerebellum and the vestibular nuclei (VN) are intact, the patient should be able to suppress the nystagmus by at least 50% (Alpert, 1974). In the presence of vermian lesions no such suppression can occur. Failure of this mechanism is referred to as "failure of fixation suppression," or, "impaired VOR suppression."

Time intervals between caloric irrigations

It is the recommendations of both ANSI (1999), and BSA (1999) that a minimum of 5 minutes elapse between irrigations. In practice, the clinician may take a more practical approach. That is, if the right cool caloric irrigation elicits a low-amplitude peak SPV, e.g., only 4°/s, it probably will be possible to conduct the left cool irrigation sooner than 5 minutes. Thus, it is recommended that the clinician examine the eyes for residual caloric nystagmus in the interval between irrigations. Seeing none, it probably is safe to conduct the next caloric irrigation.

Special considerations

Caloric testing in the presence of a tympanic membrane perforation

Water caloric irrigations are contraindicated where a breach in the continuity of the TM has occurred. In these instances air caloric testing is recommended. However, the presence of the unilateral perforation means that heat transmission to the ear with the perforation will be enhanced relative to the ear with the intact TM. This means that caloric ear asymmetry measures, e.g., measures of unilateral weakness and directional preponderance (DP), are invalid in the presence of a significant TM perforation. In fact, what has been reported is that the effect of the heated air for the warm caloric test blowing through the perforation is to, initially, evaporate moisture in the middle ear cavity, thus cooling the middle ear and causing an opposite-beating nystagmus than expected (Barber et al., 1978). Once the moisture in the middle ear cavity has evaporated, the nystagmus direction becomes as expected. In most cases, the information that is requested is whether the ear with the TM perforation has any function at all. In these instances, ear-specific information might be available with vHIT.

Caloric testing where the tympanic membrane is intact but the bony anatomy has been surgically modified

A slightly different situation exists where the TM is intact but the mastoid bone has been surgically modified. In these cases, heat transmission to the horizontal semicircular canal can occur with short latency and be of much larger magnitude than normal (Fig. 9.3). If caloric testing is to be conducted on the surgically modified ear, a 5-second irrigation should be conducted first. If heat transmission has been augmented by surgery, the caloric response will occur immediately and the magnitude will be great. If there is little or no response to the 5-second irrigation, the full 20-second (250 mL) irrigation can be conducted and the nystagmus response recorded.

Caloric testing for patients with severe hearing impairments

Communication before, during, and after the caloric irrigation is challenging where patients are severely or profoundly hearing-impaired. In these cases it is best to establish a code for when to begin conducting alerting tasks. For example, "When I tap you on the shoulder I would like for you to begin counting forward by 7 s and when I tap you on the shoulder again you can stop."

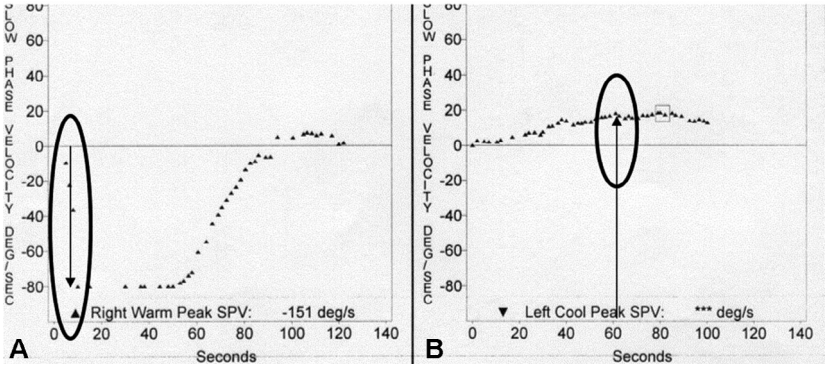

Fig. 9.3. Caloric velocity profile for a patient with a surgically modified ear (**A**: canal wall down mastoidectomy) compared to the opposite unmodified ear (**B**). Notice that within 5 seconds of the warm-water irrigation, the caloric velocity for the modified ear has reached the system upper limits.

Head-tilt caloric test

The reader should be aware that attempts have been made to extract more information from the caloric test by repositioning the head after the caloric irrigation has stopped (Aoki et al., 2009). The authors reported that, for right-ear irrigations, orientation of the patient's head 45° toward the irrigated ear activated the anterior semicircular canal and produced an upbeating nystagmus for cool irrigations and downbeating nystagmus for warm caloric irrigations. Alternately, orientation of the patient's head away from the irrigated ear following caloric irrigations produced a downbeating nystagmus for cool irrigations and upbeating nystagmus for warm caloric irrigations.

Although the investigators reported success with this technique, the present authors have not been able to reproduce their findings.

ANALYSIS AND INTERPRETATION

We will now turn our attention to the analysis of the responses produced by the caloric irrigations. We will follow the same order as was done in the section on the methods of performing the various protocols that can be used in clinical situations.

Bithermal protocol

The intensity of the induced nystagmus is described by its peak SPV. This is the part of the nystagmus that is the representation of the VOR, while the fast or quick phase of the nystagmus represents an involuntary saccade generated by the paramedian pontine reticular formation in the brainstem to reset the eye for its next compensatory movement in the direction opposite the horizontal canal being stimulated. In the computerized video-nystagmography/electronystagmography systems on the market today, this analysis takes place automatically. When done manually, this amounts to calculating the slope of the slow-phase portion of the nystagmus trace, with the units of the slope being degrees per second, i.e., the velocity of the eye during that movement. As shown in Figure 9.1, each SPV value can be displayed to present the velocity profile generated by the thermal irrigation, either stimulating or inhibiting the neural activity of the horizontal canal being irrigated. As characterization of the nystagmus response, a 10-second interval is used to calculate the average maximum SPV for the response to either the warm or cool irrigation, as shown in Figure 9.1.

Once the four SPV average maximums are calculated (as indicated in Figure 9.1), the values are inserted into the Jongkees equation:

$$\{[(RW+RC)-(LW+LC)]/(RW+RC+LW+LC)\} \times 100$$

where RW = right warm; LW = left warm; RC = right cool; LC = left cool.

The percentage value that results from this equation expresses the degree of "unilateral weakness" (UW %). The preferred term for this now is left or right reduced vestibular response. The primary purpose for this analysis is to determine if either the left or right horizontal canal is showing a reduced response, i.e., hypofunction compared to the other side. The other possible outcome of the analysis that uses the absolute value of SPV, for each of the irrigations, would be to determine if one or both of the peripheral responses is hyperactive or whether both are responding in a weakened manner and therefore are hypoactive.

A number of studies have been performed over the years to determine the upper limit for the percentage asymmetry and the majority suggest this should be set between 20% and 25%, as this is the range for two standard deviation values above the mean. For a complete

review of the pertinent studies that have established this range, the reader is referred to Barin (2015b). All labs have to determine how they want to set their normative cutoff within this range. As with the percentage differences, there are again a number of pertinent studies that Barin (2015b) reviews that have established the limits for the absolute value of the SPV. The recommendation is to use individual cutoff limits for each of the sums of the irrigations per ear.

Stockwell (1993) recommends that the total response from each ear needs to be less than 12 °/s to define bilateral hypofunction. For a cutoff regarding hyperactivity, it is suggested that both cool irrigations should exceed 50°/s or SPV be greater than 80°/s for each of the warm irrigations (Barber and Stockwell, 1980). Alternatively, it has been suggested by Jacobson and Newman (1993) that hyperactivity be defined as greater than 99°/s for the sum of the cool irrigations, and/or a total of 146°/s for the warm irrigations, and/or a total of 221°/s for the sum of all four irrigations (see Table 9.2 for a summary of these different recommendation).

Unilateral hypofunction occurs when the caloric asymmetry exceeds the 25% cutoff. Assuming that the technique was such that equal stimuli were used for the irrigations, this finding is used to identify the likely side of a vestibular lesion, i.e., the side of the hypofunction. The source for this finding can be any number of disorders, ranging from vestibular neuronitis, to other acquired pathologies of the vestibular labyrinth, to hereditary, trauma, or tumor processes (Barin, 2015b).

The magnitude of caloric-induced nystagmus is probably controlled by the cerebellar midline and VN. It follows that impairments that disable this suppressive function would produce a disinhibited or hyperactive response to vestibular stimulation (Fredrickson and Fernandez, 1964; Baloh et al., 1975). However, it might be rightly expected that, when it occurs, hyperactivity is a bilateral phenomenon. This means that hyperactivity should occur for both ear caloric irrigations. The phenomenon should be consistent and be present, along with abnormally increased VOR gain during rotational testing. It is the authors' experience that interpreting a caloric test as hyperactive without the same occurring on rotational testing invariably produces a false-positive outcome.

Lastly, the consideration of bilateral hypofunction is one of significant concern. This type of disorder, once verified with the findings of sinusoidal rotary chair (Shepard et al., 2015a) via abnormal phase lead independently of the rotary chair gain values, can be an explanation for general unsteadiness when walking in challenging situations such as poor lighting and / or an uneven surface and complaints of oscillopsia. Interestingly, there can be situations where the criteria for caloric bilateral weakness can be met, yet sinusoidal rotary chair is completely normal. In this case it is assumed that the caloric values obtained for that particular individual are normal. When one considers the significant variability in the use of the absolute values of the SPV, there would be those individuals who make up that lower portion of the normal distribution that falls below the typical two standard deviation limit set for normal responses.

Table 9.2

Normal reference ranges of common caloric variables

	Common	Alternative
Unilateral weakness (UW)	<25%	20–30%
Directional preponderance (DP)	<30%	25–50%
Gain asymmetry	<25%	30%
Bilateral weakness	Total of warm and cool irrigations from the right and left ears <12°/s	Sum of right- and left-ear responses <22–30°/s
Hyperactivity	Total SPV of right ear ≥140°/s Total SPV of left ear >140°/s	Individual peak SPV of right cool and left cool caloric > 50–60°/s Individual peak SPV of right warm and left warm caloric >80°/s
Fixation suppression	>60%	>50–70%

Adapted from Barin (2008b).
SPV, slow-phase velocity.

Directional preponderance and gain asymmetry

Directional preponderance

Two additional parameters can be obtained from the caloric analysis: DP and gain asymmetry (GA). These are both related to identifying a bias in the system that produces a stronger nystagmus response in the right-beating or left-beating direction compared to the other direction. The DP is, in the vast majority of cases, explained by a persistent, pre-existing, direction-fixed, spontaneous nystagmus that produces a baseline shift (Halmagyi et al., 2000). In this situation the nystagmus produced by a given irrigation has the spontaneous nystagmus added to it when in the same direction and subtracted from the response when in the opposite direction.

The formula for DP is a variation on the Jongkees equation, where the sum of the maximum average SPV for the irrigations that produce right-beating nystagmus is subtracted from the sum of the maximum average SPV that produce left-beating nystagmus, divided by the sum of the four irrigations, multiplied by 100, and expressed as a percentage.

$$\{[(LW+RC)-(LC+RW)]/(LW+RW+LC+RC)\} \times 100 = \%DP$$

where RW = right warm; LW = left warm; RC = right cool; LC = left cool.

The criterion for an abnormal DP varies more widely in the literature than reduced vestibular response, ranging from 19% to 30% (Barin, 2015b). Barin speculates that this may be a result of DP being made up of two components: the bias from pre-existing, direction-fixed nystagmus and an intrinsic strength differential in the production of nystagmus beating to the left versus to the right with the thermal irrigation component. The studies by Baloh and Honrubia (2001) and Jacobson and Newman (1993) suggest abnormal cutoffs of 30% and 27% respectively. The authors would suggest that laboratories should select a cutoff between 27% and 30% for DP.

The general interpretation is that an isolated DP is a nonlocalizing finding, as with spontaneous or positional nystagmus. However, to carry this one step further, if the study does not show abnormalities that could be suggestive of central vestibular system involvement (Eggers, 2015; Shepard et al., 2015b), then the DP indicates a bias in response to the thermal caloric that is more likely to be of a peripheral vestibular system asymmetry that has not been compensated for centrally. If a DP is seen with indications of central vestibular system involvement, a peripheral interpretation cannot be used and the bias is rather produced by a central system lesion.

Gain asymmetry

The last of the parameters that can be obtained from thermal caloric irrigations is GA. As mentioned above, this is the other component that goes into making up the overall value of DP. In effect, GA is the bias in percentage once all four of the irrigation responses are normalized for any baseline shift from pre-existing, direction-fixed nystagmus. Using the same formula for DP%, the baseline shift, if there is one, is subtracted from the nystagmus intensities in the same direction and added to the nystagmus intensities beating in the opposite direction.

For example, a patient diagnosed with likely vestibular neuronitis on the left has a persistent, spontaneous direction-fixed right-beating nystagmus noted only with visual fixation removed with average SPV of 8°/s. Water thermal caloric irrigations produced the following responses: RW = 38°/s – right-beating, LW = 8°/s – left-beating, RC = 20°/s – left-beating, LC = 12°/s – right-beating. The use of the equations for UW% and DP% return the following: UW = 49% left reduced vestibular response, DP = 28% right DP.

To calculate the GA, the right-beating 8°/s baseline would be subtracted from the irrigations that produced right beats (RW and LC) and added to the irrigations that produced left beats (LW and RC) and then the formula for DP% would be recalculated, this time, with the normalization, the GA = 1% to the right. Barin (2015b) suggests that the cutoff for GA should be set at 25% and therefore in this example there is no significant GA and hence no intrinsic bias, with the DP being the result of the uncompensated right-beating nystagmus.

Figure 9.4 shows the four caloric responses for a patient who has no baseline nystagmus, yet one still can see that the resultant DP is a significant 78.8% to the left. In this case the baseline average SPV = 0°/s and therefore the GA in this example is 78.8%. This implies that there is a significant intrinsic bias that produces the greater left-beating nystagmus than right-beating when the ears are stimulated with the thermal caloric irrigations. When investigated further, only a small percentage of patients with a clinically significant GA (values >25–30%) were shown to have central vestibular involvement (Halmagyi et al., 2000).

Normal thermal caloric irrigations

When the results of the caloric irrigation test is fully normal for all the parameters discussed above (unilateral weakness, DP, and GA), as well as having absolute values of SPV within the normal ranges listed above, what can be interpreted from that study? First, it needs to be recognized that the normal thermal caloric study does not equate to normally functioning peripheral vestibular systems. Recall from the discussion above that the caloric test primarily gives information about the horizontal semicircular canals and then only in the very-low-frequency response range over which the horizontal canals respond. Secondly, it is not known what level of peripheral asymmetry is required for a patient to start having symptoms. Therefore, an asymmetry that is less than 25% and persistent may be significant in the symptomatic patient but does not meet criteria for a significant asymmetry based on statistical studies.

Bilateral peripheral hypofunction

In the discussion above, criteria for determining bilateral peripheral hypofunction were presented, i.e., less than 12°/s SPV for each ear, based on the sum of the two

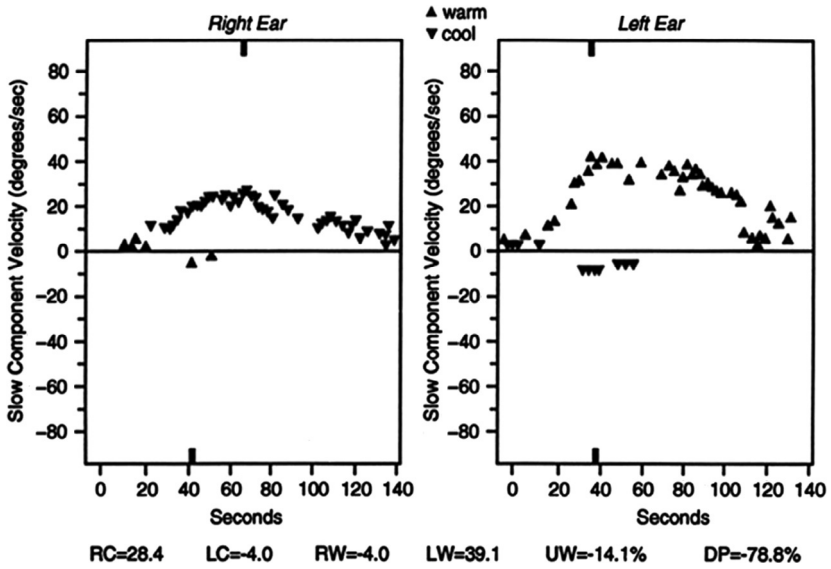

Fig. 9.4. See Figure 9.1 for description. In this figure the average maximum slow-component velocities (SCV) for each of the irrigations are listed across the bottom of the figure, along with the value for unilateral weakness (UW) and directional preponderance (DP). See the text for the case represented by this figure. RC, right cool; LC, left cool; RW, right warm; LW, left warm.

caloric irrigations. One needs to ask if a test of caloric responses meeting this criterion for warm and cool irrigations is both necessary and sufficient for defining the patient as having bilateral hypofunction.

Let's consider two examples to answer this question. The first example is a patient with four water caloric irrigations with absolute responses 6–8°/s maximum average SPV. The responses showed nystagmus in the correct directions for the temperature of irrigation used. Based on the criteria above, the patient could be a mild bilateral hypofunction. If these responses do represent bilateral peripheral pathology, then we would expect rotational chair responses to show an abnormally large phase lead of greater than 68° at 0.01 Hz, independent of the gain values (Shepard et al., 2015a). The phase lead in this patient was 82° at 0.01 Hz, but with fully normal rotational chair gain. Therefore, these findings would be consistent with a mild, low-frequency bilateral hypofunction.

In the second example, the patient had all four caloric responses of 7–10 °/s. Yet, the rotary chair findings are fully normal. In this case the lack of any abnormal phase lead would strongly argue against bilateral peripheral pathology. This patient's responsiveness on caloric irrigations was considered normal for this patient, even though below the lower limit for the two standard deviation range.

Therefore, the caloric test meeting criteria for bilateral hypofunction is necessary but not sufficient to define a patient with bilateral hypofunction when the caloric weaknesses are mild in degree, but below the cutoff values. An additional study such as a sinusoidal rotary chair or possibly the vHIT should be used to define the mild bilateral hypofunction.

Caloric dilemmas

These relate to a matter of interpretations rather than a change in the protocol of the test. The first relates to the ability to determine the extent of remaining function in a single peripheral vestibular system. The second is the determination of a peripheral vestibular system that shows simultaneous signs for both a paretic and irritative lesion.

Determination of unilateral peripheral vestibular function

Consider the following patient example. A 55-year-old male has been appropriately diagnosed with right-sided Ménière's disease. He had failed conservative treatment options and finally underwent a right-side vestibular nerve section. His hearing was preserved during the surgery, yet he had no more than 3 months without spontaneous events of vertigo. While the spells were milder than previous events, he was continuing with spontaneous spells of vertigo with auditory complaints on the right that would last for 1–3 hours. The managing surgeon's question is whether they were too conservative with the nerve section and did not cut enough of the vestibular portion of the eighth nerve, leaving residual neural function. The patient is sent for further vestibular testing with the question, "Is there any residual function on the right side?"

VEMP responses were absent on the right and the vHIT showed significantly reduced gain for all three canals on the right. Rotary chair showed abnormal phase and an appropriate asymmetry with normal gain, but one must remember that, with the left side functioning normally, these findings do not allow determination of residual function on the right. You are, therefore, left with the caloric as the only test for unilateral residual function. If the caloric study shows no apparent response, does that equate to no residual function? The answer is "no," remembering that the caloric is only effective for low-frequency evaluation of the peripheral horizontal-canal system. Caloric responses were obtained, giving the following results:

Pre-irrigation he had a 5°/s spontaneous left-beating response that had been seen throughout the rest of the video-nystagmography.

LW: 25°/s left beat
RW: 0°/s no response other than the 5°/s left beat at the first of the trace and then nothing throughout the remainder of the tracing – certainly no right beats
RC: 7°/s left beats
LC: 20°/s right beats
R ice-water irrigation over 15 seconds = 10°/s left beats

To this point, is it convincing that the right periphery is without any response? One could clearly argue that the use of the right ice-water irrigation produced a response that may be considered an increase over the spontaneous left-beating nystagmus noted prior to caloric irrigations. More convincing is the fact that the right warm had to generate right-beating nystagmus to a level of 5°/s in order to counter the spontaneous left-beating nystagmus seen at the start of the irrigation that reduced over a short interval.

The next step to help with the argument that residual function is noted would be to repeat the ice-water irrigation, but this time with the patient in a prone rather than supine position. In the prone position an ice-water irrigation to the right should now produce a right-beating nystagmus. When performed, the right ice-water irrigation in the prone position did provoke a 5°/s right-beating nystagmus. The overall impression of these results would be to suggest that there is low-frequency residual function remaining in the right peripheral system.

Paretic lesion with irritative status

Refer to Figure 9.5 for the following case example to introduce this interpretive dilemma that can occur with the caloric test results. The caloric results shown are from a 37-year-old female who is strongly suspected of Ménière's disease on the left. She has a low-frequency fluctuating, sensorineural hearing loss with spontaneous spells of vertigo lasting 2–4 hours with accompanying auditory symptoms on the left. She has no complaints of an auditory nature on the right. On her video-nystagmography she had a spontaneous left-beating nystagmus that was persistent at 7–10°/s SPV throughout the study with visual fixation removed. The caloric findings in Figure 9.5 show a 51% left reduced vestibular response along with a 32% left DP. Yet, one of the rules of nystagmus is that it always beats toward the more neurally active side. If that is the case, how can a side with

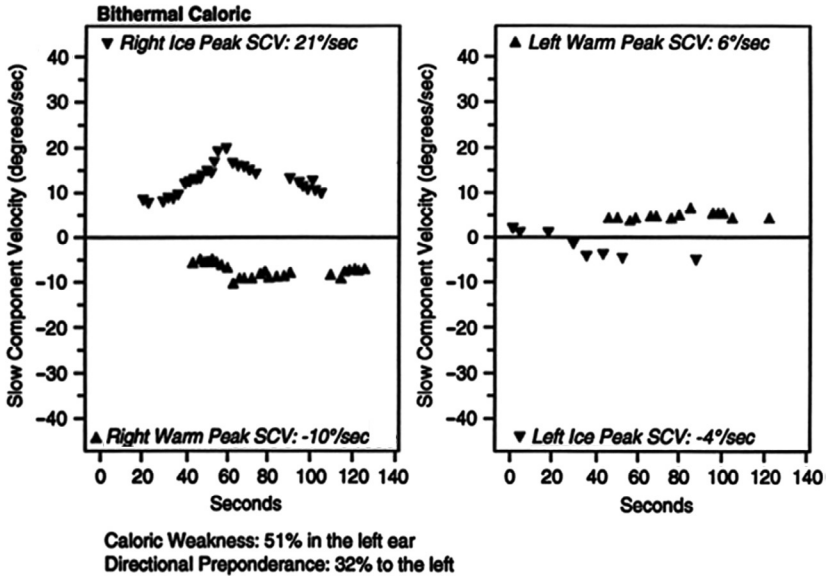

Fig. 9.5. See Figure 9.1 for description. In this figure the values for unilateral weakness (UW) and directional preponderance (DP) are shown at the bottom of the figure. See text for the case represented by this figure. SCV, slow-component velocity.

such a significant weakness result in spontaneous nystagmus throughout the video-nystagmography that is clearly represented by the DP to the weaker side?

The answer to this gets to the meaning of a caloric weakness. The concept of the caloric test is that it is not a measure of the intrinsic neural strength but the responsiveness to an exogenous stimulus. That being the case, the example above indicates that the intrinsic strength of the neural activity is stronger on the left side (the lesion side – an irritative lesion) given the spontaneous nystagmus beating toward that side. Yet, when the left ear is stimulated with warm and ice water, as shown in Figure 9.5, it has very minimal response to these stimuli compared to the responsiveness of the right side – hence the caloric "weakness" or, better phrased, the reduced vestibular response. The interpretation of this combination would be a left peripheral hypofunction (paretic lesion) in an irritative state.

EXPECTED CALORIC TEST RESULTS FROM ACUTE UNILATERAL DEAFFERENTATION THROUGH STATIC COMPENSATION

It is possible to predict the outcome of caloric testing following a profound unilateral peripheral impairment. These patients include those with superior vestibular neuritis and those who have had unilateral surgical destruction of the end organ or superior vestibular nerve. During phase 1 (acute phase) the patient will generate a destructive spontaneous nystagmus, where the fast phase beats toward the unaffected ear. This spontaneous nystagmus will result in a bias in the direction of the fast phase for all four caloric irrigations. Accordingly, it is common for patients to generate a DP toward the direction of the spontaneous nystagmus fast phase. It also is common for the patient not to generate caloric nystagmus for irrigations to the affected ear. Thus, in acute stages the patient is expected to generate a contralesional beating DP and an ipsilesional unilateral weakness.

For phase 2 (suppression phase), the connections between the structures at the cerebellar midline and the VN, and, the connections between the two VN are responsible for an attenuation of the tone in the contralesional VN. The attenuation of spontaneous activity in the VN on the unaffected side produces a low net difference in resting tone. The low net difference yields little, if any, spontaneous nystagmus in light, or in a vision-denied condition. At this point, the patient may show bilaterally reduced caloric responses. From a behavioral perspective, the patient may behave like someone who has sustained a permanent bilateral peripheral injury. Thus, at this stage the patient may complain, not so much of vertigo, but instead of gait ataxia and oscillopsia.

Once static compensation is complete, the spontaneous activity will continue to be absent in the ipsilesional end organ. However, there will be present tonic activity in the ipsilesional VN and it will be of a magnitude that is equal to that in the contralesional VN. At this point, central suppression has been withdrawn and spontaneous nystagmus is absent. However, the patient will, forever, generate a unilateral weakness on the affected side.

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Chapter 10

Vestibular-evoked myogenic potentials

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Abstract

The vestibular-evoked myogenic potential (VEMP) is a short-latency potential evoked through activation of vestibular receptors using sound or vibration. It is generated by modulated electromyographic signals either from the sternocleidomastoid muscle for the cervical VEMP (cVEMP) or the inferior oblique muscle for the ocular VEMP (oVEMP). These reflexes appear to originate from the otolith organs and thus complement existing methods of vestibular assessment, which are mainly based upon canal function. This review considers the basis, methodology, and current applications of the cVEMP and oVEMP in the assessment and diagnosis of vestibular disorders, both peripheral and central.

BACKGROUND

The vestibular apparatuses are small organs that lie within the temporal bone and are therefore inaccessible to direct assessment in human subjects. The potent motor effects arising from the labyrinths were first appreciated by means of local destruction (Camis, 1930), including the unexpected finding that destruction bilaterally had less severe effects than unilateral lesions. The vestibular end organs are innervated by the superior and inferior divisions of the vestibular nerve (Shute, 1951). The utricle, horizontal canal, and superior canal pass their afferents though the superior division of the nerve and the saccule and the posterior canal via the inferior division. A small portion of the saccular afferents travel via Voit's nerve to the superior division of the nerve (Gacek and Rasmussen, 1961). Vestibular afferent projections terminate either in the vestibular nuclei or the vestibulocerebellum (Wilson and Peterson, 1978). The major descending tracts are the medial and lateral vestibulospinal tracts, but projections to the spinal cord also travel through reticulospinal pathways (Goldberg et al., 2012).

Vestibular sound sensitivity

One notable early experiment indicating that the vestibular apparatus might respond to (loud) sounds was the work by von Békésy (1935). A variety of modulated tones were used in normal volunteers and an estimate made of the sound intensity required for vestibular activation – sound pressures of the order of 500–1000 dyn/cm^2 (equivalent to 128–134 dB sound pressure level (SPL)). Von Békésy showed the effect was not due to cochlear activation by transiently deafening his subjects.

In 1963 Bickford et al. reported a "new audio motor system in man" with latencies of 8–10 ms in cervical muscles that clearly distinguished it from startle (25 ms) and voluntary responses. This report importantly recognized that the short latency implied an oligosynaptic pathway, identified the dependence upon tonic muscle activation, and also that the response was of myogenic (electromyogram: EMG) origin. It soon became evident that the response required an intense click stimulus and did not depend upon the cochlea, thus an origin from vestibular

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receptors was proposed (Bickford et al., 1964; Cody et al., 1964). Although initially presented mainly as a source of unwanted artefact, Cody et al. (1964) recognized the possible value of the test and clearly distinguished its properties from those of the vertex response evoked by sound. Townsend and Cody (1971), based upon their clinical observations, proposed an origin from the saccule.

THE CERVICAL VESTIBULAR-EVOKED MYOGENIC POTENTIAL

Properties

Current interest in the vestibular-evoked myogenic potential (VEMP) as a clinical investigation was prompted by the report of Colebatch et al. (1994), who moved the recording site from the inion to the sternocleidomastoid (SCM). The SCM provided two advantages over the inion: the reflex could be unambiguously attributed to a single muscle and the laterality could be easily determined. The authors demonstrated that the response to loud clicks consisted of two separable parts: an early positive–negative response (p13-n23) which occurred ipsilaterally to the ear stimulated and a later, bilateral response. Studies of patients with selective auditory and vestibular lesions supported a vestibular origin for the p13-n23 potential. The high sound threshold and dependence upon tonic muscle activity, previously reported for the inion response, were confirmed. SCM activity was measured using full-wave rectified EMG activity and the change in amplitude of the p13-n23 response with the level of rectified EMG was remarkably linear. The findings of Young et al. (1977) of a lower threshold for saccular receptors to sound, as well as the report by Didier and Cazals (1989) of saccular afferents being excited by loud clicks in guinea pigs, led the authors to propose a saccular origin for the click-evoked cervical VEMPs (cVEMPs).

Once a reliable response pathway had been defined, other methods of stimulation were investigated. Clicks are not the only form of air-conducted (AC) sound that has been shown to be effective and tone bursts have been used to investigate the tuning of the response. Here caution is required, because the middle ear has potentially significant filtering effects and a distinction needs to be made between tuning of the middle-ear–vestibular system as distinct from the vestibular receptors themselves. Frequency tuning of the cVEMP has been widely studied (e.g., Murofushi et al., 1999; Todd et al., 2000; Welgampola and Colebatch, 2001a; Akin et al., 2003), with the conclusion that there is a broad range of tuning, maximal around 400–1000 Hz, for the combined middle-ear–vestibular response. Stimuli within this resonant frequency range are therefore more efficient and allow lower intensities to be used (Rosengren et al., 2009).

Soon afterward it was found that an impulsive bone-conducted (BC) stimulus, consisting of a tap to the forehead using a tendon hammer, also evoked short-latency, bilateral (for midline taps), positive–negative responses in SCM (Halmagyi et al., 1995). BC sound/vibration (Sheykholeslami et al., 2000) was subsequently also shown to be effective. These forms of stimulation were thought to have their greatest application in subjects with conductive hearing loss, a condition which severely attenuated AC-evoked VEMPs. Welgampola et al. (2003), using a standard B71 bone conductor applied just behind the ear, showed that vestibular-dependent, short-latency biphasic responses were evoked bilaterally, although larger ipsilaterally (Fig. 10.1). The hearing level (HL) intensity of the BC stimulus was much lower than for AC, implying that it was relatively more effective for vestibular receptors than for cochlear ones (Welgampola et al., 2003). A broadly similar tuning curve to AC stimulation was shown, but with low-frequency enhancement. The latter could not be fully defined due to limitations of the B71 output. More powerful minishakers, with wider-frequency responses than audiometric bone vibrators, have allowed more detailed investigation of frequency and impulsive effects. For example, using a minishaker, Todd et al. (2008a) showed enhancement of cVEMP amplitude with lower frequencies of stimulation, with a peak around 100 Hz. Although the tendon hammer has the virtue of simplicity, impulses derived from a minishaker or other vibrator have at least two clear advantages – the intensity can be altered without compromising the trigger and both positive (motor movements toward subject, like the tendon hammer) and negative (motor movement away from subject) forces can be applied, allowing the direction of acceleration to be independent of the side of application.

The final type of VEMP stimulus is galvanic vestibular stimulation (GVS) – a low-intensity DC current, which has been used for many years to activate the vestibular end organs (e.g., Fitzpatrick and Day, 2004). A current of about 4 mA, 2 ms long, and delivered to the mastoid process is effective and short enough to avoid severe stimulus artefact. However, a special subtraction technique (of traces with relaxed versus contracted SCM muscle) is required to remove the remaining stimulus artefact (Watson and Colebatch, 1998). Irregularly discharging afferents are most sensitive to this stimulus and the effect appears to be at the level of the nerve afferent ending (Goldberg et al., 1984). As the stimulus is thought to activate the nerve rather than the end organ, GVS-evoked VEMPs have been proposed to potentially distinguish between receptor and neural disorders (Murofushi et al., 2003), although this may not hold for chronic disorders, as permanent receptor damage may change the sensitivity of

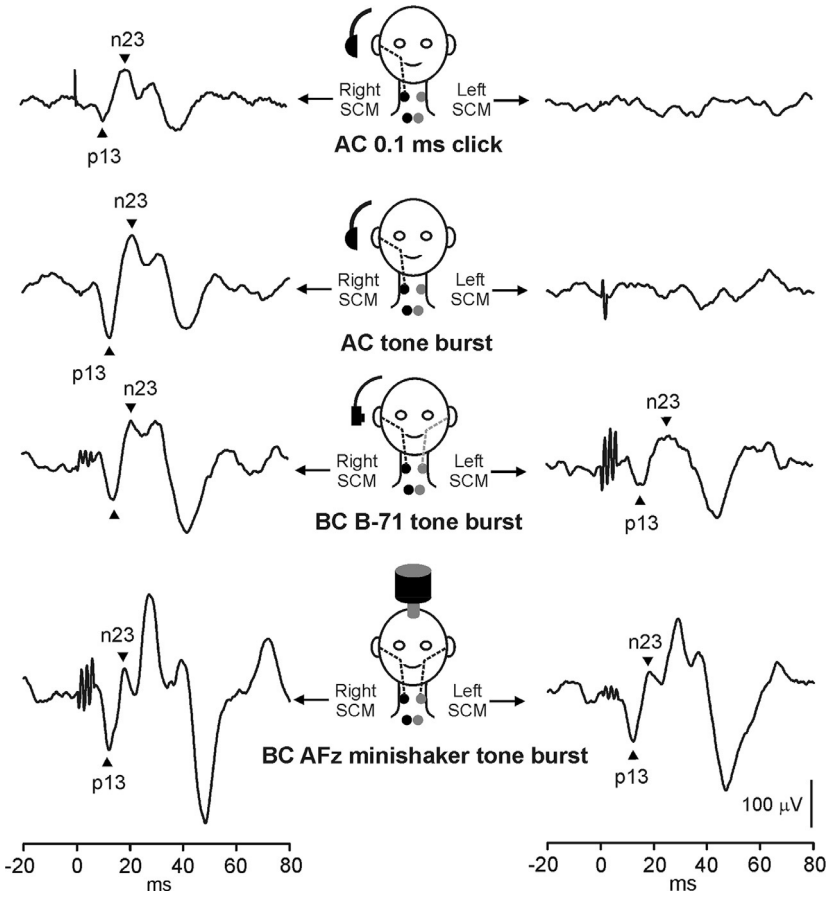

Fig. 10.1. Cervical vestibular-evoked myogenic potentials evoked by a series of four different stimuli. The two forms of air-conducted (AC) stimuli (upper two rows), 0.1 ms clicks and 500 Hz, 2 ms tone bursts at 105 dB $L_{Aeq,1s}$, delivered to the right ear, evoke p13-n23 responses ipsilateral to the stimulus. The B71 bone vibrator (third row) evokes bilateral p13-n23 responses, larger on the side of stimulation, due to spread of vibration bilaterally (stimulus: 500 Hz, 6 ms tone burst at 10 V peak). Midline bone vibration delivered to the forehead at AFz using a minishaker (bottom row) evokes similar-sized p13-n23 responses bilaterally (stimulus: 500 Hz, 6 ms tone burst at 20 V peak). $L_{Aeq,1s}$, equivalent A-weighted sound energy presented over 1 s; AFz, location midway between Fpz and Fz in the international 10-20 system; SCM, sternocleidomastoid.

the vestibular nerve. However, due to the technical difficulty involved, VEMPs evoked by GVS have not been widely adopted in clinical contexts.

Electrophysiologic investigations in animal preparations have confirmed the presence of a short-latency inhibitory postsynaptic potential in the motoneurones innervating the ipsilateral SCM in response to stimulation of both the saccule and the utricle (Kushiro et al., 1999). Only utricular afferents had an effect on the contralateral side, evoking an excitatory postsynaptic potential. The latter may explain the short-latency crossed negativity seen in some normal subjects in response to acoustic stimulation (Welgampola and Colebatch, 2001b). The pathway to the SCM motoneurones appears to be mediated through the medial vestibulospinal tract, similar to the projection from the semicircular canals (Fukushima et al., 1979; Fig. 10.2).

Population responses and age effects

Welgampola and Colebatch (2001b) carried out an early study on normative values for cVEMPs. They examined 70 healthy adults, aged 25–85 years old, using clicks, head taps, and galvanic-evoked responses. There was an increase in threshold for clicks with age, associated with a reduction in corrected amplitudes (peak-to-peak unrectified values divided by the mean rectified EMG), such that the average amplitude for the eighth decade was less than half that for the third. Over the age of 60, responses were sometimes absent on one side, but below 60 the range of amplitude asymmetry ratios was less than 35%. The mean p13 latency was 12.0 ms and showed no correlation with age. Tap-evoked cVEMPs were larger and fell more slowly with age, while galvanic-evoked reflexes also declined significantly with

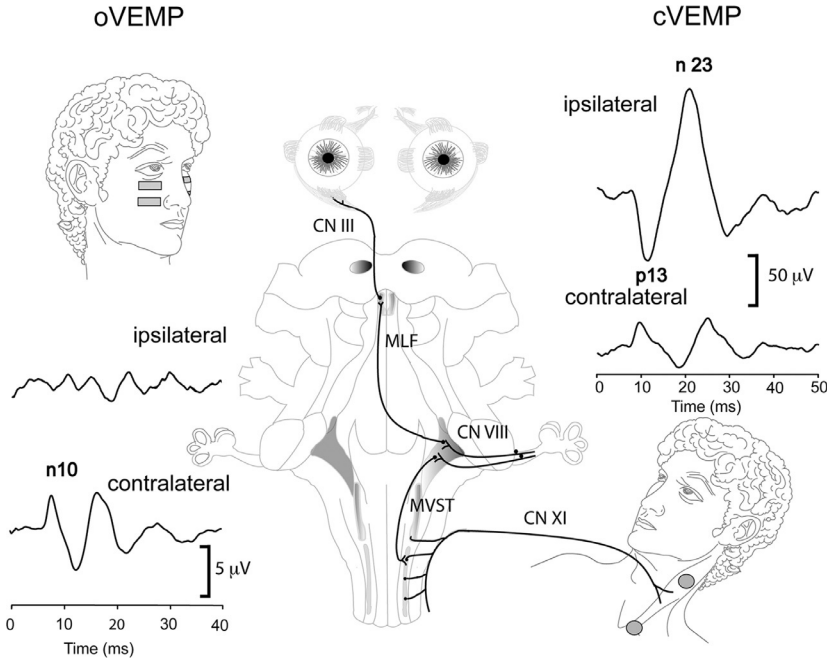

Fig. 10.2. The pathways thought to underlie the cervical vestibular-evoked myogenic potential (cVEMP) and ocular VEMP (oVEMP), following left-sided stimulation. For the cVEMP (right side of figure), the vestibular afferents synapse in the vestibular nucleus and descend via the medial vestibulospinal tract (MVST) to synapse on the motoneurons innervating the ipsilateral sternocleidomastoid, evoking the p13-n23 response. For the oVEMP (left side of figure), the fibers ascend from the nucleus and cross the midline, projecting to the contralateral inferior oblique muscle via the medial longitudinal fasciculus (MLF) and evoking the n10 response. CN, cranial nerve.

age. Welgampola and Colebatch proposed that degeneration of end organs and their afferents was likely to be the basis of the age-related changes. Subsequent studies have confirmed the significant age effects on cVEMP amplitude and threshold (Basta et al., 2007; Brantberg et al., 2007; Rosengren et al., 2011; Piker et al., 2013). Further analysis of age effects showed two patterns of change with age (Colebatch et al., 2013). Responses to high-frequency stimuli (AC or BC 500 Hz) fell significantly with age, on average by 12% per decade over the age of 20, while taps and impulsive stimuli, with low-frequency content (<100 Hz), were significantly less affected.

Limited information is available about the properties of VEMPs in infants and children, although testing is clearly possible with pediatric subjects and the technique appears to be well tolerated. Sheykholesami et al. (2005) demonstrated that it is possible to record cVEMPs from normal neonates and the cVEMP is present in children of all ages (Picciotti et al., 2007; Zhou et al., 2014). Specific techniques are needed to ensure adequate SCM activation in younger children, but the technique has proven useful in diagnosis (Zhou et al., 2014).

THE OCULAR VESTIBULAR-EVOKED MYOGENIC POTENTIAL

Properties

Stimulation of the vestibular organs with sound, vibration, or galvanic current produces small eye movements that can be measured with sensitive magnetic coil systems. The ocular VEMP (oVEMP) represents the electric activity produced by the extraocular muscles during this eye movement (Todd et al., 2007; Welgampola et al., 2009). Although the evoked eye movements are very small, oVEMPs can be recorded from surface electrodes placed close to the eyes, as the abrupt nature of the stimulus produces a synchronous change in muscle activity. Studies have shown that the surface potential is distinct from the corneoretinal dipole (Rosengren et al., 2005; Todd et al., 2007) and is not a blink reflex (Smulders et al., 2009). oVEMPs are generally largest when recorded from beneath the eyes during up-gaze (e.g., Govender et al., 2009), and under these conditions originate primarily from the inferior oblique (IO) muscle (Weber et al., 2012).

The oVEMP consists of a series of waves beginning at short latency. When a single ear is stimulated with AC

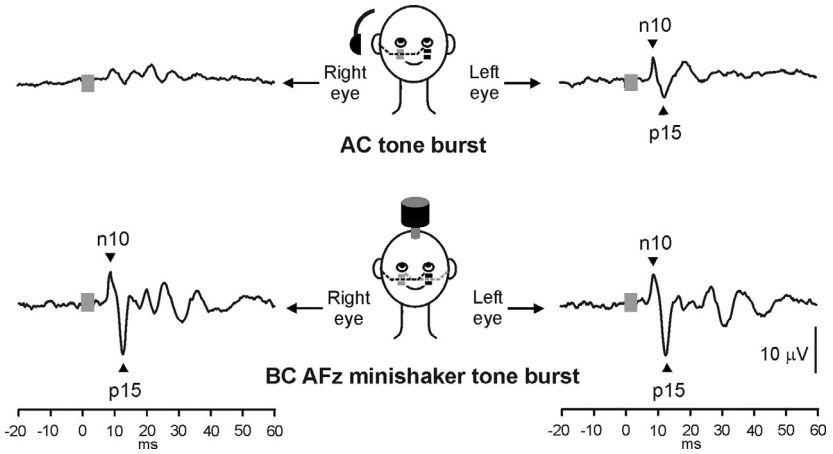

Fig. 10.3. Ocular vestibular-evoked myogenic potentials evoked by two commonly used stimuli. In the upper half the effect of a unilateral tone burst given to the right ear is shown (500 Hz, 2 ms, 105 dB L_{Aeq}). The stimulus evokes an n10 response from the opposite eye and a smaller ipsilateral response. In the lower half, a midline bone-conducted (BC) stimulus evokes bilateral n10 responses (500 Hz, 2 ms tone burst at 20 V peak), likely to be the superimposition of both ipsilateral and contralateral effects. AC, air-conducted.

sound, the clearest response is recorded under the contralateral eye, suggesting a predominantly contralateral projection (Chihara et al., 2007). The response begins at approximately 7 ms and its first peak occurs at approximately 10 ms (Fig. 10.3). The polarity of the initial peak is negative for most of the commonly used vestibular stimuli, and the response is therefore termed n10. The n10 is followed by a positive peak at approximately 15 ms (p15) and further negative and positive peaks at intervals of about 5 ms. Recordings from patients with bilateral vestibular loss usually show complete absence of responses, suggesting that all of the peaks are vestibular-dependent (Todd et al., 2009). In patients with unilateral vestibular loss, activation of both ears simultaneously with BC stimulation evokes an n10 response predominantly under the eye opposite the intact ear, again indicating a contralateral projection (Iwasaki et al., 2007). There is often a small residual negativity under the ipsilateral eye (Todd et al., 2007), possibly originating from nearby extraocular muscles, and the later potentials are also usually preserved in these patients (Iwasaki et al., 2007).

The properties of the oVEMP change with gaze direction, most likely due to changing contributions from the extraocular muscles. As myogenic potentials spread widely around the head (Rosengren et al., 2005; Todd et al., 2008b), a bipolar montage, with electrodes placed beneath the eyes, is used to provide a more selective recording from the inferior extraocular muscles (Todd et al., 2007). Using this electrode montage, the n10-p15 response is largest during superomedial gaze (Chihara et al., 2007; Govender et al., 2009). oVEMPs can also be recorded with gaze depression (Govender et al., 2009), but are smaller, have prolonged latency, and may originate predominantly in the inferior rectus (IR) muscle instead of the IO (Rosengren et al., 2013). Likewise, oVEMPs have also been recorded with closed eyes (Chihara et al., 2007; Huang et al., 2012), but prevalence is low and the myogenic origin is probably mixed.

oVEMPs can be recorded in patients of all ages, including children (Chou et al., 2012) and the elderly (Iwasaki et al., 2008). However, like the cVEMP, oVEMP responses tend to become smaller and less prevalent with increasing age (e.g., Iwasaki et al., 2008; Tseng et al., 2010; Rosengren et al., 2011; Agrawal et al., 2012; Chang et al., 2012). This is a particular problem for oVEMPs evoked by AC sound, as they are typically smaller than those evoked by BC stimulation, leading to a high rate of absent responses in normal older subjects (Piker et al., 2011) and reducing the clinical utility of the AC reflex. Age effects have also been shown for oVEMPs evoked by BC stimulation, but appear to depend upon the type of stimulus. oVEMPs evoked by tendon hammer taps and low-frequency pulses delivered with a minishaker are relatively robust against age effects (Nguyen et al., 2010; Colebatch et al., 2013), while those evoked by sine waves and short-duration square waves appear to be more susceptible (Iwasaki et al., 2008; Chang et al., 2012). Effects of age have also been found on oVEMP latency (i.e., prolonged peak latency with increasing age: Rosengren et al., 2011; Chang et al., 2012), but not symmetry (Tseng et al., 2010; Piker et al., 2011). Gender does not appear to affect oVEMPs evoked by sound or vibration (Piker et al., 2011; Rosengren et al., 2011).

Similarly to the cVEMP, the mean preferred stimulus frequency for the oVEMP evoked by AC sound is around 500–1000 Hz (Chihara et al., 2009; Park et al., 2010; Murnane et al., 2011), while for individuals the best frequency can vary widely, between approximately 150 and 1500 Hz (Lewis et al., 2010; Zhang et al., 2011a). Overall, tuning is similar for both the oVEMP and the cVEMP, though a recent study reported concordance of only 43%, with discordant tuning nearly always resulting in higher preferred frequencies for the oVEMP (Taylor et al., 2012a). Fewer studies have examined the preferred stimulus frequency for BC oVEMP stimuli, although many clinicians use tendon hammers or square-wave pulses rather than sine waves. The available studies suggest that the best frequency is somewhat lower than that for AC sound, around 100–250 Hz (Chihara et al., 2009; Todd et al., 2009; Donnellan et al., 2010; Zhang et al., 2012a).

The site of stimulation and stimulus polarity have significant effects on the properties of the BC oVEMP. In particular, altering the direction of head acceleration has profound effects on the reflexes (e.g., Todd et al., 2008a; Lin et al., 2009; Holmeslet et al., 2011; Jombik et al., 2011). Several studies have examined the effects of gravity on the oVEMP, by altering the orientation of the head and body during the test in either the pitch (Govender et al., 2009; Wang et al., 2014) or roll axes (Iwasaki et al., 2012; Gürkov and Kantner, 2013; Taylor et al., 2014); however, there is currently no consensus about potential gravity effects.

ELECTROGENESIS OF VEMPs

The cVEMP is produced by a brief inhibition of the ipsilateral SCM muscle. Colebatch and Rothwell (2004) recorded the activity of single motor units in normal human volunteers and found a reduction or gap in firing in the SCM ipsilateral to the AC sound or cathodal galvanic stimulus. The inhibition occurred at a similarly short latency (~12 ms) to the surface p13 peak and had a very short duration (~3–4 ms). Although the cVEMP recorded at the surface is biphasic, both the p13 and n23 components are likely to be produced by the single period of muscle inhibition (Fig. 10.4), as both potentials are correlated with the magnitude and duration of the initial motor unit inhibition, rather than any increase or recovery of activity (Rosengren et al., 2015). In addition, mapping studies have shown that the p13 response behaves like a traveling wave, i.e., the latency of the p13 increases with increasing distance of the recording electrode from the motor point, and thus the potential represents the progressive spread of inhibition of motor unit firing along the muscle toward the tendons (Colebatch, 2012). In contrast, the n23 response behaves more like a standing wave, i.e., the latency

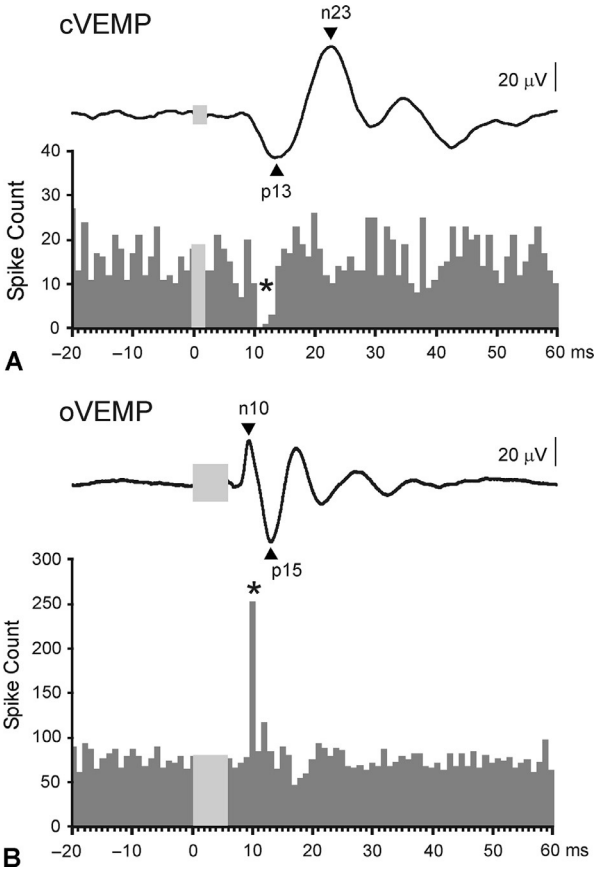

Fig. 10.4. Single motor unit histograms for (**A**) the cervical vestibular-evoked myogenic potential (cVEMP) and (**B**) ocular VEMP (oVEMP). (**A**) The activity of a single motor unit was recorded from within the ipsilateral sternocleidomastoid muscle, while the cVEMP surface response was recorded simultaneously (stimulus: air-conducted tone burst of 500 Hz, 2 ms, 105 dB L_{Aeq}). The asterisk shows a significant decrease in activity, indicating that the cVEMP is caused by an inhibition of the muscle. (**B**) The activity of multiple motor units recorded simultaneously from the inferior oblique muscle during neutral gaze is shown (stimulus: bone-conducted tone burst of 500 Hz, 4 ms, 20 V peak). The accompanying oVEMP surface response was recorded separately during maximal upgaze. The asterisk shows a significant increase in motor unit activity, indicating that the oVEMP is caused by an excitation of the muscle. Light gray areas are periods of stimulus artefact. (Both sets of data from SM Rosengren and KP Weber, unpublished.)

remains relatively constant as the electrode is moved and the surface potential is mainly produced by the momentary dipole generated by the arrival of the inhibitory response at the muscle–tendon junction (Lateva et al., 1996).

For the oVEMP, surface recordings under different stimulation and recording conditions suggested an origin predominantly in the IO muscle contralateral to the stimulated ear. Excitation of the IO muscle as the basis of the

oVEMP was recently confirmed by Weber et al. (2012), who recorded single motor unit responses evoked by AC and BC sound in the IO and IR muscles of normal subjects. The earliest responses in IO were excitatory and occurred at 10.5 and 13.3 ms for BC and AC sound, respectively. While the IR was also excited by the BC stimulus, responses in this muscle were delayed by 4–5 ms compared to the IO, suggesting that the muscles were reciprocally active and that the n10 surface response did not come from the IR muscle. The temporal profile of the IO motor unit response closely matched that of the surface oVEMP recorded during up-gaze, suggesting that, while contributions from the other extraocular muscles could not be ruled out, the oVEMP recorded beneath the eyes during up-gaze was primarily produced by an excitation of the IO muscle.

AFFERENTS RESPONSIBLE FOR VEMPs

There are several lines of evidence about which vestibular afferents are responsible for cVEMPs and oVEMPs. These include animal studies of the effects of AC and BC stimulation on vestibular afferents and the projections to the neck and eye muscles, and human studies of the effects of selective nerve lesions on the reflexes. Cautious interpretation is required, due to the different species and methods used in animal studies and the possibility of incomplete lesions in human clinical studies.

Studies have suggested that the otoliths, and the saccule in particular, are especially sensitive to AC sound. Young et al. (1977) showed in squirrel monkeys that all of the vestibular organs could be activated by AC sound, though the saccule had the lowest threshold. Subsequent studies also demonstrated greater activation of otolith fibers by AC sound and have confirmed that it is primarily the irregular vestibular afferents that are affected (McCue and Guinan, 1994; Murofushi and Curthoys, 1997; Carey et al., 2004; Zhu et al., 2011, 2014; Curthoys et al., 2012). However, there is disagreement about the extent to which semicircular canal afferents are activated. Curthoys et al. (2012) reported that otolith afferents were much more sensitive than canal afferents, while Zhu et al. (2011, 2014) described a graded relationship, with the saccule being most sensitive and the posterior canal least sensitive (saccule > utricle > anterior canal > horizontal canal > posterior canal). Despite this debate about the normal ear in animals, there is clear evidence that semicircular canal afferents are activated by AC sound in the presence of an experimental third labyrinthine window (e.g., Carey et al., 2004). There is less animal evidence about the sensitivity of the vestibular organs to BC stimulation. Young et al. (1977) reported that the otoliths were less sensitive than the semicircular canals to skull vibration. In contrast, Curthoys et al. (2006) showed that the irregular fibers of both otoliths were preferentially activated, and vibration-sensitive afferents could be traced to both otoliths (Curthoys et al., 2012). As a result of the above evidence, VEMPs are considered to originate primarily in the otolith organs.

cVEMP origins

cVEMPs evoked by AC sound are thought to originate mainly in the saccule because of the higher sound sensitivity of the saccule compared to the other organs, combined with evidence from animal studies about the projections to the SCM neck muscles as well as studies in human subjects, including both normal subjects and patients with selective lesions of the superior and inferior nerves. All three semicircular canals and the utricle inhibit the ipsilateral SCM and excite the contralateral SCM, while saccular afferents inhibit the ipsilateral SCM, but have no known projection to the contralateral side (Kushiro et al., 1999; Uchino and Kushiro, 2011). As the cVEMP evoked by AC sound is usually a strictly unilateral inhibition of the ipsilateral SCM muscle, this is consistent with an origin from the saccule. However, the ipsilateral cVEMP is sometimes accompanied by a crossed excitatory response in the opposite SCM, albeit with smaller amplitude and higher threshold (Welgampola and Colebatch, 2001b). Based on the known SCM projections, this suggests that other organs sometimes contribute at higher intensities. As the otoliths are more sensitive to AC sound, the utricle is the most likely origin of this “crossed response.” However, in patients with third-window syndromes, the anterior semicircular afferents are thought to contribute to the observed large crossed responses (Watson et al., 2000; Rosengren et al., 2008). AC cVEMPs are usually preserved in patients with vestibular neuritis, which often selectively affects the superior nerve portion (e.g., Govender et al., 2011). Sheykholeslami and Kaga (2002) reported 7 patients with anomalies of semicircular canals who all had normal AC cVEMPs, supporting an otolith origin.

cVEMPs evoked by BC vibration or head taps are also thought to originate predominantly in the otolith organs. However, the relative contributions from the saccule and utricle have not been determined and may depend upon properties of the BC stimulus. As BC stimuli act directly on the vestibular hair cells through linear acceleration of the head and soft tissues within the skull, VEMPs evoked by BC stimulation are bilateral and highly dependent upon the direction of acceleration. In patients with complete vestibular loss in one ear, cVEMPs evoked by BC impulsive stimuli are often bilateral, with opposite polarity on the affected side, suggesting that the remaining

utricle might make a larger contribution, as the saccule does not have bilateral projections to the SCM muscle (Brantberg et al., 2003).

oVEMP origins

oVEMPs evoked by both AC and BC stimulation are thought to originate in otolith afferents in the superior vestibular nerve. This is because patient studies show that oVEMPs are absent or reduced in patients thought to have relatively selective lesions of the superior nerve caused by vestibular neuritis (Iwasaki et al., 2009; Curthoys et al., 2011; Govender et al., 2011; Shin et al., 2012). Stimulation of utricular afferents activates the IO muscle in cats, but it is not clear if this projection is ipsilateral (Uchino et al., 1996) or contralateral (Suzuki et al., 1969). In contrast, although sacculo-ocular projections have been demonstrated (e.g., Chan et al., 1977; Goto et al., 2004), they have been shown to be relatively weak (Isu et al., 2000). All utricular afferents, but only some afferents from the anterior region of the saccule, course through the superior vestibular nerve, suggesting that utricular afferents are likely to provide the dominant input for the oVEMP. However, it is possible that the saccule also contributes to the oVEMP, or even provides the dominant input with some types of stimuli, as the two otoliths are preferentially activated by linear acceleration in different directions (Fernández and Goldberg, 1976).

A recent study of patients with vestibular neuritis studied with AC and high- and low-frequency BC stimuli (Govender et al., 2015) was able to estimate the upper limits of contributions of saccular and utricular afferents to cVEMPs and oVEMPs. Their calculations showed that the AC 500 Hz cVEMP was predominantly of saccular origin, that BC 500 Hz and AC 500 Hz activated similar populations of otolith fibers, and impulsive stimuli activated utricular fibers most strongly. The oVEMP was predominantly of utricular origin for all stimuli.

MECHANISM AND PHYSIOLOGIC ROLE

Von Békésy (1935) proposed that eddy vortices might be the mechanism by which loud sound stimulated vestibular receptors, but the mechanism of action of AC stimuli is still not clear. The reduced thresholds for VEMPs in patients with large vestibular aqueducts (Sheykholeslami et al., 2004; Merchant et al., 2007; Taylor et al., 2012b) raises the possibility that the normal sound sensitivity of vestibular afferents is in part a consequence of sound energy traveling from the oval window to the vestibular aqueduct (Merchant et al., 2007). McCue and Guinan (1994) confirmed the presence of polarization of responses to clicks as well as characteristic tuning curves. They subsequently proposed (McCue and Guinan, 1995) that the most likely candidates for this resonance were either the otolithic membrane (cf. Todd et al., 2009) or the sensory epithelium. BC stimulation of the otolith organs is likely to work through inertial accelerations of the otolith membrane, given that this is the method of physiologic activation by gravity. Support for this comes from the direction-specific effects of skull acceleration for both the cVEMP (Rosengren et al., 2009) and the oVEMP (Todd et al., 2007). Resonance around 100 Hz is present and can be modeled using properties of the utricle (Todd et al., 2009) and the isolated utricle shows a resonant peak between 300 and 400 Hz (Dunlap and Grant, 2014). Todd et al. (2009) also modeled the higher resonance frequencies shown for AC stimulation using properties of the saccule, and responses of the saccule in this range have been observed (e.g., Ashcroft and Hallpike, 1934).

VEMP responses are believed to be short-latency fragments of vestibulocollic and vestibulo-ocular reflexes (VOR) originating from otolith afferents (see above). Direct recordings of the eye movements induced by 500 Hz stimulation indicate that, while there is considerable interindividual variation, AC stimulation induces elevation, extorsion, and abduction of the contralateral eye, whereas BC stimulation at the mastoid with a similar stimulus induces depression, extorsion, and abduction (Todd et al., 2007; Welgampola et al., 2009). Given the evidence that irregularly discharging otolith afferents are the main source of VEMPs, it is to be expected that the reflex effects of VEMPs may be understood in terms of otolith-collic and otolith-ocular reflexes. Direct stimulation of the saccule and utricle produces different eye movements depending upon the region of macula stimulated (Fluur and Mellström, 1970a, b). Selective whole-nerve stimulation showed strong contralateral ocular rotation induced by utricular nerve activation, as well as the ability to follow high frequencies of stimulation (Suzuki et al., 1969).

VORs, the best known being the rotational VOR, have as their major role the stabilization of the visual axes in space in response to unexpected perturbations. The otoliths are excited by linear acceleration (Fernandez and Goldberg, 1976), with the saccule mainly excited by vertical acceleration and the utricle by acceleration in the horizontal plane, corresponding to their orientations in the skull. In the case of the utricle, excitation can occur either by linear acceleration to one side or, through the action of gravity, tilt to the other. The appropriate response to these two types of disturbance may be quite different and how this ambiguity is resolved is not fully understood. VEMPs evoked by impulsive stimuli, such as a tendon hammer tap or an impulse from a minishaker, represent phasic accelerations similar to those that occur physiologically during normal movements of walking and running (Pozzo et al., 1991).

Otolith-ocular reflexes in response to linear accelerations in the horizontal plane, reflecting utricular sensitivity, may induce either tilt reflexes or a translational linear VOR (LVOR). The former is the appropriate response to a tilt, the latter to a linear translation. The translational LVOR is a relatively recent discovery (Angelaki, 2004), and the two reflexes may even originate from different parts of the utricle (Leigh and Zee, 2006). Whole-body linear acceleration, a situation that should favor the translational LVOR, evokes little torsion (Aw et al., 2003), but does evoke a horizontal ocular movement beginning at just over 30 ms. Given the structure of the head and neck – crudely, a weight on a support – one might expect that linear accelerations of the head itself would most often represent tilts and that pure linear translations would be rarer. The tonic otolith-ocular tilt reflex is thought to have a low gain, and a low-pass frequency response, but this may apply only to the tonic reflex. Colebatch et al. (2014) concluded that oVEMPs evoked by impulsive lateral head translation were likely to represent tilt VOR responses, based in part on the patterns of torsion obtained. Given that the trunk was fixed in these experiments, such a physiologic response would be appropriate. On the other hand, Todd et al. (2012), who studied oVEMPs evoked by fore–aft linear accelerations of the whole body, concluded that these were likely to be manifestations of the translational LVOR.

Vestibulocollic reflexes are best characterized for rotations, while linear acceleration effects are less well characterized (Goldberg and Cullen, 2011). Utriculocollic reflexes have been reported to facilitate ipsilateral neck flexors and extensors, consistent with a role in the LVOR (Ikegami et al., 1994), although the opposite connectivity has also been reported (Wilson et al., 1977). Impulsive lateral head accelerations evoke ocular responses more consistent with the tilt reflex than the LVOR (Colebatch et al., 2014). AC stimuli predominantly excite saccular afferents and evoke an inhibitory response in the SCM (Colebatch and Rothwell, 2004). Both whole saccular nerve (Goto et al., 2004) and AC stimuli evoke an upwards eye movement, although this is not invariable (Todd et al., 2007; Welgampola et al., 2009). These findings are consistent with a saccular reflex to compensate for sudden head drops. Sacculocollic reflexes also appear to be related to changes in gait speed with age (Layman et al., 2015).

METHODOLOGY FOR RECORDING CVEMPS AND OVEMPS

Stimuli and safety

The recording equipment for VEMPs is similar to other devices used for clinical neurophysiologic studies. AC sound is the typical cVEMP stimulus and is particularly suited to diagnosing superior canal dehiscence (SCD). AC stimuli must be generated using calibrated equipment because the intensities used are high and could be potentially harmful to hearing if not controlled. Peak intensity values are preferable to root mean square levels as safe limits are specified in these units. Ideally sound intensity should be measured using specific equipment, but for the TDH49 headphones a "nominal" calibration of 140 dB SPL for 5 V input can be assumed to be correct within 1–2 dB (manufacturer's specifications). The most widely used AC stimuli are 500 Hz tone bursts or 0.1 ms clicks. Using brief stimuli, not exceeding 140 dB SPL peak intensity for AC stimulation and minimizing stimulus repetitions should ensure that there are no adverse effects on hearing (Colebatch and Rosengren, 2014). Calibration in SPL is also preferable to HL as this measure, as well as the safe limits of exposure, is better defined using SPL intensities. Tone bursts between about 400 and 1000 Hz produce larger reflexes than clicks delivered with the same sound energy due to tuning effects. However, care is required when setting the intensity and duration of the stimulus, as the total energy content of the waveform needs to be considered (Rosengren et al., 2009).

BC stimulation was initially achieved using bone oscillators like the B71, but currently a minishaker such as the Bruel and Kjaer model 4810 is preferred for its greater output and frequency range. However, for both, a suitable amplifier is needed. Stimulus intensity, frequency, and duration should be specified. Calibrating the 4810 or other minishaker in force level requires an artificial mastoid. The phase of movement must be determined (i.e., whether a positive voltage moves the shaft toward or away from the motor), as this is not uniform. The most widely used BC stimuli are 500-Hz tone bursts delivered to the midline at AFz, Fz, or to the mastoids (Sharbrough et al., 1991). The mastoid is very suitable for reflexes evoked by tendon hammer taps or impulsive lateral stimulation. For 500 Hz BC stimulation there is little benefit to be gained in terms of amplitude by using more than one cycle (Lim et al., 2013). Brief stimuli with short rise times are also preferable as they minimize electromechanical stimulus artefact and produce responses with short, tightly grouped latencies. Due to the sensitivity of VEMPs to the direction of head acceleration, BC stimuli should be delivered with fixed polarity, while for AC stimulation the polarity can be alternated to reduce stimulus artefacts. For BC stimulation, a positive polarity, i.e., one which accelerates the minishaker rod toward the skull (similar to a tendon hammer), typically produces shorter latencies.

From the earliest observations it has been clear that stimulus intensity is a critical factor in evoking a cVEMP. Dennis et al. (2014) showed that the p13 and n23 responses were not well fit using linear regression of reflex amplitude against stimulus intensity (in dB) but

rather, an acceptable linear response was obtained when the log of the reflex amplitude was used, implying a power law relationship (Todd et al., 2008a). For the oVEMP, the amplitude in normal subjects also follows a power law, although this only applies to the n10-p15 response once a threshold has been exceeded (Dennis et al., 2014).

cVEMP methodology

Recently there has been an attempt to develop standardization of cVEMP methodology (Papathanasiou et al., 2014). Surface electrodes should be applied using an active-reference montage, with the active electrode ideally positioned over the motor point of the muscle or nearby (Colebatch, 2012) and the reference over the medial or lateral clavicle. Asking subjects to rotate their heads makes the muscle easy to visualize. EMG amplification by around 2000× (66 dB) and filtering between 10 Hz and 2 kHz are typical. Usually 100–200 stimulus presentations are averaged. Peri-trigger recording (i.e., recording some EMG prior to the stimulus) is desirable to assess the level of background "noise" as well as to estimate the level of tonic muscle activation, free of any evoked response. The most critical elements in recording cVEMPs are the stimulus type and intensity (discussed above) and the degree of activation of the SCM and its measurement. Although there are semiquantitative approaches to controlling the level of muscle contraction (e.g., pressing on a blood pressure cuff), that should improve the symmetry of activation on the two sides (Vanspauwen et al., 2006), quantitative methods are to be preferred, as they provide a direct measurement of muscle activity. They also produce values that can be compared between laboratories. A relatively simple method of correcting for differences in muscle activity is to divide the p13-n23 peak-to-peak amplitude by the level of full-wave rectified and averaged EMG derived from the same recording electrodes (Fig. 10.5). This method ignores any offset to the relationship between amplitude and activation and a certain level of activation is required to ensure reliable measurements (Rosengren, 2015). An elementary error is to calculate the full-wave rectified value after averaging – this leads to an underestimation of the true level of full-wave rectified activity and produces values that depend upon the number of trials averaged.

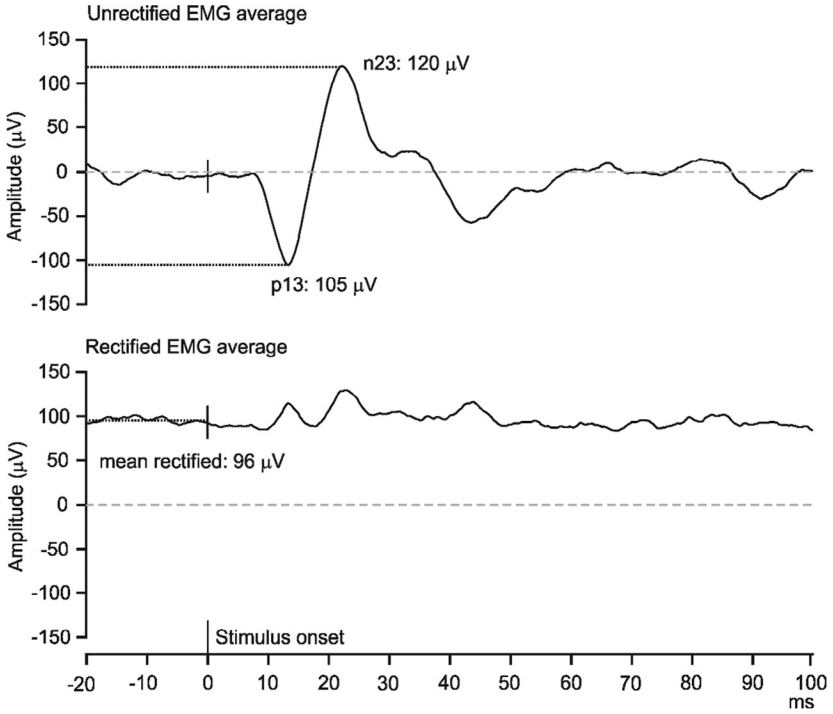

Fig. 10.5. Unrectified average (upper half) and full-wave rectified average (lower half) from sternocleidomastoid. The stimulus was given at time 0, 20 ms after the onset of the average. The prestimulus period serves two functions. In the upper, unrectified average, a flat baseline with little electromyogram (EMG) "noise" enables clear identification of the p13 and n23 peaks. In the lower, rectified average, the prestimulus period is used to determine the average level of activation (mean rectified EMG), unaffected by any evoked response. A simple method to correct for differing levels of activation is to express the p13-n23 amplitude as a ratio of the mean rectified activity, here giving 2.34 (225/96). Note the level of rectified activity is sufficient to give reliable corrected values (Rosengren, 2015). (Modified from Rosengren et al., 2010.)

oVEMP methodology

The oVEMP has broadly similar stimulation and recording requirements to the cVEMP (Fig. 10.3), though some stimuli are less suitable for oVEMPs. In particular, while BC stimulation produces robust cVEMPs in most normal volunteers, oVEMPs evoked by AC stimulation are small, have a higher threshold, and are often absent, especially in older patients. The high rate of absent responses for AC oVEMPs is a significant problem for its clinical application. While oVEMPs evoked by BC stimulation are typically larger and more robust, this depends on stimulus properties.

oVEMPs are usually recorded from a pair of electrodes placed beneath the eye in a vertical line. This bipolar arrangement reduces the potential impact of distant sources and provides a more selective recording of IO muscle activity than a referential montage (Todd et al., 2007). Alternative montages have recently been investigated, e.g., with the active electrode placed more laterally, and have found larger, though more variable, amplitudes (Sandhu et al., 2013). The advantage of the standard montage is that it appears to provide a relatively pure recording of the IO muscle, which receives a crossed projection from the otoliths.

oVEMPs can be recorded with the patient seated upright or reclined. The more critical factor is the level of gaze elevation, which is best kept above approximately 20°. Gaze can be standardized at a fixed angle by providing visual targets, or maximized by asking subjects to look upwards as far as possible. In clinical contexts, the test should be repeated using maximal gaze if the oVEMP is absent when first tested at a lower gaze angle. While factors such as fatigue, nystagmus, head tilt, and alcohol intoxication can have attenuating effects on oVEMP amplitude, the reflex is not abolished by these conditions as long as a sufficient degree of up-gaze is maintained during the test (Lin and Young, 2014; Rosengren et al., 2014). Although the oVEMP is not a blink reflex, patients often blink during the first couple of stimuli. However, these responses habituate very quickly under typical recording conditions and only very rarely contaminate the average. The initial trials can be deleted to avoid this.

As the oVEMP is approximately an order of magnitude smaller than the cVEMP, a higher gain is required. The frequency content of the oVEMP is higher than the cVEMP, as the reflex tends to oscillate at about 100 Hz, and thus low-pass filter settings should be the same as or higher than for the cVEMP. The recording window can be the same or shorter than for the cVEMP, and it is useful to include a pre-stimulus recording to help confirm that the baseline is sufficiently flat to ensure the recorded peaks are reliable.

VEMP measurement

For the cVEMP, the p13 and n23 components of the cVEMP are measured at the response peaks. Peak-to-peak amplitude is calculated, and is corrected for the level of tonic activation when possible, giving a dimensionless ratio (or corrected amplitude). For the oVEMP, the first biphasic components are usually measured: either the n10 or the n10-p15 peak-to-peak amplitude. For both reflexes, amplitude and symmetry are usually the main measurements of interest, but note should also be made of the latency of the peaks and their threshold (if SCD is suspected). Symmetry is typically calculated by the Jongkees formula: (larger – smaller)/(larger+smaller). The smaller amplitude is usually the abnormal one, but not invariably (e.g., SCD causes enlarged responses). Latency is most relevant to central abnormalities.

As stimulus properties such as intensity, frequency, shape, duration, and rise time have significant effects on the normal ranges of amplitude and latency for both cVEMPs and oVEMPs, it is recommended that clinics establish their own normative data sets.

ROLE IN DIAGNOSIS

An abnormality affecting the cVEMP or oVEMP indicates a lesion along the vestibulocollic (cVEMP) or vestibulo-ocular (oVEMP) reflex pathways. Unilateral absence of both responses localizes the lesion to the end organ, primary afferents, or nerve root entry zone (assuming there is no conductive hearing loss if an AC stimulus is used). Delayed latencies for both reflexes can be encountered in demyelinating neuropathies affecting the vestibular nerves or in central disorders. Using three-dimensional video head impulse test (vHIT), oVEMPs, and cVEMPs, it is now possible to test all five vestibular end organs noninvasively. VEMPs, particularly when combined with vHIT, calorics, and audiometry, will often produce a characteristic disease profile that enables diagnosis of the underlying vestibular disorder.

Superior canal dehiscence and third-window syndromes

Very soon after the initial report of the cVEMP, it became clear that subjects with what was then called Tullio syndrome – sound-induced vertigo and nystagmus – showed specific changes on VEMP testing, namely, reduced thresholds. Colebatch et al. (1998) reported that 7 patients with symptoms and signs of Tullio phenomenon all showed lower thresholds for their cVEMPs than for their asymptomatic ears or for 25 controls. Galvanic-induced sway responses were essentially normal, localizing the abnormality to the periphery. This syndrome is now recognized to be nearly always due to a defect in

the bone overlying the superior semicircular canal (Minor et al., 1998) and, while this may be recognized radiologically, it is not always clear whether the radiologic changes are of functional significance (e.g., Watson et al., 2000). A typical abnormality on VEMP testing confirms that the radiologic finding is likely to be functionally significant (Fig. 10.6).

Amplitudes of cVEMPs are increased but overlap with normal values (Brantberg et al., 1999; Rosengren et al., 2008; Welgampola et al., 2008), probably as a consequence of it being an inhibitory reflex. Responses at abnormally low thresholds have however been repeatedly confirmed for SCD using AC stimuli (Fig. 10.6). Zhou et al. (2007) evaluated 65 patients for possible SCD and found that abnormal AC cVEMPs showed over 90% sensitivity and specificity. One patient with low thresholds had posterior canal dehiscence, indicating that the VEMP changes are indicative of an abnormal "third window" and not, strictly, its location. Welgampola et al. (2008) showed significantly reduced thresholds for cVEMPs (similar to those for oVEMPs) in patients with SCD and, importantly, reported that the thresholds returned to normal with successful treatment (see also Niesten et al., 2013). Roditi et al. (2009) agreed that abnormal cVEMPs were a better indicator of disturbed physiology than radiologic findings alone and pointed out the value of the cVEMP in bilateral cases. Brantberg and Verrecchia (2009) reported that showing a large-amplitude response to a weak AC stimulus, below the level of saturation, can be as effective as measuring the actual thresholds.

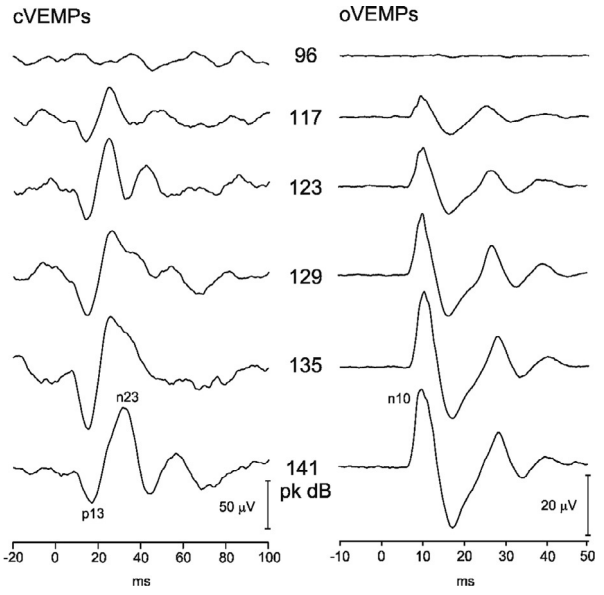

Fig. 10.6. Cervical vestibular-evoked myogenic potentials (cVEMPs) and ocular VEMPs (oVEMPs) from a patient with superior canal dehiscence, using a 500 Hz air-conducted tone. The peak sound pressure level is shown in the middle of the figure. Both reflexes show an abnormally low threshold, but the oVEMP amplitude is also much greater than normal (cf. Fig. 11.3). Note differing calibrations for the two reflexes. (Modified from Rosengren et al., 2008.)

With the development of the oVEMP, an excitatory reflex, it became clear that amplitude differences shown with oVEMPs were a more reliable guide to SCD than for the cVEMP. Rosengren et al. (2008) and Welgampola et al. (2008) both showed that the amplitudes of AC- and BC-evoked oVEMPs at standard stimulus intensities were much higher when compared to controls than were cVEMP amplitudes, but had similar thresholds. The high oVEMP amplitudes in SCD are likely to be due in part to an effect of superior canal afferents themselves, whose thresholds to sound stimulation drop dramatically with experimental dehiscence (Carey et al., 2004). BC stimuli also show abnormalities in SCD, although the threshold reductions appear to be less marked than for AC stimuli (Welgampola et al., 2008). The optimum stimulus has not been extensively investigated and higher frequencies than those normally used may be even more specific (Zhang et al., 2011b, 2012b; Manzari et al., 2013).

VEMPs appear to have an established role in the management of patients with SCD. The demonstration of pathologic sound sensitivity confirms the significance of radiologic findings and can be a guide to the symptomatic side in bilateral cases. Pre- and postoperative observations can confirm the effectiveness of surgery. VEMP testing, and thereby consideration of SCD as an alternative diagnosis, should be considered in cases of suspected otosclerosis and perilymph fistula where operative treatment is considered necessary, as SCD may mimic features of these conditions.

Reduced thresholds are not unique to SCD. Large vestibular aqueducts are associated with mildly reduced VEMP thresholds to AC stimuli (Sheykholeslami et al., 2004; Merchant et al., 2007; Taylor et al., 2012b). A minority of patients with perilymph fistulas have the Tullio phenomenon, loosely defined (Fox et al., 1988), and a case of perilymph fistula with a low-threshold VEMP has been reported (Hermann and Coelho, 2014), although it is not clear if this is typical. Both these conditions need to be considered in the differential diagnosis of low AC thresholds. Conversely, the presence of SCD or the rarer posterior canal dehiscence (Aw et al., 2010) needs to be considered in all cases with unequivocally abnormally low thresholds.

Acute vestibular syndromes

Vestibular neuritis

Presenting with sudden severe and prolonged vertigo without hearing loss, unidirectional spontaneous

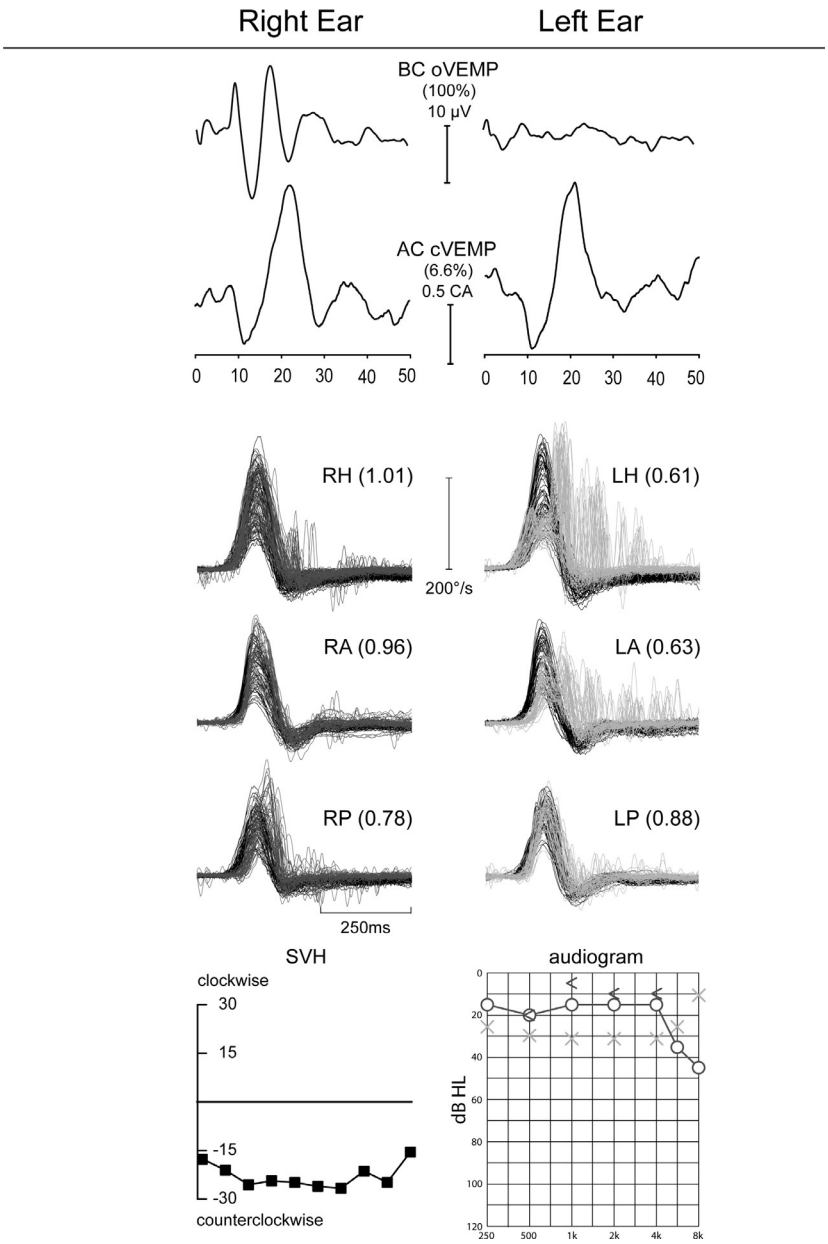

Fig. 10.7. Typical findings for vestibular neuritis affecting the superior division of the left vestibular nerve. Stimulation of the left ear evokes a normal cervical vestibular-evoked myogenic potential (cVEMP: asymmetry ratios given in paraentheses; CA, corrected activity) but no ocular VEMP (oVEMP). Right-sided stimulation is normal. Below are shown the typical findings for the visual head impulse test (reduced gain of the left horizontal and anterior canals), the ipsiversive deviation of the subjective visual horizontal (SVH) on repeated measurements and the (normal) audiogram. BC, bone-conducted; AC, air-conducted; RH, LH, right and left horizontal canal; RA, LA, right and left anterior canal; RP, LP, right and left posterior canal; HL, hearing loss.

nystagmus, and a positive HIT, vestibular neuritis is an acute, self-limiting vestibulopathy. The dysfunction is selective and usually affects the afferents traveling in the superior division of the vestibular nerve more severely than those in the inferior division (Fetter and Dichgans, 1996; Fig. 10.7). As a consequence, the cVEMP is usually relatively spared (Murofushi et al., 1996), while the oVEMP is attenuated or abolished, whether evoked by 500 Hz stimuli via AC or BC origin (Govender et al., 2011, 2015). If the whole nerve is affected or in the much rarer inferior form of vestibular neuritis, the cVEMP is attenuated (Halmagyi et al., 2002; Kim and Kim, 2012). The pattern of involvement of the oVEMP, the cVEMP, or both can indicate superior, inferior, or pan vestibular neuritis (Govender and Colebatch, 2011).

Magliulo et al. (2014) studied 40 subjects with vestibular neuritis within 10 days of symptom onset, using vHIT, cVEMPs to AC 500 Hz tones and oVEMPs to BC stimuli, and reported that 55%, 40%, and 5% of subjects had complete, superior, and inferior vestibular neuritis. These authors used raw cVEMP amplitudes and an amplitude criterion (rather than an asymmetry ratio) for determining the normality of VEMPs. While 80% of subjects had absent or reduced oVEMPs on the affected side, only 47.5% had absent or reduced cVEMPs. A study of acute vestibular neuritis (within 2–5 days of onset) by Walther and Blödow (2013), which also used raw cVEMP amplitudes, showed absent or asymmetric AC oVEMPs and AC cVEMPs in 65% and 40% of subjects. In a retrospective review of 703 patients with acute vestibular neuritis, Kim and Kim (2012) reported 9 subjects with inferior vestibular neuritis, most of whom had spontaneous torsional downbeating nystagmus, impaired posterior vHIT ($n=7$) and absent or asymmetric AC cVEMPs (6 of 8) but preserved oVEMPs (4 of 4).

Govender et al. (2015), in a predominantly prospective study, showed that both AC and BC 500 Hz stimulus-evoked oVEMPs showed similar sensitivities for the detection of vestibular neuritis – with over 80% abnormalities for AC-evoked oVEMPs, the majority of whom had cVEMPs amplitude ratios within the normal range. The use of both modalities of stimulation improved sensitivity. Impulsive stimuli, such as head taps, show more abnormalities of the cVEMP in vestibular neuritis (Brantberg et al., 2003; Govender et al., 2011, 2015), presumably due to strong activation of utricular afferents projecting to the SCM. The cVEMP also appears to be more often abnormal with herpes zoster oticus, particularly if patients have vestibular symptoms (Lu and Young, 2003).

Brainstem and cerebellar stroke

Strokes could potentially affect VEMP pathways by infarction of the labyrinth, vestibular nuclei, or vestibulospinal tracts. An early study that compared cVEMPs in controls, isolated cerebellar strokes ($n=19$), and brainstem strokes ($n=15$) reported no abnormalities in cerebellar strokes and a low prevalence of delayed peak latencies ($n=2$) in brainstem stroke (Pollack et al., 2006). Later, Choi et al. (2014) found a 41% and 33% prevalence in cVEMP and oVEMP abnormalities in isolated cerebellar infarcts, with a nearly threefold increase in the prevalence of abnormalities in those patients who also had an ocular tilt reaction signifying involvement of the graviceptive pathways.

Both posterior inferior cerebellar artery (PICA) and anterior inferior cerebellar artery (AICA) strokes can present as acute vestibular syndromes, usually accompanied by additional physical signs that enable their recognition. Weng and Young (2014) found abnormal cVEMPs in 36% and 75% of tested ears in PICA and AICA strokes; oVEMPs were abnormal in 57% of PICA and 50% of AICA ears tested. Hearing loss (commonly observed in AICA stroke) was a better separator of these two syndromes than the pattern of VEMP abnormalities. Ahn et al. (2011) also found a 50% prevalence of absent or asymmetric AC cVEMPs in AICA strokes, in addition to hearing loss and canal paresis on caloric testing. Isolated vestibular nucleus infarction can occur with either PICA or AICA stroke and may present with isolated spontaneous vertigo and horizontal-torsional spontaneous nystagmus and, sometimes, bidirectional gaze-evoked nystagmus. Kim et al. (2014) reported 2 such patients, both of whom had significant ipsilesional AC cVEMP and oVEMP asymmetry and bilateral (ipsilesional > contralesional) head impulse deficits in horizontal and posterior canal planes.

Recently Oh et al. (2013) undertook a large study ($n=52$) of AC oVEMPs in brainstem lesions inclusive of strokes, in which they found a 54% prevalence of abnormalities, mostly when the lesions occupied the dorsomedial brainstem. They hypothesized that involvement of the medial longitudinal fasciculus, crossed ventral tegmental tract, and oculomotor nuclei were responsible for these abnormalities. Heide et al. (2010) examined AC cVEMPs in 29 subjects with brainstem stroke and reported 41% abnormalities mostly localized to the dorsolateral medulla or lateral part of the lower pons. They attributed these findings to lesions affecting the spinal accessory nucleus and vestibular nucleus.

Episodic and recurrent vertigo

Menière's disease

Menière's disease (MD) is characterized by attacks of vertigo lasting from minutes to hours, with fluctuating low-frequency cochlear hearing loss, tinnitus, and aural pressure. Early MD before the onset of aural symptoms ("vestibular MD") is difficult to separate from vestibular migraine (VM). Ipsilesional reduction in AC cVEMP reflex amplitude has been widely reported in MD, with a prevalence of 35–55% (de Waele et al., 1999; Huang et al., 2011; Taylor et al., 2011). When AC cVEMPs are bilaterally present in MD, the ear with the smaller cVEMP is not necessarily the affected one: the AC cVEMP can be augmented in early MD (Young et al., 2002), perhaps because the hydropic sacculus presses against the stapes footplate, enhancing saccular sensitivity to AC sound. An enhanced cVEMP with an ipsilateral canal paresis may suggest early MD (unpublished observations). As the disease advances, cVEMPs tend to disappear (Young et al., 2003), but can reappear or become

enlarged with glycerol or furosemide, which are drugs that would be expected to reduce endolymphatic hydrops (Murofushi et al., 2001; Seo et al., 2003; Ban et al., 2007). Fluctuation of the cVEMP during an acute attack, i.e., disappearance or attenuation of cVEMPs during the first 24 hours after symptom onset and reappearance of responses after 48 hours, has also been documented (Kuo et al., 2005). Rauch et al. (2004), using tone bursts with a two-cycle rise and fall delivered at 13 Hz, recorded the lowest average cVEMP thresholds at 500 Hz in controls. Compared with controls, affected MD ears had significantly increased cVEMP thresholds and less tuning at 500 Hz. Even unaffected ears of MD subjects showed elevated thresholds compared with normal subjects. Kim-Lee et al. (2009) observed that the frequency peak amplitude ratio, i.e., the ratio between raw peak-to-peak cVEMP amplitudes at 1000 Hz and 500 Hz, lies above 0.7 in 93.5% of MD ears and falls below 0.7 in 95% of controls. Winters et al. (2011) examined AC oVEMP tuning characteristics in controls and MD and recorded the highest amplitudes and lowest thresholds at 500 Hz followed by 1000 Hz. In affected ears of MD patients, the optimal frequency had shifted to 1000 Hz. Tuning alterations may prove a diagnostically useful reflex measure in MD. AC oVEMPs, AC cVEMPs, BC cVEMPs, and BC oVEMPs are abnormal in MD in a descending order of prevalence (Huang et al., 2011; Taylor et al., 2011).

Vestibular migraine

VM can present with episodic spontaneous or positional vertigo lasting seconds to days. Studies that examine VEMP attributes in VM are few and are mostly based upon data collected prior to the publication of the Bárány Society's diagnostic criteria (Lempert et al., 2012). Baier et al. (2009) recorded cVEMPs to 400 Hz / 100 dB normal HL tone bursts and found bilateral reduction in VEMP amplitudes when compared with age- and gender-matched controls, but did not statistically compare VEMP asymmetry ratios. Zaleski et al. (2015) compared AC cVEMPs and oVEMPs in VM patients and controls. Subjects with VM had no significant differences in raw cVEMP amplitudes, amplitude asymmetry, or latencies. In contrast, oVEMP prevalence was lower in VM compared with controls (72% vs. 100%) and amplitude asymmetry was significantly higher. Taylor et al. (2012c), in contrast, found no significant differences in AC click- and BC tap-evoked cervical and ocular VEMPs between VM and controls. Using tone bursts at octave frequencies between 250 and 2000 Hz, cVEMP and oVEMP were compared in controls, VM, and MD. For both the oVEMP and cVEMP, frequency tuning characteristics of VM did not differ significantly from age-matched controls. The optimal frequencies for VM, unaffected MD ears, and controls were 500 Hz and 1 kHz, but affected MD ears tuned to 1 kHz. The ratio of cVEMP amplitudes at 0.5 and 1 kHz, VEMP asymmetry ratio using 0.5 kHz stimuli, and caloric tests combined separated VM from MD with a sensitivity of 90.0% and specificity of 70.0%.

Benign paroxysmal positional vertigo

Benign paroxysmal positional vertigo (BPPV) is characterized by a unique positional nystagmus profile that enables bedside diagnosis. An early study by Murofushi et al. (1996) reported that in BPPV secondary to (superior) vestibular neuritis, AC cVEMPs were usually preserved, as the inferior vestibular nerve, which innervates both the saccule and the posterior canal, has to be intact in order to generate vertigo by activation of posterior-canal afferents.

AC cVEMPs with ipsilaterally absent, attenuated, or delayed responses have since been identified in up to 52% of posterior-canal BPPV patients (Akkuzu et al., 2006; Hong et al., 2008; Korres et al., 2011; Eryaman et al., 2012), but methodologic issues, including variability in control of SCM activation, small sample sizes, and patient selection criteria, limit the interpretation of these findings. A study by Lee et al. (2013) that did not specifically separate idiopathic from secondary causes of BPPV reported a 10% prevalence of abnormal oVEMPs or cVEMPs in nonrecurrent BPPV but 25% and 30% prevalence in recurrent BPPV. Yang et al. (2008) found absent AC cVEMP responses as well as delayed p13n23 latencies when compared with controls. Although the number of maneuvers required to treat did not correlate with the degree of latency prolongation, absent VEMPs did correlate with a greater number of treatments. There is a report that otolith function may improve following particle repositioning (Seo et al., 2013).

Other peripheral and central vestibular abnormalities

Gentamicin treatment

Intratympanic gentamicin injections are used to treat intractable vertigo in MD. In most patients, AC cVEMPs are reported to be within the normal range before treatment and are very often abolished following treatment, frequently after only a single dose (de Waele et al., 2002; Picciotti et al., 2005; Helling et al., 2007; Ozluoglu et al., 2008). The posttreatment AC cVEMP was more often abolished than the caloric response or shift in subjective visual vertical, suggesting that the saccule may be more sensitive to gentamicin than other parts of the vestibule (Picciotti et al., 2005; Helling et al.,

2007). However, the AC cVEMP was not correlated with residual vertigo attacks, indicating that it is not a reliable indicator of treatment success. In a study comparing AC with GVS stimulation, after a single injection 92% of ears lost cVEMPs to AC sound, while 32% and 46% lost cVEMPs to low-intensity GVS at 1 month and 2 years (de Waele et al., 2002). Although the caloric responses and vertigo attacks returned over time in some patients, this did not occur in patients with abolished GVS cVEMPs, suggesting that the GVS cVEMP may be a useful indicator of adequacy of gentamicin ablation. The AC cVEMP is also likely to be abolished in systemic aminoglycoside toxicity and could potentially be used to noninvasively monitor patients receiving aminoglycoside therapy.

Bilateral vestibulopathy

Bilateral vestibulopathy may be the consequence of ototoxic aminoglycosides, bilateral MD, meningitic processes, autoimmune or idiopathic disorders. VEMPs may constitute a useful component of vestibular assessment in these patients, but their preservation does not prevent vertical oscillopsia (Brantberg and Löfqvist, 2007).

Multiple sclerosis

cVEMP abnormalities are present in 31–70% of patients with multiple sclerosis, often consisting of delays (Shimizu et al., 2000; Versino et al., 2002; Alpini et al., 2004; Bandini et al., 2004; Patkó et al., 2007), and in most studies there is little correlation with radiologic findings. oVEMPs ascend to the midbrain and are frequently abnormal in the presence of internuclear ophthalmoplegia (Rosengren and Colebatch, 2011). Gazioglu and Boz (2012) found a 45% abnormality rate for oVEMPs and only 18% for cVEMPs in a group of 62 patients with definite multiple sclerosis. Rates of abnormality were higher with signs or a history of brainstem involvement and with higher disability.

Hearing loss with imbalance/vertigo

Vestibular schwannomas and cerebellopontine angle meningiomas

Studies that combine cVEMPs and oVEMPs indicate that both responses can be abolished or attenuated in subjects with schwannoma, with similar prevalences of ~50–70% for AC cVEMP and BC oVEMP (Kinoshita et al., 2013; Chiarovano et al., 2014; Taylor et al., 2015). The prevalence of both VEMP modalities is significantly correlated with maximal tumor diameter. Neither test correlates with the nerve of origin of the vestibular schwannoma at surgery (Suzuki et al., 2008). Large and medium-sized tumors (>14 mm in diameter) most commonly demonstrate vestibular test abnormalities referable to both divisions of the vestibular nerve (92%) and only rarely point to involvement of a single division (Taylor et al., 2015). AC cVEMPs may also be abolished or attenuated in schwannoma patients with normal brainstem-evoked potentials (Matsuzaki et al., 1999) and even in patients with normal audiometry (Taylor et al., 2015). Thus, VEMPs constitute a valuable addition to the noninvasive test battery that should be offered to patients presenting with symptoms such as monaural tinnitus, muffled hearing loss, and unexplained imbalance suspicious for a schwannoma. A single small study that compared cerebellopontine angle meningiomas and schwannomas found a similar prevalence of VEMP abnormalities in these two tumors (Su et al., 2013).

CVEMPs and oVEMPs in conjunction with three-dimensional vHIT could prove valuable when evaluating residual vestibular function before schwannoma surgery. Since those with near-normal preoperative function could be at risk of developing an acute and perhaps a chronic unilateral vestibular deafferentation syndrome, having these test profiles could help surgeons plan pre- and postoperative management. Controlled vestibular deafferentation with intratympanic gentamicin before surgery, followed by vestibular pre-habilitation, has been validated as a method of minimizing postsurgical vestibular symptoms (Magnusson et al., 2007).

Otosclerosis and middle-ear disease

Disease of the middle ear and its contents usually leads to conductive hearing loss and an air–bone gap of 15 dB or more leads to attenuation of AC VEMPs (Halmagyi et al., 1994). Otosclerosis is characterized by conductive hearing loss, absent acoustic reflexes, and, less commonly, vertigo. AC cVEMPs are frequently absent but may be recordable in 21–29% of ears. The likelihood of AC VEMP attenuation is proportional to the degree of conductive hearing loss (Tramontani et al., 2014). Subjects with otosclerosis who develop vertigo and imbalance have a significantly higher prevalence of BC cVEMP abnormalities (absent responses: 90%) than those who are symptom-free (6.6%), indicating that otosclerosis could affect otolith function, thereby attenuating the VEMP (Saka et al., 2012).

The use of VEMPs allows the recognition of inner-ear causes of apparent conductive hearing loss (e.g., Picavet et al., 2009). Zhou et al. (2012) found that VEMP thresholds correctly classified all but 3 of 120 patients with air–bone gaps into either middle-ear pathology or inner-ear and other pathology, the latter including SCD and enlarged vestibular aqueducts.

Sudden hearing loss and vertigo

Sudden sensorineural hearing loss refers to a 30 dB or greater increase in hearing threshold across three or more adjacent frequencies within a period of 24–72 hours and could be caused by disorders affecting the entire labyrinth (labyrinthitis), ischemia affecting the labyrinthine artery, or immune-mediated inner-ear disorders. Iwasaki et al. (2005) reported a high prevalence of AC cVEMP abnormalities (77%) in sudden sensorineural hearing loss when compared with caloric asymmetry (45%). Based upon the preservation of galvanic cVEMPs in all tested patients, they hypothesized the labyrinth to be the site of the lesion. Nagai et al. (2014) found a higher prevalence of asymmetric AC cVEMP (41.5%) compared with BC oVEMPs (9.3%), while Fujimoto et al. (2015) found cVEMPs, oVEMPs, and calorics to be abnormal in 64%, 43%, and 52% of subjects respectively. Absence of oVEMPs was associated with a poorer prognosis in the study of Nagai et al. (2014).

CONCLUSION

In the 20 or so years since its initial description, the VEMP – to date, principally the AC cVEMP – has established an important role in the diagnosis and assessment of vestibular disorders. One clear contribution is in the recognition, assessment, and differential diagnosis of "third-window" abnormalities. However, its contribution is such that VEMP testing has a role as an additional assessment of most patients presenting with dizziness and vertigo and it should also be considered in those presenting with disorders of hearing and balance. Its applications, particularly the use of various BC stimuli and the oVEMP, are still yet to be fully defined.

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Chapter 11

Audiometry and other hearing tests

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Abstract

Hearing tests of the peripheral auditory system are well established and the pure-tone audiogram is generally regarded as the screening test of choice in adults. It allows the distinction to be made between conductive, i.e., outer- and middle-ear, and sensorineural, i.e., cochlear, hearing loss, and also to describe the configuration of the hearing thresholds in terms of severity and the frequency affected. Electrophysiologic testing with auditory potentials, e.g., the auditory brainstem response, can identify sites of lesion in the eighth nerve, brainstem, and more centrally. However, it is only in the last two decades that a battery of central auditory tests has been established that can probe the central pathways in more details, i.e., when the pure-tone audiogram may be normal, and yet the patient still has symptoms of hearing dysfunction.

This chapter not only describes the tests available to identify a peripheral and/or a central lesion causing hearing difficulties, but also the clinical information required and details of the otologic assessment that add further diagnostic information directing the choice of tests available. Where an understanding of the anatomophysiologic mechanisms of audition or the physical basis of a test is required to understand the test, this is also included.

Assessment of hearing is best made with both otologic (structural) and audiologic (functional) information. This is because of the particular interrelationship between structure and function in the auditory system. Thus, clinic examination as well as audiometric evaluation is required to assess hearing. This chapter will look briefly at the clinic examination explaining the association with hearing loss, and then in detail at the audiologic test battery.

Audiologic tests characterize abnormalities within the auditory system, establishing the level of the lesion and quantifying the loss. Specifically, the purpose of the testing is to:

- quantify the audiometric threshold at each frequency
- differentiate conductive from sensorineural hearing loss
- differentiate cochlear from retrocochlear abnormality
- identify central auditory dysfunction in the brainstem, midbrain, or auditory cortex
- identify any nonorganic hearing impairment (Fig. 11.1).

CLINIC EXAMINATION

The history taken from the patient needs to include the questions listed in Table 11.1.

The medical examination will be guided by the anamnesis, but should include appearance of the facies, i.e., xanthelasma, plethora, syndromal features; tenderness of the superficial temporal arteries; auscultation of the supraclavicular fossae and carotid arteries in the neck; blood pressure measurement; evidence of thyroid dysfunction; assessment of affect, intellectual performance, and memory capabilities; and assessment of central language functions. For the patient in the neurology clinic or ward, a full neurologic examination is of course mandatory.

EXAMINATION OF THE EAR

This includes inspection of the auricle and otoscopic examination of the external auditory meatus (EAM)

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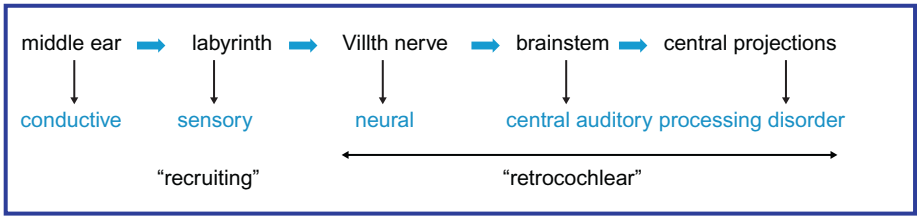

Fig. 11.1. Types of hearing loss associated with site of lesion along the auditory pathway.

Table 11.1

Questions to be asked when taking the clinical history

Hearing loss
• Date of onset
• Gradual or sudden
• Stable, progressive, or fluctuating
• Unilateral or bilateral
Past medical history
• Noise exposure (occupational, social, gunfire)
• Ear/head trauma; surgery to the ear
• Administration of ototoxic drugs
• Infections (mumps, measles, meningitis)
• Birth and neonatal history
• Family pedigree (syndromal or nonsyndromal)
• Neurologic disorder
Associated symptoms
• Aural fullness, pain, discharge
• Tinnitus (pitch, pulsatile, clicking)
• Diplacusis, hyperacusis, distortion
• Vertigo

and tympanic membrane (TM), the latter offering a window into the middle-ear cleft.

The external ear

The auricle is essentially vestigial, slightly enhancing the collection of sound and directing it toward the TM and middle ear.

Developmental abnormalities of the auricle should be identified because of the possible association with other ear abnormalities and associated hearing loss. Anotia (absence of auricle and EAM, microtia (auricle smaller than normal and probably misshapen), and polyotia (e.g., two auricles facing each other) may be seen.

Acquired causes of abnormalities of the auricle include hematoma (following a blow on the ear, commonly found in rugby players and boxers); acute dermatitis (an extension of EAM infection with auricular desquamation – weeping eczema); squamous and basal cell carcinoma (triggering a search for lymphadenopathy).

The external auditory meatus

Inspection of the EAM and TM can be carried out with either a hand-held otoscope or the binocular microscope with the patient upright. The speculum should be introduced carefully into the external ear canal with the pinna held between the thumb and forefinger of the examiner's hand and gently retracted backward to straighten out the curve in the cartilaginous meatus. The speculum should then be directed around the circumference of the canal, looking for debris or foreign bodies, inflammation and, in particular, for defects of the posterior or attic wall.

Presence of obstructing wax or debris

If wax (or other aural debris) completely obscures the view of the TM, the wax may be impacted. As this can cause a conductive hearing loss, the wax should be removed (Fig. 11.2). This is with a Jobson Horne probe, a Cawthorne wax hook, or use of Tilley's dressing forceps with suction microscopy in the hands of an otologist, i.e., ear, nose, and throat surgeon or audio-vestibular (AV) physician, or, if nonimpacted, by syringing by an audiologist or trained practice nurse. If the wax is particularly hard, it may need softening using warm olive oil or 5% sodium bicarbonate drops applied topically for 1 week in advance of wax removal. Contraindications to syringing are:

- the presence of ear infection
- when the ear is known to have had a perforation
- when the history indicates the ear is suspected of having a vulnerable TM, e.g., post tympanoplasty or myringoplasty.

Aural debris is best removed by suction microscopy, with any discharge being sent to the microbiology laboratory for microscopy and culture.

Congenital abnormalities of the EAM include narrowed, stenosed, and atretic canals that may be associated with other abnormalities. Atresia is found in 1–2/100 000 births and is frequently associated with hearing loss. Examples of acquired abnormalities are otitis externa (infections include Staphylococcus, Pseudomonas aeruginosa, Aspergillus niger, and Candida albicans; the vesicular eruption of herpeszoster virus may be seen in the auriculotemporal division of the

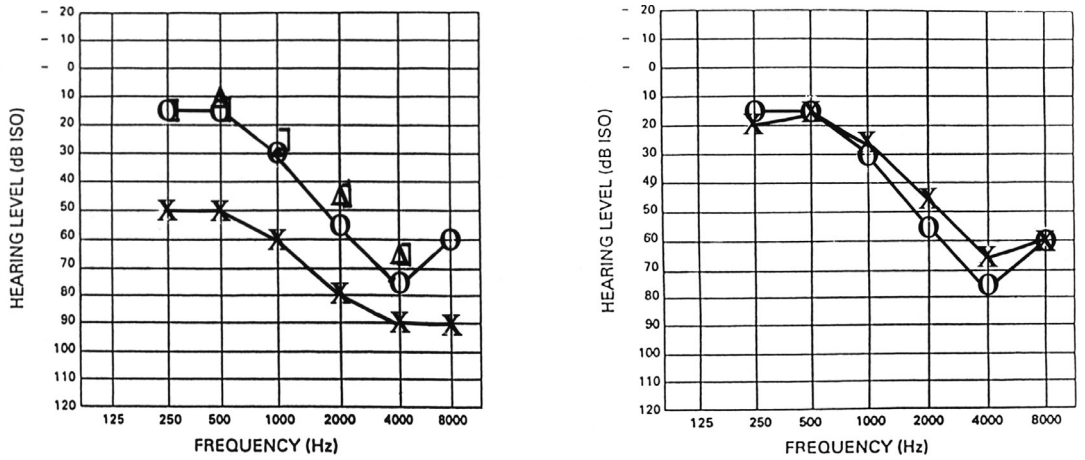

Fig. 11.2. Pure-tone audiometry before (**A**) and after (**B**) syringing. (**A**) Impacted wax on the left (thresholds indicated by X) by comparison with thresholds in the right ear (thresholds indicated by O): auditory thresholds are raised on the left by an average of 24 dB. (**B**) Following wax removal, auditory thresholds on the left have improved by an average of 32 dB. N.B.: After wax removal, patient has a pure-tone audiogram compatible with age-related and noise-induced hearing loss.

trigeminal nerve in the Ramsay Hunt syndrome) and are frequently associated with conductive hearing loss. Osteoma (discrete, white, rounded excrescences of bone) and exostoses (multiple small osteomata frequently found in people who swim or dive regularly) can also be seen.

Fistula test

This sign should be sought in all dizzy patients, particularly those with chronic middle-ear disease. It is elicited in those patients with a fistula to the labyrinth where there is transmission of air pressure changes from the EAM via the middle ear, causing endolymph movement within the vestibular end organ and resulting in nystagmus. Raised pressure causes a conjugate deviation of the eyes toward the opposite ear, and with maintenance of pressure, a corrective fast eye movement will be introduced and resulting nystagmus will be toward the affected ear. The pressure may be raised by finger pressure on the tragus, but more accurately using tympanometry to induce a precise pressure whilst observing the eyes for nystagmus.

The tympanic membrane

The standard landmarks and features of the TM should be identified: the central position of the handle of the malleus, the distinction between the pars flaccida and pars tensa of the drum, and the identification of the long process of the incus and stapedius tendon, which may be visible in transparent membranes.

Perforations

Those of the pars tensa are classified as marginal or central (Fig. 11.3A) according to whether the annulus of the TM forms part of the circumference of the perforation.

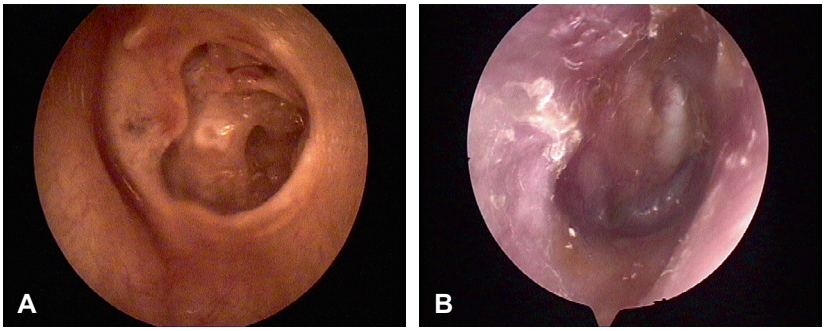

Fig. 11.3. (A) Large, "safe," central perforation of the left tympanic membrane with normal, dry middle ear mucosa. (B) Cholesteatoma of the left tympanic membrane/middle ear. There is a large perforation extending to the annulus and a watery discharge is seen inferiorly. The middle ear mucosa is inflamed and epithelial cysts (chloesteatoma) are seen. This is an "unsafe" ear. (By courtesy of Dimitris Kikidis, 1st Otolaryngology Clinic, University of Athens.)

Defects of the epitympanic recess (pars flaccida) are described as attic perforations and characterised as small or large. If the perforation is marginal, the position of the perforation is described as anterior, inferior or posterior. Very large central perforations are described as sub-total and very large marginal perforations as total. "Safe" perforations are dry and do not include the annulus of the tympanic membrane. "Unsafe" perforations are wet and inflamed middle ear mucosa is visible through the perforation (Fig. 11.3B).

Color

Normally the TM has the appearance of mother of pearl. The light reflex is found anteroinferiorly, where reflection of the examining light occurs. This may be lost if the membrane is thickened. If hyaline degeneration with deposition of calcium occurs in the middle layer of fibrous tissue, the appearance is described as tympanosclerotic. In acute suppurative otitis media the color is a bright cherry red.

Position

The TM may become retracted when there is a chronic lowering of pressure in the middle ear, such as when there is chronic obstruction of the eustachian tube. The handle of the malleus is drawn inward and there is retraction of the TM toward the medial wall of the middle ear. In severe cases the membrane is stretched around the long process of the incus and the head of the stapes. At worst, the membrane is plastered against the promontory. A fluid level may be visible if secretory otitis media has resulted from the reduction of middle-ear pressure (MEP). The TM may bulge outwards with increased MEP, e.g., acute suppurative otitis media.

Abnormalities of the tympanic membrane and middle ear

Congenital abnormalities

- Fused malleus and incus
- Incus fixed to posterior bony annulus
- Congenital stapes fixation and grossly deformed stapes
- Absent stapedius tendon
- Uncovered seventh nerve
- Partial bony plate formation.

Acquired abnormalities

Acute otitis media

Acute otitis media is frequently associated with upper respiratory tract infections. Common causative organisms include pneumococcus, Haemophilus influenzae, and Moraxella catarrhalis. There is an exudative phase associated with a conductive hearing loss and a negative MEP and a recovery phase when the middle ear becomes well ventilated again.

Chronic otitis media

Chronic otitis media may develop from acute otitis media and be associated with TM perforation, incus necrosis, myringostapediopexy, malleus head fixation, cholesteatoma, and tubotympanic disease. The size and location of a perforation determine the degree of hearing loss – a large perforation in general is associated with a greater degree of hearing loss. The location of the perforation generally distinguishes "safe" from "unsafe" perforations, the marginal perforation being the "unsafe" perforation and likely to be associated with cholesteatoma.

Cholesteatoma

Cholesteatoma is a cyst lined with squamous epithelium that can arise in an ear undergoing long periods of negative MEP. Cysts are likely to begin in the attic of the ear and extend into the mastoid antrum. They are associated with "unsafe," marginal perforations when the cyst penetrates the TM. They can penetrate the bone with which they come into contact, and lead to intracranial complications by eroding through the dura of the middle or posterior fossa, or into the lateral sinus or the horizontal semicircular canal. The facial nerve may be eroded in the middle ear or mastoid.

Tubotympanic disease

Tubotympanic disease is characterized by recurrent infections rather than persistent infections and by odorless discharge. A central TM perforation and a break in the ossicular chain or malleus fixation are regarded as "safe" and unlikely to be associated with cholesteatoma.

Otitis media with effusion

Otitis media with effusion (OME) is recognized by the presence of an air–fluid level in the middle ear and a bluish discoloration of the TM. In adults the presence of bilateral OME should trigger investigation for neoplastic obstruction in the nasopharyngeal end of the eustachian tube. In children OME is more commonly known as "glue ear." Hemotympanum may be seen after a head injury associated with a temporal bone fracture, or with barotrauma associated with scuba diving.

Otosclerosis

Otosclerosis is an autosomal-dominant condition associated with gene TGBF1 that can be identified during the

osteoblastic phase by hyperemia of the middle-ear promontory, visible through the TM as a rosy glow, known as Schwartze's sign. It is associated with a conductive hearing loss due to fixation of the stapes footplate (but, characteristically with no air–bone gap at 2 kHz, known as a Carhart notch). Absent stapedius reflexes are a feature early in the progression of the disease and the TM compliance peak is low.

Head trauma

Head trauma can lead to a variety of outer, middle-, and inner-ear abnormalities depending on the presence of a fracture of the petrous temporal bone. If there is bloody otorrhea, audiometry is mandatory and may show a conductive hearing loss, but also a sensorineural hearing loss associated with labyrinthine concussion.

Glomus tympanicum tumor

Glomus tympanicum tumor is identified as a vascular mass behind the TM and the patient may describe pulsatile tinnitus. In such cases audiometry may show a conductive hearing loss and the tympanogram may be pulsatile.

Tuning fork tests

Traditionally tuning fork tests have been used in the clinic to distinguish conductive from sensorineural loss. However, with the widespread availability of pure-tone audiometry, these tests are less used clinically. The most commonly used tuning forks are those tuned to 256 and 512 Hz. Lower frequencies produce a vibrotactile stimulus that leads to misleading hearing thresholds.

Two general principles apply:

1. The inner ear is more sensitive to sound conducted by air than by bone.
2. In pure conductive hearing loss, the affected ear is less subject to environmental noise and is more sensitive to bone-conducted (BC) sound.

Rinne

The 512-Hz tuning fork should be struck two-thirds of the way along its tines (to minimize distortion products) against a hard but elastic mass, e.g., a rubber pad (otherwise overtones may be produced). The fork is then held perpendicular to the long axis of the EAM with its closest tine within 1 cm of the entrance to the meatus. The patient is asked to report if s/he can hear the sound. The fork is then immediately transferred behind the ear, with the base soundly pressed to the bone overlying the mastoid. The patient is asked which sound is louder, that "in front of the ear" or that "behind the ear."

Positive Rinne (AC > BC). The Rinne is described as positive if the sound in front of the ear (air-conducted (AC) sound) is reported as louder than that behind the ear (BC sound). In an ear with a normal conductive mechanism, AC sound will be perceived as louder than BC sound. A positive test is found in a normally hearing ear or with a sensorineural hearing loss.

Negative test (AC < BC). The Rinne is described as negative if the sound in front of the ear is reported as quieter. If it is negative, this indicates a significant conductive component (>15 dB hearing level (HL)). A false-negative Rinne can occur if there is a severe sensorineural hearing loss in the tested ear. In this situation, the BC stimulus is heard in the nontested ear because of intracranial transmission, and BC sounds will be greater than AC sound. Masking of the nonaffected ear is then performed using a Bárány box, delivering white noise and raising the threshold of hearing, so that BC sound cannot be heard. The Rinne is best used as a test for conductive hearing loss, but has a high specificity and a low sensitivity.

Weber

The Weber test is used in conjunction with the Rinne test and is most useful in patients with unilateral hearing loss. The aim is to identify the better-hearing cochlea. The 512-Hz tuning fork is struck and placed in the midline on either the forehead or the vertex. The patient is asked if the sound is heard louder in one ear or equally in both ears. In a normally hearing patient, the tone is heard centrally. Otherwise, the sound is heard on the side of the better cochlea unless there is a conductive hearing loss, in which case the tone may be heard in the poorer-hearing ear.

AUDIOLOGIC TESTS

Baseline audiometric tests

Pure-tone audiometry

The cornerstone of audiologic testing is the pure-tone audiogram (PTA) and is used as a screening test for hearing loss. The aim is to establish hearing thresholds and, if abnormal, to distinguish between conductive and sensorineural hearing loss. Accurate air and bone conduction sound audiometry, masked where necessary (see below, under masking), shows the existence and extent of any hearing loss. It is best used in conjunction with tympanometry and measurement of stapedius reflex thresholds.

The PTA involves the measurement of the threshold of hearing, i.e., the lowest intensity at which sound

can just still be heard across a range of frequencies audible to the human ear. It is a subjective measure of hearing, and if the patient is unable or unwilling to cooperate, additional objective audiologic investigations, such as otoacoustic emissions and auditory evoked responses, are essential to provide objective measures of hearing.

Physical characteristics of sounds audible to the human ear

Table 11.2 identifies the characteristics of pure tones (sound pressure waves) as heard by the human ear, by frequency and intensity.

The magnification amplitudes, the equivalent decibel measurement, and an example of an equivalent sound, as heard by the human ear, are shown in Table 11.3. The unit for expressing the relative intensity of sound is a decibel (one-tenth of a bel) and is plotted on a logarithmic scale along the y-axis of the audiogram.

Manual audiometry

As a psychoacoustic (subjective) measurement, the results may be biased by particular methods of conducting the test and a standard protocol needs to be followed.

Table 11.2

Characteristics of pure tones (sound pressure waves) as heard by the human ear, by frequency and intensity

Sound pressure waves, i.e., pure tones
Frequency
• Lowest audible 20 Hz
• Highest audible 30 000 Hz
Intensity
• Measured as decibels (log factor of intensity)
• 0 dB is defined as the quietest audible sound. The range is –10 dB to 120 dB (painful sound threshold)

Table 11.3

Decibel levels of sounds

Magnitudes of amplification	Decibels	Sounds
100 000 000 000 000	140	Jet engine
1 000 000 000 000	120	Aircraft propeller
10 000 000 000	100	Rock drill
1 000 000 000	90	Heavy vehicle
10 000 000	70	Private car
1 000 000	60	Conversation
1000	30	Soft music
10	10	Leaf rustle
1	1	Barely audible

Pure-tone audiometry is carried out in a soundproofed room, as low-frequency thresholds are particularly affected by any ambient noise in the room. Pure tones are delivered through headphones (for air conduction thresholds) or a bone conductor applied to the mastoid process (for bone conduction thresholds). The pure-tone oscillator can be set to one of several different frequencies, and the level of the signal adjusted according to a calibrated scale from –10 to +90 dB HL. The threshold of hearing for a pure tone at a particular frequency is defined as the lowest level of sound that can still be heard on at least 50% of presentations. In manual audiometry the tone is presented in 5-dB steps in an ascending manner, i.e., increasing in intensity until the threshold is reached. The subject is required to respond to the quietest tone, this being recorded as the AC or BC hearing threshold for that frequency. For bone conduction, the ear not being tested is masked with narrow-band noise centered on the test frequency, because the intra-aural attenuation for BC sound is negligible.

For clinical purposes, air conduction threshold values better than 20 dB HL are considered to be normal. Bone conduction thresholds significantly better than air conduction thresholds indicate a disorder affecting transmission of sound through the middle ear into the inner ear, i.e., conductive hearing loss, whereas raised bone and air conduction thresholds that are similar imply sensorineural hearing loss.

Masking

The amount of sound lost in transcranial transmission is variable, the attenuation range in adults for air conduction being 40–85 dB and for bone conduction 5–15 dB. To ensure that the threshold obtained using PTA is indeed from the test ear and not the nontest ear, masking noise is applied to the nontest ear in certain situations. In air conduction audiometry, the masking noise is presented through the earphone opposite to the ear being tested. In bone conduction audiometry, the usual procedure is to deliver the masking noise via an insert earphone. Narrow-band noise centered on the frequency of the test tone is most effective.

Masking is needed at any frequency where:

1. the difference between the left and right ear air conduction thresholds is 40 dB or more when using headphones
2. the unmasked bone conduction threshold is better than the air conduction threshold of either ear by 10 dB or more. The worse ear (by air conduction) would then be the test ear and the better ear would be the nontest ear to be masked

3. the bone conduction threshold of one ear is better by 40 dB or more than the unmasked air conduction threshold attributed to the other ear.

The "shadowing" technique of determining the true auditory threshold is the most commonly used masking technique, but is not described in detail here.

The results of pure-tone audiometric measurement are plotted according to the following standard format:

- X = left-ear air conduction threshold
- O = right-ear air conduction threshold
- Δ = unmasked bone conduction threshold (plotted on the audiogram on the side where the bone conductor has been placed)
- [= right masked bone conduction threshold
-] = left masked bone conduction threshold.

Examples of audiograms are shown in Figure 11.2 (a mixed hearing loss where the conductive component in the left ear (A) improves to match the air conduction threshold of the right ear after removal of wax (B)) and in Figure 11.4 (audiograms typical for a variety of medical conditions causing hearing loss). Table 11.4 identifies the characteristics of a conductive hearing loss such as seen in Figure 11.4B, and Table 11.5 identifies the characteristics of a sensorineural hearing loss.

PTA descriptors of hearing loss

Severity.

- Normal: better than 20 dB HL
- Mild: between 20 and 40 dB
- Moderate: between 41 and 70 dB HL
- Severe: between 71 and 90 dB HL
- Profound: in excess of 90 dB HL.

Frequency.

- Low-frequency (250 and 500 Hz)
- Mid-frequency (1000 and 2000 Hz)
- High-frequency (4000 and 8000 Hz).

Thus, the sensorineural loss shown in Figure 11.5 would be a symmetric, mid- to high-frequency hearing loss of mild to moderate severity with additional 4 kHz notching.

Where quoted, the average hearing loss refers to the average of the three thresholds, 500, 1000, and 2000 Hz.

Acoustic immitance measurement (tympanometry)

Tympanometry, or measurement of the acoustic immitance of the ear, obtains information about the state of the middle ear as a function of ear canal pressure.

Acoustic immitance represents the difficulty encountered by a sound wave (acoustic energy) as it is transmitted through the ear. "Stiffness" of the ear is the characteristic that maintains its shape and brings about restoration after a force has been applied. Compliance is the reciprocal of stiffness and represents the mobility of the middle-ear system. Acoustic immitance identifies high-impedance middle-ear abnormalities, e.g., otitis media and otosclerosis, and low-impedance abnormalities such as ossicular interruption.

The advantages of tympanometry are that it is objective and thus requires no behavioral response; it is noninvasive and well tolerated; and it is quick and inexpensive.

Principles of acoustic immitance

A variable-intensity, low-frequency pure tone (220–226 Hz), generated by a miniature sound source, is delivered to the EAM by means of a flexible tube connected to one of three orifices in a probe tip assembly. The other two components are a tube connected to a pump that alters the ear pressure in the EAM measuring the pressure manometrically; and a tube that conducts sound waves from the EAM to a microphone for transduction to electric activity. The electric signal represents sound pressure level. It is compared with a reference voltage delivered by the impedance meter and the comparison is registered on a balance meter.

The probe assembly is inserted into the EAM to make an airtight seal. In a normal ear, the MEP will range from +50 to –50 mmH2O (adults) +50 to –100 mmH2O (children). The tympanogram is obtained by varying the external meatus pressure from –600 to –200 daPa and is now recorded automatically, giving a hard copy and also evidence of rhythmic fluctuations in compliance due to conditions such as tensor tympani myoclonus or the pulsatile tympanogram of a glomus tumor.

Middle-ear compliance

When the EAM pressure is at MEP, the measured compliance is primarily that of the air in the EAM plus that of the middle-ear structures. If the EAM pressure is increased significantly above MEP (e.g., MEP + 200 mmH2O), the measured compliance of the middle-ear structures becomes very small in comparison to the air in the EAM, and the measured compliance is approximately equal to that of the air in the EAM. If this value is subtracted from the maximum compliance obtained when MEP equals EAM pressure, this difference will be approximately equal to the compliance of the middle ear. Normal values range from 0.3 to 1.5 mL of equivalent volume.

If the eustachian tube fails to ventilate the middle ear, negative ear pressure develops in the air spaces of the temporal bone. This is thought to happen because of: (1) gases diffusing from the air into the cells because of unequal concentration of gases in the air and in the middle-ear tissues; and (2) the movement of fluid by cilia

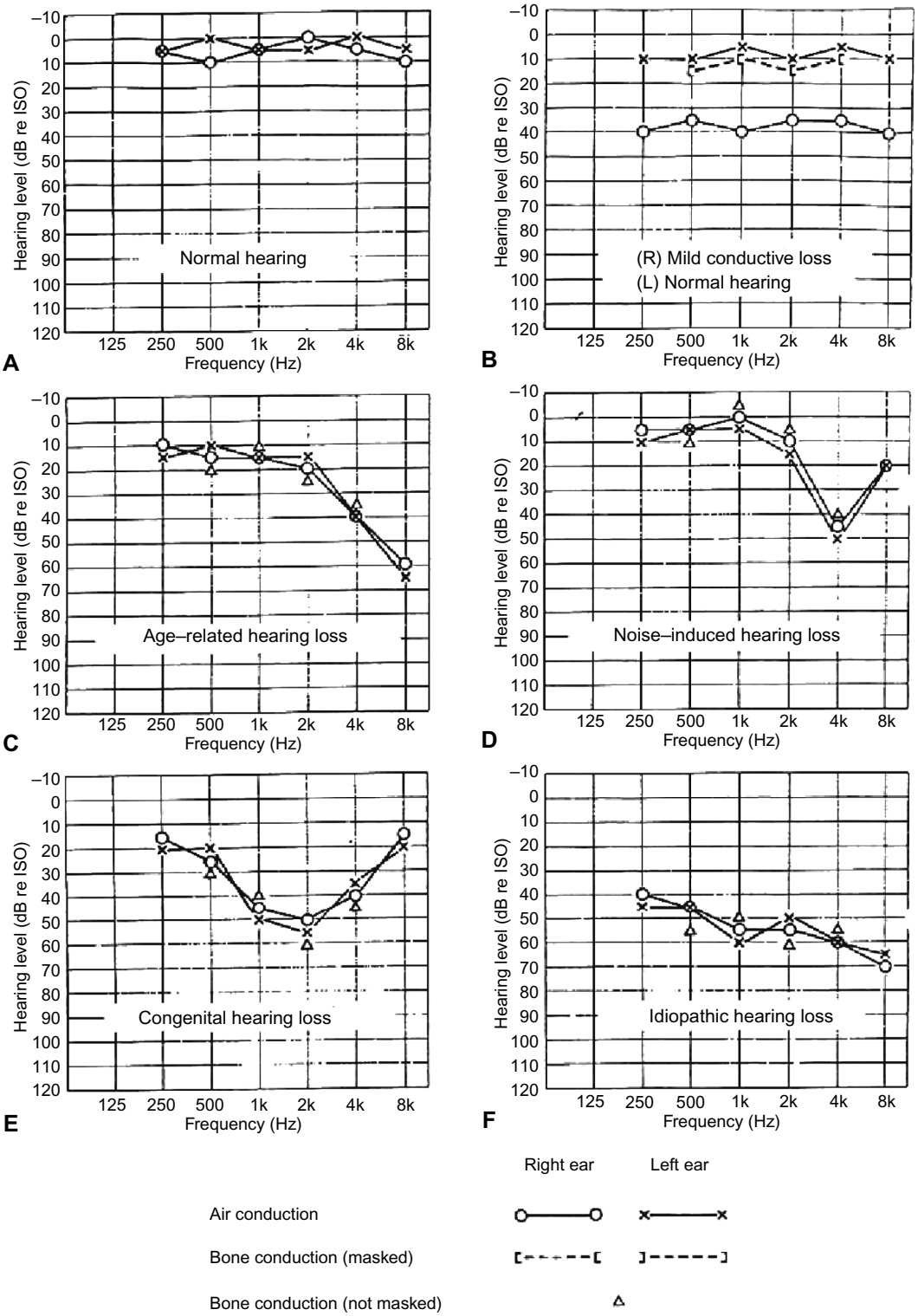

Fig. 11.4. Specimen pure-tone audiograms: (A) normal hearing; (B) unilateral conductive hearing loss; (C) age-related loss; (D) noise-induced hearing loss; (E) congenital hearing loss; (F) idiopathic hearing loss.

Table 11.4

Audiologic characteristics of a conductive hearing loss

Conductive hearing loss is caused by outer-ear, tympanic membrane, or middle-ear abnormalities. It is identified by the following audiologic abnormalities:

- Negative Rinne and Weber test lateralizing to the poorer-hearing ear
- Pure-tone audiometry: raised air conduction thresholds with a difference of >10 dB or <60 dB when compared to bone conduction thresholds on pure-tone audiogram (air–bone gap)
- Abnormal tympanometry (see section on acoustic immitance measurement)
- Absent/raised stapedius reflexes in a diagonal pattern, i.e., as measured from the affected ear (see section on stapedius reflex thresholds)

Table 11.5

Audiologic characteristics of a sensorineural hearing loss

A sensorineural hearing loss is characterized by:

- Positive Rinne and Weber lateralizing to the better-hearing ear
- Raised air conduction thresholds with <10 dB difference when compared with bone conduction thresholds on pure-tone audiogram
- Normal tympanometry
- A recruiting pattern of stapedius reflex thresholds when compared to audiometric thresholds

out of the closed eustachian tube, thereby increasing the effective middle-ear volume and leading to a negative MEP (Davies, 2003).

High-impedance abnormalities

1. Perforated TM: flat tympanogram with middle-ear compliance >2.5 up to 4.5 mL
2. Middle-ear effusion: high impedance with a flat pressure peak inversely correlated with amount of middle-ear effusion
3. Ossicular fixation: shallow tympanic peak, MEP peak around 0 mL (type As).

Low-impedance abnormalities

1. Thin, atrophic TM, i.e., flaccid: high tympanic pressure peak with sharp notching
2. Ossicular disruption: high tympanic pressure peak, low static impedance measurements.

Tympanometric shapes

The most commonly used classification system was introduced by Liden and modified by Jerger, with Feldman (1976) describing an analytic approach:

- Type A is normal – the peak immitance is at or near 0 daPa.
- Type AD shows an unusually high peak pressure, e.g., a flaccid TM or ossicular discontinuity.
-

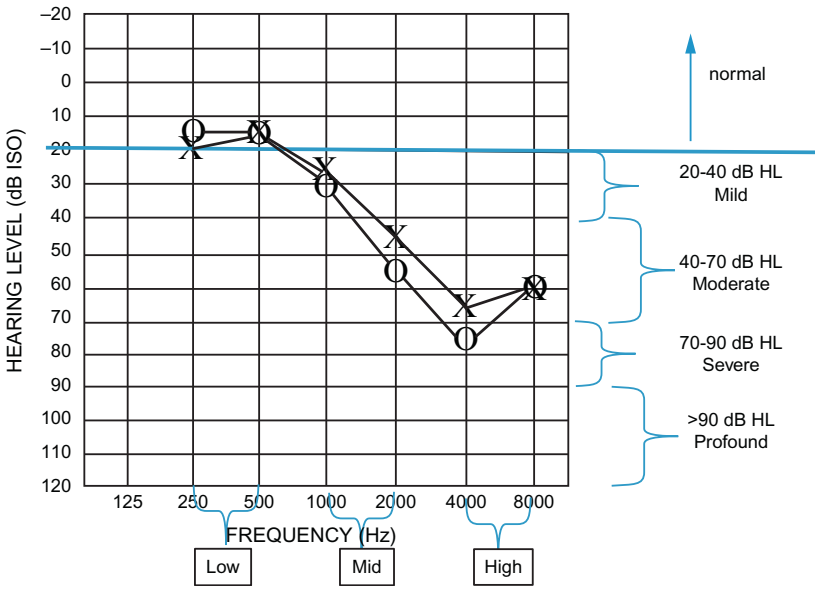

Fig. 11.5. Pure-tone audiogram descriptors of hearing loss (HL) by severity and frequency.

Type AS shows a reduced pressure peak, e.g., ossicular fixation and some forms of otitis media.

- Type B shows a flat pressure peak such as with a middle-ear effusion or other space-occupying lesions of the middle ear. Alternatively this may be seen with obstructed wax.
- Type C shows a negative peak pressure and indicates negative MEP, such as with a retracted eardrum.
- Type D shows sharp notching, characteristic of scarred eardrums or hypermobile TM.
- Type E is characterized by broad, smooth notching and is most commonly found in cases of partial or complete ossicular discontinuity.

Stapedius reflex thresholds (measured by tympanometry)

Stapedius reflex measurements provide information about the middle and inner ear, in addition to the eighth and seventh nerve (proximal to the innervation of stapedius) and brainstem function. Dynamic changes which result from contraction of stapedius in response to stimuli of 500, 1000, 2000, and 4000 Hz, at intensities of 70–115 dB sound pressure level, are measured and thresholds for activation documented. There is an afferent limb to the stapedius reflex involving the TM, middle ear, cochlea, and eighth nerve, and also an efferent limb involving the seventh nerve, middle ear, and TM with cross-over in the brainstem at the level of the superior olive complex (Fig. 11.6). The stapedius reflex can be measured both ipsilaterally and contralaterally.

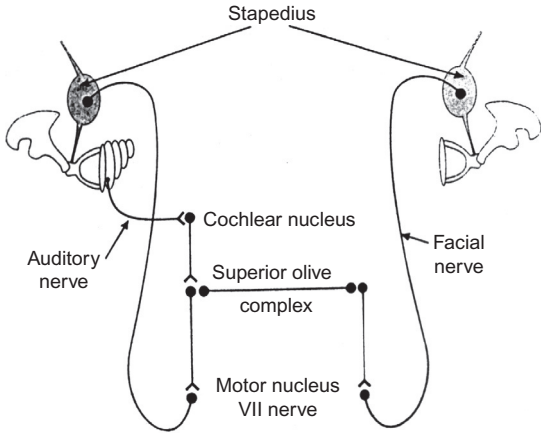

Fig. 11.6. Diagram of stapedius reflex showing afferent limb of the reflex involving the tympanic membrane (TM), middle ear (ME), cochlea and eighth nerve and the efferent limb involving the seventh nerve, ME and TM, with cross-over in the brainstem at the level of the superior olivary complex.

When presented with a high-intensity sound stimulus, the stapedius and tensor tympani muscles contract. The stapedius stiffens the ossicular chain by pulling the stapes of the middle ear away from the oval window of the inner ear and the tensor tympani muscle stiffens the ossicular chain by loading the TM when it pulls the malleus in toward the middle ear The contraction of the stapedius muscle stiffens the middle ear, thus decreasing middle-ear admittance, which can be measured by tympanometry. It is thought that the reflex provides limited protection of the organ of Corti against excessive stimulation (particularly the lower frequencies).

Definition of stapedius reflex threshold abnormality

Stapedius reflex thresholds arise from stimulation across the four frequencies 500, 1000, 2000, and 4000 Hz and are measured both ipsi- and contralaterally, and threshold abnormalities are identified according to the criteria below (Cohen and Prasher, 1992):

1. >15 dB difference at two adjacent frequencies when compared to the opposite ear
2. >115 dB.

Significance of stapedius reflex threshold abnormalities (Fig. 11.7)

1. normal
2. unibox: afferent pathway lesion
3. diagonal: efferent pathway lesion, i.e., middle-ear abnormality or seventh-nerve paralysis (when the lesion is proximal to the innervation of the stapedius)
4. vertical: afferent pathway lesion, i.e., eighth-nerve lesion with sufficient hearing impairment that the stapedius reflex cannot be elicited, i.e., vestibular neuroma
5. L-shaped: otosclerosis, i.e., mixed pattern
6. full house: brainstem abnormalities, or bilateral middle-ear disease.

Recruitment

Measurement of stapedius reflex thresholds can also identify loudness recruitment, one of the hallmarks of cochlear impairment. The objective finding is an abnormal growth of response with sound level. Typically the stapedius reflex is triggered by sound levels 60 dB louder than the hearing threshold. Thus, when the hearing thresholds are raised and yet the stapedius reflex is recruited at only 30–40 dB above, recruitment is identified.

A	Probe right	Probe left	NORMAL
Ipsilateral stimulation	N	N	
Contralateral stimulation	N	N	

D	Probe right	Probe left	VERTICAL
Ipsilateral stimulation	Abn	N	
Contralateral stimulation	Abn	N	

B	Probe right	Probe left	UNIBOX
Ipsilateral stimulation	Abn	N	
Contralateral stimulation	N	N	

E	Probe right	Probe left	INVERTED **L*
Ipsilateral stimulation	Abn	Abn	
Contralateral stimulation	N	Abn	

C	Probe right	Probe left	DIAGONAL
Ipsilateral stimulation	Abn	N	
Contralateral stimulation	N	Abn	

F	Probe right	Probe left	FULL HOUSE
Ipsilateral stimulation	Abn	Abn	
Contralateral stimulation	Abn	Abn	

Fig. 11.7. Patterns of abnormal stapedius reflexes. N, normal; ABN, abnormal.

Abnormal stapedius reflex decay

The full tension of the stapedius muscle cannot be maintained in response to continued stimulation. The tension drops to about 50% of its maximum value after a few seconds. Abnormal decay of the stapedius reflex is an indication of eighth-nerve abnormalities.

Speech audiometry

Speech audiometry assesses auditory discrimination as opposed to auditory acuity, requiring the subject to repeat standard word lists delivered through headphones at varying intensities. The responses are scored to provide an assessment of auditory discrimination that, together with other tests, is valuable in distinguishing conductive from sensorineural hearing impairment (in sensorineural hearing loss there is a roll-over effect, i.e., with increasing intensity, the percentage of correctly identified words diminishes). This is of particular value in assessing the efficacy of hearing aids. Speech recognition tests are also an essential item of the test battery for identification of auditory neuropathy, as speech intelligibility scores are poorer than can be explained by pure-tone thresholds.

Causes of cochlear (sensorineural) hearing loss (Luxon, 2008)

Genetic hearing loss

Many genes with autosomal-dominant, -recessive, and mitochondrial inheritance have been reported, in addition to genetic aberrations giving rise to X-linked hearing. Many of these forms of genetic hearing impairment present either in a nonsyndromal or syndromal pattern (Willems, 2000; Nance, 2003).

Age-related hearing loss, characterized by progressive deterioration of auditory sensitivity with age, is the leading cause of adult auditory impairment. Specific genes predispose individuals to environmental triggers affecting various molecular mechanisms underlying changes in auditory function. Specifically, a mitochondrial mutation (A1555G) has been identified with an increased susceptibility to aminoglycoside-induced hearing loss (Usami et al., 1998).

Autosomal-recessive hearing loss

Autosomal-recessive hearing loss accounts for approximately 40% of all cases of childhood hearing loss and

manifests as stable, profound, congenital/prelingual impairment. There may be marked intrafamilial variation in the severity of the loss and audiology is generally normal.

Autosomal-dominant sensorineural hearing loss

Autosomal-dominant sensorineural hearing loss is uncommon in prelingual profound hearing impairment, but is well recognized in families with hearing loss of various configurations, differing ages of onset, and differing rates of progression.

Syndromic hearing loss

More than 100 syndromes have been reported with associated hearing impairment. Many of these present in childhood, but hearing loss associated with certain syndromes can progress or, indeed, become apparent in adult life.

Metabolic disease

Genetic studies have defined the relationship of diabetes and hearing loss in mitochondrial mutations and in mutations of the WFS1 gene in the Wolfram syndrome of hearing impairment, diabetes mellitus, and optic atrophy. Renal failure is commonly associated with hearing loss. Ototoxicity from disease, drugs, and axonal uremic neuropathy have all been implicated as possible etiologies, while both dialysis and renal transplantation have been reported to be associated with recovery of hearing impairment.

Drugs

Many drugs produce ototoxicity, including chloroquine, loop diuretics, aminoglycosides, and salicylates. Platinum-based chemotherapeutic agents, in addition to the aminoglycosides, have been shown to damage the hair cells of the inner ear, while vincristine sulfate has been shown to produce bilateral cochlear nerve damage. Thalidomide has been demonstrated to produce aplasia of the eighth nerve in association with a Michel aplasia of the inner ear.

Acoustic trauma

Noise-induced permanent threshold shift is a common and preventable cause of sensorineural hearing loss, associated with hazardous occupational and/or recreational exposure to noise or acoustic trauma, e.g., gunfire and explosions. Characteristically, the maximal loss is at 4000 Hz, with a notched configuration to the audiogram. With time, the adjacent frequencies gradually deteriorate, but it is rare for a hearing loss greater than 70 dB to be the result of occupational noise exposure.

Acute barotrauma

Acute barotrauma associated with diving, depressurization in aircraft, and explosions may give rise to TM hemorrhage into the middle ear, with conductive hearing loss or perilymph fistula which is commonly associated with auditory and vestibular symptoms.

Physical trauma

Physical trauma (head injury) may lead to middle-ear, inner-ear, eighth-nerve, and/or central auditory loss. In mild and moderate head injuries, auditory abnormalities, commonly high-frequency sensorineural loss, are found in 50% of cases. Labyrinthine concussion and both longitudinal and transverse fractures of the petrous temporal bone may result in sensorineural and/or conductive hearing loss.

Menière's disease

This disorder is less common than originally thought; many of the cases are now being re-diagnosed as vestibular migraine. However, the diagnosis is clear when the patient describes acute attacks of intense vertigo and vomiting, sudden hearing loss, unilateral tinnitus, and aural fullness. The hearing loss is initially fluctuant and measurement of stapedius reflex thresholds shows a recruiting hearing loss.

Autoimmune inner-ear disease (Agrup and Luxon, 2006)

Autoimmune inner-ear disease refers to a presumed autoimmune condition in which there is sudden or rapidly progressive hearing loss in the absence of any other neurologic or systemic immunologic abnormalities. Cogan's syndrome is a rare, presumed autoimmune disorder, affecting the eye and the ear, with systemic manifestations including lymphadenopathy and cardiorespiratory involvement. Vogt–Koyanagi–Harada syndrome is a rare condition characterized by bilateral uveitis with cutaneous and neurologic features (cerebrospinal fluid pleocytosis) and auditory abnormalities. Susac's syndrome is a rare microangiopathy resulting in encephalopathy, retinopathy, and hearing loss, and is assumed to have an autoimmune basis. The encephalopathy causes prominent headache, personality change, paranoia, confusion, and cognitive impairment.

About one-third of cases of Behçet's syndrome have predominantly high-frequency cochlear hearing loss and vestibular involvement. Other systemic autoimmune

conditions associated with deafness include systemic lupus erythematosus, ulcerative colitis, scleroderma, polyarteritis nodosa, Sjögren's syndrome, giant cell arteritis, and Wegener's granulomatosis (Rudge, 1983; Overell and Lindhall, 2004).

Electroacoustic and electrophysiologic tests

Auditory evoked potentials can span activity from the full length of the auditory pathway, from cochlear hair cells to cerebral cortex. The methods use separate auditory potentials that are time-locked to the stimulus from background noise. The timing and waveform of activity vary among different levels of the auditory pathway and the orientation and position of the generators vary along the pathway. Therefore, electrode locations, filter settings and analysis times can be set up to selectively record activity from a specific generator along the auditory pathway and help site pathology.

Electrocochleography

Transtympanic electrocochleography (ECochG) is used to measure cochlear potentials and is essentially a surgical technique. Using a microscope, a needle electrode is inserted through the TM (if intact) and placed on the promontory of the middle ear. As the technique represents a near-field recording, transtympanically recorded cochlear potentials are 20 times larger in amplitude than those recorded noninvasively from an electrode in the ear canal. The major components and measures derived from an ECochG in response to alternating polarity clicks are: (1) the step-like negative deflection from baseline at the beginning of the record, known as the summating potential, followed by (2) a major negative peak, known as N1, called the cochlear compound action potential. Typically, ECochG is used to measure the ratio between the summating and action potentials and is most commonly used in the diagnosis of Menière's disease, when the summating potential to action potential ratio is greater than 30% (in the normal population it is significantly smaller).

Cochlear microphonics

Cochlear microphonics represent the early components of the acoustic brainstem responses, occur in the 0.7–1 ms window poststimulus, and show similar waveform characteristics to the stimulus. They are a far-field reflection of auditory activity of the eighth nerve in response to an acoustic stimulus. The response is cancelled out when performing auditory brainstem-evoked responses (ABR) by using alternate polarity clicks, thereby generating a "microphonic-free" ABR. Cochlear microphonics (Fig. 11.8) are best determined by reversing the click phase at 5–25 ms from condensation to rarefaction. By overlaying the responses to condensation and rarefaction clicks, the cochlear microphonics can be visualized (Berlin et al., 1998).

Transtympanic ECochG indicates that the phase reversal to the click stimulus occurs at the level of the cochlea itself, and therefore the presence of cochlear microphonics is indicative of a preneural response to sound. Cochlear microphonics in the presence of an abnormal ABR are typical of an auditory neuropathy (Sininger and Oba, 2001).

Otoacoustic emissions

An otoacoustic emission (OAE) is a low-intensity, mid-frequency sound, generated from within the inner ear by the active movement of the outer hair cells. OAEs were

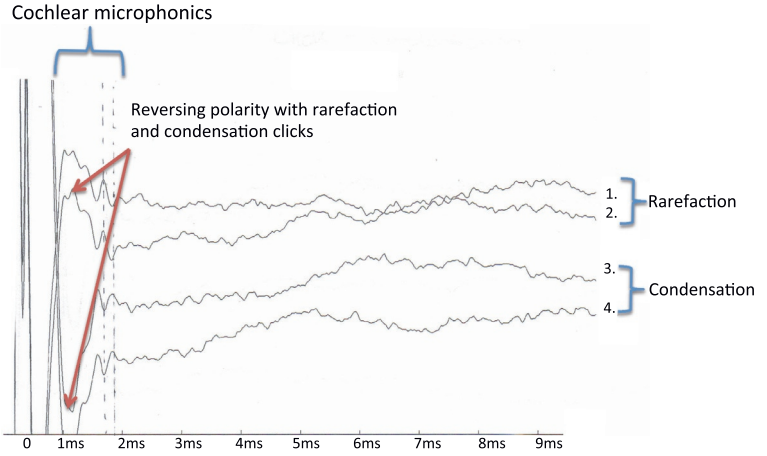

Fig. 11.8. Reversing auditory brainstem-evoked response (ABR) polarity with rarefaction and condensation clicks: cochlear microphonics and flat ABR seen in baby with auditory neuropathy spectrum disorder.

first demonstrated experimentally in 1978 (Kemp, 1978). Transient evoked OAEs (TEOAEs) are often used in the clinic as a measure of normal cochlear function. OAEs disappear after the inner ear has been damaged, but persist after section of the eighth nerve, and thus OAEs have been used to demonstrate auditory neuropathy.

TEOAEs are evoked by stimulation with transients at 80–86 dB summating potential and are captured in the first 20 ms after presentation of the stimulus. They are deemed present if the response amplitude is >4 dB greater than background noise. They can sometimes be reduced despite a normal audiogram and are regarded as a more sensitive test of cochlear hearing. False negatives occur if a conductive loss is present.

Figure 11.9 compares the audiograms of a patient with Menière's disease with the respective TEOAEs.

OAEs with contralateral suppression

The efferent auditory system is a neural network that is now well recognized, although some of the functions of this pathway are not yet clear. Information from higher auditory nuclei is relayed via olivocochlear efferents that connect the olivary complexes to the inner and outer hair cells of the cochlea (Guinan, 1996). With presentation of noise to the contralateral ear, OAEs generated by the outer hair cells of the cochlea can be suppressed. The pathways of this neural network that cross the brainstem, the medial and lateral olivocochlear bundles, are depicted diagrammatically in Figure 11.10.

Suppression of OAEs is found when a contralateral masker is applied during OAE measurement. Abnormal suppression is identified if noise (set to a level 5 dB louder than the click) presented to the contralateral ear fails to reduce the OAEs by 1 dB or more (Murdin and Davies, 2008). If abnormal, this implies a lesion in either afferent pathway from the contralateral ear or efferent pathway on the ipsilateral side (Fig. 11.10).

Acoustic brainstem-evoked responses

Auditory potentials evaluate processing lower in the brain (auditory brainstem response audiometry), whereas others assess functioning higher in the brain (middle-latency responses, late auditory evoked responses, auditory cognitive, or P300 responses).

ABRs are detected by surface electrodes, and represent electric activity transmitted by the eighth nerve and brainstem auditory relay centers in the 10 seconds immediately after an acoustic stimulus (Jewett et al., 1970). There has been long-standing debate about most of the generators of the ABR waveforms, and only wave I has definite attribution – to the cochlea. Wave II is thought to arise from the cochlear nucleus, whilst waves III, IV, and V are considered to arise from generator sites within the brainstem auditory pathways.

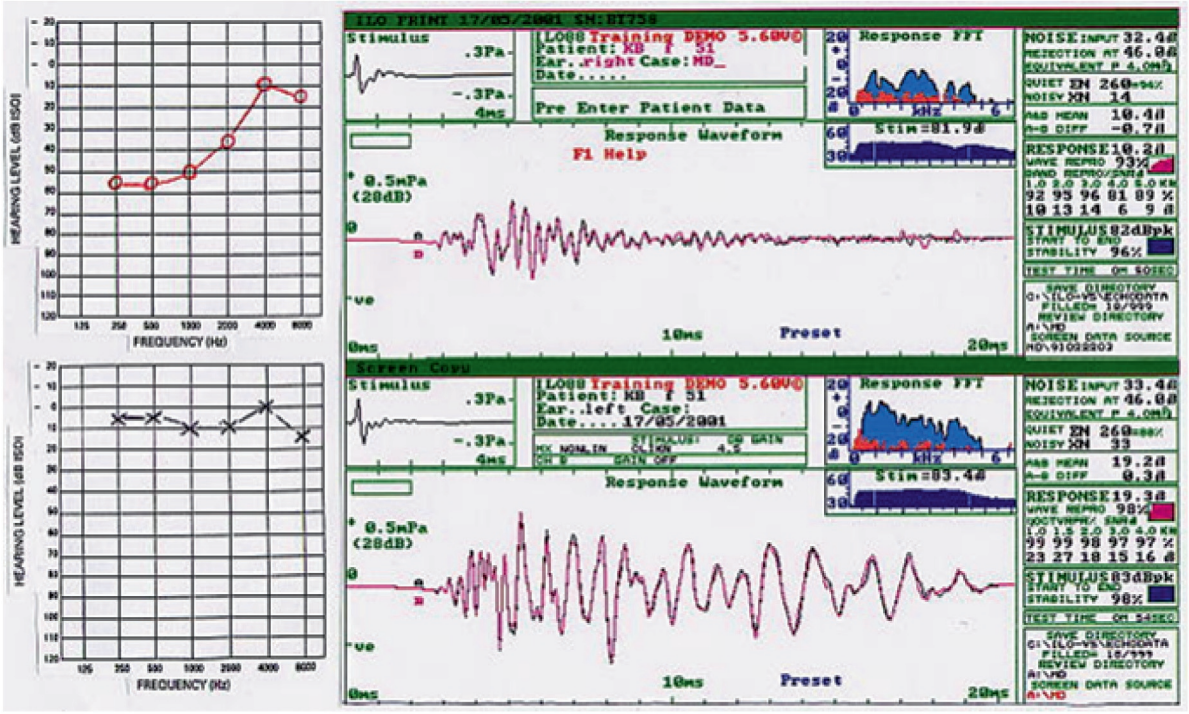

Fig. 11.9. Pure-tone audiogram (showing raised thresholds in the right low frequencies) and otoacoustic emissions (right comparatively lower than the left) of a patient with right Menière's disease.

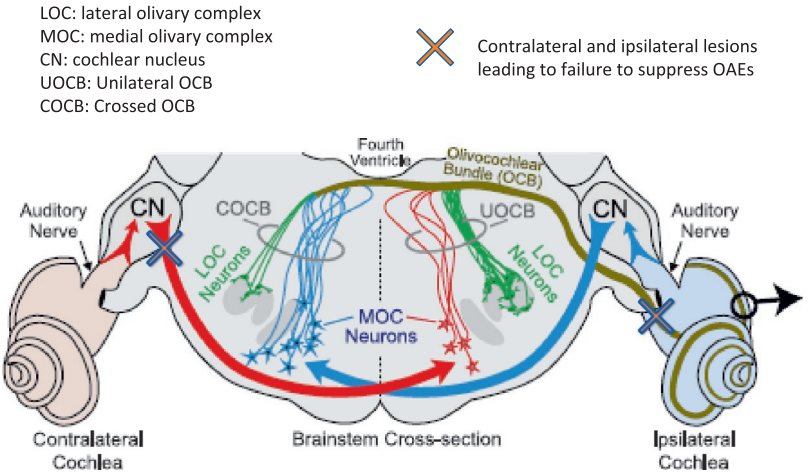

Fig. 11.10. The medial and lateral olivocochlear systems showing contralateral and ipsilateral lesions leading to failure to suppress otoacoustic emissions. (Modified from Guinan, 1996 with permission from Springer Science and Business Media.)

Two protocols can be followed depending on the purpose of the ABR: in the neuro-otology clinic, ABRs with stimulus intensity of 90 or 100 dB are recorded both ipsi- and contralaterally (Fig. 11.11). Measurements are made of the absolute latencies of the waveforms and the interwave latencies, identifying any abnormalities. Interaural wave latencies and interwave intervals are compared. Prolongation of the I–III interval can be seen in auditory nerve and cochlear nucleus pathology. Prolongation of the III–V interval is usually indicated when pathology is sited above the level of the cochlear nucleus, while absent IV and/or V waves are found in cases with involvement of the mid-upper pons. Interaural latency comparisons of wave V are of value in the diagnosis of vestibular schwannoma, but may not be useful in detecting brainstem involvement. An absent ABR of the patient with auditory neuropathy may be explained by the altered temporal synchrony of the auditory brainstem pathway.

In the audiology clinic, for neonates, or others who cannot perform subjective audiometry, threshold ABRs are recorded to determine the level of hearing (Fig. 11.12A). Latency intensity series can be seen in Figure 11.12B. The wave V latency shortens with maturation of the eighth nerve and is considered to reach permanent values by the age of 12 months.

As an example of how abnormal electroacoustic and electrophysiologic tests can be combined alongside the PTA and speech audiometric thresholds, the eighth-nerve pathologies known as auditory neuropathy spectrum disorder (ANSD) are described below.

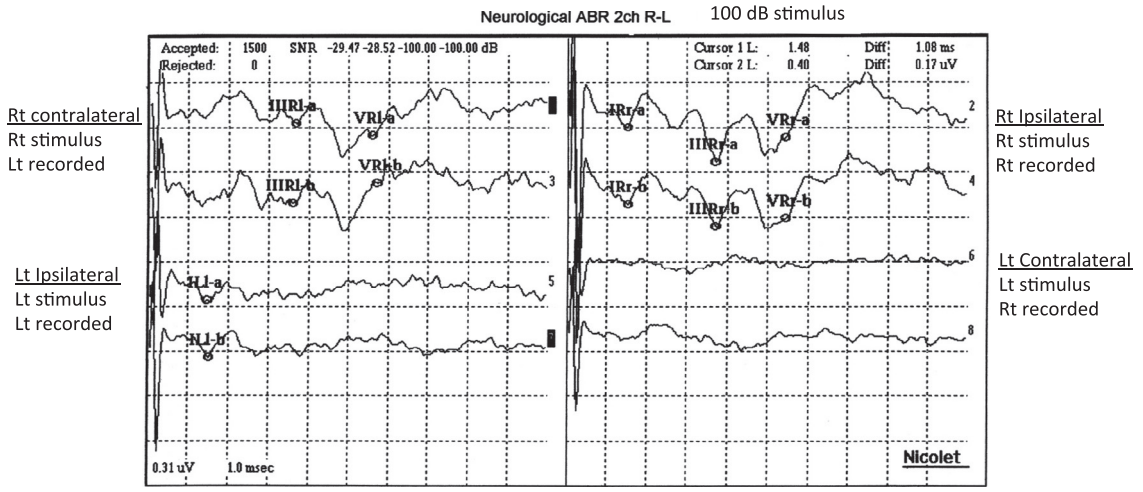

Fig. 11.11. A neuro-otologic auditory brainstem-evoked response showing both ipsi- and contralaterally recorded waveforms in a patient with multiple sclerosis and left eighth-nerve pathology (absent waveforms on both left stimulated recordings except for wave I on the left ipsilateral trace). Duplicates of each recording condition are performed to ensure reproducibility.

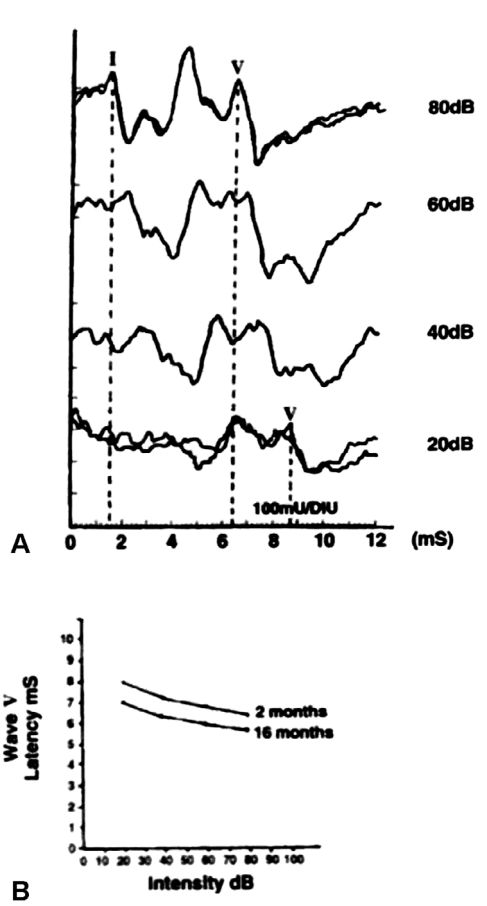

Fig. 11.12. (A) A normal threshold series in a 16-month-old baby, i.e., still present at 20 dB. (B) Latency intensity series for a 2-month and a 16-month-old baby, showing eighth-nerve maturation effects, i.e., decreasing latency of wave V with increasing age.

Auditory neuropathy spectrum disorder

ANSD is the term that has been developed to describe a group of heterogeneous disorders with similar auditory test results. Common features are disordered synchronization of sound and intact preneural hearing. Patients say they can identify the speech sounds and the language used, but they cannot understand the words. Difficulties are always more marked in noisy environments when there are competing signals and the severity of the hearing impairment may be variable and can range from transient, intermittent, to stable and deteriorating (Sininger et al., 1995).

On audiometric evaluation, inconsistent measures of hearing are found: paradoxic ABR (Kraus et al., 1984; Starr et al., 1996) and behavioral audiometry tests, i.e., where hearing sensitivity (PTA thresholds) is better than might have been expected from the ABR. Both OAEs and cochlear microphonics are normal.

The loudness of sound is relatively well perceived, but the synchronization of acoustic signals is not adequate to evoke an ABR, to suppress the contralateral OAEs, or elicit the stapedius reflex. Table 11.6 (Stein et al., 1996; Madden et al., 2002) shows the typical audiologic abnormalities of ANSD, Table 11.7 shows the genetic cause of ANSD, and Table 11.8 shows the acquired causes of ANSD (Davies, 2008).

AUDITORY PROCESSING DISORDERS

Central auditory processing disorders can manifest in both children and adults with difficulties with word recognition, environmental sounds or music, and with uncertainty about what an individual hears, despite the presence of normal hearing thresholds (Bamiou et al.,

Table 11.6

Auditory neuropathy spectrum disorder: typical audiologic abnormalities

Auditory brainstem-evoked responses	Absent or severely abnormal
Cochlear microphonics	Normal
Pure-tone thresholds	Normal to severe impairment
Otoacoustic emissions/distortion product otoacoustic emissions	Normal
Contralateral suppression of otoacoustic emissions	Absent
Stapedius reflexes	Absent

Table 11.7

Genetic causes of auditory neuropathy spectrum disorder

Nonsyndromal
- Otoferlin (OTOF) gene
- Delayed maturation

Syndromal

Plus peripheral neuropathy
- Charcot–Marie–Tooth (hereditary motor and sensory neuropathy)
- Roma gypsies (NDRG1 gene)
- Neurofibromatosis type 2
- Refsum's

Minus peripheral neuropathy
- Arnold–Chiari
- Usher's
- Mitochondrial MELAS/CPEO
- Branchio-otorenal

MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; CPEO, chronic progressive external ophthalmoplegia.

Table 11.8

Acquired causes of auditory neuropathy spectrum disorder

Infection
• Herpes zoster/herpes simplex (Ramsay Hunt; Bell's palsy); cytomegalovirus
Basal meningitis
• Pneumococcal, meningococcal, *Haemophilus*, tuberculosis, cryptococcosis
Postinfective (Guillain–Barré)
Vasculitic/granulomatous
• Systemic lupus erythematosus, rheumatoid arthritis, sarcoid, Behçet's
Demyelination
• Multiple sclerosis (eighth-nerve, brainstem)
Neoplasia
• Vestibular schwannoma, meningioma, cerebellopontine angle lesion, carcinomatosis, radiotherapy
Metabolic
• Uremia, Paget's disease, organic mercury, cisplatin, hemosiderosis

2001). Katz (1992) described central auditory processing as "what we do with what we hear." Patients may experience difficulties listening in background noise or with people conversing, understanding degraded or rapid speech, following oral instructions, localizing sounds, or perceiving music. They also may have language and other disorders, professional and academic problems and behavioral, emotional, social, and other difficulties.

Central auditory processes are the auditory system mechanisms and processes responsible for the following behavioral phenomena (Jerger and Musiek, 2000):

1. sound localization and lateralization
2. auditory discrimination
3. temporal aspects of audition, including temporal resolution, temporal masking
4. temporal integration and temporal ordering
5. auditory performance with competing acoustic signals
6. auditory performance with degraded signals.

It is the ability of the brain to process incoming auditory signals. The brain identifies sounds by analyzing their distinguishing physical characteristics, frequency, intensity, and temporal features. These are features we perceive as pitch, loudness, and duration. Once the brain has completed its analysis of the physical characteristics of the incoming sound or message, it then constructs an "image" of the signal from these component parts for comparison with stored "images." If a match occurs, we can then understand what is being said or we can recognize sounds that have important meanings in our lives (sirens, doorbells, crying, etc.).

A detailed history of the auditory complaints is needed as patients may deny the presence of hearing complaints as they do not always attribute difficulties to hearing problems. Features of auditory complaints may help define the diagnosis, e.g., in cases of cortical deafness, in which the patient has abnormal hearing thresholds because of bilateral auditory cortex lesions, and in auditory agnosia, of speech, music, and environmental sounds, which may be isolated or in combination. Thirdly, identification of specific auditory complaints (e.g., specific pitch difficulties or music-related problems) guides the choice of tests and provides some clues to the site of the lesion.

Electrophysiologic tests

Middle-latency response

The middle-latency response generator sites are presumed to be within thalamocortical pathways to the auditory cortex. Sensitivity and specificity of middle latency responses for central auditory pathology are reasonably good, and the test is therefore valid and objective in assessment of central auditory dysfunction, but sleep and sedation may affect responses.

Cortical-evoked auditory responses

Cortical- or late-evoked auditory responses are the most effective method of defining auditory thresholds at each frequency in a patient who is unable or unwilling to cooperate; they are essential in legal cases, in which nonorganic loss should always be considered.

Psychophysical tests

Binaural integration tests

These encompass those tests that require the interaction of both ears in order to effect integration of information separated by time, intensity, or frequency factors to the two ears. This unification of auditory information is presumed to occur in the brainstem, and these tests are thought to be sensitive to brainstem pathology.

Masking level difference

A stimulus is applied to both ears (words or pulsed pure tones) at the same time as a broadband masking noise is delivered to the two ears. The patient is tested under two conditions, a homophasic and an antiphasic condition. In the former, the signal, the stimulus, and noise are presented in phase, whereas in the antiphasic condition one of the two signals is presented 180° out of phase. Subtracting the thresholds established in the homophasic condition from that found in the antiphasic condition

represents the masking level difference (normal tends to be 6 dB or less). This is considered to be a "release from masking" occurring at the level where information from the two ears is first integrated.

Dichotic speech tests

In these tests different speech items are presented to both ears either simultaneously or in an overlapping manner and the patient is asked to repeat everything that is heard (divided attention) or repeat whatever is heard in one specified ear (directed attention). The more similar and closely acoustically aligned the test items, the more difficult the task.

The ipsilateral pathways are weaker and tend to be suppressed and neural impulses travel up the more dominant contralateral pathways to reach the auditory reception area. Typically, contralateral ear effects are noted with lesions of the auditory cortex, whereas left-ear defects are noted in patients with lesions within the interhemispheric pathways.

Dichotic Digit Tests

One of the more commonly used tests in this category is the Dichotic Digit Test (Musiek, 1983). The patient is asked to listen to four numbers presented to the two ears at comfortable listening levels. In each test item two numbers are presented to one ear and two numbers are presented to the other ear. An example of a test stimulus from the dichotic digits test would be: "5" is presented to the right ear at the same time "1" is presented to the left ear. Then the numbers "9" and "6" are presented simultaneously to the right and left ears. The patient is asked to repeat all numbers heard and a percent correct score is determined for each ear and compared to age-appropriate norms.

Monaural low-redundancy speech tests

Due to the richness of the neural pathways in our auditory system and the redundancy of acoustic information in spoken language, a normal listener is able to recognize speech even when parts of the signal are missing. However, this ability is often compromised in the individual with central auditory processing disorders. Monaural low-redundancy speech tests represent a group of tests designed to test an individual's ability to achieve auditory closure when information is missing. The speech stimuli used in these tests have been modified by changing one or more of the following characteristics of the speech signal: frequency, temporal, or intensity characteristics.

An example of a test in this category is the Compressed Speech test (Beasley et al., 1972). This is a test in which the speech signals have been altered electronically by removing portions of the original speech signal. The test items are presented to each ear individually and the subject is asked to repeat the words that have been presented. A percent correct score is derived for each ear and these are compared to age-appropriate norms. Monaural presentation of degraded stimuli is sensitive to cortical lesions, in which case contralateral ear defects are commonly noted.

Temporal patterning tests

These tests involve feature detection, frequency, or duration discrimination and acoustic contour recognition. The patient is asked to label the patterns perceived, then linguistic processing is also tapped. These tests have been shown to be sensitive to compromise of the auditory cortex in the right hemisphere (responsible for processing of the acoustic contour of the patterns). If a verbal response is required, the test is sensitive to lesions in the left hemisphere (responsible for verbally labeling the patterns perceived) and/or the interhemispheric pathways.

Frequency Pattern Sequences test (Musiek and Pinheiro, 1987)

This is one of the temporal patterning tests used frequently. The test items are sequences of three tone bursts that are presented to one or both ears. In each of the sequences, two tone bursts are of the same frequency, while the third tone is of a different frequency. There are just two different frequencies used in this test: one is a high-frequency sound and the other a low-frequency sound. The subject therefore hears patterns, such as high-high-low or low-high-low, and is asked to describe the patterns heard. As with other central tests, the test items are presented at levels (50 dB sensation level) that are comfortable and percent correct scores are obtained and compared to norms. The test assesses primarily right-hemisphere function.

Causes of central auditory processing disorders

1. Genetic causes. These include syndromes that affect brain structure or make the brain more susceptible to damage. The genetic basis of these auditory processing deficits observed with other developmental disorders remains unclear.
2. Neurologic conditions such as tumors, stroke, and multiple sclerosis.
3. Auditory deprivation, e.g., following OME or other type of peripheral hearing loss.
4. In the presence of other higher-order disorders, such as attention deficit disorder, dyslexia,

specific language impairment – although in these cases no causal link has been established.
5. Age-related changes of the central auditory system, distinct from age-related cochlear hearing loss or cognitive decline.
6. Finally, some forms of tinnitus and musical hallucinations, attributed to abnormal activity of the auditory cortex.

Cortical hearing impairment

The primary auditory cortex lies in the anterior–posterior transverse temporal gyrus of Heschl. Each ear has bilateral representation in the auditory cortex, and thus it is possible to remove the nondominant hemisphere in humans without significant effect on either the PTA or the discrimination of distorted speech.

In some cases, the primary auditory deficit predominates, and these cases are described as true cortical deafness. In this situation, a patient may present with no subjective experience of hearing, and demonstrate profound hearing loss on pure-tone audiometry. This may be misdiagnosed as peripheral if electroacoustic and electrophysiologic testing is not conducted. For example, otoacoustic emissions and ABR will demonstrate normal peripheral auditory function. However, abnormal central auditory function will be identified by the later auditory evoked potentials, specifically the middle-latency response N1 and P2 waves.

Auditory agnosia

Auditory agnosia was defined originally as a selective disorder of sound recognition: "I can hear you talking, but I cannot translate it." This group can be further subdivided into several different clinical presentations: those who are unable to recognize a particular type of sound, e.g., speech, music, or particular environmental noises, such as a dog barking, and those who are unable to discriminate at all between verbal and nonverbal sounds. Most cases correspond to the wider definition, with impairment of all modalities of auditory function. Nonetheless, there are also cases of verbal auditory agnosia ("word deafness"), in which speech perception is severely impaired, while recognition of nonverbal material such as musical tunes embedded within environmental noise remains intact.

Interhemispheric lesions

Patients with surgical section of the posterior corpus callosum demonstrate a typical pattern of auditory processing test results, termed the auditory disconnection profile. Characteristically, they have normal performance on monaural low-redundancy speech tests, left-ear deficits on dichotic speech tests, and bilateral deficits on temporal pattern testing.

CONCLUSION

This chapter not only describes the tests available to identify a peripheral and/or a central lesion causing hearing difficulties, but also the clinic information required and details of the otologic assessment that add further diagnostic information directing the choice of tests available. Where an understanding of the anatomophysiologic mechanisms of audition or the physical basis of a test is required to understand the test, this is also included.

Hearing tests of the peripheral auditory system are well established and the PTA is generally regarded as the screening test of choice in adults. Electrophysiologic testing with auditory event-related potentials is used to help identify sites of lesion in the eighth nerve, brainstem, and more centrally. In the last two decades a battery of central auditory tests has been established that can probe the central pathways in more detail, i.e., when the PTA may be normal, and yet the patient still has symptoms of hearing dysfunction. It is hoped that this chapter will have roused the interest of the clinician to explore the auditory system further by clinic assessment and choice of an appropriate test battery when faced with a patient presenting with symptoms of hearing dysfunction.

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Chapter 12

Rotational testing

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Abstract

The natural stimulus for the semicircular canals is rotation of the head, which also might stimulate the otolith organs. Vestibular stimulation usually induces eye movements via the vestibulo-ocular reflex (VOR). The orientation of the subject with respect to the axis of rotation and the orientation of the axis of rotation with respect to gravity together determine which labyrinthine receptors are stimulated for particular motion trajectories. Rotational testing usually includes the measurement of eye movements via a video system but might use a subject's perception of motion. The most common types of rotational testing are whole-body computer-controlled sinusoidal or trapezoidal stimuli during earth-vertical axis rotation (EVAR), which stimulates primarily the horizontal semicircular canals bilaterally. Recently, manual impulsive rotations, known as head impulse testing (HIT), have been developed to assess individual horizontal semicircular canals. Most types of rotational stimuli are not used routinely in the clinical setting but may be used in selected research environments. This chapter will discuss clinically relevant rotational stimuli and several types of rotational testing that are used primarily in research settings.

The natural stimulus for the semicircular canals is rotation of the head. Head rotation may also stimulate the otolith organs. Vestibular stimulation usually induces eye movements via the vestibulo-ocular reflex (VOR). Cohen (1984a, b) has reviewed the history of using rotational testing to assess vestibular function. Typically, whole-body rotation uses sinusoidal or trapezoidal trajectories. Head-only rotation uses sinusoidal or, more recently, impulsive trajectories. The orientation of the subject with respect to the axis of rotation and the orientation of the axis of rotation with respect to gravity together determine which labyrinthine receptors are stimulated for particular motion trajectories. Rotational testing usually includes the measurement of eye movements via a video system but may use a subject's perception of motion. Perceptual data are somewhat variable and not especially useful for quantitative analysis.

The most common types of rotational testing are whole-body computer-controlled sinusoidal or trapezoidal stimuli during earth–vertical axis rotation (EVAR), which stimulates primarily the horizontal semicircular canals bilaterally. This type of testing is considered a standard vestibular function test (Fife et al., 2000). Recently, manual impulsive rotations, known as head impulse testing (HIT), have been developed to assess individual horizontal semicircular canals (Weber et al., 2008; MacDougall et al., 2009, 2013). The HIT has widespread clinical applicability. There are numerous other types of rotational testing, some of which are discussed below.

Although the eye movement responses to rotation depend upon the specific vestibular receptors being stimulated, several other factors that influence the eye movement response include: (1) whether or not the rotation of the head is active or passive; (2) the visual condition, i.e.,darkness vs. a subject-stationary target vs. an earth-stationary target; and (3) level of alertness. Some rotational stimuli are especially technically challenging to deliver, difficult for subjects to tolerate, or produce eye movement responses difficult to measure and analyze. Most types of rotational stimuli are not used routinely in the clinical setting but may be used in selected research environments (Table 12.1). This chapter will discuss

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Table 12.1 Types of rotational testing

Orientation of head re axis of rotation	Orientation of axis of rotation re gravity	End organs stimulated	Comments
Yaw (on-axis)	Earth–vertical	Semicircular canals (primarily horizontal canals)	Most common clinical stimulus; postrotatory head tilt stimulates otolith organs
Yaw (eccentric off-axis rotation)	Earth–vertical	Unilateral otolith (primarily utricle) at constant velocity	"Unilateral centrifugation," "Off-axis rotation"
Pitch	Earth–vertical	Semicircular canals (primarily vertical canals)	"On-side" rotation
Roll	Earth–vertical	Semicircular canals (primarily vertical canals)	Induces dynamic ocular counter-rolling
RALP/LARP planes	Earth–horizontal	Semicircular canals (vertical)	Induces a complex eye movement
Yaw	Off-vertical/ earth–horizontal	Otolith organs and semicircular canals if not at constant velocity	"OVAR" if off-vertical tilt $<90°$; "barbecue" if earth–horizontal (tilt $= 90°$)
Pitch	Earth–horizontal	Otolith organs and semicircular canals if not at constant velocity	"Head-over-heels" rotation
Roll	Earth–horizontal	Otolith organs and semicircular canals if not at constant velocity	Static tilts induce ocular counter-rolling

RALP, right anterior, left posterior; LARP, left anterior, right posterior; OVAR, off-vertical axis rotation.

clinically relevant rotational stimuli. Figure 12.1 illustrates three types of yaw rotational stimuli and highlights the importance of the orientation of the rotation axis with respect to gravity.

EARTH–VERTICAL AXIS ROTATION

EVAR is the most common clinically useful rotation test. EVAR is performed with the subject seated upright in a rotational chair affixed to a computer-controlled rotational device. The upright orientation of the subject with respect to the axis of rotation constitutes a yaw rotation (Fig. 12.1A). With the orientation of the axis of rotation aligned with gravity, i.e., earth–vertical, a purely semicircular canal stimulation is accomplished (Fig. 12.1B, panel A). EVAR in darkness generally causes nystagmus, which can be analyzed to assess the VOR independently of vision. Eye movements are usually recorded with video-oculography and analyzed by computer. The most common rotational velocity trajectories for EVAR are: (1) trapezoidal rotation, sometimes called step rotation, consisting of a gradual acceleration to a constant-velocity rotation sustained for approximately 1 minute followed by a rapid deceleration to a stop during which eye movements are recorded; (2) sinusoidal rotation, consisting of a periodically alternating rotational velocity; and (3) impulsive rotation, a recently described technique consisting of a rapid acceleration to a peak velocity followed by a gradual deceleration.

Trapezoidal EVAR consists of multiple rotations using velocities of different magnitude. Sinusoidal stimulation typically consists of sinusoids of different frequencies ranging from approximately 0.01 Hz to 1.0 Hz at one or more peak velocities. Trapezoidal rotation is designed to deliver an abrupt rotational acceleration or deceleration to assess the transient response of the VOR, whereas sinusoidal rotation is designed to assess the steady-state response of the VOR. Eye movements induced by trapezoidal testing are analyzed to yield an estimate of the magnitude, timing, and symmetry of the response, known as gain, time constant, and directional preponderance, respectively. The analysis of eye movements induced by sinusoidal EVAR is also designed to yield estimates of magnitude, timing, and symmetry of the VOR, known as gain, phase, and directional preponderance. The eye movements induced by EVAR are typically nystagmoid and are analyzed by first removing quick components of the vestibular nystagmus to isolate the vestibular slow components, which are thought to reflect the activity of the peripheral vestibular system (Fig. 12.2). The velocity of the slow components over time is concatenated and compared to the rotational stimulus. For trapezoidal stimulation, the induced slow-component eye velocity is typically characterized by an exponentially decaying trajectory. Estimates of VOR magnitude and time constant are based on a best fit of an exponential function to the slow-component velocity. The ratio of the magnitude of the exponential response to

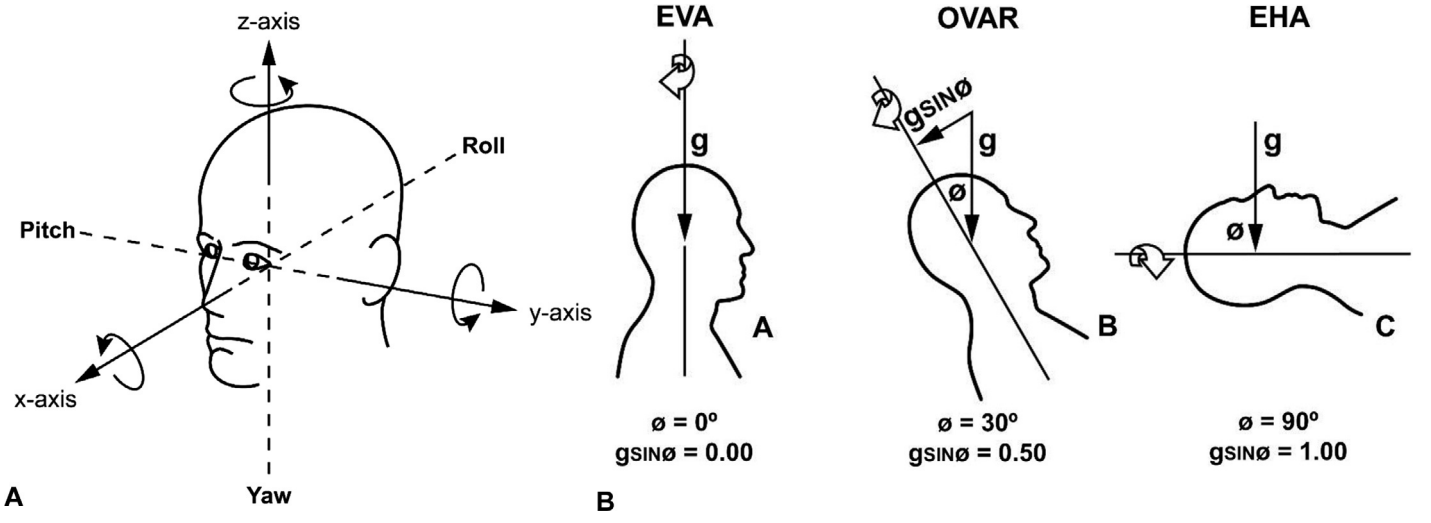

Fig. 12.1. Orientation of subject and stimulus for three types of yaw rotation. (**A**) Orientation of the subject to the axis of rotation. Yaw is equivalent to rotating the head left and right, like saying "no"; pitch is equivalent to nodding the head up and down, like saying "yes"; roll is equivalent to tilting the head from ear to shoulder. (**B**) Orientation of the axis of rotation with respect to gravity. For earth–vertical axis rotation, the axis of rotation is oriented along gravity. For off-vertical axis rotation (OVAR), the axis of rotation is tilted with respect to gravity. For earth–horizontal axis rotation, which is an extreme example of OVAR, the axis of rotation is perpendicular to the direction of gravity. From Furman (2010).

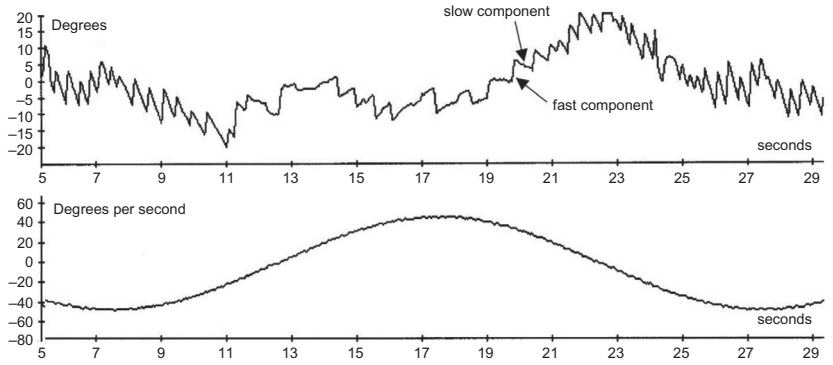

Fig. 12.2. Nystagmus induced by earth–vertical exis rotation at 0.05 Hz. The nystagmus alternates its direction from right-beating to left-beating to right-beating. A slow component and a fast component of the nystagmus are labeled. Note that the rotational stimulus is shown below the eye position trace. From Furman (2010).

Table 12.2

Normative data for earth–vertical axis rotation

Test items	Normative limits ($\mu \pm 2$ seconds)	Number of cases, reference
Sinusoidal testing		
Gain		
0.05 Hz, 60°/s	0.20–0.80	$n=20$ (Baloh et al., 1984)
0.05 Hz 60°/s	0.13–0.77	$n=10$ (Hess et al., 1985)
0.05 Hz, 50°/s	0.24–0.85	$n=38$ (Van der Stappen et al., 2000)
0.05 Hz, 60°/s	0.38–0.98	$n=167$ (Peterka et al., 1990b)
Phase		
0.05 Hz, 60°/x	6–14°	$n=20$ (Baloh et al., 1984)
0.05 Hz, 60°/s	2–20°	$n=10$ (Hess et al., 1985)
0.05 Hz, 50°/s	–1–18°	$n=38$ (Van der Stappen et al., 2000)
0.05 Hz 50°/s	–1.9–24°	$n=50$ (Wall et al., 1984)
0.05 Hz 60°/s	0.8–20.2	$n=167$ (Peterka et al., 1990b)
Directional preponderance		
0.05 Hz, 60°/s	≤15%	$n=208$ (Peterka et al., 1990b)
0.05 Hz, 50°/s	≤24%	$n=38$ (Van der Stappen et al., 2000)
Trapezoidal testing @ 90°/s		
Gain	0.33–0.72	$n=20$ (Theunissen et al., 1986)
Time constant	11–26 ×	$n=20$ (Theunissen et al., 1986)
Directional preponderance	≤22%	$n=20$ (Theunissen et al., 1986)
Trapezoidal testing @ 100°/s		
Gain	0.27–0.99	$n=43$ (Baloh and Honrubia, 1990)
Time constant	5–19.4 seconds	$n=43$ (Baloh and Honrubia, 1990)

the magnitude of the rotational stimulus velocity yields an estimate of VOR gain. The time constant of the exponential decay is used to provide an estimate of the VOR time constant. A comparison of the magnitude to the right and to the left provides a measure of directional preponderance.

For sinusoidal testing, the analysis of slow-component eye velocity also provides estimates of magnitude and timing of the VOR via measures of gain and phase rather than gain and time constant. Directional preponderance of the VOR using sinusoidal stimulation is estimated based on the amount of asymmetry in the sinusoidal eye velocity response to a symmetric sinusoidal rotational stimulus. For sinusoidal testing, the estimates of gain and phase are based on the best fit to a sinusoid through the slow-component eye velocity. Linear systems theory can be used to relate the transient response measures of gain and time constant to the steady-state measures of gain and phase. This correspondence does not exist for directional preponderance, as this measure reflects a nonlinearity in the VOR. Table 12.2 provides normative data for EVAR for both trapezoidal and sinusoidal stimulation.

The usefulness of the parametric measures of the VOR described above depends upon the clinical or research setting. Gain of the VOR reflects the overall sensitivity of the horizontal semicircular canal-ocular reflex. Reduced gain can be seen in patients with reduced vestibular function unilaterally or bilaterally (Jenkins et al., 1982). Abnormalities of VOR time constant and phase generally reflect the presence of unilateral peripheral vestibular dysfunction, although some central disorders can be associated with changes in time constant and phase (Jenkins et al., 1982). A directional preponderance reflects a dynamic VOR asymmetry and often can be seen in the setting of either peripheral or central vestibular disease (Baloh et al., 1989). Generally, a directional preponderance is associated with active symptoms in patients with vestibular disorders. Impulsive EVAR is a recently described technique to assess unilateral semicircular canal function using whole-body rotation (Furman et al., 2014). Impulsive EVAR uses a rotational stimulus comparable to that used with head-only impulsive testing, i.e., the HIT, which is discussed later in this chapter. Preliminary results suggest impulsive EVAR is a reliable, repeatable technique that can be used to assess unilateral horizontal semicircular canal function. The advantages of impulsive EVAR as compared to the HIT include the absence of neck stimulation, the longer duration of the stimulus, which yields more data, and the lower jerk of the stimulus. The obvious disadvantage of impulsive EVAR is the need for expensive, laboratory-based equipment.

OFF-VERTICAL AXIS ROTATION

The term off-vertical axis rotation (OVAR) refers to rotational stimulation using an axis of rotation that is not earth–vertical (Fig. 12.1B, panel B). During OVAR, the orientation of the subject changes continuously with respect to gravity; the amount of off-vertical tilt determines the portion of earth's gravity that is applied in the plane perpendicular to the axis of rotation according to a cosine rule. Regardless of the orientation of the axis of rotation with respect to gravity, if the subject is rotated about the body-vertical axis, the rotation is considered "yaw." During yaw OVAR, the component of gravity that is applied in the plane perpendicular to the axis of rotation will primarily stimulate the utricles as they lie in nearly a horizontal body plane. Thus, for yaw OVAR, there is a nonzero component of gravity in the head-horizontal plane that continuously changes its orientation with respect to the subject's naso-occipital and interaural axes. It is this changing orientation with respect to gravity, leading to a linear acceleration of constant magnitude but changing direction sensed by the otolith organs. For a 30° tilt, the component of gravity in the plane perpendicular to the axis of rotation, and thus in the head horizontal plane for yaw OVAR, is gSIN30, which equals 0.5 **g**. For a 90° tilt, i.e., earth–horizontal axis (EHA) rotation (Fig. 12.1B, panel C), gSIN90, i.e., the entire force of gravity, i.e., 1.0 **g**, rotates in the subject's horizontal plane.

As for EVAR, rotational velocity during OVAR can either be constant or vary sinusoidally. To better understand the response of the VOR to OVAR, it is convenient to consider the interaural and naso-occipital components of the OVAR stimulus separately. For constant-velocity OVAR, both the interaural and naso-occipital projections of the gravity vector vary sinusoidally. For sinusoidal OVAR, however, the interaural and naso-occipital projections of the stimulus are complex since they can be represented by a transcendental function of a transcendental function. For constant-velocity OVAR, the acceleration-sensitive semicircular canals are stimulated by the initial acceleration but eventually stop responding. Thus, only the otolith organs are stimulated continuously. For sinusoidal OVAR, both the semicircular canals and the otolith organs are stimulated continuously.

OVAR can be performed using one of two basic paradigms, namely tilt then rotate (T,R) or rotate then tilt (R,T). Thus, OVAR can be performed in one of four ways: (1) constant-velocity T,R; (2) sinusoidal T,R; (3) constant-velocity R,T; and (4) sinusoidal R,T. Conceptually, T,R is the most easily understood because the orientation of the subject with respect to the axis of rotation and the orientation of the axis of rotation with respect to gravity is positioned prior to the onset of the stimulus. Sinusoidal T,R produces a continuous stimulation of both the semicircular canals and the otolith organs and can be useful for assessing dynamic semicircular canal–otolith interaction. Constant-velocity T,R is a far less useful paradigm because the semicircular canals only respond to the initial rotational acceleration and then their response decays exponentially. Thus, the stimulus during the first 60 seconds of rotation consists of a decaying semicircular canal stimulation and a continuous otolithic stimulation. Although constant-velocity T,R can yield data regarding the influence of otolithic stimulation on the time constant of the semicircular canal response, the most useful portion of the stimulus occurs after the semicircular canal response has decayed, so that pure otolithic influences can be measured. Unfortunately, because OVAR causes nausea (Furman et al., 1992; Denise et al., 1996), the initial 60 seconds of constant velocity OVAR produces significant discomfort without providing much useful data. A constant-velocity R,T paradigm, however, can overcome this problem of producing nausea needlessly while waiting for the semicircular canal response to decay. That is, by rotating at constant velocity about an earth–vertical axis until the semicircular canal response decays and then tilting the subject,

pure otolithic responses can be measured with minimal nausea.

Postrotational responses at the end of a constant-velocity OVAR paradigm reflect the interaction of a semicircular canal stimulus caused by the rotational deceleration and a static otolith stimulus caused by the nonvertical orientation of the subject. Note that, when rotation ceases, the subject is stopped in one of four tilted positions, i.e., nose up, nose down, right ear down, or left ear down. Thus, the two OVAR paradigms that are the most useful are sinusoidal T,R and constant-velocity R,T. Similar to EVAR, sinusoidal testing is usually performed at several frequencies between 0.02 and 1.0 Hz and constant-velocity testing is often performed at 30, 60, or 90°/s.

Yaw OVAR, unlike yaw EVAR, induces vertical and torsional eye movement in addition to horizontal eye movement (Kamura and Yagi, 2001). The analysis of horizontal eye movement recordings obtained during OVAR is designed to yield a parameterization of the otolith-ocular reflex and of semicircular canal–otolith interaction. The analysis method for sinusoidal OVAR is identical to that used for sinusoidal EVAR. Specifically, after using the technique illustrated in Figure 12.2 to generate slow-component velocity, responses are used to estimate the gain, phase, and symmetry of the responses. For the analysis of constant-velocity OVAR responses, the analysis begins the same way, i.e., the generation of slow-component velocity traces. Then, the slow-component velocity vs. time records are used to estimate the nonzero baseline, the so-called "bias" component, and the sinusoidal so-called "modulation component" (Darlot et al., 1988; Furman et al., 1992). There are no standardized methods for analyzing the nonhorizontal eye movements induced by OVAR. The gain of the response to sinusoidal OVAR, like the gain of the response to sinusoidal EVAR, reflects the sensitivity of the VOR. The phase of the response to sinusoidal OVAR, like the phase of the response to sinusoidal EVAR, reflects the dynamic characteristics of central vestibular processing. The symmetry of the response to sinusoidal OVAR, like the symmetry of the response to sinusoidal EVAR, reflects the equality of the propensity for leftward vs. rightward eye movements. The bias component of the response to constant-velocity OVAR consists of the nonperiodic component of the slow-component eye velocity, whose direction is usually opposite to that of the OVAR. That is, for clockwise constant-velocity OVAR, in which persons are rotated towards their right, the slow-component eye velocity response usually has a nonzero component towards the left, i.e., a left bias. Superimposed on this bias component is a sinusoidally varying "modulation" component. The horizontal bias component represents the desired eye movement since it reflects the most appropriate response to a constant-velocity rotation, namely a constant-velocity eye movement. On the contrary, the horizontal modulation component of the response to constant-velocity OVAR is unwanted and reflects the unsuppressed horizontal eye movement generated by the misperception that the head is being oscillated linearly along an interaural axis. Note that both the bias and modulation components represent purely otolithic responses, since the semicircular canal response decayed exponentially and the testing is performed in darkness, so no visual stimulation exists. Postrotatory OVAR responses are analyzed in a manner identical to those following cessation of EVAR. For OVAR, however, the time constant of the decay of postrotatory nystagmus reflects the combined effects of a semicircular canal stimulus and a static otolith stimulus, which foreshortens the response (Koizuka et al., 1996).

Unlike EVAR, which is considered part of the standard test battery for tertiary balance centers, OVAR has not emerged as a useful clinical test modality. Major limitations of OVAR testing include its propensity for producing intolerable nausea (Furman et al., 1992; Denise et al., 1996), especially during constant-velocity rotation, which is the most useful paradigm for assessing the otolith organs. Also, studies have shown that responses to OVAR appear to be insensitive to unilateral loss of peripheral vestibular function (Denise et al., 1996; Furman et al., 2003), further reducing its clinical utility. Another related factor that reduces the incentive to develop OVAR into a clinical test is the emergence of other otolith organ tests, notably vestibular-evoked myogenic potentials. Despite these issues, OVAR retains its place in the realm of research because it is a safe and relatively convenient means of stimulating the otolith-ocular reflex (Furman and Redfern, 2002), can easily be combined with visual stimuli to assess visual–otolith interaction (Furman and Mendoza, 1996) (see below), and induces complex vertical and torsional eye movements that potentially could provide objective information about spatial orientation.

UNILATERAL CENTRIFUGATION/OFF-AXIS ROTATION

Unilateral centrifugation, also known as eccentric or off-axis rotation, can be used to assess unilateral utricular function. This technique, which was first described by Wetzig and Reiser (1990) and advanced by Clarke and Engelhorn (1998), uses earth–vertical axis yaw rotation with the axis of rotation placed through one of the otolith organs. In this way the utricle that is at a distance from the axis of rotation is subjected to a centripetal and small tangential force, while the other utricle, which is placed on

the axis of rotation, does not experience any linear force aside from gravity. To produce a large-enough stimulus to induce a measurable torsional eye movement, rotational velocities need to exceed about 300°/s. For example, at 400°/s, the off-axis utricle is subjected to a centripetal force of about 0.4 **g**; this corresponds to an equivalent roll tilt of about 22°. In some laboratories, the subject is first rotated on-axis to a constant velocity to allow the semicircular canal response to decay and then is slowly translated to align either the right or left utricle with the axis of rotation. After measuring the response to this off-axis stimulus, the subject is slowly translated back to being on-axis and then to an eccentric position to align the other utricle with the axis of rotation. In other laboratories, subjects cannot be translated during rotation and must be positioned prior to rotation. This requires several rotational trials, which can lead to motion sickness. Off-axis rotation induces ocular torsion that can be measured using three-dimensional videooculography. An alternative method of assessing the response to off-axis rotation is to measure subjective visual vertical during rotation. Eccentric off-axis rotational responses are abnormal in persons with unilateral vestibular loss (Wuyts et al., 2004). Despite the ability of eccentric off-axis rotation to measure vestibular function in each ear separately (placing it in the same class as caloric testing and vestibular-evoked myogenic potential testing), the complexity of the equipment and the motion sickness that is often induced by the stimulus relegate off-axis rotation to a technique that is unlikely to become widely accepted.

VISUAL–VESTIBULAR INTERACTION

As noted above in the discussions of EVAR and OVAR, in addition to the ability to assess the VOR in darkness, rotational testing can be used to assess visual–vestibular interaction (VVI) (Baloh et al., 1976, 1984). VVI consists of VOR fixation (VOR-fix), often called VOR suppression, and the visual VOR (VVOR). There is controversy as to whether or not VVOR testing provides information beyond that obtained from testing ocular motor function and the VOR separately. Specifically, VOR-fix is thought to reflect the ability to use pursuit eye movements to cancel the VOR, and many studies indicate a strong correlation between pursuit abilities and VOR-fix (Demer, 1994). Nonetheless, VOR-fix is a direct way to measure the ability to suppress or cancel the VOR and may provide additional information regarding central vestibular function. VVOR is thought to reflect the ability to use optokinetic-induced eye movement to augment the VOR (Baloh and Demer, 1993). Analogous to the relationship between pursuit and VOR-fix, VVOR is correlated with optokinetic nystagmus. VVI can be measured for both EVAR and OVAR, i.e., visual stimuli can be combined with both semicircular canal and otolith organ stimulation. Generally, VVI is performed using sinusoidal EVAR and also can be performed with both sinusoidal and constant-velocity OVAR. For EVAR at 0.05 Hz, VOR-fix gain is generally very small, i.e., less than 0.1, whereas VVOR gain is near 1.0 (Furman and Cass, 1996). For sinusoidal OVAR, VVI responses are similar to those for EVAR. However, for constant-velocity OVAR, the modulation component of the otolith-ocular response, i.e., the sinusoidal modulation of eye position, appears to be more resistant to suppression than either the bias component during OVAR or eye movement induced by EVAR (Furman and Mendoza, 1996). Also, during VVOR testing using constant-velocity OVAR, there is a modulation of eye velocity superimposed on the constant-velocity baseline response that seems to reflect an enhanced modulation component (Furman and Mendoza, 1996). Studies of VVI using EVAR in patients with cerebellar disease indicate a cerebellar-dependent impairment of VOR-fix. Studies of VVI using EVAR in patients with peripheral vestibular disorders indicate no abnormalities (Baloh et al., 1984).

In general, advanced age seems to have a small adverse effect on EVAR, OVAR, and VVI. Specifically, with advanced age, responses to EVAR sinusoids have a larger phase lead and shorter time constant (Peterka et al., 1990a, b; Paige, 1994; Baloh et al., 2001), responses to OVAR have a smaller bias component and a larger modulation component (Furman and Redfern, 2002), and VVI testing shows a reduced ability to suppress/cancel the VOR (Demer, 1994).

HEAD-ONLY ROTATIONAL TESTING

Another type of rotational testing uses rotation of only the head and not of the entire person. This type of testing is called head-only rotational testing (HORT) (Jell et al., 1982; Fineberg et al., 1987; Demer et al., 1990; Goebel et al., 1991; Hoshowsky et al., 1994) for sinusoidal movement and HIT for rapid unidirectional head movement. HORT and HIT are usually performed while seated. HORT can use either EVA yaw (Fig. 12.3A) or EHA pitch. HORT can be active, i.e., head movement is generated volitionally by the subject being tested, or can be passive, i.e., with the examiner rotating the subject's head. For active rotations, subjects are usually cued regarding when to move their head, e.g., by an auditory stimulus. Because of the limited range of motion of the head on the neck, the frequency of HORT is limited to a range of about 1–5 Hz and the amplitude of HORT is limited to a peak velocity of about 150°/s. Eye movements induced by HORT (Fig. 12.3B) are based primarily upon the VOR, but influences from the neck via the cervico-

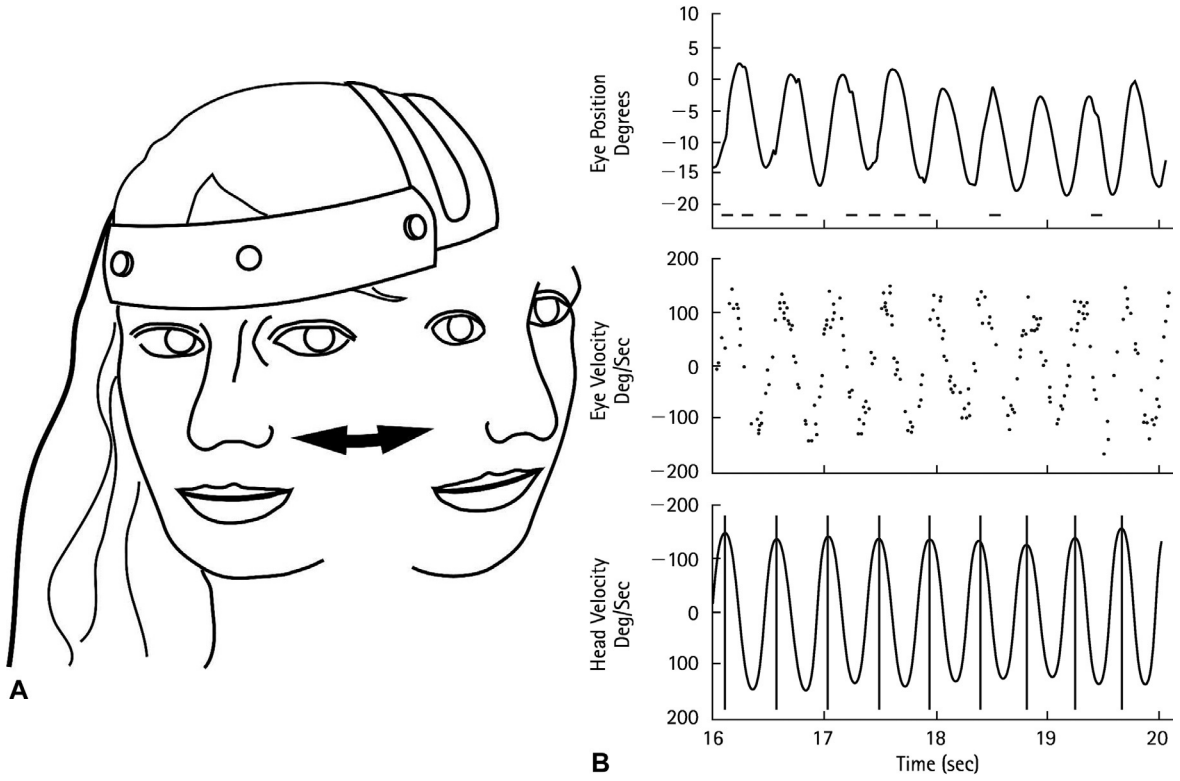

Fig. 12.3. Head-only rotation. (**A**) Head-only rotation-measuring device showing a headband with a rotational velocity sensor. (**B**) Eye movements induced by head-only rotation at a frequency of about 2 Hz. The bottom trace shows the yaw rotational velocity of the head measured with the rotational velocity sensor shown in (**A**); the vertical lines in the bottom trace indicate the computer-determined beginning and end of each cycle of the quasi-sinusoidal movement. The top trace shows horizontal eye position measured with electro-oculography; the horizontal dashes below the top trace indicate the location of computer-determined fast components. The middle trace shows the computer-determined slow-component eye velocity for the eye movements in this example of head-only rotational testing. From Furman (2010).

ocular reflex and, especially for active HORT, influences from volitional, "feed-forward" mechanisms, must be considered. Despite these limitations, HORT has been used to provide a measure of the VOR without the requirement of a large, expensive rotational chair. Despite the commercial availability of HORT, the technique has not gained widespread use (Cheung et al., 1996). The primary reasons for the lack of wide use of HORT are that: (1) subjects often find it difficult to move their head at multiple specific frequencies, especially higher frequencies; (2) the VOR at higher frequencies is often preserved despite abnormal VOR function overall, so that HORT is not especially helpful clinically (Jenkins et al., 1982); (3) HORT, like EVAR, stimulates both labyrinths simultaneously and thus, even when abnormal, does not provide lateralizing information; and (4) HORT provides a somewhat contrived laboratory measure of the VOR rather than a functional measure of the VOR.

HIT, unlike HORT, has found wide clinical use by overcoming some of the key limitations of HORT. HIT uses examiner-delivered passive impulsive unidirectional movements to take advantage of Ewald's second law. In particular, rapid unilateral movements in one of the three canal planes excites the semicircular canal nerve toward which the head is rotated and suppresses the opposite semicircular canal nerve in that plane. In this way, HIT can provide canal-specific information, something that can only be accomplished otherwise for the horizontal canal using the caloric test. Further, HIT can be adapted for testing the vertical semicircular canals. Whereas horizontal HIT has been used extensively (MacDougall et al., 2013), technical issues limit the applicability of the vertical HIT. These issues concern both the stimulus delivery and data analysis. HIT requires an experienced examiner, especially for vertical canal testing. Most patients, especially older patients, have limited range of motion of the head, especially for pitch and roll. This limited vertical range of motion limits the ability to achieve the velocities required to suppress the normal activity from the canal being inhibited.

A further challenge for the vertical HIT is how to record and analyze the eye movement induced by the

stimulus. Oblique movements of the head designed to stimulate one vertical semicircular canal at a time induce a complex eye movement with both vertical and torsional components. The HIT is likely to continue to be useful clinically as a means of assessing semicircular canal function, especially horizontal semicircular canal function. As the equipment for HIT testing is relatively inexpensive and is easily transportable, testing requires only a few minutes, and does not require dedicated space, the availability of the HIT will continue to grow. Direct comparisons with caloric testing suggest that the HIT provides clinically valuable information. Although the caloric test appears to have a higher sensitivity (Mahringer and Rambold, 2013; Zellhuber et al., 2013; Bell et al., 2014; McCaslin et al., 2014), the HIT is less disturbing and better tolerated.

COMPUTERIZED ROTATIONAL HEAD IMPULSE TESTING

Computerized rotational HIT (crHIT) is a cross between whole-body EVAR and head-only HIT testing. crHIT uses a high-torque rotational chair to deliver whole-body rotational impulses while eye movements are recorded using infrared video-oculography, comparable to that used for EVAR, HORT, and HIT. Still in the research phase, preliminary results suggest that crHIT yields results similar to those from HIT but overcomes several challenges. Specifically, crHIT does not stimulate the neck, yields more data per impulse, and is more comfortable. The obvious disadvantage of crHIT is the need for expensive, laboratory-based equipment.

CONCLUSION

Rotational testing consists of angular motion of the head. The orientation of the head with respect to the axis of rotation and the orientation of the axis of rotation with respect to gravity determine which of the vestibular end organs are stimulated. In this chapter, the most commonly used rotational stimulus, i.e., yaw EVAR and yaw OVAR, are discussed. EVAR is used clinically to assess the functional status of the angular VOR. OVAR is generally reserved for research, especially with the advent of newer, more sensitive otolith tests. HORT, which uses sinusoidal movement, and HIT, which uses rapid unidirectional rotations, do not require costly equipment and can be performed at the bedside. Although HORT has limited clinical utility, HIT is now widely available as it provides lateralizing information. crHIT is a recently described technique that combines whole-body EVAR with the impulsive trajectory of the HIT.

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Chapter 13

An overview of vestibular rehabilitation

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Abstract

Data related to the efficacy of vestibular rehabilitation and its evolution as an intervention are provided. Concepts and various treatment strategies are described, with explanations of why people with uncompensated peripheral and central vestibular disorders might improve with rehabilitation. Various tests and measures are described that are commonly used to examine patients and determine their level of ability to participate in their environment. Factors that affect recovery, both positively and negatively, are described in order to better prognosticate recovery. A case utilizing many of the principles discussed is included to provide insight into how to utilize vestibular rehabilitation with a person with an uncompensated peripheral vestibular loss.

VESTIBULAR REHABILITATION

In the 1940s, Cawthorne and Cooksey introduced an exercise-based technique- known as vestibular physical therapy (VPT) for the management of vertigo (Cawthorne, 1944; Cooksey 1946). Later on, a number of controlled, prospective trials reported the effectiveness of VPT in patients with vestibular hypofunction (Shumway-Cook and Horak, 1989; Horak et al., 1992; Krebs et al., 1993; Cohen and Kimball, 2003) Recently, a Cochrane review reported moderate to strong evidence that VPT is safe and effective for persons with peripheral vestibular dysfunction (McDonnell and Hiller, 2015).

The use of VPT in the management of persistent dizziness and vertigo in persons with vestibular dysfunction has exponentially increased over the last 25 years. Reduction of vertigo and improvements in gaze stabilization, postural control, functional activities, and quality of life are the aims of VPT. The major components of VPT include gaze stabilization (vestibulo-ocular reflex (VOR)), balance-retraining, habituation, and substitution exercises (Shumway-Cook and Horak, 1989; Cohen and Kimball, 2004; Herdman et al., 2007).

These exercises are utilized in different ways for different vestibular lesions. The VOR adaptation exercises are used to assist in compensation for persons with unilateral vestibular deficits (Herdman, 1989). VPT can provide strategies that teach individuals with bilateral vestibular hypofunction to cope with their disorder (Kasai and Zee, 1978; Bronstein and Hood, 1986). Another common treatment technique includes various repositioning maneuvers for benign paroxysmal positional vertigo (BPPV), which physical therapists are trained to perform (Epley, 1992; Herdman, 1997). Another major category of treatments discussed will refer to patients who are visually sensitive to movement after a vestibular disorder. This condition has been called many things in the literature, including visual vertigo (Bronstein, 2005), space and motion phobia, space and motion discomfort, (Jacob et al., 1993), or persistent postural perceptual dizziness (Staab, 2015).

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VPT consists of balance exercises and the incorporation of head movements that may provoke dizziness. To provoke symptoms, these exercises comprise a sequence of eye, head, and body movements of increasing difficulty (Alsalaheen et al., 2013). The exercise prescription is changed as the patient improves and it is typically customized to address specific deficits. As movement specialists, physical therapists are trained to observe movement deficits and then provide an exercise program to modify the movement dysfunction.

VPT is an exercise-based technique widely used to reduce symptoms and improve function in patients with vestibular disorders (Shepard and Telian, 1995; Whitney and Rossi, 2000; Hall and Cox, 2009; McDonnell and Hiller, 2015). A customized exercise program is generally thought of as more effective than generic protocols (Herdman, 1998).

Vestibular rehabilitation team

A comprehensive vestibular rehabilitation program includes a multidisciplinary team approach. The rehabilitation team includes physical and occupational therapists, audiologists, neuro-otologists, nurses, neurologists, and psychiatrists or psychologists who all are specialized in the management of persons with dizziness. Typically, the individual vestibular exercise program is designed to restore functional activities, balance, and strength, and prevent falls. For optimal results, the physical therapist administering the vestibular exercises should be experienced in the treatment of patients with vestibular disorders. Experience in the treatment of persons with balance/vestibular disorders for the entire healthcare team is a key factor in functional recovery.

Patients with vestibular dysfunction often have seen their primary care physician, otolaryngologist, or a neurologist prior to referral to physical therapy. The neurologist or otolaryngologist interprets the vestibular function tests and the audiologist usually performs the audiometric testing. When patients are referred for VPT, the treating physical therapist often will refer to another medical team specialist for consultation and advice. If the patient has significant anxiety, panic attacks, or depression associated with the vestibular disorder, a psychiatrist or psychologist referral is necessary.

The correct diagnosis of persons with dizziness is essential to ensure optimal functional recovery. The prescription of inappropriate vestibular exercises or exercises that are too difficult/easy will delay functional recover. In addition, patients with central vestibular dysfunction may respond better to VPT if the physical therapy is combined with pharmacotherapy, especially those with migraine dizziness (Johnson, 1998).

PRINCIPLES OF RECOVERY

Vestibular adaptation, habituation, and substitution are the three important mechanisms of recovery from vestibular lesions. Cawthorne described the vestibular adaptation approach for patients with persistent disequilibrium, which is similar in other vestibular lesions (Krebs et al., 1993). Vestibular adaptation requires modification of the gain of the VOR (Shelhamer et al., 1994). Habituation (Cawthorne, 1944; Shepard et al., 1990) is a central process of learning (Thompson and Spencer, 1966) that is most commonly utilized when patients have problems with motion sensitivity. Vestibular substitution utilizes alternative mechanisms to compensate for the lost vestibular function (Herdman, 1998; Halmagyi et al., 2010). The term "vestibular compensation" is often used as a synonym for vestibular substitution (Krebs et al., 1993). To describe functional recovery the term "well compensated" is commonly used, while for a partial recovery the term "poorly compensated" is used. The term "decompensation" has been adopted (Curthoys and Halmagyi, 2007) to describe persons who may have compensated well and then may have a relapse of symptoms because of becoming sedentary or having a change of lifestyle. The presence of persistent motion-provoked vertigo is an example of a person who is poorly compensated. Such an individual might benefit from various forms of habituation exercises such as virtual reality (VR) or the use of a disco ball to decrease visual sensitivity. To promote central nervous system compensation through exercise-based techniques is the major goal of VPT (Herdman and Clendaniel, 2007; McDonnell and Hiller, 2015). The following exercise approaches (adaptation, habituation, substitution, and optokinetic training) are used to reduce impairments such as dizziness/vertigo, postural instability, and gaze instability and enhance functional recovery.

Adaptation

Adaptation exercises or visual-vestibular interaction exercises use stimuli such as head movement to promote the adaptation of the remaining vestibular system. Adaptation exercises are effective in the treatment of gaze instability and have also been shown to improve balance and reduce dizziness (Horak et al., 1992; Herdman et al., 1995).

The reduced gain of the vestibular response to head movements causes gaze instability (Herdman, 1997). The error signal induced by retinal slip, which is the image motion on the retina during head movement, is used as a stimulus to increase the gain of the vestibular response (Herdman, 1998). Horizontal or vertical head movements while maintaining visual fixation on a target

can induce retinal slip in patients with a defective VOR. The target should be placed at various distances from the person's eye (Herdman et al., 1995). The most effective head movements are horizontal (yaw plane) and vertical (pitch plane) head movements. However, head movements in the roll plane do not cause sufficient changes in the VOR gain (Herdman, 1998).

There are various methods to improve the effectiveness of vestibular adaptation during head movements. Instead of sudden large errors, use of gradually increasing amplitudes of retinal slip during training is more effective (Schubert and Zee, 2010). Showing a target that is moving in the opposite direction of the head while moving the head either horizontally or vertically (VOR $\times$ 2) will increase the magnification factor and the duration of exposure to retinal slip (Herdman, 1998). Various training frequencies cause the greatest change in VOR gain, hence, a wide range of head movement frequencies should be used in the exercise program (Lisberger et al., 1983; Herdman, 1997). A gradual increment in error signal is recommended to induce greater adaptive changes in the VOR gain to retinal slip (Schubert et al., 2008). In order to provide otolithic input, patients should move their head in various directions (Tiliket et al., 1993; Herdman, 1997). Herdman (2007) recommends that exercises for gaze stability should be performed four to five times daily for a total of 20–40 minutes/day, in combination with balance and gait training. Our experience is that many people cannot tolerate 20–40 minutes of head movements a day and that less time still has value in terms of long-term recovery. During the training session, it is recommended that the room has adequate lighting (Fetter et al., 1988).

Habituation

Habituation exercises utilize repeated exposure to symptom-provoking stimuli to reduce position-induced dizziness. A reduction indizziness can result over time following systematic exposure to mild, temporary symptoms of vertigo (Smith-Wheelock et al., 1991; Herdman, 2007).

The primary goal in patients with position-induced vertigo without a definite diagnosis but with a benign etiology is to improve the symptoms of vertigo (Shepard and Telian, 1995). The habituation of abnormal vestibular responses to rapid movements may achieve this goal (Shepard et al., 1990). Typical movements that produce the most intense symptoms are identified and a list of those exercises that reproduce these movements is provided to patients as part of their home exercise program (Shepard and Telian, 1995). The repetitive exposure to a provoking movement may cause a reduction in the magnitude of the response to repetitive sensory stimulation (Pavlou et al., 2004a).

Habituation exercises are specific to the type, intensity, and direction of the eliciting stimuli. When central compensation has developed sufficiently following exercise, symptoms will decrease (Norre and Beckers, 1989; Pavlou et al., 2004a).

Persons with bilateral vestibular loss are not appropriate for habituation exercises (Herdman et al., 2007). Certain habituation activities, such as rising rapidly, should be avoided by the elderly, as the movement may provoke orthostatic hypotension (Herdman, 2007).

Sensory substitution

Substitution exercises are utilized to enhance postural control and lessen falls by utilizing other sensory stimuli such as visual or somatosensory input to substitute for missing or decreased vestibular function (Herdman and Clendaniel, 2007). Patients depend on somatosensory signals from the lower extremities during the acute stage after unilateral loss and on visual signals during the chronic stage (Herdman, 1998). The visual inputs that emerge from large-field visual movement signals are more effective than those from focal (foveal) visual movement (Horak, 2010). Visual signals can be exceptionally destabilizing as a postural reference in patients with vestibular deficits. This phenomenon is known as visual dependency. At the point when a patient is visually dependent, a moving visual scene (e.g., trucks passing before the patient in the road) can be misinterpreted as a self-motion, and the postural modification can result in instability (Ford and Marsden, 1997). Hence, it is not ideal to encourage visual dependence by teaching the patient to focus on a stationary object and to reduce head movements while walking (Herdman, 1997) unless that is the only way that the person can ambulate without falling.

Optokinetic training

The primary goal of optokinetic training is to recreate the sensory conflict experienced by patients. These optokinetic exercises are intended to activate the vestibular system, providing continuous low-frequency (less than 0.3 Hz) visual information. This frequency range induces motion sickness by activating mainly the otolith system (Ressiot et al., 2013). In addition to retinal slip, other error signals induced by optokinetic visual stimuli may be used to stimulate VOR adaptation (Shelhamer et al., 1994; Herdman, 1998; Schubert and Zee, 2010). The advantage of optokinetic visual stimulation is that it does not require head movement and can be produced using a light-emitting diode stimulus or oscillation of an optokinetic drum (Herdman, 1998). Unidirectional optokinetic training improves vestibular responses in the same direction. Hence, optokinetic or combined vestibular-optokinetic training may enhance the VOR

gain in unilateral peripheral vestibular dysfunction (Pfaltz, 1983). Both foveal and full-field stimuli work effectively (Shelhamer et al., 1994).

TYPES OF PATIENTS WHO IMPROVE WITH VESTIBULAR PHYSICAL THERAPY

Vestibular rehabilitation has been shown to be an effective treatment for patients with dizziness and balance disorders (Shepard and Telian, 1995; Whitney and Rossi, 2000; Hall and Cox, 2009; McDonnell and Hillier, 2015). Tee and Chee (2005) reported that individuals with a stable unilateral peripheral vestibular loss with incomplete central compensation benefited most from VPT. VPT is also effective in patients with stable bilateral vestibular loss (Tee and Chee, 2005). However, the treatment strategies are different for unilateral and bilateral dysfunction.

The objective of VPT is to encourage compensation after peripheral and central vestibular disorders with the aim of reducing symptoms of dizziness and vertigo, enhancing balance, and encouraging return to previous activities of daily living. A growing body of evidence supports the effectiveness of VPT in a variety of conditions (Table 13.1). In addition, other evidence shows that VPT can be more effective than medication alone for long-term improvements in symptoms and function (Horak et al., 1992). The following section discusses conditions that typically respond successfully to VPT.

COMMON PERIPHERAL VESTIBULAR CAUSES OF DIZZINESS

Benign paroxysmal positional vertigo

BPPV is characterized by short duration of vertigo activated by a change in the position of an individual's head with respect to gravity with symptoms typically lasting less than 1 minute (i.e., the nystagmus fatigues with repeated stimulation of the semicircular canal). BPPV is the most widely recognized vestibular disorder, representing one-third of vestibular diagnoses in the general population (von Brevern et al., 2007).

In BPPV, calcium carbonate particles (otoconia) become displaced into the canals from the otolith organs, causing changes in the fluid dynamics of the canals. There are two essential theories for the mechanisms of BPPV. The first is cupulolithiasis (Schuknecht, 1969), in which the displaced otoconia get attached to the cupula, weighting this membrane. The change in the orientation of the canal in respect to gravity causes deflection of the cupula, which excites or inhibits the ampullary organ. The second is canalithiasis (Hall et al., 1979), in which the otoconia is free-floating within the canals. When the orientation of the canals in respect to gravity changes, the otoconia move to the lowest part of the canal, producing a drag on the endolymph, causing fluid pressure on the cupula, which activates the ampullary organ, resulting in the sensation of spinning with a change of head position. Please see Chapter 18 for specfics about the repositioning maneuvers.

Table 13.1

Types of patients who benefit from vestibular physical therapy

Peripheral	Central
Benign paroxysmal positional vertigo (Epley, 1992; Bhattacharyya et al., 2008; Helminski et al., 2010)	Stroke (Cowand et al., 1998; Brown et al., 2001; Suarez et al., 2003)
Vestibular neuronitis (Shepard et al., 1990; Horak et al., 1992; Tokumasu et al., 1993; Gillbody et al., 1994; Telian and Shepard, 1996; Cowand et al., 1998; Bamiou et al., 2000; Black et al., 2000; Hahn et al., 2001; Corna et al., 2003; Pavlou et al., 2004b; Dominguez, 2005; Perez et al., 2006; Halmagyi et al., 2010)	Brain injury/concussion (Herdman, 1990; Gurr and Moffat, 2001; Hoffer et al., 2004, 2007, 2009; Alsalaheen et al., 2010; Naguib and Madian, 2014)
Labyrinthitis (Shepard et al., 1990; Horak et al., 1992; Vitte et al., 1994; Yardley et al., 1998; Bamiou et al., 2000; Hahn et al., 2001; Strupp et al., 2001; Corna et al., 2003; Cohen and Kimball, 2004; Topuz et al., 2004; Swartz and Longwell, 2005; Clendaniel, 2010; Kao et al., 2010; Mohammad et al., 2010)	Vestibular migraine (Cass et al., 1997; Johnson, 1998; Wrisley et al., 2002; Gottshall et al., 2005a)
Vestibular schwannoma (Herdman et al., 1995; El-Kashlan et al., 1998; Badke et al., 2002; Enticott et al., 2005; Magnusson et al., 2009)	Multiple sclerosis (Zeigelboium et al., 2008)
Menière's disease (Clendaniel and Tucci, 1997; Dowdal-Osborn, 2002; Gottshall et al., 2005b, 2010; Magnusson et al., 2009)	Parkinson disease (Zeigelboium et al., 2009)
Bilateral vestibular loss (Krebs et al., 1993; Herdman, 1997; Gillespie and Minor, 1999; Brown et al., 2001; Herdman et al., 2007)	Presbystasis (disequilibrium of aging) (Jung et al., 2009)
Movement or visually provoked dizziness (Rine et al., 1999; Pavlou et al., 2004a)	Cerebellar degeneration/disorders (Gill-Body et al., 1997; Kelly et al., 2001; Brown et al., 2006)

Menière's disease

Menière's disease is the commonest cause of vertigo of otologic origin proposed to be due to dilation and sporadic rupture of the endolymphatic compartment of the inner ear. It is clinically characterized by ipsilateral fluctuating low-frequency hearing loss, tinnitus, aural fullness, and episodic vertigo (Strupp and Brandt, 2009). Endolymph hydrops is thought to be the pathologic basis of Menière's disease, either because of an excessive production or a minimum absorption of the endolymph (Strupp and Brandt, 2009). The pressure within the endolymphatic compartment increases and causes sporadic rupturing of the membrane separating the endolymphatic compartment of the inner ear.

VESTIBULAR PHYSICAL THERAPY EXAMINATION

According to the model of disability that was proposed by the *International Classification of Functioning, Disability and Health* (ICF) (World Health Organization, 2001), patients' disability is a result of the impact of multiple factors that healthcare professionals should take into consideration when evaluating and treating patients. These factors include the impairment itself (any problem in body function or structure) with its sequelae on patients' activities and participation. Additionally, the contextual factors with its components, personal and environmental factors, play an important role in facilitating or inhibiting patients' activities and participation (World Health Organization, 2001).

Vestibular disorders are among the most disabling diseases that lead to activity limitations and participation restrictions (Cohen, 1992; Yardley et al., 1998, 2003; Yardley, 2000; Monzani et al., 2001; Neuhauser et al., 2005; Mira, 2008; Vogel et al., 2008). Therefore, it is critical to evaluate every component of the ICF model that applies to persons with vestibular disorders who are referred to physical therapy.

History

The process of examination and evaluation of patients with vestibular disorders begins with a detailed medical history and a full systems review. The information gathered during the history taking is essential to assisting the examiner in organizing all factors necessary to understand the deficits in the patient's vestibular system and its effects on functional performance. Additionally, the patient's experience in describing the spells of dizziness, vertigo, or imbalance is very informative and may guide the healthcare professional to the appropriate next step.

Starting with open questions about the patient's medical status is usually recommended in history taking. A complete history of the patient's home, work, and community environment as well as other relevant health issues and their impact on the patient's social status should be reviewed as well, particularly when evaluating an elderly patient.

Many words can be used by persons with vestibular disorders when describing what they feel, such as motion in the head (floating, swimming, or spinning sensation), a sense of rotation (in linear motion or tilting directions), imbalance (disequilibrium, drop attacks, or falling), visual blurring (oscillopsia), ringing in the ear, and autonomic symptoms (malaise, nausea, and vomiting) (Fetter, 2000). Some of these expressions suggest peripheral vestibular disorders while others indicate central vestibular disorders (Table 13.2) (Baloh, 1998). The physical therapist needs to determine the triggers of the patient's symptoms. There are certain environments that may increase symptoms in people with vestibular disorders, such as crowds, malls, and cinemas (Cohen, 2006). Additionally, the trigger could be an activity that initiates the symptoms, such as driving, looking up or down, using the computer, turning in bed, shopping, bathing, or dressing (Cohen et al., 2000; Beidel and Horak, 2001; Redfern et al., 2001; Cohen, 2006).

Examination

Examining patients with vestibular abnormalities is complex. The examination process should be comprehensive to all disability elements, including tests and measurements that quantify impairment of the vestibular disorder, activity limitations, participation restrictions, and contextual factors. The examination of the vestibular system should be performed by an experienced physical therapist. The physical therapist can utilize patient-provided information, such as environmental and personal history, and create a tailored examination.

Vestibulo-ocular reflex testing

The VOR is responsible for clear vision during head motion and this is achieved by moving the eyes in the opposite direction of head movement. A vestibular evaluation should include the evaluation of gaze stabilization (VOR functioning), static/dynamic visual acuity, and head coordination, as well as tests for smooth pursuit, saccadic eye movements, and rapid head thrusts (impulses).

Gaze stabilization

To begin evaluating VOR function/gaze stability, a visual target is presented to the patient and the patient is asked to move the head in vertical (pitch) and then in horizontal (yaw) directions with instructions for varying the head speed. A person with normal VOR function will be able

Table 13.2

The common words used by persons with vestibular disorders to describe their symptoms and their interpretation

Patient's words	What the words suggest
Spinning	The patient could have a central or peripheral vestibular disorder, although spinning of short duration often suggests benign paroxysmal positional vertigo if there are no central findings
Headache	Patients' vestibular disorders often complain of an occipital or bitemporal headache. Tension headaches are described as a ring around the head or in the frontal area. Migraines can be very severe, tend to be unilateral, and may cause sensitivity to light, sound, and motion
Swimming sensation in the head	This is a nonspecific term that can suggest that there is a peripheral vestibular or central nervous system dysfunction
Dizziness	This is a nonspecific term that can be related to anxiety, orthostatic hypotension, medication side-effects, or a mild peripheral or central vestibular disorder
My vision is jumping	This suggests oscillopsia. The visual surroundings will jump with oscillopsia, which usually suggests a peripheral vestibular disorder of both ears
I am tired	This is a very common complaint in persons with vestibular or balance disorders
My neck hurts	This is more common in central vestibular disorders than peripheral disorders. It is often seen with people with whiplash, labyrinthine injuries, or concussion
I feel like everything is moving when I am in a busy environment with motion and distractions	This complaint of space and motion discomfort is common in persons with migraine, anxiety/panic, and in persons with peripheral vestibular disorders
People tell me that my head is not straight	This is sometimes seen in central vestibular disorders and also with head trauma. This is rarely seen in persons with peripheral vestibular disorders
I feel like I am going to fall	This is common in patients with peripheral or central vestibular disorders. Patients with anxiety may develop a fear of falling despite being stable on examination
I can't walk straight	This can be seen with a peripheral vestibular disorder, or with a central vestibular disorder
I am having trouble reading	If the problem exists only with head movement, it may suggest a vestibular abnormality, particularly bilateral vestibulopathy. When occurring at rest it may result from spontaneous nystagmus. It might be helpful to test visual acuity with a vision chart

to maintain the gaze without the target blurring at frequencies up to 2 Hz. The patient with VOR dysfunction will be unable to maintain a fixed gaze or this test will induce a horizontal gaze-evoked nystagmus, indicating a peripheral or central vestibular lesion (Fetter, 2000; Furman et al., 2010).

Static/dynamic visual acuity

Visual acuity is first tested statically by asking the patient to read an acuity chart down to the lowest line possible, i.e., until unable to identify all of the letters on a particular line. Acuity is then tested dynamically by the examiner standing behind the patient, flexing the patient's head forward approximately 20–30°, and oscillating the patient's head 20–30° each direction at a rate of 2 Hz. The patient is then asked to read the chart again, down to the lowest possible level during the passive head movements, as described above. A loss of three lines dynamically compared to statically is suggestive of either a central or peripheral lesion affecting the VOR (Longridge and Mallinson, 1987).

Smooth pursuit

For smooth pursuit, the patient is asked to follow a slowly moving target 18 inches (46 cm) from the nose while keeping the head stationary. The target is moved through 30° of motion to the right, left, and in upward and downward directions from head-neutral. If any abnormality is detected, it should be recorded as a corrective saccade. This abnormality typically indicates cerebellar dysfunction (Fetter, 2000).

Saccadic eye movement

To evaluate saccadic eye movement, two targets are placed 18 inches (46 cm) from the patient's nose and 15° left and right of the nose, followed by vertical eye movements on to the target at 15° up and down. The patient is asked to keep the head stationary but to quickly move the gaze back and forth. The examiner should be careful to note undershoots or overshoots of the target and in which direction these occur, as they could indicate an abnormality in the cerebellum or brainstem (Fetter, 2000), for which magnetic resonance imaging or

computed tomography scan is required to determine the area affected if otherwise unknown. Always assure that the patient is paying attention to the task and repeat the saccadic eye movements to ensure that the patient cannot accurately perform the saccadic task.

Rapid head thrusts (head impulse test)

To evaluate for an impaired VOR resulting from a peripheral lesion, rapid head thrusts can be performed (Halmagyi and Curthoys, 1988). To perform this test, the patient is seated and should be relaxed. First, the patient's cervical passive range of motion is checked by the examiner. Next, the patient is told to remain focused on a target object in front. The examiner then quickly, but over a small amplitude, moves the patient's head rapidly. The examiner should be looking for the patient's capability to maintain fixed gaze and for any corrective saccades. If a corrective saccade does occur, the direction should be noted (Halmagyi and Curthoys, 1988). The direction in which you are turning rapidly is the ear that is being tested.

The Dix–Hallpike maneuver

The Dix–Hallpike maneuver has been utilized for over 70 years and is the diagnostic test for BPPV. Since BPPV is common, the Dix–Hallpike is incorporated into the examination of everyoner who complains of positional dizziness. Lawson et al. (2005) have reported that BPPV is commonly seen in syncope clinics, as most patients are referred with suspected cardiovascular complications, yet BPPV may be the primary cause of the positional dizziness. The Dix–Hallpike is performed in the following manner: the person turns the head 45° to the side while seated and then the patient is brought down into the head-hanging position approximately 20–30° over the edge of the table. The examiner observes for nystagmus, which is typically a torsional upbeating nystagmus. The posterior canal is the most commonly affected canal, followed by the horizontal and the anterior canals (Cohen, 2004). The sidelying test is an alternative to the Dix–Hallpike test. The sidelying test may be slightly more sensitive than the Dix–Hallpike. For persons with limited mobility, the sidelying test may be the option of choice.

Vestibulospinal reflex (VSR) testing

A thorough vestibular examination should also include assessment of the VSR, including balance, gait, and mobility. Static tests include the Romberg, tandem Romberg, standing on toes or on one leg, and standing on foam rubber (Fetter, 2000). The function of the dynamic VSR can be examined using tandem walking, rapid turns, and responses to external perturbations. However, a complete examination of strength, range of motion, sensation, and postural control is also critical (Fetter, 2000).

Romberg and tandem Romberg tests

The Romberg is a test that was designed to assess proprioception in the lower extremities. It is performed by asking the patient to put the feet together and cross the hands over the chest. The patient is to maintain this stance position at first with the eyes open and then eyes closed for 20–30 seconds. A positive Romberg is most commonly caused by a peripheral sensory neuropathy. Tandem Romberg can also be performed by asking the patient to place one foot directly in front of the other and remain still (Rossiter-Fornoff et al., 1995). The tandem Romberg position is very difficult for older persons, even those living in the community.

Single-leg stance

Single-leg stance is a common and easily administered test that requires no additional equipment (Bohannon et al., 1984). The subject is asked to stand on each leg individually for a specified amount of time, usually 30 seconds, and imbalance or falling is reported. While single-leg stance is partially a test of strength in each lower extremity, it can be a difficult test for older adults to perform because of distal proprioception loss or lower-extremity weakness.

Sensory integration testing

The visual, vestibular, and somatosensory systems are responsible for providing the brain with the sensory information that needs to be integrated to determine the position of the body in space (Shumway-Cook and Woollacott, 2007). The interaction among the three sensory systems is critical to have normal postural control and locomotion in various environments. There are different ways of testing this interaction, but the most utilized ones are the Clinical Test of Sensory Interaction and Balance (CTSIB) (Shumway-Cook and Horak, 1986), the sensory organization test (SOT) (Clendaniel, 2000), and portions of the Balance Evaluation Systems Test (BEST) (Horak et al., 2009).

The Clinical Test of Sensory Interaction and Balance

The CTSIB is a simple method to assess sensory organization in the standing position using a piece of foam and a dome (modified Japanese lantern) (Shumway-Cook and Horak, 1986). For this test the patient is asked to stand on a firm surface under three conditions: (1) with the eyes

open; (2) with the eyes closed; and (3) with a visual conflict dome. The results can be reported in either the magnitude of sway and occurrence of a fall or by timing the patient's ability to stand (for a maximum of 30 seconds). These procedures are then repeated with the patient standing on a foam surface.

A modified version of the test has been adopted without the portion that requires the conflict dome. It includes only the eyes-open and eyes-closed portions of the test on a firm surface, then on a foam surface (Whitney and Wrisley, 2004; Wrisley and Whitney, 2004). Individuals with vestibular disorders have been shown to have difficulty maintaining balance during the performance of the CTSIB conditions that include visual and support surface manipulation (Nashner et al., 1982). The CTSIB has been validated in older adults (Anacker and Di Fabio, 1992), people with vestibular disorders (Cohen et al., 1993; Weber and Cass, 1993), and stroke survivors (Di Fabio and Badke, 1990).

The Sensory Organization Test

The SOT is a quantitative and objective test that aims to identify postural control deficits while standing caused by the sensory components of balance (Clendaniel, 2000). For the SOT, the patient is placed on a force plate that can rotate up and down surrounded by a moveable wall. During this test, visual and somatosensory elements change to present the subject with six different sensory conditions: (1) stable or (2) unstable standing surface; (3) eyes open or (4) eyes closed; and (5) stationary or (6) moving visual surroundings. If a subject falls while the eyes are closed and the support surface is moved (condition 5) or if the patient falls with the eyes open but both the standing plate and the visual surroundings are moved (condition 6), the subject may have a vestibular dysfunction. Younger individuals performed better than older adults on the SOT (Cohen et al., 1996). However, older adults without vestibular dysfunction scored better than older adults with vestibular disorders on the SOT (Pedalini et al., 2009). The SOT has been validated in younger individuals (Wrisley et al., 2007), older adults (Ford-Smith et al., 1995), persons postconcussion (Broglio et al., 2008), and people with vestibular disorders (Whitney et al., 2006; Cohen and Kimball, 2008).

The Balance Evaluation Systems Test

The BEST is a 36-item test that targets six balance control systems. One of these items is the "incline toes up–eyes closed" test that targets the interaction of sensory inputs and examines the ability of patients to maintain standing postural control with sensory manipulation (Horak et al., 2009). The patient is asked to close the eyes while standing on a firm surface followed by standing on an inclined board (10° angle) with eyes closed. Imbalance and sway are observed during the absence of visual input and the absence of visual input while standing on an angled support surface. People with vestibular disorders were found to have difficulty in maintaining balance and being oriented to vertical in the second condition (Horak et al., 2009).

ACTIVITIES AND PARTICIPATION

There is no clear distinction between activities and participation components in the ICF (World Health Organization, 2001; Jette et al., 2003). Healthcare professionals depend heavily on self-reported tools to assess participation since patients are able to describe their performance in the community (Shumway-Cook and Horak, 1986).

Participation testing

The evaluation of participation in people with vestibular disorders at the societal level is an important area to address. Participation can be assessed using questions about the level of difficulty the patient faces in performing daily-living activities (eating, dressing, bathing, reading, and sleeping), outdoor activities (driving and working), as well as recreation and leisure activities. Most self-report tools used with people with vestibular disorders include activities and participation, body functions, and environmental factors (Alghwiri et al., 2011). The Vestibular Activities and Participation (VAP) measure is the only measure to date that includes activities and participation items exclusively, was developed based on the ICF, and has been translated and cross-culturally validated in three languages (German, English, and Arabic) (Alghwiri et al., 2011, 2012, 2013; Grill et al., 2013; Mueller et al., 2015).

Vestibular Activities and Participation measure

After linking eight common vestibular questionnaires to the ICF (Alghwiri et al., 2011), the VAP was developed to represent a disease-specific scale that quantifies activity limitations and participation restriction in persons with vestibular disorders (Alghwiri et al., 2012). The VAP is a 34-item questionnaire that includes items from the activities and participation categories of the ICF. The VAP was recently shortened to 12 items (Mueller et al., 2015). The VAP demonstrated excellent reliability and validity in people with vestibular disorders across cultures (Alghwiri et al., 2012).

Activities-specific Balance Confidence scale

The Activities-specific Balance Confidence (ABC) scale was originally developed for the geriatric population to

provide a description of activity difficulty and fear of falling (Tinetti et al., 1994; Powell and Myers, 1995). The ABC includes 16 activities with various levels of difficulty that range from walking around the house to walking on icy sidewalks (Powell and Myers, 1995). The ABC scoring scale extends from 0% (indicating no confidence) to 100% (indicating complete confidence) in performing the task without any difficulty. The ABC has been validated in older adults (Powell and Myers, 1995; Lajoie and Gallagher, 2004), persons with vestibular disorders (Whitney et al., 1999; Legters et al., 2005; Friscia et al., 2014), and stroke survivors (Botner et al., 2005).

Dizziness Handicap Inventory

The Dizziness Handicap Inventory (DHI) is a 25-item questionnaire that assesses the self-perceived handicap caused by dizziness in patients with vestibular disorder (Jacobson and Newman, 1990). The DHI has three domains – functional, emotional, and physical – that cover aspects of dizziness and disequilibrium. The response scale used in the DHI is "yes/sometimes/no," scored as "4/2/0" respectively. The psychometric properties of the DHI have been examined and found to be good to excellent (Jacobson and Newman, 1990; Fielder et al., 1996; Enloe and Shields, 1997). In a recent review, the DHI was found to be one of the most frequently used self-reported measures in people with vestibular disorders (Fong et al., 2015).

Activities testing

The examination of functional activities that patients can or cannot perform in their daily life is essential to determine their level of disability. The examiner can start with more static tasks and proceed to dynamic testing based on the patient's ability.

Reaching tasks

One valuable tool available to physical therapists that reveals stability, particularly for older patients, is reaching tests. These tests require less time and effort to perform and can be utilized in community health screening situations to identify those at risk for falls. For the functional reach test, subjects are asked to stand and reach forward with their right hand as far as they can without moving their feet and return to the starting position without falling (Duncan et al., 1990). The distance that the subject is able to successfully move is measured by a tape measure attached to the wall. Those subjects who are able to reach only 6 inches (15 cm) or less are at increased risk of falling in the next 6 months (Duncan et al., 1992).

The Multi-Directional Reach Test (MDRT) is another valuable reach test that provides information on stability not only in a forward direction but also left, right, and backwards (Lamoureux et al., 2001). A yardstick is placed on a tripod and is lined up with the subject's acromion. The subject is then asked to reach forward, backward, left, and right as far as possible. According to Lamoureux et al. (2001), the MDRT is a valid and reliable measure of "limits of stability."

The Timed Up and Go test

The Timed Up and Go (TUG) is a gait-based test (Podsiadlo and Richardson, 1991). The TUG has shown a high sensitivity (87%) and specificity (87%) for predicting falls in older adults (Shumway-Cook et al., 2000). Utilizing an assistive device, if needed, the subject is instructed to stand up from sitting, walk a distance of 3 meters, turn around, return to the starting point, and sit down again. The time required for this task is then recorded. Subjects who require more than 13 seconds to complete the task are considered to be at higher risk of falling (Shumway-Cook et al., 2000). The TUG is not only time-efficient but is also an informative tool that provides the examiner with information about multiple aspects of balance, including the patient's ability to stand from sitting, walk, turn around, and sit from standing.

The Berg Balance Scale

A commonly utilized examination tool for static and dynamic balance (sitting and standing) is the Berg Balance Scale (BBS) (Berg, 1989; Berg et al., 1992). The BBS is a quantitative measure of balance during functional activities. Subjects are asked to reach, bend, transfer from one chair to another, stand with their feet apart, stand with their feet together, stand with their feet in tandem position with eyes open and with eyes closed, reach down, and stoop down to pick something up from the floor (Berg, 1989). Each item receives a grade on a 0–4 scale, where 0 indicates the subject is unable to complete the task and 4 is the highest grade obtainable, where each grade is given specific criteria to meet. The BBS has been shown to be reliable and have construct validity (Wang et al., 2006; Conradsson et al., 2007).

When reporting results of the BBS, several different cutoff scores have been suggested. When the test was originally designed, a score of >45 was considered to be predictive of future falls (Thorbahn and Newton, 1996). However, Muir et al. (2008), in their evaluation of the BBS, felt that the test was a better predictor of multiple fallers. They reported a score of 40 would predict multiple falls as well as falls that were more likely to cause harm to the patient. Prior to Muir's study, Shumway-Cook et al. (1997) reported that, in their study,

a score of 36 or less was 100% predictive of a fall within the next 6 months in the geriatric population. The BBS has demonstrated concurrent validity when compared to the Dynamic Gait Index (DGI) in persons with vestibular disorders (Whitney et al., 2003).

Dynamic Gait Index

The DGI was developed to examine the ability of patients to maintain functional balance during the performance of activities during gait (Shumway-Cook et al., 1997). The DGI integrates rotational head movements (up and down and from side to side) into gait testing. Therefore the DGI is a very informative test in people with vestibular disorders (Wrisley et al., 2003). The rotational head movements utilized during the test can help to point to specific impairments and potential interventions in people with vestibular disorders. Each of the eight items on the DGI is graded on a scale from 0 to 3, indicating normal, mild, moderate, or severely impaired performance (Shumway-Cook and Woollacott, 1995). Although the DGI has been shown to moderately predict future falls, sensitivity and specificity are only 55% and 65% respectively (Shumway-Cook et al., 1997). The DGI has been validated in older adults (Shumway-Cook et al., 1997; Romero et al., 2011), people with vestibular disorders (Whitney et al., 2000, 2003; Wrisley et al., 2003), people with multiple sclerosis (McConvey and Bennett, 2005), individuals with brain injury (Simon and Harro, 2004), people with Parkinson's disease (Dibble and Lange, 2006), and stroke survivors (Galgon et al., 2004; Jonsdottir and Cattaneo, 2007). Moreover, the DGI has been translated and validated across cultures into Arabic (Alghwiri, 2014) and Portuguese (De Castro et al., 2006).

The Functional Gait Assessment

The Functional Gait Assessment (FGA) is a balance measure that has been developed based on the DGI (Wrisley et al., 2004). The FGA has 10 items: seven of them were taken from the DGI and three difficult balance items were added to improve the psychometric properties of the DGI and prevent a ceiling effect. The FGA has been validated in older individuals (Wrisley and Kumar, 2010), people with vestibular disorders (Wrisley et al., 2004), stroke survivors (Thieme et al., 2009; Lin et al., 2010), and people with Parkinson's disease (Leddy et al., 2011). Moreover, the FGA has been translated and validated in German (Thieme et al., 2009).

Gait speed

Gait speed is a very powerful measure of health. Studenski et al. (2011) have reported that gait speed can predict mortality, i.e., the slower you go, the worse you are. Gait speed should be recorded in all persons with vestibular disorders. Vestibular impairment has been reported as one of the main intrinsic factors that lead to falling (Pothula et al., 2004; Agrawal et al., 2009). Therefore, functional gait should be examined in people with vestibular disorders. When selecting an appropriate evaluation tool for functional gait, a therapist should take into consideration the main purpose of the gait evaluation and the current abilities of the patient. The examiner should consider whether the patient has had a history of falls as well as whether the patient is currently utilizing an assistive device.

Moreover, it is important to ask the patient to report any dizziness spells during the performance of the test and stop the task immediately for safety purposes. When interpreting the results, the therapist must take into consideration how the deficits on the test interact with the patient's functioning.

A thorough examination of functional gait necessitates multiple assessment tools. While some tools focus on gait speed, others may look at gait pattern and the level of assistance needed, whereas different tools combine other tasks with walking, such as changing gait speed (DGI), walking with head turns (DGI and BEST), negotiating obstacles (four-step square test) (Dite and Temple, 2002), and stair climbing (DGI and BBS). Moreover, complex walking tests that challenge attention and require higher cognitive ability, such as the walking and talking test (Camicoli et al., 1997; Verghese et al., 2002), can be added to the battery of gait examination. In regard to gait speed, the examiner should be cautious when dealing with older adults, since it has been reported that changing gait speed by 0.1 m/s significantly changed safety in older adults (Shumway-Cook et al., 2007).

The Locomotor Sensory Organization Test

The Locomotor Sensory Organization Test (LSOT) is a newly proposed paradigm to assess dynamic postural control during walking under similar sensory manipulation conditions to the original SOT (Chien et al., 2014). In the LSOT, a treadmill with two embedded force plates as well as a VR environment that represents a moving corridor were used. Additionally, body markers were placed on toe and heel and the three-dimensional motion of body parts was captured using a specialized camera system. For the purpose of visual manipulation, specialized goggles were used to reduce the intensity of light. The LSOT includes six conditions: condition 1 requires the patient to walk normally; in condition 2, visual input is reduced by stopping the VR as well as asking the patient to wear goggles; in condition 3, the speed of the VR is randomly varied; in condition 4, the speed of the treadmill is varied; in condition 5, visual input is

reduced as explained above, in addition to manipulation of the treadmill speed; finally, in condition 6, the speed of both the VR and the treadmill is varied.

The results of examining 10 healthy young individuals revealed mirror findings between the SOT during standing and LSOT during walking, indicating that sensory mechanisms also contribute to maintaining postural control during walking (Chien et al., 2014). Although this test is not available clinically, many physical therapy clinics have treadmills and VR software and hardware is becoming less expensive. The use of VR is already being used in VPT clinically (Alahmari et al., 2014; Meldrum et al., 2015). It is not clear if the LSOT will demonstrate long-term value because of its high cost.

FACTORS THAT AFFECT FUNCTIONAL RECOVERY

Persons with peripheral and/or central vestibular dysfunction can have variable outcomes. Comorbid dysfunction of the visual or proprioceptive systems will complicate rehabilitation. Table 13.3 lists several factors that can negatively affect outcome for persons with vestibular disorders. Diagnosis alone will affect outcome.

At present, persons with complete bilateral loss will have lifetime complaints of oscillopsia and gait dysfunction. Technology is being developed to assist persons with bilateral vestibular loss (Lewis, 2015), but currently their prognosis for functional recovery is limited due to the lack of function of the vestibular apparatus. Oscillopsia can be disabling during driving and head movements, although one report says that persons with bilateral loss can drive safely (MacDougall et al., 2009). Most patients report that when they hit a bump in the road, their vision blurs. Individuals report that everything jumps in their visual field and some patients report that they feel that they have a "bobble head" on top of their shoulders. At the moment, there is little that can be done to assist with the oscillopsia.

Table 13.3

Negative prognostic factors

Peripheral neuropathy (decreased distal sensation)
Migraine
Cognitive dysfunction
Anxiety
Comorbid disease (spinal stenosis, diabetes, renal disease, back/neck pain)
An inability to move (paralysis, head/neck immobilization)
Pre-existing eye disorders (strabismus, macular degeneration, glaucoma, cataracts)
Obsessive-compulsive disorder
Perfectionistic personality
A feeling of "fogginess"
Persons who are visually motion-sensitive prior to or after the vestibular insult
A feeling that the patient cannot get better
Fear of falling
Fear of movement

There is hope that a vestibular prosthesis will diminish oscillopsia in patients with bilateral vestibular loss (Dandy's syndrome). Postural instability is also a concern for persons with bilateral loss, who may suffer from frequent falls (Herdman et al., 2000). The use of a vibrotactile vest appears to be promising for persons with bilateral loss. Providing an early-warning system that they are at their limit of stability may help to prevent falls and there is some preliminary work that suggests that gait is improved with vibrotactile feedback in persons with vestibular dysfunction (Wall et al., 2009). The vibrotactile vest may be especially helpful for patients with cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS) (Szmulewicz et al., 2014). Patients with CANVAS have impairments of the VOR, smooth-pursuit, and optokinetic reflex. With their impaired distal sensation, they are also at greater risk for falling than those with only Dandy's syndrome. Recent evidence suggests that CANVAS may be a recessive disorder with late-life onset (Szmulewicz et al., 2014). Fall prevention is imperative for this group of patients and devices such as the vibrotactile vest may hold promise to enhance their postural control during functional activities.

Treatment can be challenging if patients have comorbid factors that negatively affect rehabilitation, regardless of the presenting diagnosis. It may take longer to improve and may require greater skill of the treating physical therapist to recognize and manage the comorbid factors within the treatment plan. Some of the comorbid factors that affect outcome may need to be managed by multiple disciplines such as by a psychologist or psychiatrist. Patients with migraine often require medical intervention in addition to physical therapy, while those with severe anxiety may need psychotherapy and sometimes medication. Generally, it is thought that, after the acute phase, the use of vestibular suppressants should be minimized (Horak et al., 1992). Early on for symptom management vestibular suppressants may be essential, but continued use of vestibular suppressants while undergoing a physical therapy exercise program may slow functional recovery (Strupp et al., 1998).

TREATMENT OF PATIENTS WITH VESTIBULAR DISORDERS

An individualized exercise program is developed in order to address the deficits identified during the physical therapy examination. Education about the individual

vestibular condition is an essential element of all vestibular exercise programs, as are support and encouragement in order for the patient to move more within the limits set by the physical therapist. Gaining the patient's trust is an essential element in recovery, as patients are often asked to make themselves dizzy and are encouraged to stretch the limits of their postural stability.

Progression-of-balance exercises are complex, as few people start with exactly the same postural control or dizziness deficits. Klatt et al. (2015) recently suggested a systematic method of exercise progression that included different "buckets" of exercise, with various modifiers to make the exercise easier or more difficult. The buckets consisted of: firm static standing, foam static standing, gait, modified center of gravity, VOR, and weight shifting. All of the exercises could be modified by head movement, changes in the environment, divided attention, foot stance, the surface, visual input, static versus dynamic standing, gait, and eye/head movements.

An exercise prescription is always provided for the patient to perform at home. Generally, patients are asked to perform their exercises two to three times a day for up to 10–15 minutes a day. Recently, it was determined that there was no difference in exercises provided by the physical therapist both online and with a written home exercise program. Patients generally do not like to exercise, so the importance of exercise needs to be emphasized. An ongoing randomized trial in persons over the age of 50 will soon answer the question of whether exercises provided on the web are effective for persons with chronic dizziness.

There are five types of exercises that have evolved in the treatment of individuals with dizziness and balance disorders: (1) adaptation; (2) habituation; (3) substitution; (4) postural control; and (5) optokinetic exercises. Not all patients need all types of exercises in their exercise prescription. Lacour and Bernard-Demanze (2014) recently reported that adaptation exercises were the optimal exercise for persons with unilateral hypofunction. The goal of the adaptation exercise is to minimize retinal slip in order to enhance the gain of the VOR. The VOR gain is typically low in patients with unilateral hypofunction and in animal and human studies the VOR gain increases with VOR exercises. The VOR $\times 1$ exercise consists of the person focusing on a target (either near or far) with various backgrounds (typically, a plain white background progressing to complex patterns) while moving the head in the pitch and yaw planes. Exercises typically start at slow speed, progressing to faster speed as long as the visual target remains in focus, without a significant increase in symptoms within 15–20 minutes of the cessation of the exercise program. The VOR exercises are progressed from sitting to standing to walking and may be performed during dual tasking (walking and talking or doing a mental task). Dizziness and balance are monitored with all activities. The goal is to reduce symptoms and improve postural control.

Little is known about how and if habituation works. Patients are often asked to repeat movements that increase symptoms, with the goal of "habituating" symptoms and improving function. Habituation presently is most commonly used in the form of optokinetic training.

Substitution is most commonly used with individuals with little to no remaining vestibular function and has been observed in those who compensate well with unilateral loss. Persons with vestibular hypofunction appear to benefit from the use of substitution. Schubert et al. (2010) reported that patients with bilateral vestibular hypofunction use saccades to compensate for the loss of VOR function, resulting in a decrease in oscillopsia.

Postural retraining is utilized with persons who are at risk of falling or who demonstrate instability. Slow gait speed (<0.8 m/s) suggests that gait training is indicated. Exercises that challenge balance in standing are utilized with head still or moving and in various stance positions on level and compliant surfaces. Various gait exercises are practiced, such as walking at different speeds, walking and turning, walking with head movements in the pitch and yaw position, and walking and talking.

Optokinetic training is being used especially for patients with visual motion sensitivity. Some patients complain of having difficulty walking in a grocery store, a train station, or a shopping mall. Bright, fluorescent, or flashing lights often bother the patient who is very sensitive to motion. Optokinetic training, in the form of moving stripes, disco balls, and VR scenes have been used successfully to help to modulate the symptoms of motion discomfort. Some experts have suggested calling this motion discomfort persistent "postural-perceptual dizziness" (Bittar and Lins, 2014). Optokinetic training must be carefully dosed, as one can increase the patient's symptoms rapidly. The results appear to be promising as another form of exercise for the person with vestibular dysfunction.

VPT treatment frequency and duration have not been well studied. It appears that persons with relatively uncomplicated unilateral vestibular hypofunction can be treated over a 4–6-week period with good results. Persons with bilateral vestibular hypofunction, especially those with complete loss, appear to take longer to improve. Generally, most people are treated one on one for approximately 45 minutes to 1 hour per session, especially if they are practicing balance tasks. As it is common for persons with vestibular disorders to fall, the patient is carefully guarded in order to prevent falls, especially when challenging the postural control system with a new exercise.

Treatment frequency is much less understood in persons with central disorders. Although the literature is expanding related to VPT and central conditions, it is difficult to describe how frequently and for how long a person needs to be seen. Central vestibular disorders are complex and present differently, so it is more difficult to compare findings between studies. In a large case series of persons with various diagnoses by Brown et al. (2006), they all improved, but not on all measures. Patients with cerebellar dysfunction improved the least. Alsalaheen et al. (2010) reported that in persons with chronic concussive symptoms the range of treatment visits was 2–13 visits over a range of 7–181 days.

CONCLUSION

The growing body of evidence related to physical therapy for vestibular disorders suggests that people improve faster with VPT versus no intervention. Persons with vestibular disorders may develop psychologic dysfunction and fear of movement the longer they experience vestibular symptoms. Early intervention is advised and customized programs appear to be superior to a generic exercise program. The support of the physical therapist is most likely a factor in the recovery of persons with uncompensated vestibular disorders.

ILLUSTRATIVE CASE

An 83-year-old woman was referred to VPT with a diagnosis of right uncompensated peripheral vestibular loss. Her symptoms of nausea, vomiting, and dizziness started suddenly 4 months ago. The patient's present chief complaint was nausea, feeling off balance, and also of visual blurring with a change of head position. She had stopped driving and traveled 1 hour to the clinic. She had an 80% caloric weakness on the right, normal positional testing, normal oculomotor testing, and normal hearing. She was seen 3 days ago in the vestibular clinic by the neurologist who then referred her for VPT for treatment of uncompensated right vestibular neuritis. The patient takes no medication and was very active before her vestibular event.

The patient was seen in physical therapy and stated that she had lost at least 10 lb (4.5 kg) over the last 4 months (unintentionally) and that she is nauseous whenever she eats. She feels that her balance is off but that her biggest problem is her nausea. At rest she had nausea that she rated as 3 out of 10, increasing to 7–8 at meal times.

She does not want to take traditional medicine for her nausea. The patient does, however, try to self-medicate from the local health food store and has tried everything that they have to offer to try to decrease her symptoms of nausea, including ginger and peppermint. The peppermint has helped her but she still has symptoms (Amato et al., 2014).

The patient has no past medical history of migraines or anxiety disorder. Her vision is corrected with glasses and she has no history of eye disease. She was very active in her church and cooked food on a volunteer basis for seniors who were unable to get out of their home. The patient has not fallen and has not had any near falls.

During the exam, the patient had an inability to keep a target in focus with head movement, suggesting that she was still experiencing retinal slip. She was asymptomatic with VOR cancellation and had a negative head impulse test, head shake nystagmus test, Dix–Hallpike test, and roll test. Saccades and smooth-pursuit movements appeared normal without an increase in symptoms. Vergence was age-appropriate. With dynamic visual acuity testing, the patient lost four lines and became symptomatic.

She also was unstable and veered during gait with head movements in both the pitch and the yaw plane. Her DGI score was 18/24 and her FGA score was 22/30. She was unable to stand on a high-density foam pad and fell within 1–2 seconds with her eyes open and closed. Standing with feet together on a stable surface was normal (30 seconds). Strength, range of motion, and sensation were normal. Her blood pressure was 125/70 mmHg.

Her DHI score was 46 and her ABC score was 60%, suggesting that she has moderate impairment and that she may be at risk of falling. The patient's dizziness at rest was 4/10 and increased to 7/10 with head movements. Her visual blurring and her nausea will be priorities for her invention program. Her first exercise prescription included performing VOR × 1 exercises slowly at home and walking with head turns, and she was asked to perform a walking program as she was not getting out of her home alone without her daughters. The patient was also advised to try sea bands to see if they could decrease her nausea (Allais et al., 2012).

Upon return to the clinic, she had less dizziness and stated that her dizziness felt "better" after doing the VOR × 1 exercises. Her nausea was slightly improved over the past week.

Over the next 4 weeks the patients was seen four more times. At her fifth visit, she no longer stated that she had nausea. She was eating normally and stated that she always felt "better" after she did her VOR × 1 exercises. By "better," she meant that her vision was clearer. At discharge (visit 5), she had no nausea, a normal dynamic visual acuity test (she lost only two lines), could stand on foam with eyes closed for 25 seconds, her DGI was 22/24, her FGA was 27/30, the ABC was 85%, and her DHI score was 12. Although all of her scores were not "perfect," the patient felt that she was back to baseline and that she had reached her goals. She was discharged and told to call if she had any additional concerns related to her dizziness, balance, or nausea.

The patient was very compliant with her exercise program. It is often difficult to get patients to perform exercises that increase their symptoms of dizziness, yet this patient was willing to try the exercises at home. Sometimes older adults must be seen more frequently in the clinic because of their fear that their dizziness will increase or that they will fall when performing the exercises. The support of this woman's daughters, who attended each session, may have helped this woman to comply. Her activity gradually

increased over the 5 weeks that she was seen and she was encouraged to get out of the house as much as possible in order to begin to resume her normal schedule. It is possible that the visual blurring from her vestibular neuritis may have been driving her nausea and that, as her retinal slip decreased, she became less nauseous. The patient had not improved for the previous 4 months and was not provided any new medication by the neurologist, suggesting that the graduated exercise program and eye exercises may have been the driving force in her functional recovery.

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Chapter 14

Principles of vestibular pharmacotherapy

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Abstract

Ideally, vestibular pharmacotherapy is intended, through specific and targeted molecular actions, to significantly alleviate vertigo symptoms, to protect or repair the vestibular sensory network under pathologic conditions, and to promote vestibular compensation, with the eventual aim of improving the patient's quality of life. In fact, in order to achieve this aim, considerable progress still needs to be made. The lack of information on the etiology of vestibular disorders and the pharmacologic targets to modulate, as well as the technical challenge of targeting a drug to its effective site are some of the main issues yet to be overcome. In this review, my intention is to provide an account of the therapeutic principles that have shaped current vestibular pharmacotherapy and to further explore crucial questions that must be taken into consideration in order to develop targeted and specific pharmacologic therapies for each type and stage of vestibular disorders.

THE "BLACK BOX," OR THE QUEST FOR PROOF BY INFERENCE

It is a somewhat difficult, if not hazardous, task to establish an exhaustive review of vestibular pharmacotherapy. Current pharmacopeia originates from empiric approaches, based upon assumptions that have not always been verified, rather than from accurate and well-defined biologic actions, founded on established molecular mechanisms. The main issue that has to be faced is the lack of information on the etiology and time course of most vestibular impairments. It is even more difficult to invoke notions of specificity or selectivity of action in relation to available drugs. In most cases, we often try to reconcile the observed (or expected) therapeutic effects with the molecular properties of the drugs. The aim is to assign to the compounds a mode of action, and eventually to speculate about pathophysiologic mechanisms that remain, most of the time, impossible to decipher on the basis of available diagnostic tools and medical devices. Moreover, the molecular mechanisms involved in the shaping and transfer of the vestibular information have still to be completely deciphered. This has resulted in a problematic gap in the current knowledge of available and appropriate pharmacologic actions that would efficiently control vestibular input, both on healthy and damaged sides. A further issue derives from the fact that there is no suitable pharmacokinetic protocol to verify the presence and fate of administered compounds at the sites of targeted actions. In addition, we do not know the best therapeutic windows to achieve the optimum effect of administered drugs. Moreover, current clinical approaches are incapable of confirming or disproving the long-term effects of therapy. Ultimately, the modalities of vestibular pharmacotherapy also depend on regional rules dictated by national medical leaders and health authorities. This being so, most antivertiginous treatments lack specificity and may engender side-effects. The result is a lack of efficacy with regard to the targeted symptoms or pathologies.

DEFINITION AND OBJECTIVES OF VESTIBULAR PHARMACOTHERAPY

Vestibular pharmacotherapy consists of the administration of active compounds and medications for the treatment of acute or chronic vestibular disorders. It intends to

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alleviate the different vertigo symptoms, to protect the vestibular end organs in pathologic situations, and possibly to repair damaged tissues, with the aim of restoring vestibular function. Another goal is to promote the reactive processes that support vestibular compensation. All the different classes of compounds are usually systemically administered. The administration *per os* is by far the most common. Intravenous application and occasionally suppositories are recommended in case of severe nausea and vomiting. Local (transtympanic) drug administration remains restricted to corticosteroid treatments of inner-ear inflammations and to destructive treatments with ototoxic compounds in persistent and intractable Menière's disease.

PRINCIPLES OF VESTIBULAR PHARMACOTHERAPY AND MAIN DRUG CATEGORIES

Among the various action principles in vestibular pharmacotherapy, two main categories may be distinguished. A first category, referred to as "symptomatic treatments," includes drugs that are intended to alleviate vertigo symptoms. These include dizziness, nausea, and vomiting that often accompany vestibular disorders and nystagmus as their main clinical sign. A second category is composed of different approaches referred to as "causal treatment." The aim of these treatments is to counteract the causes – most often assumed, but not confirmed – of the different types of vestibular pathologies. This category includes antibiotics, antiviral, and anti- inflammatory approaches and medications designed to improve inner-ear blood perfusion or to stimulate vestibular compensation. Other approaches, referred to as "destructive," are used to reduce or suppress vestibular function, especially in patients with intractable Menière's disease. Other therapeutic approaches under development, that aim to protect the integrity of the vestibular end organs under pathologic conditions or to stimulate the repair of the vestibular sensory network, will be mentioned in the last part of this chapter.

In the present review, I have chosen to classify the main compounds used in vestibular pharmacotherapy according to the mode of action for which they are prescribed (symptomatic or causal treatments). For additional and more complete information on the assumed mechanisms of action of these drugs, readers are referred to the outstanding reviews by Soto and Vega (2010) and Huppert et al. (2011). The first review presents the antivertigo drugs according to their molecular and cellular properties: modulators of membrane receptors and neurotransmitters, as well as compounds acting on voltage-gated ionic channels (Figs 14.1 and 14.2). This rational approach reconciles the idea of a modulation of pharmacologic targets expressed throughout the vestibular sensory pathway with the assumed antivertigo potential of these compounds. The second review classifies antivertigo drugs in alphabetic order, with mention of their class and doses used, indications, and contraindications in order to facilitate their use by the clinician.

Symptomatic treatments

Vestibular suppressants

The principle of vestibular suppression consists in modulating the molecular effectors expressed throughout the vestibular sensory network, in order to control the sensory information generated in the vestibular end organs and transmitted to the vestibular nuclei through the vestibular nerve. This strategy, which dates back to the works of Bárány at the turn of the 20th century (Bárány, 1935), relied on the assumption that the vertigo episodes observed in Menière patients resulted from a transient unilateral hyperexcitability of primary vestibular neurons, in response to unknown vestibular dysfunction. The logical countermeasure proposed by Bárány consisted in counteracting this hyperexcitability by blocking the nerve influx. With this aim, he administered to Menière patients antagonists of voltage-gated sodium channels such as lidocaine. This vestibular suppressant operation later evolved into local administration through transtympanic applications because of cardiac or neurologic risks. It was designed as vestibular anesthesia or inner-ear anesthesia (for review, see Adunka et al., 2003). Since these pioneering works, a number of clinical studies have confirmed the benefits of vestibular anesthesia. However, this approach has not become a standard protocol in the management of the acute vertigo episodes or other vestibular disorders, such as unilateral vestibular deafferentation (uVD) syndromes (Rahm, 1962; Gejrot, 1963; Sakata et al., 1984; Fradis et al., 1985; Halmagyi et al., 2010). This may be due to the risks of inappropriate vestibular suppressant effects. Vestibular suppressant action, when performed outside the period of unilateral hyperexcitability, or excessive inhibition of the affected side, would lead to amplification of the vestibular imbalance and subsequent exacerbation of the vertigo syndromes, rather than to their reduction. On the other hand, to achieve an alleviating effect in uVD syndromes, vestibular anesthesia needs to be applied to the healthy ear. However, the modulation of vestibular function currently remains the basis of most antivertigo treatments. Its expected therapeutic output relies more on a general reduction, through combined peripheral and central actions, of the imbalance of activity between contralateral labyrinths and vestibular nuclei that occurs under pathologic situations (Curthoys and Halmagyi, 1995; Dieringer, 1995; Hain and Uddin, 2003; Jones

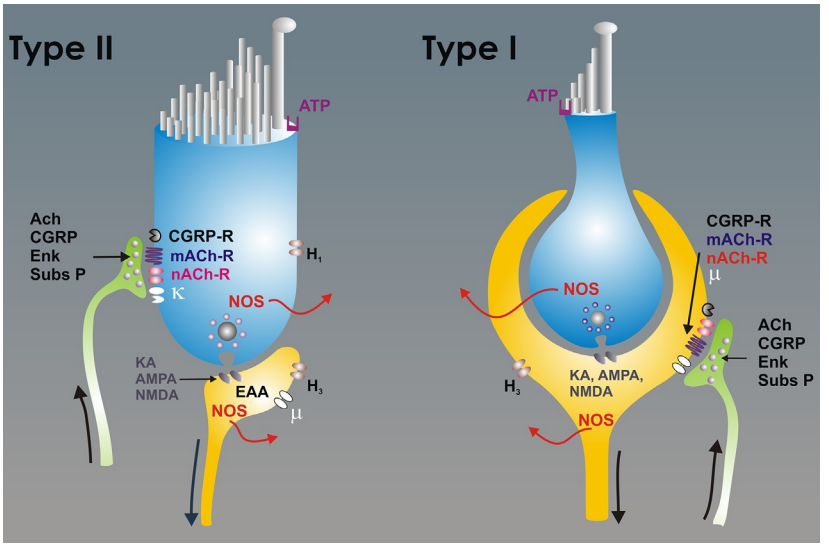

Fig. 14.1. Synaptic relationships of type I (right) and type II (left) hair cells. The type I hair cells are characterized by the large-calyx afferent innervation that covers its basolateral surface. The efferent fibers make synaptic contacts with the external surface of the calyx in the afferent neuron. In type II hair cells, the afferent neurons form bouton-type synapses, and the efferent neurons make synaptic contact directly upon the hair cell body. The hair cell to afferent synapse uses glutamate as the principal neurotransmitter. At the postsynaptic cell glutamate interacts with several subtypes of excitatory amino acid (EAA) receptors, including *N*-methyl-D-aspartic acid (NMDA), α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionic acid (AMPA), kainic acid (KA), and metabotropic receptors. The efferent neurons are primarily cholinergic, and acetylcholine (Ach) released from afferent neurons interacts with muscarinic (mACh) and nicotinic (nACh) receptors. The efferent neurons also release calcitonin gene-related peptide (CGRP), substance P (SubsP), and enkephalins (Enk), which act on specific receptors (in the case of the enkephalins κ opioid receptor in the hair cells and μ opioid receptors in the afferent neurons). Both the hair cells and the afferent neurons express nitric oxide synthase (NOS) and nitric oxide (NO). Hair cells also express H1 histamine receptors and the afferent neurons H3 histamine receptors. The hair cells typically express purinergic receptors (ATP) in their apical portion. (Reproduced from Soto and Vega, 2010, with permission from Bentham Science Publishers.)

et al., 2009; Halmagyi et al., 2010). Conventional antivertigo drugs are classified into three main groups: antihistamines, anticholinergics, and benzodiazepines (Table 14.1). Calcium channel antagonists, which are less widely used, can also be added to this list. These substances are currently used for fast symptomatic action, including reduction of nystagmus, dizziness, vomiting, and postural imbalance.

Antihistamines

Antihistamines are historically among the first antivertigo drugs and constitute today a large part of the vestibular pharmacopeia (McCabe et al., 1973; Lacour and Sterkers, 2001; Soto and Vega, 2010). Diphenhydramine, meclizine, cyclizine, and promethazine, all displaying antagonist actions on type 1 histamine receptors (H1R), are among the most widely used antivertigo drugs in the treatment of vestibular disorders in the USA. They are mainly prescribed to alleviate acute vertigo symptoms and to prevent kinetosis (Huppert et al., 2011). Betahistine, which is both an antagonist of type 3 histamine receptors (H3R) and an H1R agonist, is the standard treatment for the long-term management of Menière disease (Lacour and Sterkers, 2001) out of the USA. H1R antagonists were the first to be demonstrated as significant regulators of the vestibulo-ocular reflex in patients displaying chronic vestibular disorders (Jackson and Turner, 1987). Dimenhydrinate (H1R antagonist with molecular properties close to diphenhydramine) reduces both the duration and intensity of acute vertigo episodes, as confirmed by meta-analysis of several randomized, double-blind controlled studies (Schneider et al., 2005; Thormann et al., 2013).

Nevertheless, a number of questions remain open regarding the molecular and cellular mechanisms that support these antivertigo effects, as well as the effective site of action of the drugs. Several studies in animals have demonstrated that the application of histamine receptor modulators was able to modulate the firing activity of vestibular nuclei neurons (Kirsten and Sharma, 1976; Lacour and Sterkers, 2001; Zhang et al., 2008). A number of studies have reported the expression of different histamine receptors in the vestibular end organs and primary neurons (Botta et al., 2008; Tritto et al., 2009). Others have demonstrated modulation of the neuronal excitability after application of H1R and H3R

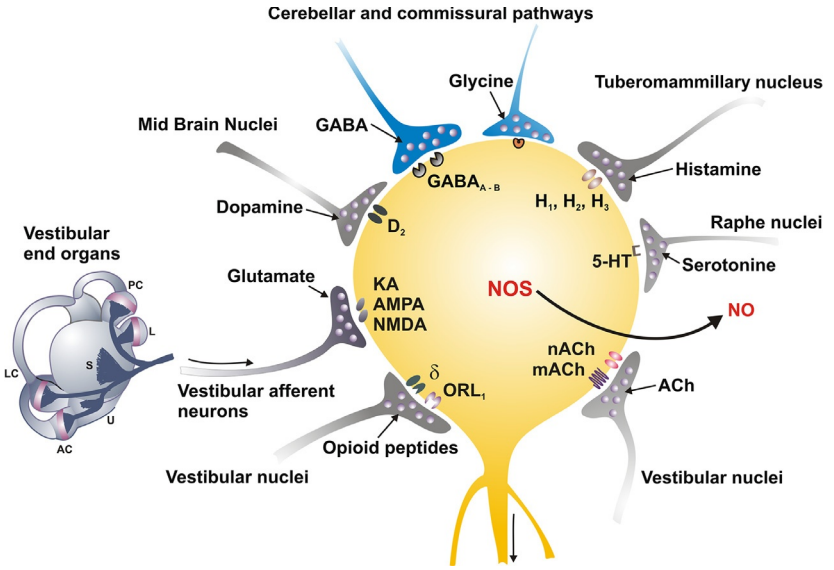

Fig. 14.2. Complexity of synaptic input impinging on vestibular nucleus neurons. The neurons of the nuclei are heterogeneous and not all cells necessarily receive all types of synaptic influences. The main synaptic input to the vestibular nuclei neurons is from the vestibular primary afferents, mediated by glutamate that interacts with *N*-methyl-D-aspartic acid (NMDA), α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionic acid (AMPA)/kainic acid (KA), and metabotropic receptors. Vestibular nuclei also receive glutamatergic synapses originating from spinal cord neurons. GABAergic fibers originating primarily from the cerebellum and from the contralateral vestibular nuclei impinge on the vestibular nucleus neurons, activating GABA-A and GABA-B receptors. Histaminergic fibers originating from the tuberomammillary nucleus act on H1, H2, and H3 receptors. Serotonergic fibers originating from the raphe nuclei activate 5-HT$_1$ and 5-HT$_2$ receptors. Intrinsic and commissural connections give rise to glycinergic fibers acting on glycine inhibitory receptors. The output of the vestibular nuclei neurons is primarily by glutamatergic and cholinergic projections, but GABAergic and glycinergic projections have been demonstrated also. Finally, the vestibular nucleus neurons express nitric oxide synthase (NOS) and may produce nitric oxide (NO) as a cellular messenger. ACh, acetylcholine; nACh, nicotinic acetylcholine; mACh, muscarinic acetylcholine; GABA, gamma-aminobutyric acid; ORL, opioid receptor-like. (Reproduced from Soto and Vega, 2010, with permission from Bentham Science Publishers.)

Table 14.1

Vestibular depressants

Compounds	Administration	Class
Lidocaine	Transtympanic	Anesthetic
Diphenhydramine	*Per os*	Antihistamine
Meclizine	*Per os*	Antihistamine
Cyclizine	*Per os*	Antihistamine
Promethazine	*Per os*	Antihistamine
Scopolamine	*Per os*/ transcutaneous	Anticholinergic
Atropine	*Per os*	Anticholinergic
Diphenidol	*Per os*	Anticholinergic
Diazepam	*Per os*	Benzodiazepine
Lorazepam	*Per os*	Benzodiazepine
Clonazepam	*Per os*	Benzodiazepine
Nimodipine	*Per os*	Calcium antagonist
Nitrendapine	*Per os*	Calcium antagonist
Verapamil	*Per os*	Calcium antagonist
Cinnarizine	*Per os*	Calcium antagonist
Flunarizine	*Per os*	Calcium antagonist

antagonists (Housley et al., 1988; Tomoda et al., 1997; Guth et al., 2000). The real questions remaining are whether antivertigo drugs administered systemically are able to reach action sites that are potentially important for the control of vestibular information, and whether histamine receptors really mediate their antivertigo effect. It cannot be ruled out that the acknowledged antivertigo effect of H1R antagonists may occur via their well-known anticholinergic action (Hain and Uddin, 2003). Only studies based on local antihistamine applications (in the brainstem or directly to the vestibule), associated with regular pharmacokinetic studies, will provide suitable answers to these questions.

Today, the development of novel antivertigo treatments based on modulators of histamine receptors is moving towards H1R antagonists with negligible sedative effect, or towards the use of modulators of other categories of histamine receptors. The antivertigo potential of type 4 histamine receptor (H4R) antagonists is currently under study. These strong modulators of the vestibular primary neurons' excitability have shown

significant antivertigo properties in animal models of uVD (Desmadryl et al., 2012; Wersinger et al., 2013). Due to their lack of sedative effect, this compound family may become the next generation of antivertigo drugs, if their benefit is confirmed in humans.

Anticholinergics

Anticholinergics, such as scopolamine or atropine, both muscarinic receptor antagonists, are among the most widely used drugs in the pharmacologic treatment of vestibular disorders. Scopolamine is also one of the most effective compounds in the prevention of motion sickness. However, as for antihistamines, it is not known whether its action is central or peripheral or if it has a combined effect at both levels (Wackym et al., 1996; Ishiyama et al., 1997). Both nicotinic and muscarinic acetylcholine receptors are expressed in vestibular end organs (Wackym et al., 1995, 1996; Anderson et al., 1997; Elgoyhen et al., 2001), as well as in vestibular nuclei (Matsuoka and Domino, 1975; Pérez et al., 2009). At the periphery, these different receptors are involved in the complex modulation of vestibular afferents by efferent fibers (Goldberg and Fernández, 1980; Valli et al., 1984; Bernard et al., 1985; Highstein and Baker, 1985). The efficacy of scopolamine in alleviating acute vertigo episodes was demonstrated in randomized, double-blind, controlled clinical studies in vestibular patients (Babin et al., 1984). Similarly, its effect in preventing kinetosis is significant versus placebo, but does not differ significantly from other vestibular suppressants such as antihistamines or voltage-gated calcium channel antagonists (Spinks et al., 2007). Because of its significant side-effects (blurred vision, behavioral disorders, and dry mouth), there is a tendency for oral administration of scopolamine to be replaced by transcutaneous applications (Renner et al., 2005; Nachum et al., 2006). The administration of diphenidol in Menière patients has also demonstrated significant reduction of vertigo symptoms compared to placebo (Futaki et al., 1975). This effect may result, as for scopolamine, from its antagonist properties against muscarinic receptors (Varoli et al., 2008).

Benzodiazepines

Benzodiazepines are used in the symptomatic treatment of acute vertigo episodes to reduce nausea and vomiting (Huppert et al., 2011). They are also used in the prevention of kinetosis (McClure et al., 1982). The main benzodiazepines used for antivertigo treatment are diazepam, lorazepam, and clonazepam. Their fast action in reducing nystagmus was demonstrated in humans (Blair and Gavin, 1979; Padoan et al., 1990) and is attributed to a central action similar to gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter of vestibular neurons. However, it cannot be ruled out that benzodiazepines may act through a peripheral action, as $GABA_A$ receptors have been shown to be expressed in mammal vestibular end organs (Rezaee et al., 1999; Meza, 2008). The benefits of benzodiazepines in vertigo patients may also result from their anxiolytic effect (Zajonc and Roland, 2005). Use of benzodiazepines as antivertigo medication is essentially restricted to the USA. Recently they have been less widely used because of their serious side-effects, such as addiction, loss of memory, and risk of falling (Funderburk et al., 1988). Another GABAergic substance is baclofen, which acts as a $GABA_B$ agonist. Several nonrandomized clinical studies have demonstrated the reduction of periodic alternating nystagmus by baclofen (Stahl et al., 2002; Straube et al., 2004; Straube, 2005). This effect may result from the inhibition of central vestibular neurons via the antagonization of $GABA_B$ receptors (Zee, 1985).

Calcium channel antagonists

The voltage-gated calcium channel antagonists also belong, although to a lesser extent, to the family of vestibular suppressants. They are used mostly for acute vertigo episodes but they may also have the potential to prevent vestibular migraine. The majority of calcium channel antagonists used as antivertigo medication are dihydropyridine derivatives. Because these compounds specifically block the voltage-gated calcium channels restricted to the vestibular end organs, it is widely accepted that their effect is essentially peripheral (Soto and Vega, 2010). The calcium channel antagonists used as antivertigo medication are nimodipine, nitrendipine, and verapamil (Lassen et al., 1996; Hain and Uddin, 2003; Scholtz et al., 2004). Cinnarizine and flunarizine, which both display an antihistaminic action, are also used in the treatment of vertigo symptoms, especially in vestibular migraine (Lepcha et al., 2014). A multicenter, randomized, double-blind, controlled study has demonstrated that *per os* administration of cinnarizine and nimodipine significantly reduced the frequency of vertigo attacks of vestibular origin (Pane-Pianese et al., 2002).

Other compounds

Other compounds or combinations of compounds have shown significant antivertigo effects upon oral or intravenous administration during the acute phase. This applies to acetylleucine, which has demonstrated significant alleviation of vertigo symptoms in animals (Leau and Ducrot, 1957) and humans (Ferber-Viart et al., 2009). Treatments combining H1R antihistamine and

calcium channel antagonists also showed significant benefits (Novotny et al., 1995). Amphetamines are sometimes used in combination with anticholinergics as antimotion sickness drugs. In animals, D-amphetamine has been reported to reduce the excitability of vestibular nuclei neurons through central action (Kirsten and Sharma, 1976). Its use may be of interest in the treatment of vestibular disorders, as amphetamines also accelerate vestibular compensation, perhaps by stimulating the general activity of the patient (Peppard, 1986).

Antiemetics

Administration of antiemetic compounds is sometimes proposed in parallel to other active compounds in order to alleviate the neurovegetative reaction involved in most vestibular disorders (Miller and Grélot, 1996). Antiemetics are generally administered *per os*, except in the case of excessive vomiting, for which rectal or intravenous administration is recommended (Table 14.2). The antiemetic pharmacology associated with vertigo treatment is based on the use of setrons (antagonists of the 5-HT_3 receptors: ondansetron, granisetron), dopaminergic antagonists (metoclopramide, domperidone), and antihistamines that combine both antivertiginous and antiemetic properties. These different compounds display both central action at the vomiting control site in the area postrema and peripheral action on gastric mobility (Miller and Leslie, 1994). Through these different actions, these compounds promote rapid emptying of the stomach. Meclizine and promethazine – both antihistaminics – also display antiemetic properties. Their effect may occur through the antagonization of both dopamine and muscarinic receptors (Minor et al., 2004; Zajonc and Roland, 2005). It should be noted that dopamine receptor antagonists may be contraindicated in the treatment of vestibular disorders, because of the effect of phenothiazines in slowing vestibular compensation (Petrosini and Dell'Anna, 1993).

Table 14.2

Antiemetics

Compounds	Administration	Class
Ondansetron	*Per os*	Setron
Granisetron	*Per os*	Setron
Metoclopramide	*Per os*	Antagonist DOPA
Domperidone	*Per os*	Antagonist DOPA
Promethazine	*Per os*	Antihistamine
Meclizine	*Per os*	Antihistamine

CAUSAL TREATMENTS

In contrast to symptomatic treatments, causal treatments are intended to counteract the underlying pathologic processes, in order to limit the extension of tissue damage and related functional alterations of the vestibular labyrinth. Upcoming treatments under development have been designed to preserve the different cell types involved in the generation and transfer of the vestibular sensory information, while others are intended to stimulate their regeneration.

Antibiotics and antivirals

Antibiotics are commonly used in clinical situations where the labyrinth is likely to be suffering from bacterial superinfection (acute otitis media in children with vertigo, vertigo in patients with chronic otitis media and cholesteatoma and postoperative vertigo symptoms after opening of the labyrinth). Penicillin A plus clavulanate or third generation of cephalosporin are commonly used. In most cases, antibiotics are administered through oral or intravenous routes. However, their real benefit for vestibular recovery is not clearly established (Pellegrini et al., 2012). Aminoglycoside antibiotics are used in patients with intractable Menière's disease regarding their ototoxic properties. Antiviral approaches rely on the assumption that a significant proportion of vestibular neuritis (the name of which literally refers to inflammation of the vestibular nerve) results from the reactivation of the herpes simplex virus (Arbusow et al., 1999; Theil et al., 2003). This viral reaction may affect the vestibular ganglia, the vestibular nerves, and, more generally, the whole labyrinth or a combination thereof (Walker, 2009; Jeong et al., 2013). This results in unilateral loss of vestibular sensory information and vertigo. This hypothesis is supported by the demonstration of the expression of CD8-positive lymphocytes, cytokines, and chemokines concomitantly to vertigo (Derfuss et al., 2007). The most widely used treatment is the administration of valacyclovir, often in association with corticotherapy, in the first hours following the onset of the vestibular neuritis symptoms (Strupp et al., 2004). While the therapeutic benefits of this approach have been demonstrated, they are rather attributed to corticosteroids. Therefore, the question of the real benefit of the antiviral treatments is as yet unresolved (Strupp et al., 2004; Amber et al., 2012).

Anti-inflammatories: corticosteroids

Inflammation is a reactive process that has often been suspected to cause inner-ear dysfunction (Ruttin, 1909; Nylen, 1924; Dix and Hallpike, 1952). The terms vestibular neuritis or labyrinthitis literally refer to inflammation of the vestibular nerve or the whole labyrinth,

respectively. It is only recently that the involvement of an inflammatory process in vestibular neuritis has been confirmed (Kassner et al., 2011), consistent with the long-time standard corticosteroid-based treatment of this condition (Walker, 2009). Although used as standard treatment in most patients with uVD syndromes, the clinical benefit of corticosteroid-based treatments using intravenous or transtympanic administration has been strongly questioned because of their limited clinical efficacy (Shupak et al., 2008; Goudakos et al., 2010; Fishman et al., 2011). Functional restoration following vestibular neuritis is often incomplete, even after steroid treatment (Mandala and Nuti, 2009; Strupp and Brandt, 2009), resulting in a permanent dynamic deficit of the vestibulo-ocular reflex that cannot be fully compensated by other mechanisms (Halmagyi and Curthoys, 1988; Curthoys and Halmagyi, 1995). Intratympanic steroids to reduce the frequency and severity of the vertigo symptoms in Menière's patients have been gaining popularity. Up to now, however, there is limited evidence to support the effectiveness of such an approach in this pathology (Phillips and Westerberg, 2011). It should also be noted that, similarly, a meta-analysis of clinical studies has shown a lack of effect of steroids in patients with sudden hearing loss (Wei et al., 2013).

Peripheral vasodilators

In his famous study, C.S. Hallpike was one of the first to speculate that acute vertigo episodes in Menière patients are associated with vestibular ischemia that could result from impairments of the blood circulation following endolymphatic hydrops (Hallpike and Cairns, 1938). The principle of vasodilation of the arteries irrigating the inner ear has been pursued since then, with the aim of improving the perfusion of the inner ear and limiting damage to the vestibular detectors. The vasodilator properties of histamine were the basis of the first treatments of episodic vertigo and other forms of inner-ear dysfunction (Fischer, 1991). The observed benefits resulted in the development of betahistine, an analog of histamine for oral administration. First references to the clinical use of betahistine in the treatment of vertigo refer to its use in the management of patients who underwent unilateral vestibular neurectomy (McCabe et al., 1973). In terms of the pharmacologic treatment of Menière disease, betahistine (H3R antagonist) has for several decades remained the most widely used drug in Europe. However, its therapeutic action is not fully understood. Beside its action in increasing inner-ear blood flow, demonstrated in animals (Martínez, 1972; Dziadziola et al., 1999), the antivertigo effect of betahistine may also depend on central neuromodulatory actions on the vestibular nuclei neurons, and also on the peripheral action of vestibular primary neurons via its antagonist effect on the H3R (Lacour and Sterkers, 2001; Desmadryl et al., 2012; Lacour, 2013). The real therapeutic benefit of betahistine is however still questioned, as a systematic Cochrane review of clinical studies in Menière patients was inconclusive (James and Burton, 2001).

Recently, two studies offered significant insight into the pharmacologic management of Menière disease. At very high doses and over a prolonged administration period, i.e., 480 mg/days for several years, betahistine also demonstrated therapeutic benefit with regard to the frequency of vertigo episodes in severely affected Menière patients (Lezius et al., 2011). These benefits were, however, associated with serious side-effects. Betahistine administered at doses of 24 mg/day between 3 and 90 days in neurectomized Menière patients demonstrated significant benefits in improving vestibular compensation (Redon et al., 2011).

Destructive pharmacotherapies

The principle of vestibular neurectomy was first proposed by J.M. Charcot as the therapy "*de la dernière chance*" [the last resort] in the treatment of Menière disease (Charcot, 1874). The benefits of this approach (Miyazaki et al., 2005) were closely associated with the risks of complications of an intracranial procedure (Thomsen et al., 2000). The main advantage of vestibular neurectomy over chemoablative procedures is that a neurectomy disrupts the connection of the Scarpas's vestibular ganglion to the vestibular nuclei. This connection may be the basis for vestibular plasticity via plasticity of the histamine H3R, and may explain differences in the course of vestibular compensation after vestibular neurectomy and chemical ablation (Dutheil et al., 2011; Tighilet et al., 2014). Chemical labyrinthectomy progressively developed over time as the standard therapeutic method in the management of intractable Menière's disease, first on the basis of the work of Schuknecht using parenteral application of streptomycin (Schuknecht, 1956; Wilson and Schuknecht, 1980), then through local transtympanic applications of gentamicin (Nedzelski et al., 1993). The clinical benefit of the transtympanic gentamicin is now widely acknowledged and has been confirmed by a series of randomized, double-blind clinical studies (Cohen-Kerem et al., 2004; Pullens and van Benthem, 2011; Huon et al., 2012). However, extensive research is currently dedicated to the question of which dose of the drug is required to prevent acute vertigo episodes, while preserving hearing (for review, see Daneshi et al., 2014).

The question of the best therapy is directly associated with the fact that we still do not know the pathophysiologic mechanisms that cause Menière's disease, and even

less those of the antivertigo effect of gentamicine. A review proposed an attractive hypothesis regarding the etiology of Menière's disease (Foster and Breeze, 2013). Returning to the hypothesis originally proposed by C.S. Hallpike in 1938 for an ischemic source of the Menière symptoms (Hallpike and Cairns, 1938), the authors proposed that the iterative attacks of vertigo might result from transient alterations of the vestibular blood perfusion inducing ischemia of certain areas of the sensory epithelia. Excitotoxic consequences of the ischemia on the synaptic contacts between vestibular hair cells and their cognate afferents in turn could trigger hyperexcitability in part of the vestibular nerve fibers. This situation may support the different symptoms encountered during acute vertigo episodes, and especially so-called irritative nystagmus. Over time, repeated local ischemia would eventually result in loss of hair cells, synapses, and sensory neurons, leading to progressive hearing and vestibular impairment. Eventually, as such patchy damages gradually become confluent, they may lead to the late stage of Menière's disease. In this scenario, the ototoxic effect of gentamicin might affect preferentially damaged epithelial zones (i.e., having experienced transient ischemia), which would lead to the suppression of the irritative foci and effectively alleviate the vertigo symptoms from the early stages of the disease, unfortunately without treating its cause.

Antivertigo drugs with undefined therapeutic actions

Ginkgo biloba has been used for many years in the treatment of vestibular disorders in many countries. However, its action mechanisms and therapeutic benefits have yet to be clarified (Cesarani et al., 1998). A recent double-blind controlled study performed in a mixture of vertigo patients, which compared ginkgo with betahistine, reported similar improvement of vertigo symptoms of treatment in both groups (Sokolova et al., 2014). The results were however inconclusive, as a placebo control was lacking and the efficacy of betahistine is unproven.

FUTURE DIRECTIONS OF VESTIBULAR PHARMACOTHERAPY

Lack of specificity and lack of efficacy

The diversity and heterogeneity of the compounds used in the pharmacologic treatment of vestibular disorders, as well as the history of their use as antivertigo drugs, illustrate the fact that current pharmacotherapy results more from an empiric approach than from systematic and controlled pharmacologic strategies. In practical terms, the patient who suffers from a vestibular disorder will be administered, from the onset of the first symptoms and throughout the progression of the disease, a series of compounds that are often very different, sometimes with conflicting effects (e.g., agonist and antagonists of H1R in the same prescription!), or others where the risks of interaction have not been fully recognized. This situation is perfectly illustrated in the treatment of vestibular neuritis, for which, often, a cocktail of drugs, combining antivertiginous, antiemetic, antiviral, and anti-inflammatory medication, is given, with the aim of covering all the aspects and possible causes of a poorly understood disease. It comes as no surprise that the lack of specificity of such strategies usually results in a lack of therapeutic benefit.

HOW TO IMPROVE THE SPECIFICITY AND EFFICACY OF VESTIBULAR PHARMACOTHERAPY?

The question now is to know in which direction to develop vestibular pharmacotherapy in order to treat each type and stage of vestibular impairment. To achieve this objective requires overcoming several stumbling blocks. First, it is necessary to decipher the etiology of the different types of vestibular disorders. Several ongoing studies on animal models of vestibular impairments have been attempting to understand how a vestibular injury develops within the vestibule and how its characteristics (pathogenic substrate, severity, time course) govern the heterogeneity of the vertigo symptoms. Financial support for this type of project is essential, since it is through this process that we can hope to identify potential drug targets. At a time when increasing control on medications is imposed by the health authorities, it is essential to identify the mechanisms and pharmacologic targets that are truly modulated by antivertigo compounds. The essential question of using incompatible or even antagonistic drugs to treat acute vertigo episodes and to promote central compensation was recently raised by an elegant animal model (Beck et al., 2014).

Then, it is crucial to define the preferential sites to target with active compounds for optimum therapeutic benefit, while minimizing the risks of side-effects. This applies both to the effective control of vertigo attacks and to the optimization of central compensation mechanisms. To achieve this aim, original approaches using local administration (transtympanic or intrathecal drug administration) in animal models of the respective human disorders (Dutheil et al., 2009, 2013) constitute a suitable approach to discriminate between central and peripheral actions of drugs such as betahistine or vestibular suppressants. The improvement of the methods and techniques of administration of active compounds and the development of pharmacokinetic studies deserve similar priority.

Our ability to transport a compound towards its active site and to control its presence and fate over time is essential to improve vestibular pharmacotherapy. The pioneering work of A. Salt's team in St. Louis (MO, USA) is particularly precious for understanding the kinetics of action of systemically or locally administered compounds and associating their therapeutic effects with their effective action sites (Salt and Plontke, 2009; Salt et al., 2012). One can imagine that methods involving local dosing or inner-ear imaging might soon provide clear answers to questions of adequate dosing of gentamicin for the treatment of intractable Menière's disease. To achieve these objectives, it is necessary to accurately quantify the different parameters altered during a vestibular disorder and to accurately track their progression throughout the therapy. The development of novel biomarkers of the different types and stages of vestibular impairment will be required in order to meet these expectations.

Developing novel reliable diagnostic tools and medical devices is a challenge for the upcoming years. It is only after these obstacles have been removed that we may expect an improvement in the selectivity of active compounds and the targeting of specific therapeutic actions. It is also on the basis of this information that we may develop new administration procedures corresponding to the time and space requirements of the desired therapeutic effect. The extension of the vestibular pharmacotherapy environment is eventually a prerequisite for the development of novel therapeutic agents or principles. According to preliminary data, serotonin 5HT-3 receptor antagonists (such as ondansetron) are candidate drugs for enhancing recovery from peripheral vestibular damage (Venail et al., 2012; Dyhrfjeld-Johnsen et al., 2013). Other ongoing studies are focused on promoting the restoration of the synaptic contacts between hair cells and primary neurons by stimulating the endogenous repair processes that occur within the sensory epithelia following deafferentation (Brugeaud et al., 2007; Travo et al., 2012). It might also be expected that the current boom in biotherapy studies focused on regenerating sensory cells from progenitor cells (Zine et al., 2014) will soon give rise to effective restoration of vestibular hair cells and primary neurons, thereby promoting the recovery of balance.

CONFLICT OF INTEREST

The author is scientific consultant at Sensorion Pharmaceuticals.

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Chapter 15

Acute unilateral loss of vestibular function

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Abstract

Sudden unilateral loss of vestibular function is the most severe condition that can occur in the vestibular system. The clinical syndrome is caused by the physiologic properties of the vestibulo-ocular reflex (VOR) arc. In the normal situation, the two peripheral vestibular end organs are connected to a functional unit in coplanar pairs of semicircular canals working in a push–pull mode. "Push–pull" mode means that, when one side is excited, the other side is inhibited, and vice versa due to two mechanisms. First, first-order vestibular afferents are bipolar cells. They have a tonic firing rate that is modulated up or down depending on the direction of rotation. Second, via inhibitory neural connections of second-order vestibular neurons between the vestibular nuclei (vestibular commissural system), the excited side inhibits further the contralateral side. The neural signals are encoded as the difference of the change in firing rate of the vestibular neurons modulating the tonic firing rate on both sides in opposite directions (one side up, the contralateral side down). When the head is not moving, the two peripheral vestibular end organs generate a resting firing rate, which is exactly equal on both sides. When the head is rotated, for example, to the right, the right-sided first-order vestibular afferents increase their discharge rate and the left-sided ones decrease their firing rate. This leads to increase in firing rate of also the type I second-order vestibular neurons in the vestibular nuclei, which synapse with inhibitory type II neurons on the contralateral side, further decreasing the firing rate in the second-order vestibular neurons in the contralateral vestibular nucleus. When the direction of head rotation is reversed, the behavior of the type I neurons on the two sides of the head is reversed. The same relation exists between the coplanar vertical canal afferents on the two sides of the head. When there is unilateral damage to the end organ or the vestibular nerve, the resting firing frequency is drastically reduced or even silenced on the lesioned side, thereby creating a tonic imbalance between the normal resting firing on the healthy side and the lesioned side. This tonic imbalance mimics a permanent rotation toward the healthy side (the side with the higher firing rate), resulting, via the VOR, in a slow-phase drift of the eyes toward the side of the lesion, interrupted by rapid quick-phase resetting eye movements toward the healthy side. This leads to the typical vestibular spontaneous horizontal-torsional nystagmus together with rotational vertigo and postural imbalance, with the tendency to fall toward the lesioned side. The tonic imbalance with the hallmark of spontaneous nystagmus usually recovers within days to weeks after the lesion due to the central restoration of tonic activity on the lesioned side. The dynamic changes, however, might be long-lasting when the peripheral sensors do not recover their function. This causes asymmetric VOR responses, with weaker responses when the head is rotated rapidly toward the lesioned side, leading to transient oscillopsia.

INTRODUCTION

Sudden unilateral loss of vestibular function is the most severe condition that can occur in the vestibular system. It results in a stereotyped clinical syndrome consisting of severe rotational vertigo, spontaneous nystagmus, postural imbalance, nausea, and vomiting (Dix and

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Hallpike, 1952). Acute unilateral loss of vestibular function can occur in several distinct medical conditions. Most commonly, the reason is an infection (either viral or bacterial), such as in vestibular neuritis, zoster oticus, or labyrinthitis, or traumatic, like in a fracture of the petrous bone. There is some debate about whether the lesion in acute vestibular loss is actually in the nerve (neuritis) or in the peripheral sensors themselves. Therefore, it has been agreed that the better term for the condition of sudden unilateral loss of complete or partial peripheral function should be "acute unilateral vestibulopathy." The lesion can be permanent, as in about half of cases with unilateral vestibulopathy or after trauma, or transient, as in the early stages of Menière's disease or in some cases with vestibular migraine. The condition can also be provoked iatrogenically, for example, by using an intratympanic gentamicin injection to treat Menière's disease or surgically when removing an acoustic schwannoma. For all these medical conditions there will be special chapters in this volume. The main focus of this chapter will be on the pathophysiologic changes that happen in acute unilateral loss of vestibular function and the resulting clinical signs.

To better understand the mechanisms responsible for the clinical findings in acute unilateral vestibular loss, first the physiology of the vestibular system will be reviewed, followed by the changes that occur in the pathologic condition. This can best be explained by looking at the physiology of the vestibulo-ocular reflex (VOR).

PHYSIOLOGY OF VESTIBULAR FUNCTION

The VOR ensures best vision while moving the head by stabilizing the retinal image via rotating the eyes equally and opposite to the head. An ideal VOR, that tries to compensate for any arbitrary movement of the head in three-dimensional space, would generate eye rotations at the same speed as, but in opposite direction to, head rotation independently of the momentary rotation axis of the head. The desired result is that the eye remains stable in space during head motion, enabling clear vision.

The VOR has two different physical properties. The angular VOR, mediated by the semicircular canals (SCCs), compensates for rotation. The linear VOR, mediated by the otolith organs (saccule und utricle), compensates for translation and also detects the gravitational vector, providing a reference frame of orientation in our 1-**g** environment. The angular VOR is primarily responsible for gaze stabilization. The linear VOR is most important to give information on static position of the head in space and contributes to the VOR in situations where near targets are being viewed (Lorente de No, 1933; Baloh and Honrubia, 1990).

The VOR has three main components: (1) the peripheral sensory apparatus (the labyrinths with the respective end organs); (2) a central processing mechanism; and (3) the motor output (the eye muscles) (Szentágothai, 1950). The sensory input for the generation of the VOR is provided by a set of motion sensors, which send information about head angular velocity, linear acceleration, and orientation of the head with respect to gravity to the central nervous system, primarily to the vestibular nucleus complex and the cerebellum. The output of the central vestibular system is sent via the oculomotor nuclei to the extraocular muscles and to the spinal cord to serve the VOR and the vestibulospinal reflex (VSR), the latter generating compensatory body movement in order to maintain head and postural stability, thereby preventing falls. The information goes also to several cortical structures, e.g., the posterior insular vestibular cortex, where it is further integrated with visual, proprioceptive, auditory, and tactile input to generate a best-possible perception of motion and space orientation (Grüsser et al., 1990). The performance of the VOR and VSR is monitored by the central nervous system, and readjusted as necessary by adaptive processes, with an immense capability of repair and adaptation, mainly involving cerebellar function (Lisberger et al., 1984). This provides the basis for recovery, even after permanent loss of unilateral vestibular function.

The peripheral vestibular system

The peripheral vestibular system includes the membranous and bony labyrinths, and the motion sensors of the vestibular system, the hair cells. Each labyrinth consists of three SCCs, the cochlea, and the vestibule containing the utricle and saccule. The geometric arrangement of the SCCs allows for detection of head rotation about any axis in three-dimensional space. They are positioned in three nearly orthogonal planes in the head and act as angular accelerometers working in a push–pull arrangement with the other labyrinth, with three functional pairs of nearly coplanar SCCs: (1) right and left lateral SCCs; (2) right anterior and left posterior SCCs; and (3) left anterior and right posterior SCCs.

The planes of the SCCs are close to the planes of the extraocular muscles, thus allowing relatively simple neural connections between sensory vestibular neurons of the individual canals, and motor output neurons, related to individual extraocular muscles (Blanks et al., 1975). Motion of the head is detected by the cupulae in the ampullae of the SCCs. The cupulae cause endolymphatic pressure differentials, associated with head motion, to be coupled to the hair cells embedded in the cupula. These specialized hair cells are biologic sensors that convert displacement due to head motion into neural firing.

When hairs are bent toward or away from the longest hair, the firing rate increases or decreases from a resting firing rate in the vestibular nerve (Fernandez and Goldberg, 1971; Goldberg and Fernandez, 1971). The hair cells of the saccule and utricle are located in the maculae, on the medial wall of the saccule and the floor of the utricle. The otolithic membranes are structures similar to the cupulae, but as they contain calcium carbonate crystals called otoconia, they have substantially more mass than the cupulae. The mass of the otolithic membrane causes the maculae to be sensitive to gravity and, via shear forces, to linear acceleration in all three dimensions. In contrast, the cupulae normally have the same density as the surrounding endolymphatic fluid and are insensitive to gravity. By virtue of their orientation, the SCCs and the otolith organs are able to respond selectively to head motion in any particular direction in three-dimensional space (Bach-Y-Rita, 1971).

Central processing of vestibular signals

In the normal healthy situation, the two peripheral vestibular end organs are connected to a functional unit in coplanar pairs, working in a push–pull mode. The neural signals are encoded as a change in firing rate of the vestibular neurons modulating a tonic firing rate. When the head is not moving, the two peripheral vestibular end organs generate a resting firing rate, which is exactly equal on both sides (Fig. 15.1A). In humans, the frequency of this tonic firing rate is not exactly known, whereas in squirrel monkeys this frequency is on average about 90 spikes/s (Goldberg and Fernandez, 1971). When the head is moving, the coplanar pairing of SCCs is associated with a push–pull change in the quantity of SCC output. With rotation in the plane of a coplanar SCC pair, the neural firing increases from tonic resting discharge in one vestibular nerve and decreases on the opposite site (Fig. 15.1B), with a linear sensitivity ranging from about 0.5 to 4 spikes/s/°/s of head velocity in squirrel monkeys (Goldberg and Fernandez, 1971). This leads to silencing of the inhibited side at a head velocity above 180°/s for the neurons with the weakest sensitivity (Goldberg and Fernandez, 1971). The direction of rotation is encoded as toward the side of the higher firing frequency, i.e., the excitatory direction, leading via the VOR to slow-phase velocity eye movements in the opposite direction of rotation with quick phases of nystagmus toward the side of rotation, i.e., the side with the higher firing frequency. For the lateral canals, displacement of the cupula toward the ampulla (ampullopetal flow) is excitatory, whereas for the vertical canals, displacement of the cupula away from the ampulla (ampullofugal flow) is excitatory.

There are certain advantages of the push–pull arrangement of coplanar pairing with the sensors modulating a tonic resting firing level. First, pairing provides sensory redundancy. If disease affects the SCCs from one member of a functional pair, e.g., as in vestibulopathy, the central nervous system will still receive vestibular information about head velocity within that plane from the contralateral member of the coplanar pair in both directions. Second, such a pairing allows the brain to ignore changes in neural firing that occur on both sides simultaneously, such as might occur due to changes in body temperature. Third, using two sensors in a push–pull fashion leads in physics terms to differential amplification of the incoming signal with a much better signal-to-noise ratio compared to a single sensor.

For the otolith organs, as for the SCCs, there is also a push–pull arrangement of sensors, but, in addition to

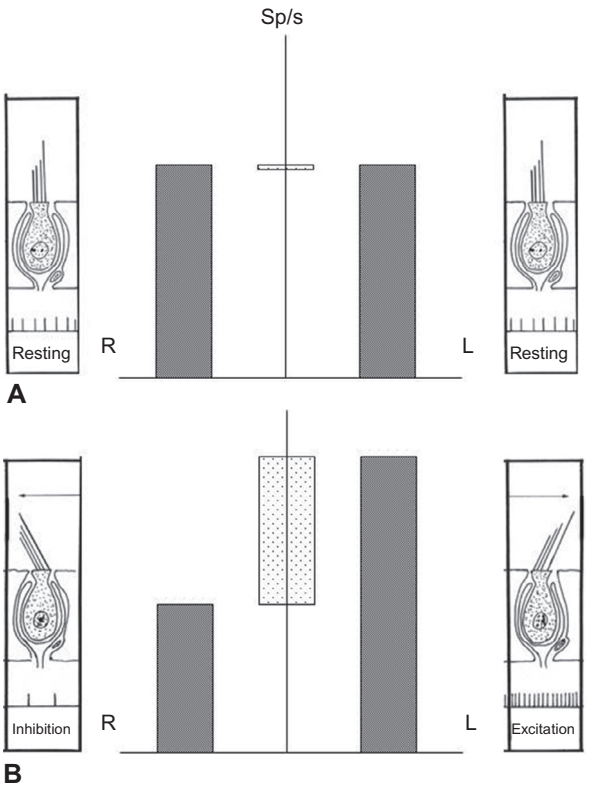

Fig. 15.1. Schematic drawing of neural activity (spikes per second: Sp/s) in the vestibular nerves of each side (R, right side; L, left side). For the lateral canals, which are shown in this example, displacement of the cupula toward the ampulla (ampullopetal flow) is excitatory. (**A**) In the normal healthy situation, when the head is not moving, the two peripheral vestibular endorgans generate a resting firing rate (solid bars), which is exactly equal on both sides. (**B**) With rotation toward the left side, the neural firing increases from tonic resting discharge in the vestibular nerve of the left lateral canal and decreases in the vestibular nerve of the right lateral canal. During rotation, the perceived head velocity corresponds to the difference in firing rate between pairs of semicircular canals.

splitting the sensors across sides of the head, the push–pull processing arrangement for the otoliths is also incorporated into the geometry of the otolithic membranes. Within each otolithic macula, a curving zone, the striola, separates the direction of hair cell polarization on each side. Consequently, head tilt results in increased afferent discharge from one part of a macula, while reducing the afferent discharge from another portion of the same macula (Suzuki et al., 1969; Fernandez et al., 1972).

There are two main targets for vestibular input from primary afferents: the vestibular nuclear complex and the cerebellum. The vestibular nuclear complex is the primary processor of vestibular input, and implements direct, fast connections between incoming afferent information and motor output neurons.

The cerebellum is the adaptive processor – it monitors vestibular performance and readjusts central vestibular processing if necessary (Robinson, 1976). At both locations, vestibular sensory input is processed in association with somatosensory and visual sensory input (Lisberger et al., 1984).

The vestibular nuclear complex consists of four major nuclei, i.e., superior, medial, lateral, and descending, and at least seven minor nuclei. This large structure, located primarily within the pons, also extends caudally into the medulla. The superior and medial vestibular nuclei are relays for the VOR. The medial vestibular nucleus is also involved in the VSR, and coordinates head and eye movements that occur together. The lateral vestibular nucleus is the principal nucleus for the VSR. The descending nucleus is connected to all of the other nuclei and the cerebellum, but has no primary outflow of its own (Brodal, 1974; Goldberg et al., 2012). The vestibular nuclei are connected via a system of commissures, which, for the most part, are mutually inhibitory. The commissures allow information to be shared between the two sides of the brainstem and implement the push–pull pairing of vestibular canals. Extensive connections among the vestibular nuclear complex, cerebellum, ocular motor nuclei, and brainstem reticular activating system convey the efferent signals to the VOR and VSR effector organs, the extraocular and skeletal muscles (Büttner-Ennever, 1981). The output neurons of the VOR are the motor neurons of the ocular motor nuclei, which drive the extraocular muscles, resulting in conjugate movements of the eyes in the same plane as head motion.

PATHOPHYSIOLOGY IN UNILATERAL LOSS OF VESTIBULAR FUNCTION

When there is unilateral damage to the end organ or the vestibular nerve, the resting firing frequency is usually drastically reduced or even silenced on the lesioned side, thereby creating a tonic imbalance between the normal resting firing on the healthy side and the lesioned side (Fig. 15.2). This tonic imbalance mimics, via the VOR, a permanent rotation toward the healthy side, i.e., the side with the higher firing rate, resulting in a slow-phase drift of the eyes toward the side of the lesion, interrupted by rapid quick-phase resetting eye movements toward the healthy side. This leads to the typical vestibular spontaneous horizontal nystagmus with a torsional component characteristic of the early stages of a unilateral vestibular lesion together with rotational vertigo and postural imbalance, with a tendency to fall toward the lesioned side (McCabe et al., 1972). In other words, the unopposed tonic firing rate of the healthy vestibular end organ produces spontaneous nystagmus and is responsible for all the unpleasant symptoms like nausea and vomiting during acute unilateral vestibular loss.

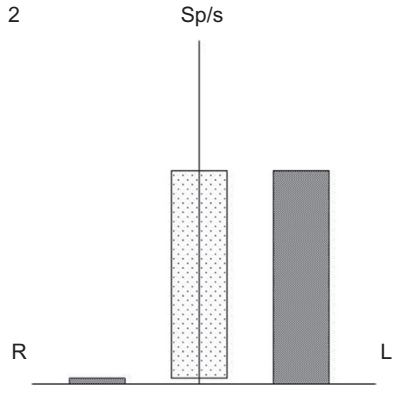

Fig. 15.2. When there is unilateral damage to the end organ or the vestibular nerve, the resting firing frequency is usually drastically reduced or even silenced on the lesioned side, which in the example shown is on the right side. This creates a tonic imbalance between the normal resting firing rate on the healthy side and the lesioned side. Sp/s, spikes per second.

Static imbalance

Spontaneous nystagmus is the hallmark of an imbalance in the tonic levels of activity mediating SCC ocular reflexes. When peripheral in origin, spontaneous nystagmus characteristically is dampened by visual fixation and is increased or only becomes apparent when fixation is eliminated, i.e., using Frenzel glasses, which blur vision and prevent the patient from using visual fixation to suppress the spontaneous nystagmus, or during ophthalmoscopy with the opposite eye occluded to prevent fixation. Note that, during ophthalmoscopy, the direction of any horizontal or vertical slow phases is opposite to the direction of the motion of the optic disc. The nystagmus can sometimes be seen or even palpated through closed eyelids.

Vestibular-induced nystagmus depends on the position of the eye in the orbit. Nystagmus arising from a peripheral lesion is more intense or may be evident only when the eye is deviated in the direction of the quick phase (Alexander's law). With central lesions, the opposite sometimes occurs, or the direction of spontaneous nystagmus might change when the eye is deviated in the direction of the slow phase. The direction of nystagmus can help differentiate between peripheral and central lesions. A pure vertical or a pure torsional nystagmus implies a central disturbance, whereas a mixed horizontal-torsional nystagmus is typical for a unilateral peripheral labyrinthine lesion.

The direction of spontaneous nystagmus in three dimensions should theoretically be the vectorial summation of the tonic activities of the healthy SCCs, since stimulation of the afferents of one singular canal produces eye movements in the plane of that canal, as is evident in benign paroxysmal positional vertigo of posterior SCC origin (Suzuki and Cohen, 1964; Baloh et al., 1987; Fetter and Sievering, 1995). Fetter and Dichgans (1996) recorded the direction of spontaneous nystagmus in three dimensions with scleral dual-search coils in 16 consecutive cases of acute unilateral vestibulopathy 3–15 days after the onset of vertigo. They showed that, in all 16 patients, the axis of rotation of the eyes of spontaneous nystagmus clustered between the expected directions for a lesion of the lateral SCC and a combined lesion of the lateral plus ipsilesional anterior SCC. In none of the patients did the spontaneous nystagmus direction indicate a combined lesion of the afferents of all SCCs on one side or a singular or combined lesion of only the vertical SCCs. However, in a follow-up study, the direction of the spontaneous nystagmus after resection of the whole eighth nerve was not much different from that after resection of only the superior branch of the vestibular nerve or that seen in vestibular neuritis (Straumann et al., 1997).

The absence of a stronger torsional component of the rotation vector in complete peripheral lesions may reflect anisotropy of oculomotor efferents of the VOR arc. There are two possible reasons for this anisotropy of the output of the VOR in the pathologic condition. First, in humans, the torsional VOR is only about half as strong as the horizontal and vertical VOR. Second, the velocity storage mechanism in the brainstem, which prolongs the time constant of the vestibular signals, enhances predominantly the horizontal VOR and is close to nonexistent in the torsional and vertical VOR (Raphan et al., 1979). Therefore, estimating the contribution of each SCC to the generation of spontaneous nystagmus by mere vector addition is insufficient and an oversimplification. The three-dimensional analysis of spontaneous nystagmus, therefore, does not permit accurate localization of a peripheral vestibular lesion. This is much better achieved with dynamic stimulation, i.e., analysis of the VOR in response to angular rotation in various directions.

Skew deviation is the hallmark of an imbalance in the tonic levels of activity underlying otolith-ocular reflexes. Skew deviation is a vertical misalignment of the eyes that cannot be explained on the basis of extraocular muscle palsy. In both peripheral and vestibular nucleus lesions, the lower eye indicates the side of the lesion. The otolith-ocular pathway crosses at the level of the vestibular nucleus, so that with lesions above the decussation the higher eye indicates the side of the lesion (Dieterich et al., 1989; Halmagyi et al., 1990b; Brandt and Dieterich, 1993). There may also be a cyclorotation, i.e., an ocular roll of both eyes, toward the side of the peripheral lesion associated with an illusion of tilt of the visual world. The head may also be tilted, usually toward the side of the lower eye. Skew deviation, cyclorotation of the eyes, and head tilt constitute the ocular tilt reaction: vestibulo-ocular and vestibulocolic components of the righting reaction in response to the lateral tilt of the head and body (Brandt and Dieterich, 1995). The ocular tilt reaction can occur with lesions anywhere in the otolith-ocular pathway but is most prominent in lesions of the central pathway above the level of the vestibular nuclei and can be completely absent in pure unilateral vestibular lesions, since each otolith organ alone provides information in all directions.

Positional testing may also exacerbate a spontaneous nystagmus. With an acute unilateral loss of labyrinthine function, the horizontal component of the spontaneous nystagmus is usually increased with the patient lying with the affected ear down and decreased with the affected ear up. This effect of gravity on the horizontal component of the spontaneous nystagmus is probably mediated by the otolith-ocular reflex, which normally produces a horizontal nystagmus in response to linear accelerations associated with translation of the head. In the case of spontaneous nystagmus due to a vestibular imbalance, the change in the pull of gravity with head tilt produces a horizontal slow-phase response that either dampens or increases the spontaneous nystagmus depending on whether the ear with the hypoactive labyrinth is up or down, respectively (Fluur, 1973).

Dynamic disturbances

Apart from the static imbalance with unilateral vestibular loss, there is also a loss of dynamic function. This dynamic disturbance is characterized by decreased and asymmetric dynamic vestibular responses. While the static imbalance with spontaneous nystagmus usually recovers within days to weeks after the lesion due to the central restoration of tonic activity on the lesioned

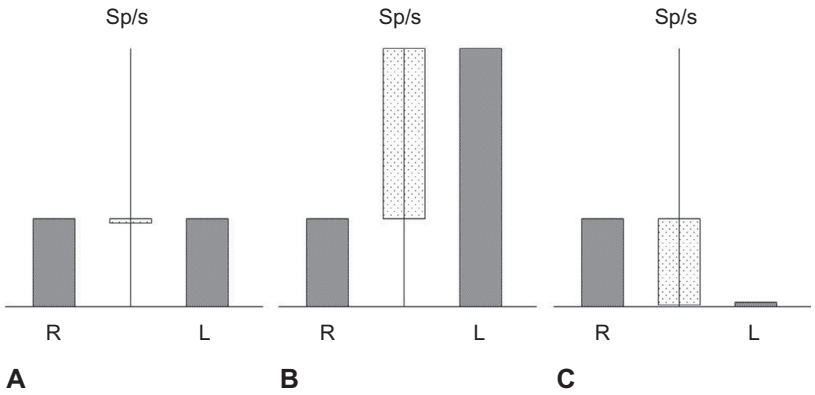

Fig. 15.3. (**A**) While the static imbalance recovers within days to weeks after the lesion due to the central restoration of tonic activity on the lesioned side (right side in this example), the dynamic disturbances are long-lasting when the lesioned peripheral sensor does not recover function. (**B**) When the head is rotated toward the healthy side (left), the firing rate can increase normally and the vestibulo-ocular reflex response might still be quite good via excitation of the healthy labyrinth, but rotation toward the lesioned side (right) will be weaker, since the tonic firing rate of the healthy side can only be reduced toward zero. (**C**) Higher rotation velocities toward the lesioned side will not adequately change the response any more due to the inhibitory cutoff when the healthy side is silenced, leading to asymmetric changes of firing rate for the two rotation directions. Sp/s, spikes per second.

side (Fig. 15.3A), the dynamic changes might be long-lasting when the peripheral sensors do not recover their function.

Until recently, caloric testing was the usual method to prove a partial or complete so-called canal paresis with the restriction that only the lateral canal function is tested with this method in the clinical routine.

With new bedside tests using rapid head rotations, the function of all six SCCs can be tested. If one side of the vestibular sensors is lost, the normal push–pull arrangement of signal transmission is also lost. In the normal condition, over a certain range of velocities, the canals work in a push–pull arrangement. However, this arrangement only pertains up to the velocity, at which the inhibited side is completely silenced. In squirrel monkeys, at velocities above 180°/s only the excited rather than the inhibited vestibular neurons can transduce these velocities. In the unilateral vestibular loss condition, the healthy SCC of a functional pair can increase the tonic firing rate when head movement excites that SCC, i.e., during movement toward the healthy side, and decrease it when the head is turned in the inhibitory direction. Thus, that SCC still can measure head movements in both directions. However, the signal transduction in the VOR is not linear any more. When the head is rotated toward the healthy side, the firing rate can increase almost normally and the VOR response might still be quite good (Fig. 15.3B), but rotation to the lesioned side will be weaker, since the tonic firing rate of the healthy side can only be reduced toward zero. Higher rotational velocities toward the lesioned side will not adequately change the response any more due to the inhibitory cutoff when the healthy side is silenced (Fig. 15.3C).

This dynamic asymmetry or nonlinearity leads to typical changes of the VOR responses that can be tested at the bedside by observing the effect of rapid head rotation on the resulting eye movements.

One simple test for dynamic imbalance uses dynamic visual acuity. First, the patient's best-corrected visual acuity is measured using a distance acuity chart with the head still and then with the head passively rotated at a frequency of about 2 Hz. Normal individuals may lose one line of acuity during head shaking; patients with a complete unilateral loss of labyrinthine function lose up to five lines and sometimes more. The possible influence of stimulation of cervical afferents, through the cervico-ocular reflex (COR), when the head is rotated on the body must be considered. In normal subjects, especially at the relatively high frequencies associated with bedside testing, the COR is rudimentary and can be ignored. In patients with bilateral loss of the function of the SCCs, however, there may be potentiation of the COR or the use of cervical afferents to trigger preprogrammed compensatory slow phases or even saccades, independently of inputs from the SCCs (Kasai and Zee, 1978).

Head-shaking nystagmus (HSN) is another way to look for an imbalance of dynamic vestibular function. This test works very well even in the chronic stage of unilateral vestibular loss or when there is only a slight asymmetry between the two sides, as in small acoustic schwannomas, where calorics might still be normal. The patient's head is actively or passively shaken vigorously about 10–15 times in the horizontal plane. With Frenzel glasses in place, one observes if any nystagmus occurs following the head shaking. Normal individuals usually have no or occasionally just a beat or two of

HSN. With a unilateral loss of labyrinthine function, however, there is usually a vigorous nystagmus with quick phases initially directed toward the healthy side and then a reversal phase with slow phases directed oppositely (Hain et al., 1987). The initial phase of HSN arises because there is asymmetry of peripheral inputs during high-velocity head rotations. More activity is generated during rotation toward the intact side than toward the affected side (Ewald, 1892; Baloh et al., 1977). This asymmetry leads to an accumulation of activity during the head shaking due to the so-called velocity storage mechanism prolonging the vestibular response by about threefold compared to the response of the peripheral sensors in the horizontal plane. The nystagmus following head shaking reflects the discharge of that activity with the nystagmus beating toward the healthy side.

Fetter and Dichgans (1996) used the three-dimensional magnetic search coil technique and a three-dimensional vestibular stimulator to test the vestibular responses in 16 patients with acute unilateral vestibular loss. They found dynamic asymmetries only during rotations about axes that stimulated the ipsilesional lateral or anterior SCCs. No asymmetry was found when the ipsilesional posterior SCC was stimulated. They concluded that, in most patients with acute unilateral vestibular lesion, there is only a partial lesion affecting the superior division of the vestibular nerve.

In a later study, using three-dimensional search coils together with head impulses, Aw and coworkers (2001) studied individual SCC function in a group of 31 patients with acute unilateral peripheral vestibulopathy. In this group, 8 patients had deficits in all three SCCs, 21 had a lateral SCC deficit or a combined lateral and anterior SCC deficit, and 2 patients had an isolated posterior SCC deficit on impulsive testing, confirming that a lesion of the superior vestibular nerve is the most common cause of acute unilateral vestibulopathy.

The most widely used bedside test is the head impulse test. One applies brief, high-acceleration head thrusts. This is best done with the eyes beginning about 15° away from primary position in the orbit and the amplitude of the head movement such that the eyes end near the primary position of gaze, thus avoiding contamination by any gaze-evoked nystagmus. The patient is usually instructed to look carefully at the examiner's nose, or, especially in elderly patients, at a distant target, since even normal elderly subjects sometimes have problems producing an adequate vestibular response when fixating near targets, thereby resulting in a false-positive, i.e., pathologic, head impulse test. The examiner looks for a corrective "overt" catch-up saccade immediately after the head has reached the final position as a sign of an inadequate compensatory slow phase. When interpreting an abnormal response, one must consider the potential adaptive readjustment in VOR function that may occur when a subject habitually wears a spectacle correction. Farsighted individuals (with hyperopia) increase their VOR gain owing to the magnification effect of a plus lens; nearsighted individuals (with myopia) decrease their VOR gain owing to the minification effect of a minus lens (Halmagyi et al., 1990a). Therefore, this test should best be performed with patients wearing their glasses.

With the recent developments in three-dimensional videooculography it became possible to use the head impulse test in all three dimensions at the bedside and thereby to test the function of all six SCCs by applying head impulses in the plane of any SCC pair and measuring the elicited response (Cremer et al., 1998). With this technique it has been shown that some patients learn to generate hidden ("covert") saccades during the head impulse as early as 75 ms after the onset of head movement. The patient thus reduces gaze error to compensate for the reduced VOR response. These covert saccades might be missed in the clinical test and lead to a false-negative head impulse test, even though they are mainly seen during active head movements (Halmagyi et al., 2003; Black et al., 2005). Interestingly, patients who learned to generate covert saccades to supply their deficient VOR are the ones who have the least subjective problems in the chronic stage of disease, most likely as a result of heaving much less oscillopsia during rapid head rotation toward the lesioned side as compared to patients without covert saccades (see also section on vestibular rehabilitation later in this chapter).

In addition to the functional testing of individual SCCs using the head impulse test, in recent years relatively simple tests to access the function of the utricle and the saccule have become available using vestibular-evoked myogenic potentials, which are discussed in Chapter 11.

VESTIBULAR TESTING IN ACUTE VESTIBULAR SYNDROME

The distinction between a unilateral peripheral vestibular loss and a central lesion mimicking a peripheral disease is of utmost importance in the emergency room because a peripheral lesion is very unpleasant but not really dangerous, whereas a central lesion is potentially life-threatening.

In the acute situation, when the patient shows strong spontaneous nystagmus, ice-water irrigation of the supposedly normal ear (the ear toward which the nystagmus is beating) should stop the nystagmus in the acute phase (reducing the tonic firing rate of the healthy side also to zero as on the lesioned side) and should only reverse the

spontaneous nystagmus in incomplete lesions, or when the lesion is not peripheral in nature (such as in unilateral cerebellar lesion) (Nelson, 1969). An immediate change of direction of a spontaneous nystagmus with ice-water calorics is the first hint of a central lesion that should lead to a thorough neuroradiologic work-up with magnetic resonance imaging, especially of the posterior fossa and the posterior circulation.

Kattah and coworkers (2009) re-evaluated acute vestibular syndrome in elderly patients with at least one vascular risk factor. They found that in this condition more than three-quarters of patients had a central lesion (ischemia, hemorrhage) and no peripheral vestibulopathy (Kattah et al., 2009). They also could show that a skew deviation, a direction-changing nystagmus depending on gaze direction, and a normal head impulse test predict a central cause of the presenting acute vestibular syndrome with a sensitivity of 100% and a specificity of 96%. This important result for the evaluation of patients the acute-onset vertigo in the emergency room has led to the acronym HINTS (head impulse (normal), nystagmus (in different directions), test for skew) as a strong suggestion for a central cause of an acute vestibular syndrome. This test battery relies on finding a normal, rather than an abnormal, head impulse test and is thus slightly counterintuitive.

TREATMENT OF ACUTE VESTIBULAR LOSS

The exact etiology of acute vestibular dysfunction is still unknown. Based on the theory of a viral infection or reactivation (similar to idiopathic facial palsy), corticosteroids have been advocated to improve or accelerate recovery. Strupp et al. (2004) published a study in which they used methylprednisolone, valacyclovir, or the combination in 141 patients with unilateral vestibulopathy within 3 days of onset of symptoms. They showed that a high-dose, short-time treatment with methylprednisolone (starting with 100 mg/day for 3 days and then reducing the dose by 20 mg/day every fourth day) can increase the rate of peripheral recovery of the end-organ function from about 50% (without treatment) to about 70% (with treatment). The treatment with valacyclovir did not show any effect, neither alone nor in combination with the corticosteroids.

However, a more recent Cochrane review by Fishman et al. (2011), including the data of four randomized controlled trials comparing corticosteroids with placebo in adults diagnosed with idiopathic acute vestibular dysfunction, involving a total of 149 participants, could not show sufficient evidence to support the administration of corticosteroids in this condition. However, all trials were small and of low methodologic quality. Although there was an overall significant effect of corticosteroids compared with placebo on complete caloric recovery at 1 month with a relative risk of 2.81, no significant effect was seen on complete caloric recovery at 12 months. In addition, there was no significant difference between corticosteroids and placebo in the symptomatic recovery of vestibular function with respect to vertigo at 24 hours and in the Dizziness Handicap Inventory score at 1, 3, 6, and 12 months. This led the authors to the recommendation that future studies should include health-related quality-of-life and symptom-based outcome measures, in addition to objective measures of vestibular improvement, such as caloric testing and video-based head impulse testing.

In the acute situation there is also in many patients a need for symptomatic treatment to reduce vertigo and accompanying neurovegetative symptoms (nausea, vomiting, anxiety). Drugs commonly used are dimenhydrinate, diphenhydramine, promethazine, meclizine, prochlorperazine, ondansetron, scopolamine, and lorazepam. There is consensus that drugs exerting a sedative effect on the vestibular system should be used only in the acute phase (in the first 24 up to maximum of 48 hours). Most agents probably affect more than one neurotransmitter system, and, in intractable cases, a combination of different types of agents may be more effective than one alone.

After 24–48 hours, any vestibular sedative drugs should be reduced or stopped and patients should be encouraged to get out of bed and increase their activities. Vestibular rehabilitation treatment should begin as early as possible, since there is evidence that early intervention with vestibular exercises facilitates a decrease in symptoms and improves gait stability compared with no exercises in patients with unilateral vestibular loss (Herdman et al., 1995; Teggi et al., 2009). However, most evidence suggests that patients will still improve even with long periods of time between the onset of the vestibular hypofunction to the initiation of exercises (Herdman et al., 2012).

VESTIBULAR REHABILITATION

The goals of vestibular rehabilitation are to: (1) decrease the patient's disequilibrium (sense of being off balance) and oscillopsia (visual blurring during head movement); (2) improve the patient's functional balance, especially during ambulation; (3) improve the patient's ability to see clearly during head movement; (4) improve the patient's overall general physical condition; and (5) enable the patient to return to a normal level of activity and participation in social life.

Already many years ago, Cawthorne (1946) and Cooksey (1946) suggested a number of equilibrium

exercises to assist in the rehabilitation of patients with vestibular disorders. Many modern vestibular rehabilitation programs are adaptations of these early suggestions. An updated version of such programs can be found in the fourth edition of the textbook *Vestibular Rehabilitation*, in the chapter by Herdman and Whitney (2014).

Several different mechanisms are involved in the recovery of function following unilateral vestibular loss. These mechanisms include cellular recovery, spontaneous re-establishment of the tonic firing rate centrally, adaptation of residual vestibular function, the substitution of alternative strategies for the loss of vestibular function, and habituation of unpleasant sensations.

If peripheral function does not recover, as in about half of the patients with acute unilateral vestibular loss, only substitution of other responses can effectively conceal the vestibular deficit and so protect the patient from experiencing oscillopsia during head movements. Such substitution is possible when there is active control of the response by the patient (Black et al., 2005). The active VOR gain is enhanced during active voluntary head movements, and during active head impulses. Patients can learn to preprogram a small eye movement response already during the ipsilesional head movement that can effectively reduce oscillopsia. The development of such a new eye–head coordination strategy can be facilitated by training with active head turns. The patient is asked to maintain gaze on an earth-fixed target while actively turning the head abruptly to left or right. Initially, there will always be an oscillopsia (seemingly moving target, when the head is moved toward the lesioned side due to the defective VOR); however, this is the error signal for the adaptive mechanisms (and should not be avoided, as many patients do). After a certain time of training, most patients learn to preprogram a small saccade to correct for the inadequate VOR and to insert this saccade during the head movement ("covert" saccade), substituting the deficient vestibular slow phase. Another way of concealing a VOR inadequacy is by a blink, which, by completely removing the retinal image, very effectively prevents oscillopsia during the head movement (Black et al., 2005; Curthoys and Halmagyi, 2014).

Patients should be encouraged to execute eye–head refixations on a regular basis (a few minutes several times a day), because the initial preference of many patients is to restrict head movements totally and to "lock" the head on the body by cocontraction of the neck muscles. This decreases the opportunity for the patient to learn any new pattern of eye–head coordination and leads in many patients to cervical pain and tension headaches, making many patients believe that their neck is the reason for ongoing dizziness after unilateral vestibular loss.

SUMMARY

Sudden unilateral loss of vestibular function is the most severe condition that can occur in the vestibular system. The clinical syndrome is caused by the physiologic properties of the VOR arc. In the normal healthy situation, the two peripheral vestibular end organs are connected to a functional unit in coplanar pairs of SCCs working in a push–pull mode. The neural signals are encoded as a change in firing rate of the vestibular neurons modulating a tonic firing rate. When the head is not moving, the two peripheral vestibular end organs generate a resting firing rate that is exactly equal on both sides. When there is unilateral damage to an end organ or the vestibular nerve, the resting firing frequency is drastically reduced or even silenced on the lesioned side, thereby creating a tonic imbalance between the normal resting firing on the healthy side and the lesioned side. This tonic imbalance mimics a permanent rotation toward the healthy side, i.e., the side with the higher firing rate, resulting, via the VOR, in a slow-phase drift of the eyes toward the side of the lesion, interrupted by rapid quick-phase resetting eye movements toward the healthy side. This leads to the typical vestibular spontaneous horizontal-torsional nystagmus together with rotational vertigo and postural imbalance, with the tendency to fall toward the lesioned side. While the tonic imbalance with the hallmark of spontaneous nystagmus usually recovers within days to weeks after the lesion due to the central restoration of tonic activity on the lesioned side, the dynamic changes might be long-lasting when the peripheral sensors do not recover their function, causing asymmetric VOR responses when the head is rotated rapidly toward the lesioned side with transient oscillopsia. With simple clinical bedside testing using the head impulse test in the planes of the SCCs, a functional evaluation of individual SCCs is possible helping clinicians to understand the complaints of vertigo in patients even in the chronic stage of disease. Effective vestibular rehabilitation programs have been developed that should be started early after the onset of the lesion. They significantly facilitate a decrease in symptoms and improve gait stability compared with no exercises in patients with unilateral vestibular loss.

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Chapter 16

Chronic unilateral vestibular loss

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Abstract

Chronic unilateral vestibular loss is a condition defined by the presence of reduced function of the peripheral vestibular system on one side, which has generally persisted for 3 or more months. The deficit is demonstrated by a reduction of the vestibular-ocular reflex either at the bedside or on laboratory testing. Though some patients with chronic vestibular loss have disabling symptoms, others are asymptomatic. Causes include a viral/postviral disorder, Menière's disease, structural lesions, ischemia, and trauma. Any other systemic or genetic disorder would be expected to involve both sides at some point.

INTRODUCTION

Vestibular disorders are common causes of dizziness symptoms (Neuhauser et al., 2005; Hillier and McDonnell, 2011) that are due to either aberrant stimulation or a lesion of the peripheral or central vestibular system on one or both sides. Chronic unilateral vestibular loss (CUVL) is a label for a broad category of vestibular disorders (Table 16.1) defined by pathologic dysfunction of the vestibular-ocular reflex (VOR) on one side. CUVL typically presumes that the lesion has been present for 3 or more months. The lesion in CUVL typically involves the vestibular nerve, though end-organ damage can also be the cause. In this chapter, the diagnostic criteria, symptoms, examination, diagnostic evaluation, and management of CUVL are described.

CHRONIC UNILATERAL VESTIBULAR LOSS CRITERIA

CUVL requires a finding indicating unilateral loss of VOR function, typically using the caloric test or the head impulse test, and that the disorder has been present for 3 or more months. Traditionally the gold-standard test is the bithermal caloric test using nystagmography to measure the maximum slow component velocity of nystagmus. An abnormal response indicating a unilateral vestibular lesion is typically a >24% reduced response on one side compared with the other normalized by the sum of all responses within the same subject, known as Jongkee's formula for vestibular paresis. The threshold for an abnormal study was developed based on results in control subjects and calculating the mean asymmetry plus two standard deviations (Baloh et al., 2011).

The head impulse test – either applied as a bedside subjective test or as a laboratory test – can also be used to identify reduced function of the VOR on one side. The head impulse test differs from the caloric test because the head impulse is a physiologic angular high-acceleration, high-frequency (2.5 Hz) stimulus, whereas caloric testing applies a nonphysiologic low-frequency (0.006 Hz) stimulus. The subjective bedside head impulse test is considered abnormal when a corrective saccade is observed after the head impulse. The laboratory test is considered abnormal typically based on a reduced VOR gain calculated by dividing eye velocity by head velocity. For control subjects, the mean VOR gain to each side has been measured as 0.98 (95% confidence interval (CI), 0.92–1.04) whereas ipsilateral mean gain in a sample of patients after vestibular neuritis was 0.59 (95% CI, 0.51–0.67) and in a sample of patients after unilateral surgical deafferentation was 0.47 (95% CI, 0.41–0.53) (Weber et al., 2008). It is important to note that the head impulse test is likely a less accurate

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Table 16.1

Some causes of chronic unilateral vestibular loss and examples of characteristic features

Disorder	Example of presentation features
Vestibular neuritis	Rapid onset of severe dizziness without other neurologic or audiologic symptoms. Exam in acute setting reveals a unidirectional horizontal nystagmus and positive head impulse test in the direction opposite the fast phase of nystagmus
Labyrinthitis	Similar presentation to vestibular neuritis, with additional feature of unilateral hearing loss
Ramsay Hunt syndrome	Similar presentation to vestibular neuritis, with additional features of unilateral hearing loss, facial nerve paresis, and vesicular eruption around the auricle and external auditory canal
Ischemic lesion	Rapid onset of dizziness symptoms, generally accompanied by other central nervous system symptoms and central ocular motor findings. Stroke in the distribution of the anterior inferior cerebellar artery can mimic vestibular neuritis and labyrinthitis
Menière's disease	Recurrent episodes of severe dizziness, plus auditory features of fluctuating and progressive unilateral hearing loss and tinnitus
Structural mass lesions (e.g., vestibular schwannoma, meningioma)	Gradual onset and progressive unilateral hearing loss, with or without dizziness
Chronic basilar meningitis (e.g., tuberculosis, fungal, syphilis)	Progressive vestibular and auditory dysfunction, often including other cranial neuropathies
Multiple sclerosis	Initial presentation can mimic vestibular neuritis. Previous or subsequent additional central nervous system focal attacks are expected
Trauma	Onset associated with blunt trauma

indicator of a pathologic process in subjects aged 70 years and older (Davalos-Bichara and Agrawal, 2014). Specifically in patients with Menière's disease, the caloric test has been shown to be a more accurate test of vestibular dysfunction compared with the head impulse test (Blodow et al., 2014; McGarvie et al., 2015). In one recent study of 22 with Menière's disease, the head impulse test results were in the normal range, even though the average canal paresis measured by the caloric test was 66% (McGarvie et al., 2015).

The caloric test and head impulse test focus on measuring the function of the horizontal canal and the pathway of the VOR via the superior division of the vestibular nerve. Less commonly, CUVL is limited to one of the vertical canals, the otolith organs, or the VOR pathways in the inferior division of the vestibular nerve. With disorders limited to the sacculus or the inferior division of the vestibular nerve, the vestibular-evoked myogenic potential test may help to define the lesion.

SYMPTOMS

The types of dizziness reported by patients with CUVL include vertiginous dizziness and nonvertiginous dizziness (Newman-Toker et al., 2007; Carlson et al., 2014). Case series in patients with vestibular schwannoma reveal that the dizziness symptoms can be characterized as vertigo, unsteadiness, lightheadedness, or nonspecific dizziness not otherwise described (Carlson et al., 2014). Though most patients with vestibular neuritis report vertigo, a substantial portion (about 20%) instead report nonvertiginous dizziness symptoms such as floating sensation or unsteadiness (Newman-Toker et al., 2007). The symptoms can also be constant or episodic.

The symptom intensity reported by patients with CUVL varies from severe to none at all, typically depending on the time course and the severity of the lesion. For example, patients with vestibular neuritis – which by definition involves unilateral vestibular loss – present with moderate to severe symptoms in the acute phase. At around 12 months after symptom onset, only about 20–30% of vestibular neuritis patients report residual symptoms, even though up to 70% (range in studies of 20–70%) have a residual CUVL as measured by the caloric test (Strupp et al., 2004; Shupak et al., 2008). In one case series of patients with vestibular schwannoma who completed a survey prior to surgical treatment, most patients reported no dizziness symptoms prior to treatment, whereas 34% reported mild dizziness and 15% reported severe dizziness (Carlson et al., 2014).

EXAMINATION

The examination in patients with known CUVL is used to further localize the lesion, gain insights into the potential etiologies, and establish and follow the course of the disorder. The general examination could identify signs of a chronic infectious process such as a middle-ear effusion or cholesteatoma. Associated peripheral facial nerve paresis suggests prior Ramsay Hunt syndrome if the onset was acute followed by some improvement, or a neoplastic process if the onset was gradual and the course progressive. Associated unilateral hearing loss suggests endolymphatic hydrops if the symptoms are episodic. Additional cranial neuropathies suggest chronic basilar meningitis (e.g., fungal, tuberculosis, syphilis), neoplastic (e.g., schwannoma, meningioma, lymphoma, glioma), or inflammatory disorders (e.g., sarcoidosis). Large cerebellopontine angle tumors commonly produce asymmetric gaze-evoked nystagmus, so-called Bruns' nystagmus, resulting from combined unilateral vestibular loss and compression of the brainstem and cerebellum. Additional focal central nervous system deficits, including central ocular motor abnormalities, would be expected with demyelinating or ischemic disorders. Next to the first and second cranial nerves, the eighth cranial nerve has the largest proportion of central nervous system myelin, perhaps making it particularly susceptible to the effects of demyelinating disorders.

The gait examination typically informs the severity of the disorder more so than providing additional localizing information in patients with CUVL. Objective gait measures include the ability to stand in place with feet together with eyes open and separately with eyes closed, stand in tandem, and walk in tandem. The timed-up-and-go (TUG) test is also a widely used standardized measure of gait function.

DIAGNOSTIC EVALUATION

A patient with a significant unilateral vestibulopathy based on laboratory testing or a positive head impulse test should generally be evaluated for a structural lesion whenever there is a progressive course or the presentation is not otherwise suggestive of a self-limited disorder such as vestibular neuritis. The test of choice for a structural lesion is magnetic resonance imaging of the brain with and without gadolinium, including fine cuts through the posterior fossa. If the findings are limited to the unilateral vestibular deficit and hearing loss, serial audiograms could be used to assess for progressive or fluctuating features.

MANAGEMENT

In the absence of a specific surgical indication, the management of CUVL is symptomatic. It can be expected that the majority of patients with a CUVL not from a progressive structural lesion will improve with time without any specific intervention (Herdman et al., 2003; Strupp et al., 2004; Shupak et al., 2008). Physical therapy can play an important role in optimizing the symptomatic and functional improvement. A meta-analysis by the Cochrane Collaboration concludes that there is moderate to strong evidence that vestibular rehabilitation is a safe, effective management for unilateral peripheral vestibular dysfunction (McDonnell and Hillier, 2015). However, there is insufficient evidence to discriminate among differing forms of vestibular rehabilitation. A basic approach involving education, demonstration, and home exercises may be effective (McDonnell and Hillier, 2015).

Despite the important beneficial effect of physical therapy programs, in some of the randomized trials only about 50% of subjects in the intervention group achieve the desired level of subjective improvement in dizziness symptoms (McDonnell and Hillier, 2015). Observational studies suggest that patient characteristics associated with less optimal improvement include greater baseline loss of vestibular function, older age, greater percentage of time symptoms interfere with activities, and anxiety or depression (Godemann et al., 2005; Herdman et al., 2012). Gender, joint problems, cardiovascular disorders, diabetes, and the number of comorbidities were not associated with a worse outcome (Herdman et al., 2012).

CONCLUSIONS

CUVL is a broad category of vestibular disorders. Patients with CUVL can be symptomatic or asymptomatic. Self-limited disorders are the most likely cause in the absence of progressive features or central nervous system exam abnormalities. Patients with CUVL typically improve with time and physical therapy interventions are safe and effective for improving symptomatic and functional outcomes.

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Chapter 17

Bilateral vestibulopathy

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Abstract

The leading symptoms of bilateral vestibulopathy (BVP) are postural imbalance and unsteadiness of gait that worsens in darkness and on uneven ground. There are typically no symptoms while sitting or lying under static conditions. A minority of patients also have movement-induced oscillopsia, in particular while walking. The diagnosis of BVP is based on a bilaterally reduced or absent function of the vestibulo-ocular reflex (VOR). This deficit is diagnosed for the high-frequency range of the angular VOR by a bilaterally pathologic bedside head impulse test (HIT) and for the low-frequency range by a bilaterally reduced or absent caloric response. If the results of the bedside HIT are unclear, angular VOR function should be quantified by a video-oculography system (vHIT). An additional test supporting the diagnosis is dynamic visual acuity. Cervical and ocular vestibular-evoked myogenic potentials (c/oVEMP) may also be reduced or absent, indicating impaired otolith function. There are different subtypes of BVP depending on the affected anatomic structure and frequency range of the VOR deficit: impaired canal function in the low- and/or high-frequency VOR range only and/or otolith function only; the latter is very rare. The etiology of BVP remains unclear in more than 50% of patients: in these cases neurodegeneration is assumed. Frequent known causes are ototoxicity mainly due to gentamicin, bilateral Menière's disease, autoimmune diseases, meningitis and bilateral vestibular schwannoma, as well as an association with cerebellar degeneration (cerebellar ataxia, neuropathy, vestibular areflexia syndrome = CANVAS). In general, in the long term there is no improvement of vestibular function. There are four treatment options: first, detailed patient counseling to explain the cause, etiology, and consequences, as well as the course of the disease; second, daily vestibular exercises and balance training; third, if possible, treatment of the underlying cause, as in bilateral Menière's disease, meningitis, or autoimmune diseases; fourth, if possible, prevention, i.e., being very restrictive with the use of ototoxic substances, such as aminoglycosides. In the future vestibular implants may also be an option.

Bilateral vestibulopathy (BVP) is one of the most frequent causes of postural imbalance and falls, in particular in the elderly. Due to its often, at first glance, "unspecific" symptoms and insidious onset and slow progression, BVP is, in many cases, overlooked or only diagnosed after a long delay. However, the diagnosis, which is based on the patient history (postural imbalance and gait disorder with no symptoms while sitting or lying down) and the clinical findings (bilaterally pathologic head impulse test and/or caloric irrigation), can be easily and reliably made and has two major therapeutic consequences: first, counseling of the patient to explain the cause of the symptoms and second, intensive, ideally daily, physiotherapy by the patient him-/herself.

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CLINICAL FEATURES

Patient history

The leading symptoms of BVP are movement-dependent postural dizziness and unsteadiness of stance and gait, which is exacerbated in the dark and when walking on uneven ground (Rinne et al., 2000; Zingler et al., 2007a; Kim et al., 2011; Brandt et al., 2013; van de Berg et al., 2015). Typically, patients are free of symptoms under static conditions when sitting or lying. About 40% of patients complain of blurred vision (oscillopsia) when walking or running (Chambers et al., 1985; Rinne et al., 2000; Zingler et al., 2007a; Kim et al., 2011); consequently they can, for instance, no longer read street signs or identify the faces of people approaching them. Oscillopsia can also occur during fast head turns to the right and left.

In the majority of patients the beginning of symptoms is insidious. When patients consult a physician they often already have a considerable vestibular deficit. Some patients report recurrent attacks of spinning vertigo, lasting seconds to minutes, in the initial phase of the disease; evidently during these phases the function of the vestibular system worsens on one side. Such a history suggests an autoimmune etiology (see below). In the case of ototoxicity due to aminoglycosides the symptoms typically occur days to weeks after the application of the drug due to delayed ototoxicity (Magnusson and Padoan, 1991).

In patients with bilateral Menière's disease the vestibular deficits occur over time, with worsening after severe attacks of vertigo, accompanied by impaired hearing. Finally, in patients with bilateral vestibular schwannoma there is often also a bilateral hypoacusis.

Bedside examination

Clinical suspicion of BVP is based on the above-mentioned key symptoms. Bedside head impulse test (HIT) typically shows a bilateral pathologic HIT, reflecting a high-frequency deficit of the angular vestibulo-ocular reflex (VOR) (Halmagyi and Curthoys, 1988; Fife et al., 2000). If the bedside HIT, which has its limitations, is not clearly pathologic, an examination with the video HIT should be performed (see below). The bedside HIT may be normal due to covert saccades (Weber et al., 2008), but may also be false positive in patients with cerebellar disorders (Kremmyda et al., 2012) and, all in all, has a quite low sensitivity and specificity (Yip et al., 2016).

Romberg test with the eyes open is basically normal, whereas gait is often broad-based. When the eyes are closed there is increased body sway during the Romberg test; this becomes more obvious during tandem standing, one-leg standing, as well as walking toe to heel. In the latter two tests there is a danger of falling. Asymmetries of the vestibular function are observed when the patient walks straight ahead with closed eyes: the direction of gait deviation as a rule indicates the side which is most or more recently affected.

Another tool to diagnose high-frequency VOR dysfunction is dynamic visual acuity, which can be measured during passive head rotation with a sensitivity according to studies from 66% to 96% (Demer et al., 1994; Schubert et al., 2002; Guinand et al., 2012b).

The ocular motor examination is normal, except in patients with additional cerebellar dysfunction, in particular, downbeat nystagmus or other cerebellar ocular signs, such as gaze-evoked nystagmus or saccadic smooth pursuit. These patients may also have limb ataxia, cerebellar ataxia of stance and gait, and/or polyneuropathy, all typical of the cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS) (Silberstein et al., 2000; Kirchner et al., 2011).

LABORATORY EXAMINATIONS

To support and to confirm the clinical diagnosis and to determine whether there is a low- and/or high-frequency deficit of the angular VOR and/or an impaired/absent otolith function the following tests are used:

- Video HIT (Bartl et al., 2009; MacDougall et al., 2009). An angular VOR gain below 0.6 on both sides is considered pathologic which, however, is not yet fully established as a cutoff. The deficit of the angular VOR can be asymmetric.
- Video oculography with bithermal (44 °C and 30 °C) caloric testing to evaluate the function of the VOR in the low-frequency range. Caloric response will be considered pathologic if the sum of bithermal maximal peak slow-phase velocity on each side is less than 6°/second. This can also be asymmetric.
- Cervical and ocular vestibular-evoked myogenic potentials (Agrawal et al., 2013; Rosengren and Kingma, 2013). Saccular function appears to be less affected than horizontal semicircular canal function in patients with BVP (Zingler et al., 2008), whereas the utricular function is correlated with horizontal canal function (Agrawal et al., 2013).

Testing of the angular VOR and otolith function reveals five groups of patients: those with (1) a combined high- and low-frequency deficit (the majority); (2) a high-frequency deficit only; (3) a low-frequency deficit only (as often found in bilateral Menière's disease); (4) an additional impaired otolith function; and (5) an impaired otolith function only (very rare) (Fujimoto et al., 2009).

Patients with BVP also have impaired visual motion perception and raised motion coherence across all velocities tested, allowing them to partially compensate for the oscillopsia (Kalla et al., 2011). Patients often also suffer

from impaired spatial memory and navigation associated with hippocampal atrophy (Schautzer et al., 2003; Brandt et al., 2005).

CLINICAL COURSE OF THE DISEASE

In the course of BVP, both labyrinths and/or vestibular nerves can be affected at the same time or sequentially; the disorder can be acute or slowly progressive, complete or incomplete, and symmetric or asymmetric. BVP can occur with or without associated hearing loss. A 5-year follow-up of more than 80 patients with BVP found that more than 80% of patients had no significant improvement in vestibular deficit regardless of etiology, type of course, sex, or age at first manifestation (Zingler et al., 2007b).

PATHOPHYSIOLOGY

The key symptoms of BVP can be explained by the loss of vestibulo-ocular (canal and/or otolith) and vestibulospinal functions.

Unsteadiness of posture and gait as well as postural imbalance, increased in the dark and on uneven ground

Due to the redundant sensorimotor control of posture, the visual system can basically substitute for any defective regulation of postural control in light. The somatosensory system also contributes to the maintenance of balance, above all via the muscle spindle afferents and the mechanoreceptors of the skin. If the contribution of the visual system (in darkness or due to visual disorders) is reduced, gait imbalance increases until the patient experiences a tendency to fall. This is further intensified if the patient walks in the dark over uneven or springy ground. A sensory polyneuropathy also reduces the somatosensory contribution to posture control and thereby exacerbates the symptoms of BVP.

Oscillopsia and blurred vision

During rapid head movements the VOR cannot maintain the target of gaze on the fovea, and thus there is an involuntary movement of the image on the retina, which is experienced as an illusory movement that reduces the visual acuity. This symptom occurs in 40% of patients (Zingler et al., 2007a). Conversely, when head movements are slow, the smooth-pursuit system is able to sufficiently stabilize the gaze in space, and no illusory movement or blurriness occurs.

Deficits of spatial memory and navigation

An intact vestibular function is important for spatial orientation, spatial memory, and navigation (Smith, 1997). Significant deficits of spatial memory and navigation as well as atrophy of the hippocampus were demonstrated in patients with BVP (Brandt et al., 2005). The rest of the memory functions were evidently not affected. In patients with unilateral labyrinthine failure, however, no disorders of spatial memory or atrophy of the hippocampus were found (Hufner et al., 2007), whereas in another study an atrophy was described (zu Eulenburg et al., 2010).

DIFFERENTIAL DIAGNOSIS

Considerations for the differential diagnosis proceed along two lines. On the one hand, it is necessary to differentiate the illness from other vestibular and nonvestibular diseases, which are also characterized by oscillopsia and/or instability of posture and gait. These are cerebellar ataxias without BVP, downbeat nystagmus syndrome, or other nystagmus syndromes leading to oscillopsia, severe unilateral vestibulopathy, functional dizziness, intoxications, vestibular paroxysmia, superior canal dehiscence syndrome, orthostatic hypotension, orthostatic tremor, unilateral vestibular deficit, normal-pressure hydrocephalus, extrapyramidal syndromes, and polyneuropathy. On the other hand, it is important to investigate the different causes and etiologies (see below) of BVP which can also have therapeutic consequences.

ETIOLOGY

The etiology of BVP remained unclear in more than 50% of patients in a case series of 255 patients (Zingler et al., 2007a; van de Berg et al., 2015). They can be assumed to have a degenerative illness (see below). The three most frequent identifiable causes of BVP were: ototoxic drugs (13%; gentamicin and other ototoxic antibiotics, anticancer chemotherapy, loop diuretics, aspirin in very high dosages (Strupp et al., 2003) or styrenes (Fischer et al., 2014)), bilateral Menière's disease (7%), and meningitis (5%). Other causes are: (1) tumors: bilateral vestibular schwannoma in neurofibromatosis type 2, meningeal carcinomatosis, infiltration of the skull base or due to tumor radiation; (2) autoimmune diseases (Arbusow et al., 1998), like Cogan's syndrome (Gluth et al., 2006), neurosarcoidosis, Behçet's disease, cerebral vasculitis, systemic lupus erythematosus, Wegener's granulomatosis; and (3) rarer causes such as bilateral labyrinth concussion or superficial siderosis.

Patients with BVP frequently have a cerebellar syndrome and downbeat nystagmus; the opposite is also true (Migliaccio et al., 2004; Zingler et al., 2007a; Wagner

et al., 2008; Kirchner et al., 2011). Such cases probably involve a neurodegenerative illness that affects the vestibular ganglia cells and the cerebellum; it often occurs with an additional neuropathy: CANVAS. This combination of symptoms occurs in up to 20% of patients with BVP (Kirchner et al., 2011; Szmulewicz et al., 2011; Pothier et al., 2012).

THERAPY

Treatment of the various forms of BVP follows four lines of action: (1) detailed explanation of the cause of the symptoms and etiology of the disease to the patient; (2) physical therapy to promote central compensation or substitution of missing vestibular function by visual and somatosensory input; (3) if possible, prophylaxis of progressive vestibular loss; and (4) if possible, improvement of recovery of vestibular function.

Informing and educating the patient

It is important to inform the patients carefully about the type, mechanism, and course of their illness. It is our experience that the diagnosis of a BVP is still established much too late, despite many visits to various physicians, a fact that only intensifies the symptoms of the patients. The disease has a pronounced negative impact on physical and social functioning, leading to deterioration of quality of life (Guinand et al., 2012a). Frequently, these subjective complaints are reduced by simply informing the patient.

Physical therapy of stance and gait

Patient response to physical therapy with gait and balance training is quite positive. This therapy alleviates the adaptation to loss of function by promoting visual and somatosensory substitution. Such substitution was proven with the help of functional imaging. It showed that larger portions of the visual and multisensory cortical areas of patients with BVP were activated during visual stimulation than in healthy persons of the same age (Dieterich et al., 2007). The efficacy of balance training was confirmed at least for patients with unilateral peripheral vestibular function disorders (Hillier and McDonnell, 2011). Treatment effects are probably smaller in patients with BVP.

Improving recovery of vestibular function

Recovery of vestibular function is possible in postmeningitis patients due to a serous nonsuppurative labyrinthitis and in individual patients with autoimmune inner-ear disease, which are diagnosed too infrequently. Although controlled prospective studies are lacking, immune treatment is theoretically expedient, if there are clinical signs of a systemic autoimmune disease, or if antibodies against inner-ear structures are detected (Schuler et al., 2003; Deutschlander et al., 2005). Initially, corticosteroids can be tried (e.g., prednisolone in doses of 80 mg/day, tapered over *ca*. 3–4 weeks). In Cogan's syndrome, initially high doses of steroids (1 gram intravenously daily for 5 days) can be given with subsequent dose reduction. If the response is inadequate or relapses occur, additional but temporary administration of azathioprine or cyclophosphamide is recommended. Besides this, treatment of the causative underlying disease is important and in individual cases also successful.

In the long term, vestibular implants can become a therapeutic option. They have had very promising results in animal studies (Merfeld and Lewis, 2012) and in pilot trials in humans (Rahman et al., 2011; van de Berg et al., 2012; Pelizzone et al., 2014; Guinand et al., 2015a, b). Recently it was demonstrated that noise-enhanced vestibular input can also improve dynamic walking stability, and this could be tried in patients with BVP (Wuehr et al., 2016).

PREVENTION

Prevention is most important for the group of patients with ototoxic labyrinthine damage, above all, due to aminoglycosides. Aminoglycoside therapy should be used only if strictly indicated and then only in a once-daily dose. Plasma levels should also be monitored. Patients with renal insufficiency, advanced age, or familial susceptibility to aminoglycoside ototoxicity are at particular risk. Ototoxic antibiotics should not be combined with other ototoxic substances, such as loop diuretics, as this can have a potentiating effect on inner-ear damage. Careful follow-ups of hearing and vestibular function are necessary during treatment, especially in meningitis. However, physicians must remain vigilant, as the ototoxic effects of gentamicin have a delayed onset, often appearing only after days or weeks.

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Chapter 18

Benign paroxysmal positional vertigo and its variants

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Abstract

Benign paroxysmal positional vertigo is a common labyrinthine disorder caused by a mechanic stimulation of the vestibular receptors within the semicircular canals. It is characterized by positional vertigo and positional nystagmus, both provoked by changes in the position of the head with respect to gravity. The social impact of the disease and its direct and indirect costs to healthcare systems are significant owing to impairment of daily activities and increased risk of falls. The first description of a patient with benign paroxysmal positional vertigo is from Robert Bárány in 1921, but the features of the syndrome and the diagnostic maneuver were well described by Dix and Hallpike in 1952. Since then, the gradually increasing interest of otolaryngologists and neurologists has led to a progressive advance in the knowledge of this labyrinthine disorder with regard to its epidemiologic, pathophysiologic, clinical, and therapeutic aspects. Despite the often effective diagnosis and treatment of most cases of benign paroxysmal positional vertigo, the physiopathologic explanations of the disease are mainly speculative. In this chapter, we describe the epidemiologic, pathophysiologic, clinical, and therapeutic aspects of benign paroxysmal positional vertigo.

INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is a common labyrinthine disorder caused by a mechanic stimulation of the vestibular receptors within the semicircular canals. It is characterized by positional vertigo and positional nystagmus (PN), both provoked by changes in the position of the head with respect to gravity. In most patients, the diagnosis is straightforward and the outcome of the treatment is very satisfactory for both the patient and physician. However, some cases present a challenge in the identification of a pathophysiologic explanation and often the treatment of those cases is less effective.

The social impact of the disease is of great importance because it is common and especially older patients experience a greater incidence of falls, depression, and impairment of their daily activities. The costs to healthcare systems and the indirect costs of BPPV are also significant (Bhattacharyya et al., 2008).

The first description of a patient with BPPV is from Robert Bárány in 1921, but the features of the syndrome and the diagnostic maneuver were well described by Dix and Hallpike in 1952. Since then, the gradually increasing interest of otolaryngologists and neurologists has led to a progressive advance in the knowledge of this labyrinthine disorder, with more than 1200 papers published on this topic in the last 25 years.

In this chapter, we describe the epidemiologic, pathophysiologic, clinical, and therapeutic aspects of the disease.

It is important to emphasize that the pathophysiologic explanations of BPPV provided here are based on the concepts of canalolithiasis and cupulolithiasis and are mainly speculative theories which are supported mostly by pathophysiologic reasoning rather than direct pathologic evidence.

EPIDEMIOLOGY

BPPV is certainly the most common cause of vertigo in adults. The lifetime cumulative incidence in the general population amounts to about 10% (von Brevern et al.,

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2007). BPPV accounts for about 15% of all equilibrium disorders, with a mean age of onset close to 60 years (Caruso and Nuti, 2005). The incidence increases in those over 60 years of age and decreases exponentially below 40, being very rare in children (von Brevern et al., 2007). Women are more commonly affected than men, in a ratio of about 2:1. BPPV is often a self-limiting disease, with spontaneous remissions that occur after days to weeks. About 1 in every 2 patients is prone to recurrences (Nunez et al., 2000). The posterior semicircular canal (PC) is by far the most commonly responsible for BPPV, as it is the most gravity-dependent. Indeed, about 70% of BPPV patients receive a diagnosis of unilateral PC-BPPV (Caruso and Nuti, 2005). Surprisingly, in almost all case studies, the right PC is more frequently affected (ratio about 1.5:1). This has been attributed to the habit of most patients of sleeping on their right side (von Brevern et al., 2004b). In 5–10% of patients, there is a bilateral involvement of the PC, and almost 90% of these are posttraumatic. About 15–20% of patients have the lateral canal (LC) variant, with no significant difference in gender or side involved.

PATHOPHYSIOLOGY

It is widely accepted that BPPV is quite often caused by otoconial debris that becomes detached from the utricular macula and enters one or more semicircular canals where they are free to move in the endolymph. Clusters of calcium carbonate crystals have been observed inside the semicircular canals during surgery performed in patients affected by BPPV (Parnes and McClure, 1992), and electron microscopic studies have confirmed that the particulate matter found inside the posterior semicircular canal consists of otoconia (Welling et al., 1997). Otoconia should dissolve in the endolymph reasonably quickly, but a high calcium concentration in the endolymph seems to slow or prevent this process (Zucca et al., 1998). The syndrome is activated when the patient's head is positioned such that the debris can enter the semicircular canals. Since dislodged otoconia are common in all semicircular canals, even in asymptomatic patients, it is likely that only when a critical mass is reached they alter the endolymphatic pressure sufficiently to displace the cupula (Kveton and Kashgarian, 1994). Once in the canal, the particles move under the force of gravity, tending to settle to its base. The debris can fall toward or away from the ampulla, thereby provoking an ampullopetal or ampullofugal deflection of the cupula, by a plunger-like action or simply because of hydrodynamic drag. This is the specific stimulus for the sensory epithelium of the crista ampullaris, the organ specialized in transducing angular accelerations. Ampullofugal deflection is excitatory for the vertical canals, since it increases the discharge rate of the ampullary nerve, and ampullopetal deflection is inhibitory. The reverse is seen in the lateral canal, where the ampullary nerve is excited by an ampullopetal deflection and inhibited by an ampullofugal one. The result of the otoconial movement in the canals is a false sense of rotation and nystagmus, even when the head is still. This is the canalolithiasis theory, proposed nearly 40 years ago (Hall et al., 1979). Otoconial clusters may also adhere to the cupula, rendering it sensitive to gravitational forces, as proposed by Schuknecht (1969) in the cupulolithiasis theory. Adhesion can probably occur on the side of the short arm or on the side of the long arm of the canals, or both. It is possible that canalolithiasis and cupulolithiasis may coexist in the same patient, as well as simultaneous involvement of more than one canal in the same labyrinth, and also bilateral involvement.

Considering physical rules, such as Pascal's principle on the physics of fluids (Epley, 1995) and according to a mathematic model (Hain et al., 2005), the mechanisms of canalolithiasis and cupulolithiasis should express very different behaviors from a clinical point of view. Indeed, a solid mass that acts like a piston in the narrow canal is able to produce much more pressure than the same mass would do if lying on the cupula. Moreover, when the head changes position, the mass gravitates to a more dependent position in the canal where it stops. As a result, the stimulus ceases and the cupula returns to its neutral position. In other words, canalolithiasis provokes an impulsive and transient stimulus to the vestibular receptors of the semicircular canal. With cupulolithiasis (heavy cupula), the cupula is instead deflected because a mass renders it heavier than the endolymph. Therefore, the stimulus should be similar to a sustained angular acceleration which keeps the cupula deflected. In summary, typical PN as a result of canalolithiasis should be abrupt in onset, paroxysmal (intense), and transient, whereas that due to cupulolithiasis should be gradual in onset, less intense, and persist as long as the provocative position is maintained, or gradually subsiding due to adaptation.

It seems logical to speculate that many variables can influence the characteristics of PN and particularly its intensity, duration, latency, and also direction. In canalolithiasis, for example, the debris can follow a relatively long path and the "piston" can be more or less leaky. On the other hand, cupulolithiasis is influenced by the weight of the clusters and whether they are attached to the apex of the cupula, where they can be more effective. The morphology of the membranous labyrinth, the spatial orientation of the semicircular canals and their radius of curvature, the angle between the cristae and

the vertical gravitational plane and other geometric features are additional elements that must be considered when nystagmus features are atypical or when therapeutic attempts fail (Della Santina et al., 2005; Bradshaw et al., 2010).

ETIOLOGY

In about 15% of cases, the symptoms begin in close relationship with a head trauma. The posttraumatic etiology includes whiplash injury, high-impact exercises, or surgery in which a drill or a scalpel is used (nasal, dental). BPPV may follow cochlear implantation (Limb et al., 2005) or stapes surgery (Magliulo et al., 2005). After a fall, especially in older people, it is sometimes difficult to ascertain whether the trauma was the cause of BPPV or whether the fall was caused by BPPV. BPPV may follow vestibular damage from a viral cause or labyrinthine ischemia. For instance, BPPV appears to be more frequent in patients who have had vestibular neuritis than in the general population, consistently affecting the PC of the same ear after the patient has recovered from the initial insult (Mandalà et al., 2010). This is possible when only the vestibular structures innervated by the superior division of the vestibular nerve and perfused by the anterior vestibular artery are affected (utricle, anterior, and lateral canal). Otoconia detach from the damaged utricle and enter the still-working posterior semicircular canal, giving rise to BPPV. Sometimes the disease initiates after prolonged bed rest, for instance, after orthopedic surgery of the legs, suggesting the hypothesis that motionlessness may predispose to detachment of otoconia. Sometimes it begins after certain positions have been held at the hairdresser or dentist or even after general surgery with prolonged positioning with the head back.

In most patients, the disease is idiopathic, since no definite etiology may be identified, even though many conditions are considered to be predisposing factors for the "spontaneous" detachment of otoconia from the utricular maculae. Aging plays an important role, since the disease is rare in childhood and frequent in the elderly. Hormonal effects and migraine may underlie the higher incidence of BPPV in females. Vasospasm of the inner ear, leading to release of otoconia, has been postulated as a mechanism (Ishiyama et al., 2000). Menière's disease also seems to predispose to BPPV (Gross et al., 2000). There is a possible association between BPPV and its rate of recurrence with the disorders of calcium metabolism and vitamin D deficiency (Vibert et al., 2003; Büki et al., 2013). It was also suggested that the incidence of BPPV could be higher at the end of winter, when serum vitamin D level is known to be low (Whitman and Baloh, 2015).

SYMPTOMS

The symptomatology of BPPV is often so typical that diagnosis can simply be made by the patient's description:

> *A few days ago, just seconds after I got out of bed, I felt the whole room spinning. It was so strong that I had to sit down again on the bed. I also had severe nausea, and thought that I must have eaten spoiled food. Lying back in bed, I had another episode of vertigo. In the following hours, I was only well when I kept my head still, but if I tried to turn in the bed or to get up, the spinning sensation returned again. The next day, I got up very slowly but I was again dizzy when I went to tie my shoes…I called my general practitioner and he suggested that I have a brain MRI [magnetic resonance imaging] and X-rays of the cervical spine. Now I am better, but every time I get up or lie down in the bed, I see the room spinning. The spinning sensation lasts for a few seconds and stops if I'm still. Doctor, do you think I have a brain tumor?*

In fact, BPPV is characterized by episodes of rotatory vertigo, since it arises from the semicircular canals. The first episode generally occurs in bed or when getting up. Vertigo recurs every time the patient's head assumes a certain position or performs a given movement. If it is triggered by lying down and/or turning in the bed, this is typical of BPPV and orthostatic dizziness is excluded. If the vertical canals are involved, vertigo is mainly provoked by head movements in the pitch plane (getting up in the morning, looking up, bending forward). The single episode of vertigo generally subsides after around 10 seconds, if the provoking position is maintained. When the lateral canals are involved, the attacks of vertigo are longer, more intense, and provoked mainly by rolling to the side while lying. In atypical forms, the vertigo may last longer, sometimes as long as the provoking position is held. The first episodes of vertigo are more intense, often accompanied by nausea and vomiting, and frighten the patient so that the duration of the attack may be overestimated. Patients with LC-BPPV are sometimes forced to lie immobile in a supine position, so it can be difficult to know whether it is a positional vertigo or not. Patients with atypical BPPV and particularly those with positional downbeating nystagmus (pDBN) complain of less specific symptoms. Some of them complain of unsteadiness instead of vertigo, especially when getting up, and dizziness when walking, which is a rare feature in those with typical BPPV (Cambi et al., 2013).

BPPV is often a self-limiting condition, with symptomatic periods lasting for days, weeks, or, rarely, months, if not treated. During this period, known as the active phase of BPPV, patients have no problems when standing up. They can drive a car, since turning the head from side to side in the sitting position does not provoke symptoms. However, some of them complain of a feeling of floating and postural instability between attacks. Recurrences of the symptomatic periods are frequent. Some patients have closely spaced active phases; in others, the asymptomatic period lasts for years. The recurrence rate has been estimated to be 15% after 1 year and up to 50% in the long term (Nunez et al., 2000). The rare chronic forms with a persistent active phase that does not resolve with repeated physical treatment cause so-called "intractable BPPV."

The disease is not associated with hearing loss or neurologic symptoms, unless secondary to other diseases. The first episode of positional vertigo is often a stressful event and can easily lead to anxiety and phobic behavior. Even though BPPV is often a self-limiting disorder, sometimes it may affect the quality of life (Lopez-Escamez et al., 2005) and has a significant socioeconomic impact (von Brevern et al., 2007). Some patients sleep in a semisitting position and avoid turning in bed to avoid dizziness, giving rise to neck discomfort that is often considered to be the cause of vertigo, particularly by general practitioners. In elderly patients, BPPV is one of the most frequent causes of falls and fractures.

DIAGNOSIS (THE CLINICAL PICTURE)

The diagnosis of BPPV can be easily reached using Frenzel glasses. In many patients, however, nystagmus can be seen without special equipment, by direct inspection of the eyes. Nevertheless, the use of video-oculography recordings is advisable, especially when PN is weak, to better appreciate the exact pattern of nystagmus, especially identification of any torsional component, and to add the possibility of a comparison in subsequent observations. The diagnostic maneuvers move the head in planes parallel to the individual canals and the resulting nystagmus often allows identification of which canal is involved, if the cupular movement is ampullopetal or ampullofugal and, possibly, where the otoconial debris is located. The most important features of PN are the direction, time course, intensity, duration, and latency. Imaging of the brain or ear is not necessary in patients with typical BPPV (Bhattacharyya et al., 2008). Further testing of the vestibular and auditory function is only indicated with the coexistence of other inner-ear diseases, such as Menière's disease and vestibular neuritis.

Posterior-canal BPPV

The posterior canal is by far the most frequently affected canal in patients with BPPV, and canalolithiasis is by far the most common mechanism. The Dix–Hallpike test is the technique used most often to detect PC-BPPV (Fig. 18.1). The patient is seated on an examination bed and the head is rotated 45° to one side. The patient is then brought into the supine position with the head hyperextended. A pillow under the shoulders of the patient or a bed with an adjustable head rest are useful to reach the correct head-hanging position, which is about 120° from the upright starting position. After nystagmus has been observed, the patient is returned to the starting position. This maneuver was devised

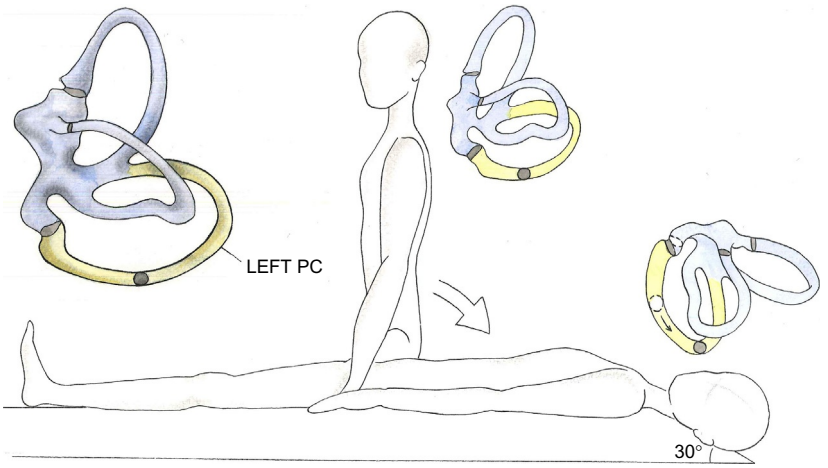

Fig. 18.1. Dix–Hallpike test for left posterior semicircular canal (PC) benign paroxysmal positional vertigo. The head is turned 45° to the left and then the patient is quickly brought into the left head-hanging position, about 30–40° below the horizontal plane. This position is maintained for at least 30 seconds, since positional nystagmus may appear after a long latency. The patient is next returned to the sitting position with the head facing forward, again observing for nystagmus. The position and movement of particles inside the PC are shown (for details, see text).

to specifically evaluate the PC, because it brings the ampulla to a higher position with respect to the canal and the canal is aligned with the plane of movement, so favoring action of the gravity vector on any debris inside the canal. It is advisable to test the left side first, since right PC-BPPV is more probable, and always to perform the test bilaterally, so as not to miss a bilateral BPPV, especially after head trauma.

The typical features of PN due to canalolithiasis of the PC are as follows.

Latency

There is a latent period between reaching the diagnostic Dix–Hallpike position and the onset of nystagmus, in most patients in the range of 2–10 seconds. Generally shorter in the early stages of the disease, it is partially explained by the delay in setting the debris in motion.

Direction and plane

These are crucial for the diagnosis. When the patient is moved to the diagnostic Dix–Hallpike position, otoconial debris falls from its starting position in the canal toward the ground and away from the ampulla, so causing an excitatory stimulus and a mixed torsional-vertical paroxysmal nystagmus consistent with the excitatory connections of the PC to the vertical extraocular muscles. The fast phase of the vertical component beats towards the forehead (up) and the fast phase of the torsional component is directed such that the upper pole of the eyes beats towards the affected lower ear.

The torsional component may appear more prominent when the patient looks toward the lowermost ear and the vertical component more prominent if the patient looks toward the uppermost ear.

Intensity and duration

Paroxysmal means that PN is rapidly increasing in intensity and then begins to decay slowly. PN is typically transitory, that is, it dissipates in 10–40 seconds, because, once the debris reaches the lowest point in the canal, the cupula returns to the primary position with its time constant, primarily due to its elasticity.

Static reversal

In some patients, when PN is particularly intense, a spontaneous reversal of its direction may occur, without any change in head position. This "secondary" nystagmus begins a few seconds after the end of the previous PN, is of low amplitude, and probably reflects adaptation to a sustained vestibular stimulus.

Dynamic reversal

When the patient is returned to the sitting position, the particles fall back in the opposite direction and cause an ampullopetal flow, which produces an inhibitory response and a less intense nystagmus in the opposite direction, i.e., downbeating, with the torsional component directed such that the upper pole of the eyes beats away from the affected ear (again geotropic). This directional change of PN is a typical feature of PC-canalolithiasis. In patients with bilateral PC-BPPV, PN is upbeating and torsional toward the lower ear in both Dix–Hallpike positions.

The possibility of a heavy cupula of the PC must be considered when the nystagmus pattern is considerably different from that described earlier. Indeed, cupulolithiasis should be characterized by a PN with the same direction (vertical-upbeating and torsional), but gradual in onset, not paroxysmal, and persisting as long as the provocative position is maintained. A gradual decline can begin after more than 1 minute (Epley, 2001). Probably the best diagnostic maneuver for cupulolithiasis is the "half Dix–Hallpike maneuver," in which the cupula is brought into a position to be maximally stimulated by the pull of gravity. The patient's head is turned 45° toward the side to be tested and then the patient is brought about 60° down to one side, instead of 120°. In this position, the cupula of the PC should be earth–horizontal. Rolling the head 180° to the other side (release position) should reveal a less intense nystagmus beating in the opposite direction, due to ampullopetal deflection of the cupula (Epley, 2001). The incidence of patients with characteristics that indicate a possible cupulolithiasis is much lower than that of patients with a typical PC-BPPV.

Lateral-canal BPPV

When LC-BPPV is suspected, one must first look for spontaneous nystagmus with the patient in the sitting position. The patient is then rapidly brought to the supine position, with the head straight (nose upward) and bent about 30° forward to bring the lateral canal into the vertical plane. A pillow or an adjustable head rest is useful. After looking for any PN, the "supine roll test" (McClure–Pagnini test) is performed by rolling the patient's head 90° to one side. The head is then rotated 180° to the other side, looking for changes in the direction and intensity of nystagmus. To avoid neck discomfort, the whole body can be rotated and also a step can be added: 90° to one side, back to neutral, and then 90° to the other side. The supine roll test acts in a plane parallel to that of the lateral canal and therefore is the best maneuver to elicit a horizontal PN due to canalo/cupulolithiasis of this canal. Other diagnostic maneuvers can be

performed to better understand the side and pathophysiology, such as the "bow and lean test" and the search for the null point (see later). Depending on the different locations of otoconial debris in the canal, LC-BPPV can be divided into two variants, the more common one with geotropic nystagmus and the less common one with apogeotropic nystagmus.

Geotropic variant

The most important feature of LC-BPPV is the finding of a horizontal, direction-changing PN provoked by the supine roll test. Rotation of the head to the pathologic side causes an intense horizontal nystagmus beating toward the lower ear. This is termed geotropic because it beats towards the ground. Generally, it is more intense and longer lasting (sometimes for more than 1 minute) than that of PC-BPPV, but again is transient. Rotation of the head to the other side provokes a less intense nystagmus toward the opposite ear, again geotropic. According to Ewald's second law, for the lateral canal, the stronger response is due to an ampullopetal movement of the cupula. Therefore the most intense geotropic nystagmus can only be due to the fall of particles toward the ampulla (excitation) and the less intense nystagmus toward the opposite ear due to the fall of particles in the opposite direction (inhibition) (Fig. 18.2). The inversion of nystagmus direction in the two different positions of the head is critical for diagnosis and can be compared with the dynamic reversal that occurs in PC-BPPV when the patient is returned to the sitting position from the Dix–Hallpike position. The phenomenon of static reversal nystagmus is much more frequent in LC-BPPV: when the excitatory nystagmus is strong, it is often followed by a reversal of direction without changing the head position. Sometimes the nystagmus reverses on both sides (Nuti et al., 1996). LC-PN seems less susceptible to habituation with repetition of the diagnostic maneuvers, even though this characteristic is often difficult to assess, due to nausea or vomiting. The latency of geotropic paroxysmal nystagmus is usually shorter than that of PC-BPPV, sometimes with no appreciable latency.

The supine roll test is quite indispensable for the diagnosis of LC-BPPV and the affected ear is revealed by the direction toward which the most intense nystagmus beats. Sometimes, however, it may be difficult to appreciate a difference between the intensity of the two sides. Other diagnostic maneuvers, which should be performed before the supine roll test, can be useful to assess the affected side. These maneuvers can also help in understanding the pathophysiology of the syndrome.

First of all, we should carefully look for spontaneous nystagmus that is sometimes detectable in the sitting position (Asprella Libonati, 2008). This is termed "pseudo-spontaneous," because there is no primary labyrinthine hypofunction. In patients with the geotropic

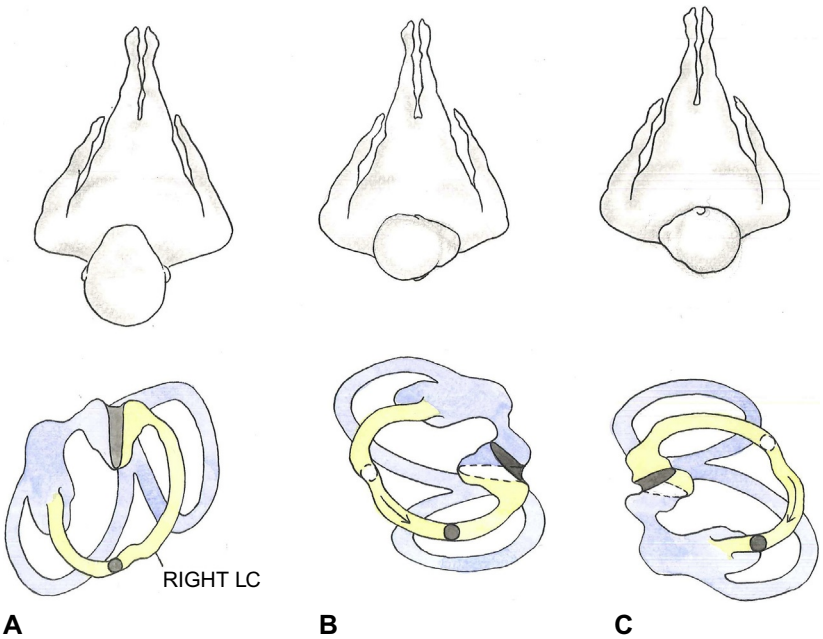

Fig. 18.2. Supine head roll test in right lateral canal (LC) benign paroxysmal positional vertigo (geotropic form). (**A**) Patient in the supine position and the head straight: particles are located in the most gravity-dependent part of the lateral canal. (**B**) Rotating the head 90° to the right side causes particles to fall toward the ampulla, producing an ampullopetal flow and intense horizontal nystagmus beating to the right, affected, ear. (**C**) Rotation of the head 180° to the left side causes particles to move in the opposite direction, producing ampullofugal flow and left-beating horizontal nystagmus (again geotropic), less intense than in (**B**).

variant, it beats towards the healthy side, is of low intensity, and generally asymptomatic. The finding of pseudo-spontaneous nystagmus is more common when patients are observed in darkness with video recordings, since it is completely inhibited by fixation. It may be revealed by a gentle shake of the head. It is strongly modulated by movements of the head in the sagittal plane, increasing its intensity with bending the head 30° backward, stopping with the head bent 30° forward, and reversing its direction if the head is further bent forward to 60°. These maneuvers are known as the Bow and Lean Test (Choung et al., 2006) or Head Pitch Test (Asprella Libonati, 2008; Califano et al., 2008). These phenomena can be explained by the anatomic position of the lateral canal in the upright position of the head. Since the anterior part of the lateral canal is angled about 30° upward from the horizontal plane, otoconial debris tends to accumulate far from the cupula when the head is bent backward (ampullofugal stimulus) and toward the cupula with bending forward (ampullopetal stimulus) (Fig. 18.3). It is also possible to provoke the unwanted transition from geotropic nystagmus into apogeotropic with bowing the head forward or with the "head-on-knees" position (Steddin et al., 1996; Lee et al., 2007). This finding has been attributed to conversion of canalolithiasis into cupulolithiasis. Actually, it is also possible that debris moves into the anterior aspect of the lateral canal.

PN can also be evoked by bringing the patient rapidly from the sitting to the supine position with the nose up. With this movement, the debris again gravitates away from the ampulla, provoking a mild horizontal nystagmus toward the unaffected ear, which is termed "lying-down nystagmus" (Nuti et al., 1996).

If geotropic PN is paroxysmal and transitory, diagnosis of LC-BPPV due to canalolithiasis is virtually certain and no differential diagnosis is required. However, there are increasing reports of persistent geotropic PN attributed to a cupula made light from debris of lower density (Bergenius and Tomanovic, 2006; Imai et al., 2014; Ichijo, 2015). Similarly to the apogeotropic variant attributed to a heavy cupula, a null point is described where the nystagmus stops when rolling the head 20–40° toward the affected ear (see later).

Apogeotropic variant

The apogeotropic variant is less common than the geotropic one. It is characterized by a PN that beats toward the ceiling when the supine roll test is performed. That is, the fast phase of nystagmus is directed to the uppermost ear.

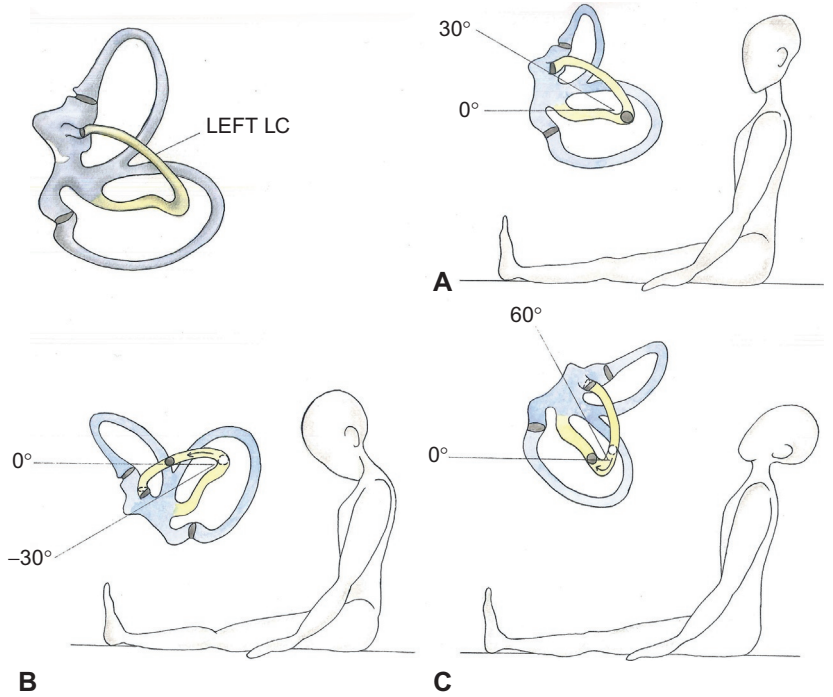

Fig. 18.3. Bow and Lean Test in left lateral canal benign paroxysmal positional vertigo (geotropic form). (**A**) With the patient in the sitting position, the angle between the horizontal plane and the plane of the lateral canal could cause particles to move away from the ampulla with "pseudo-spontaneous" beating to the right. (**B**) When bending the head about 60° forward, gravity causes debris to move towards the ampulla, producing left-beating nystagmus. (**C**) By bending the head backwards, the lateral canal is placed almost in the vertical plane, favoring the fall of particles away from the ampulla and producing right-beating nystagmus.

Also with this variant, there is often a side toward which nystagmus is more intense and one in which it is weaker. The affected side is again the one toward which the more intense nystagmus beats. There are two different theories about the pathophysiology of apogeotropic PN. The most popular theory is that of cupulolithiasis, where a mass on the cupula determines its deflection by gravity. The cupula is deflected toward the canal when the affected ear is down and in the opposite direction when the same ear is up, so provoking an inhibition and an excitation, respectively. PN should be of low to medium intensity and persistent for all the time that the critical position is held, with a slow decline due to adaptation. Latency should be absent or minimal. When the patient is lying with the head is turned about 20° towards the side of the affected ear, it is possible to find the so-called "null point" where nystagmus stops. This finding is attributed to the fact that the cupula of the lateral canal is not aligned parallel to the gravity vector when the patient lies down with the head in the nose-up position undeflected, but is laterally inclined by around 20° (Bisdorff and Debatisse, 2001). This morphologic arrangement needs to be confirmed.

An alternative theory proposes that canalolithiasis is also able to provoke apogeotropic nystagmus, if debris is located near the ampulla of the lateral canal, on its anterior part, and moving in the opposite direction with respect to the geotropic variant. Apogeotropic nystagmus due to canalolithiasis should be characterized by a brief-latency, intense PN and a limited duration.

Whatever its cause, even in the apogeotropic form, we can observe pseudo-spontaneous nystagmus, its modulation with movements of the head in the sagittal plane, and lying-down nystagmus. Its direction is, however, opposite to that found in the geotropic form. It is not uncommon to obtain the conversion of an apogeotropic nystagmus into the geotropic form during the diagnostic maneuvers or by tilting the head backward and forward (Califano et al., 2008) or by asking the patient to lie for as long as possible on the affected side. When the conversion happens, it is again more logical that otoconial debris is freely moving in the endolymph of the lateral canal (Nuti et al., 1996).

Anterior-canal BPPV

The existence of canalolithiasis of the anterior canal (AC) is still debated. Since the AC on one side is roughly coplanar to the posterior canal on the other side, the left AC is tested with a Dix–Hallpike maneuver performed on the right side. On the other hand, it was suggested that a PN from the AC can be elicited with both Dix–Hallpike maneuvers and even better in the supine straight-head-hanging position, by bringing the patient to the supine position with the head 30° (or even more) below the earth–horizontal (Bertholon et al., 2002; Casani et al., 2011). For example, in the case of left AC canalolithiasis, the right Dix–Hallpike maneuver or supine straight-head-hanging positioning provokes a backward rotation of the left AC and the fall of otoconial debris away from the ampulla. The resulting PN is mixed downbeating and torsional, with the top pole of the eyes beating towards the left pathologic ear and with the vertical component prevailing over the torsional component (Aw et al., 2005). This is consistent with the primary excitatory connections of the left AC to the ipsilateral superior rectus and contralateral inferior oblique muscles, that is, the antagonists of the muscles connected to the PC. When the patient returns to the sitting position, we expect to see a less intense nystagmus in the opposite direction, i.e., upbeating, with the torsional component directed such that the upper pole of the eyes beats away from the affected ear. The latency and duration of PN should be similar to those for PC-BPPV.

The above-described clinical pattern matches typical AC-BPPV, which is rarely seen in clinical practice. The AC is located in the higher portion of the labyrinth and it is unlikely that particles enter it unless the patient is upside-down. In any case, the condition should be short-lived, because the posterior arm of the AC descends directly into the common crus and particles should leave the canal when the patient is upright. Nevertheless, the incidence of the AC variant of BPPV has been reported to account for 2% (Korres et al., 2002) to 20% of all BPPV patients and to be even more frequent than LC-BPPV (Jackson et al., 2007). Indeed, patients presenting with atypical PN have been attributed to the AC, but other possibilities must be considered (see below). AC cupulolithiasis has not been documented (Büki et al., 2014; von Brevern et al., 2015). If it exists, the characteristics of evoked nystagmus should be the same as canalolithiasis of AC, but more persistent and less intense (see section on pDBN, below).

ATYPICAL CLINICAL FEATURES OF BPPV

In most patients, PN is typical and its pathophysiology can be reasonably understood. However, there are clinical findings that, although still in the context of BPPV, are more difficult to explain and are often very speculative.

Spontaneous nystagmus

On several occasions, the possibility of a persistent spontaneous nystagmus in LC-BPPV has been described. It is not influenced by gravity and does not change its direction with positional maneuvers. It must be differentiated from "pseudo-spontaneous" nystagmus, which is instead

modulated by movements on the sagittal and horizontal plane. Spontaneous nystagmus is attributed to jamming of the particles within a narrow segment of the LC (canalith jam or functional plugging). This event would provoke a negative or positive endolymph pressure and persistent deflection of the cupula. It often follows therapeutic procedures and more frequently affects the lateral canal, thereby provoking horizontal nystagmus. If nystagmus occurs spontaneously, with no relationship to diagnostic or therapeutic maneuvers, it is difficult to differentiate it from spontaneous nystagmus of vestibular neuritis because functional plugging of the canal can also lead to a reversible caloric paresis (Epley, 1995; von Brevern et al., 2001).

Direction-fixed positional nystagmus

This is a similar and equally rare form of LC-BPPV characterized by a PN that does not reverse its direction when the supine roll test is performed. For example, it is apogeotropic with the left ear down and geotropic with the left ear up. It is usually more intense on one side. This phenomenon has been attributed to a combination of events: simultaneous presence of masses of different density, or dimensions in the same canal and entrapment of the largest ones in the narrower part of the canal. The diagnosis of LC-BPPV is confirmed by the subsequent transformation into typical LC-BPPV (direction-changing PN), obtained with repetitive movements in the sagittal or horizontal plane (Califano et al., 2013).

Multiple-canal BPPV

The simultaneous involvement of multiple canals is possible, especially after head trauma. The most frequent finding is PN with horizontal and torsional components of similar magnitude evoked by the Dix–Hallpike test (Aw et al., 2005). Otherwise we can find, in the same session, a typical torsional-vertical PN with the Dix–Hallpike maneuver on one side and a horizontal direction-changing PN with the supine roll test (Bertholon et al., 2005). Any simultaneous combination of multiple canal involvement may also occur, but is very rare. However, not so rare is the phenomenon of "canal switch" when, during head movements and especially diagnostic and therapeutic maneuvers, debris exits out of a canal and enters another one.

Positional downbeating nystagmus

A remarkable number of patients are affected by pDBN, which is reasonably of labyrinthine origin but does not fit with the theory of AC canalolithiasis. In fact, in many patients, both Dix–Hallpike maneuvers and the straight-head-hanging positioning reveal a purely vertical PN, relatively sustained, and of low intensity. Very often, the nystagmus does not reverse its direction when the patient is returned to the sitting position, in spite of substantial vertigo or unsteadiness. Many of these patients were previously affected or will develop a typical PC-BPPV. The course of the syndrome, often characterized by a rapid and spontaneous remission, is benign and no central nervous system involvement is found at prolonged follow-up (Cambi et al., 2013). Moreover, the symptomatology is quite different from that of typical BPPV, often being characterized by fluctuating/intermittent dizziness and instability, which start in the morning and are worsened by head movements on the pitch axis. In these patients, AC involvement is possible, but other pathophysiologic mechanisms must also be considered. If pDBN is due to BPPV, it must arise from inhibition of the PC (ampullopetal movement) or excitation of the AC (ampullofugal movement).

Many hypothetic options have been proposed. One possibility is that the otoconial debris does not reach the bottom of the PC and, for some reason, is held in the distal portion with respect to the ampulla (perhaps due to the amount of debris and its relationship to the size of the lumen or the structure of the walls of the canal). The Dix–Hallpike maneuver could cause the debris to move in the ampullopetal direction, analogous to the apogeotropic PN of the LC. The nystagmus needs not change direction on sitting up if the particles are in the part of the posterior semicircular canal that is horizontal to the ground (Vannucchi et al., 2012). Debris could also be located in the short arm of the PC, causing deflection of the cupula due to debris falling into the utriculus, while the vertigo related to sitting up may be caused by debris falling back on to the cupula (Cambi et al., 2013). This is also one of the theories invoked to justify BPPV without PN (Büki et al., 2011). Furthermore, the possibility of an AC cupulolithiasis and also of a PC cupulolithiasis has been reported if the angular attachment of the cupula is different and the Dix–Hallpike maneuver is performed more deeply. However, all of these thought-provoking hypotheses cannot be proven. For more details on this topic, see Büki et al. (2014).

DIFFERENTIAL DIAGNOSIS

Positional vertigo is sometimes caused by structural lesions of the central vestibular system. These are usually excluded by the absence of neurologic signs and symptoms, but some cases are challenging. A careful examination of eye movements, including provocative vestibulo-ocular maneuvers such as head shaking, mastoid vibration, Valsalva, and hyperventilation, will often reveal "atypical features," prompting further investigation.

The two most common forms of BPPV, that is, typical PC-BPPV and LC-BPPV with geotropic paroxysmal PN, should almost never be confused with other lesions and rarely require further investigations. There are, however, rare reports of posterior canal-like PN presenting as a sign of a central lesion, though careful reading of the clinical descriptions of both symptoms and signs almost always reveals a "red flag" pointing to a central process. A re-evaluation is required when the patient is not cured despite many attempts with therapeutic maneuvers.

More attention must be given to two types of PN, since these are quite often reported in central mimics: horizontal apogeotropic PN and downbeating PN (Lee and Kim, 2010). Horizontal apogeotropic PN can be "dangerous" when it is not paroxysmal, persistent, not accompanied by vertigo and, mainly, when it fails to reverse its direction or to resolve with appropriate maneuvers or positions. A central lesion can cause pDBN when it is purely vertical, not associated with autonomic symptoms, and especially if there is no lessening of symptoms and nystagmus intensity by repeating the provoking maneuvers (Bertholon et al., 2002). As previously mentioned, pDBN quite often follows a typical PC-BPPV and disappears after a few days. When in doubt, a careful imaging of the posterior fossa should look for small lesions of the nodulus or cerebellar peduncle (Lea et al., 2014).

Since LC-BPPV may present with spontaneous or "pseudo-spontaneous" nystagmus, differentiation from acute unilateral vestibular loss is mandatory. Every patient with horizontal unidirectional spontaneous nystagmus should therefore be tested with the Bow and Lean Test and with the supine roll test to look for direction-changing PN. In fact, about 20% of patients with acute vertigo and spontaneous nystagmus in the sitting position are actually affected by LC-BPPV rather than vestibular neuritis (Asprella Libonati, 2014).

BPPV must also be differentiated from vestibular migraine (VM), an increasingly recognized cause of episodic positional vertigo. First of all, the duration of the symptomatic period is quite different: hours to days in VM patients, weeks to months in BPPV patients, if not treated (von Brevern et al., 2004a). The single episode of vertigo is usually intense and short-lasting (seconds) in typical BPPV, less intense and longer-lasting in VM patients. In contrast with BPPV, headache, photophobia, and phonophobia are very often complained of by migraine sufferers in combination with vertigo episodes. PN is the most frequent finding in the few patients seen during an acute episode of VM (Polensek and Tusa, 2010), as an isolated sign or in combination with spontaneous nystagmus (von Brevern et al., 2005). It is persistent and with low velocity of its slow phase, being difficult to detect without removing visual fixation. Conversely, typical PN in BPPV is often so strong that it can be easily seen without Frenzel glasses. PN in VM is more often horizontal, geotropic or apogeotropic, but direction-fixed, that is, it does not reverse its direction when the supine head roll test is performed. In most patients, it persists as long as the precipitating head position is maintained and is not removed or modified by physical treatment. In a small number of VM patients, PN is torsional, upbeating, or downbeating. Therefore, the most difficult differential diagnosis is probably in patients with atypical BPPV, namely those with pDBN. As already mentioned in this chapter, pDBN probably due to canalolithiasis of the vertical canals is vertical or vertical-torsional, relatively sustained, of low intensity, and very often does not reverse its direction when the head position is changed. These features correspond also quite well with those arising from a dysfunction of the central vestibular structures, like those of VM. The differential diagnosis is again helped by the presence or absence of migraine accompanying symptoms and other oculomotor signs. Moreover, pDBN of BPPV is often fatigable and many patients have already received a diagnosis of typical BPPV in the past.

TREATMENT OF BPPV

The therapy of BPPV is based on physical maneuvers and positions that are incredibly and immediately effective in most patients. When they are effective, they also serve to confirm the diagnosis and pathophysiology. The aim of physical therapy is to dislodge the otoconial debris from the semicircular canals. Therefore, it is mainly useful in patients with canalolithiasis. Therapies for PC- and LC-BPPV have been validated. On the other hand, an effective treatment for the AC variant of BPPV is still elusive.

Drugs are not indicated in BPPV, except to relieve symptoms at the beginning of the disease or during the treatment maneuvers. Surgical section of the nerve to the posterior semicircular canal and occlusion of the posterior semicircular canal have been performed, though rarely.

Physical treatment is really effective in resolving the acute phase of the disease, but does not prevent relapses. Since migraine could be a risk factor, prevention with antimigrainous drugs could be useful in patients with migraine and recurrent BPPV. Supplementation with vitamin D has been proposed, especially in women in menopause with recurrent BPPV, given the prevalence of vitamin D deficiency. These two treatments are rather speculative approaches which may be recommended in the future only when controlled trials prove their efficacy.

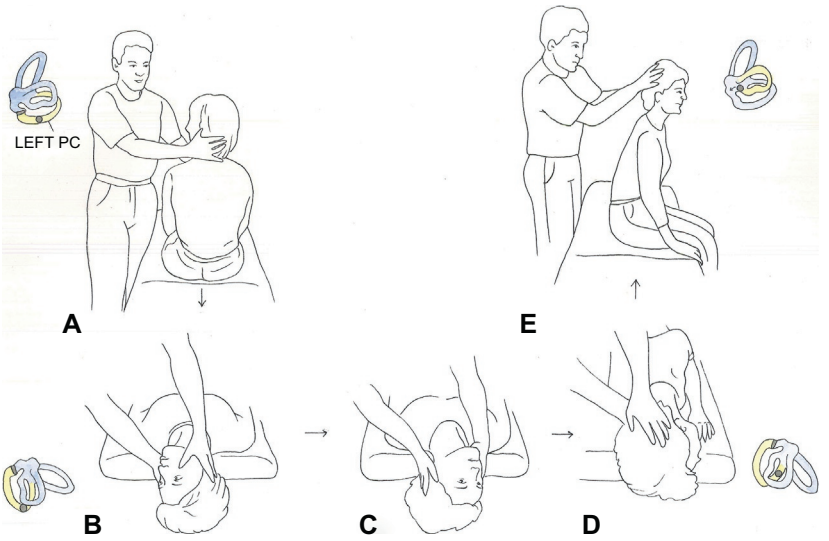

Fig. 18.4. Canalith-repositioning procedure (Epley maneuver) for left posterior semicircular canal (PC) benign paroxysmal positional vertigo. (**A**) The patient is in the sitting position and the head is turned 45° to the left. (**B**) The patient is moved into the left Dix–Hallpike position (head hyperextended). In this position, particles gravitate toward the center of the PC. (**C**) After about 30 seconds, the head is rotated 90° rightward, maintaining the hyperextension. This movement should provoke progression of debris toward the common crus. (**D**) The head and shoulders are rotated rightward another 90° until the head is face down. With this movement, particles should cross the common crus. (**E**) The patient is returned to the sitting position and then the head is turned forward and slightly tilted about 20° down. In this way, debris should enter the utricle.

Physical treatment of PC-BPPV

PC-BPPV is treated by Epley's canalith-repositioning procedure (CRP) or Semont's liberatory maneuver (Semont et al., 1988).

Canalith-repositioning procedure

The purpose of the CRP is to allow free canaliths to migrate under gravity out of the posterior canal through the common crus (Epley, 1992). The treatment consists of a series of five movements to different positions beginning with the examiner facing or standing behind the patient seated on the bed. For right BPPV, the head is rotated 45° to the right and the body moved supine with the head over the end of the table (position 1 –the same position as with diagnostic Dix–Hallpike). This position would cause canaliths to gravitate toward the center of the posterior canal. The head is then rotated 90° leftward, while maintaining neck hyperextension, until the head reaches a 45° left position (position 2). In this way, the canaliths should approach the common crus. The head and body are further rotated leftward 90° so the patient is lying on his or her left side with the head at 135° with respect to the supine position (almost looking at the floor). This third position would cause the canaliths to cross the common crus. The patient is then brought up to the sitting position with the head kept turned to the left, so that the canaliths enter the utricle (position 4). Finally, the head is turned forward with the chin down at 20° (position 5) (Fig. 18.4). The five-position cycle should provoke a nystagmus that reflects the direction in which the canaliths move. Every position is held until the nystagmus subsides, which typically takes 6–13 seconds in each position. The cycle is repeated until no nystagmus is observed. A vibrator can be applied to the ipsilateral mastoid area during at least one positioning cycle, to dislodge canaliths that might be adherent to the canal wall. Various modifications have been proposed to simplify Epley's original method, obtaining similar results in most cases (Herdman et al., 1993).

Semont's liberatory maneuver

The liberatory maneuver is a simplified version of the original treatment suggested by Semont et al. (1988). Once the affected ear has been identified with the Dix–Hallpike test, the examiner stands in front of the patient, who is seated on the side of the examining table. For right BPPV, for example, the patient's head is rotated 45° to the left, and then the patient is brought so as to lie on his or her right side, with the back of the head resting on the table. This position, also known as "side lying," or the Semont diagnostic position, is similar to the Dix–Hallpike diagnostic test and must provoke the typical vertical-torsional nystagmus caused by movement of otoconia away from the ampulla. The patient is maintained in this position for about 2 minutes and is then quickly swung 180° on to the opposite side (in a

cartwheel), maintaining the head in the same position relative to the shoulders. At the end, the patient is in the liberatory position, i.e., lying on the left shoulder with the cheekbone and nose in contact with the bed. The liberatory maneuver provokes acceleration in the plane of the PC and should provoke the exit of debris from the canal into the utricle by centrifugal inertia. The acceleration acting on the canal is important, so the duration of the swing must not exceed 1.5 seconds (Faldon and Bronstein, 2008). If too slow, the debris might fall back in the wrong direction. The expected response to the liberatory maneuver is another episode of intense vertigo and paroxysmal nystagmus with the same direction of rotation as in the provoking right Dix–Hallpike position, which is due to the movement of debris in the ampullofugal direction, toward the utricule. This is called the liberatory nystagmus and is therefore a good prognostic sign; its absence is almost always a sign that the maneuver has been unsuccessful (Nuti et al., 2000).

Since the latency of liberatory nystagmus can also be long, the patient is held in the liberatory position for at least 1 minute and then slowly returned to the sitting position with the head bent slightly forward. In this final position, neither nystagmus nor vertigo should appear. If the liberatory maneuver did not lead to liberatory nystagmus, the vertigo and nystagmus may recur when the patient is returned to the sitting position. The direction of nystagmus will be in the opposite direction to that seen in the provoking position and it can be considered a reverse nystagmus due to ampullopetal movement of otoconia back into the canal.

An evidence-based review by the American Academy of Neurology considered CRP to be an effective and safe therapy to be offered to patients of all ages with PC-BPPV (Fife et al., 2008; von Brevern et al., 2006). A class I study on the short-term efficacy of Semont's maneuver (Mandalà et al., 2012) indicated that the efficacy of both treatments is similar, with remission rates of 80–90%. Posttraumatic BPPV is significantly more difficult to treat and recurrences are significantly more common. However, outcome is good with repeated therapeutic maneuvers (Gordon et al., 2004). Complementary self-treatment at home can be suggested in case of failure of repeated maneuvers (https://www.youtube.com/watch?v=pa6t-Bpg494).

Physical treatment of LC-BPPV

LC-BPPV is also treated by physical maneuvers or positions with the aim of allowing the exit of otoconial debris under centrifugal inertia or gravity. The success of the treatment also depends on the correct identification of the affected ear, which is sometimes difficult because there may be no clear difference in the nystagmus intensity between the two sides. A wrong diagnosis can cause the otoconia to move in the wrong direction, transforming a geotropic into an apogeotropic nystagmus. Many treatments have been proposed, beginning with the barbecue rotation by Lempert (1994). In the authors' opinion, the most effective treatments for LC-BPPV with the geotropic variant are the forced prolonged position, Gufoni's maneuver, or a combination of the two.

Gufoni's maneuver

This is a liberatory maneuver conceived by Gufoni et al. (1998). When successful, it clears the labyrinth immediately. From the sitting position, with the head straight, the patient is quickly brought laterally to the healthy side and then the head is turned about 45° down, so that the nose is in contact with the bed. It is advisable to create a good deceleration as the head makes contact with the bed (Fig. 18.5). After 2 minutes in this position, the patient is returned to the upright position. The treatment should allow the particles to exit the canal under the centrifugal force created by the rapid deceleration, and by gravitation, when the head is maintained with the nose down. The maneuver should be repeated two or three times sequentially. Gufoni's treatment is a good option when the patient is moderately tolerant to vertigo. Its effectiveness was recently validated in randomized double-blind studies (Kim et al., 2012b; Mandalà et al., 2013).

Forced prolonged position

Devised by Vannucchi et al. (1997), this is a very simple and well-tolerated method that allows debris to exit the canal under gravitation. Once the pathologic side has been identified, the patient is simply instructed to lie in a supine position, then to turn on to the side of the healthy ear and to stay in this position for as long as possible, all night if possible. In this way, otoconial debris can exit the canal under gravity. This is particularly useful in patients with severe autonomic symptoms, in older people, and in obese patients or those with significant mobility limitations. Even with this method, the results are very good, with a remission rate ranging from 75% to 90% (Nuti et al., 1998; Vannucchi et al., 2005).

Treatment of apogeotropic LC-BPPV

In patients with apogeotropic PN, one option is to convert the PN into the more treatable geotropic variant, by changing the position of debris in the canal. For this purpose, it is necessary to perform Gufoni's maneuver first on the affected side. The outcome of the maneuver is verified after 30 minutes by repeating the supine head roll test. If the PN has changed its direction, becoming

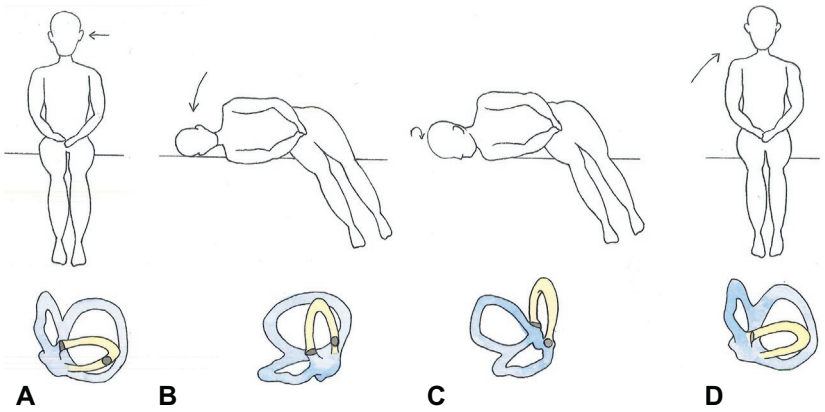

Fig. 18.5. Gufoni's maneuver for left lateral canal (LC) benign paroxysmal positional vertigo in the geotropic form. (**A**) Patient in the sitting position and debris located in the middle of the LC. (**B**) The patient is moved to the right healthy side, without changing head position relative to the shoulders. The maneuver is rapid and with deceleration as the head makes contact with the bed. With this movement, debris should move away from the ampulla. (**C**) After a few seconds, the head is rotated about 45° down to favor the exit of debris from the canal, by gravitation. (**D**) After about 2 minutes, the patient is returned to the sitting position. The maneuver can be repeated three times.

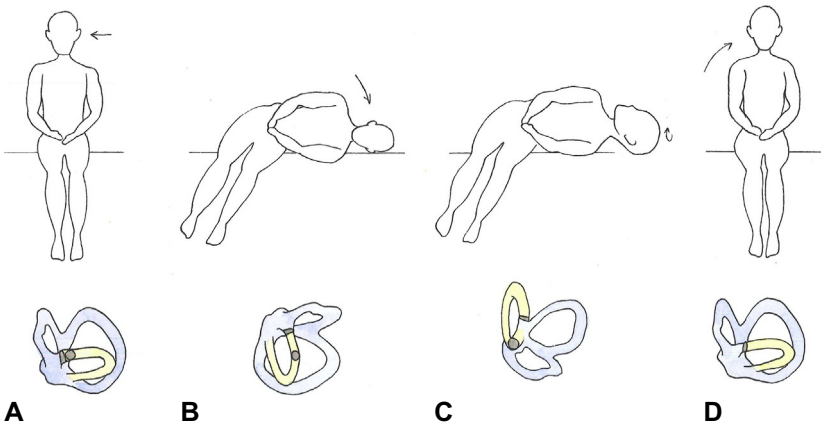

Fig. 18.6. Modified Gufoni's maneuver for left lateral canal benign paroxysmal positional vertigo in the apogeotropic form. (**A**) Patient in the sitting position and debris located close to ampulla or on the cupula. (**B**) The patient is rapidly moved to the left affected side, without changing the head position relative to shoulders. With this movement debris should move away from the ampulla. (**C**) After a few seconds the head is rotated about 45° up to favor the exit of debris from the canal. (**D**) After about 2 minutes the patient is returned to the sitting position.

geotropic and more intense with the affected ear down, the treatment will be repeated on the healthy side, patient compliance permitting. After adopting the forced prolonged position, we suggest that the patient sleeps for one night on the affected side and the following night on the opposite side. There are no controlled studies on this topic, but the authors' experience is in agreement and corroborates the canalolithiasis hypothesis, since it is unlikely that debris can detach from the cupula simply by gravity. There is also the possibility of a one-step treatment with a modified Gufoni's maneuver, as suggested by Kim et al. (2012a). The maneuver is performed on the affected ear and the patient's head is turned 45° upward instead of down (Fig.18.6).

Physical treatment of AC-BPPV

Many physical procedures have been proposed for the treatment of AC-BPPV, with the aim of dislodging canaliths from the canal. Since one AC is roughly coplanar with the PC on the opposite side, a "reverse" Epley's maneuver, starting from the healthy side, seems to be logical (Honrubia et al., 1999). Excellent results are also reported with Epley's maneuver starting from the affected side (Jackson et al., 2007). Yacovino et al. (2009), following the suggestion of Crevits (2004), proposed a maneuver that has the advantage of not requiring identification of the affected side. It is in four stages with 30-second intervals: the patient is first brought from the

sitting position to the supine head-hanging position; then, with the patient still supine, the head is tilted forward so that the chin is in contact with the chest; finally, the patient returns to the sitting position. The efficacy of this kind of treatment has been confirmed (Casani et al., 2011). Other physical treatments have been proposed for AC-BPPV (for a review, see Korres et al., 2010) but, at present, no controlled studies are available, and in our experience, their effectiveness is sometimes questionable also, considering that in about 50% of patients with pDBN, there is a spontaneous remission within a few days, without any specific treatment (Cambi et al., 2013). Home treatment with maneuvers similar to the well-known Brandt–Daroff exercises (Brandt and Daroff, 1980) and frequent checks are probably the best suggestion we can give to patients with AC-BPPV.

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Chapter 19

Menière's disease

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Abstract

Menière's disease (MD) is a chronic multifactorial disorder of the inner ear characterized by episodic vestibular symptoms associated with sensorineural hearing loss, tinnitus, and aural pressure. Epidemiologic and genomic evidence supports a genetic susceptibility with multiple biochemical pathways involved, including the endocrine system, innate immune response, and autonomic nervous system. Allergens, infectious agents, vascular events, or genetic factors could modify inner-ear homeostasis and trigger MD. The diagnosis of MD is based on clinical criteria and requires the observation of an episodic vertigo syndrome associated with low- to medium-frequency sensorineural hearing loss and fluctuating aural symptoms (hearing loss, tinnitus, and/or fullness) in the affected ear. Headache is also found during the attacks and bilateral involvement is found in 25–40% of cases. Audiologic and vestibular assessment is recommended to monitor the clinical course. The treatment of MD is symptomatic to obtain relief of vestibular episodes and preventive to limit hearing loss progression. Treatment options include sodium restriction, betahistine, intratympanic gentamicin, or steroids and eventually surgery, such as cochlear implantation.

DEFINITION

Menière's syndrome is a chronic inner-ear disorder characterized by recurrent episodes of spontaneous vertigo and fluctuating unilateral sensorineural hearing loss (SNHL), tinnitus, and aural fullness. When this set of symptoms cannot be attributed to a specifically identified cause, the syndrome is considered idiopathic and then it is referred to as Menière's disease (MD).

The diagnostic criteria for MD have been jointly formulated by the Classification Committee of the Bárány Society, the Japan Society for Equilibrium Research, the European Academy of Otology and Neurotology (EAONO), the Equilibrium Committee of the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS), and the Korean Balance Society. The classification includes two categories: definite MD and probable MD (Table 19.1). The diagnosis of definite MD is based on clinical criteria and requires the observation of an episodic vertigo syndrome associated with low- to medium-frequency SNHL and fluctuating aural symptoms (hearing loss, tinnitus, and/or fullness) in the affected ear. The episodes of vertigo have a duration of between 20 minutes and 12 hours. Probable MD is a broader concept, defined by episodic vestibular symptoms (vertigo or dizziness) associated with fluctuating aural symptoms occurring in a period from 20 minutes to 24 hours (Lopez-Escamez et al., 2015).

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Table 19.1

Diagnostic criteria for Menière's disease

Definite Menière's disease
A. Two or more spontaneous episodes of vertigo, each lasting 20 minutes to 12 hours
B. Audiometrically documented low- to medium-frequency sensorineural hearing loss in the affected ear on at least one occasion before, during, or after one of the episodes of vertigo
C. Fluctuating aural symptoms (hearing, tinnitus, or fullness) in the affected ear
D. Not better accounted for any other vestibular diagnosis
Probable Menière's disease
A. Two or more spontaneous episodes of vertigo, each lasting 20 minutes to 12 hours
B. Fluctuating aural symptoms (hearing, tinnitus, or fullness) in the affected ear
C. Not better accounted for any other vestibular diagnosis

Reprinted from Lopez-Escamez JA, Carey J, Chung WH, et al. (2015). Diagnostic criteria for Menière's disease. J Vestib Res 25:1–7 with permission from IOS Press. Available at IOS Press through http://dx.doi.org/10.3233/VES-150549.

EPIDEMIOLOGY

Although MD is considered the third most common cause of vertigo after benign paroxysmal positional vertigo and vestibular migraine (VM), it is a rare disease in the general population. The occurrence varies broadly according to the applied diagnosis criteria, source of data, and geographic and ethnic variables.

Depending on the studies, the incidence of MD ranges from 8.2 to 157 per 100 000 individuals per year (Cawthorne and Hewlett, 1954; Stahle et al., 1978; Celestino and Ralli, 1991). The prevalence of MD ranges from 3.5 per 100 000 inhabitants in Japan to 513 per 100 000 in Finland (Okafor, 1984; Wladislavosky-Waserman et al., 1984; Watanabe et al., 1995; Kotimäki et al., 1999; Havia et al., 2005; Harris and Alexander, 2010; Tyrrell et al., 2014). MD is more common in Caucasians than in other populations such as Japanese or Native Americans (Wiet, 1979; Ohmen et al., 2013).

Children are rarely affected since the disease commonly begins in the fourth or fifth decade of life, and the prevalence increases with increasing age (Stahle et al., 1991; Lee et al., 1995; Tokumasu et al., 1996; Ballester et al., 2002; Havia et al., 2005; Shojaku et al., 2005; Harris and Alexander, 2010).

There seems to be a slight female predominance, although the female:male ratio varies broadly among series (Stahle et al., 1991; Lee et al., 1995; Havia et al., 2005; Shojaku et al., 2005). No difference exists in the ratio of right to left ear. Also the proportion of patients with bilateral MD involvement increases with duration of illness (Vrabec et al., 2007; Huppert et al., 2010). Bilateral MD has been reported in 25–40% of affected individuals (House et al., 2006). Bilateral MD is associated with increased vestibular symptoms and has a negative impact on health-related quality of life (Lopez-Escamez et al., 2009).

MD patients suffer from other disorders that are considered MD comorbidities. These include allergic and autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, and ankylosing spondilytis (Derebery and Berliner, 2010; Derebery, 2011; Gazquez et al., 2011; Tyrrell et al., 2014). Several authors have found a high prevalence of migraine in patients with MD as compared to age- and sex-matched controls (Radtke et al., 2002; Shin et al., 2013). It seems that migraine is more common in patients with MD whose family history includes episodic vertigo (Cha et al., 2007).

When at least one first- or second-degree relative fulfills criteria for MD, familial MD (FMD) is diagnosed. Family history is observed in 5–15% of sporadic cases in populations of European descent (Morrison et al., 2009; Vrabec, 2010; Hietikko et al., 2013; Requena et al., 2014). An autosomal-dominant pattern of inheritance with incomplete penetrance is commonly found, although genetic heterogeneity has been described in FMD (Requena et al., 2014). A family history of migraine or SNHL, isolated or as a part of an episodic vestibular syndrome, is also observed in some cases, suggesting an incomplete phenotype (Requena et al., 2014).

ETIOLOGY AND PATHOPHYSIOLOGY

Human temporal bone studies have linked MD symptoms to the accumulation of endolymph within the cochlear duct (scala media) and the sacculus in the inner ear. It is believed that this endolymphatic hydrops (EH) begins with a disturbance of the ionic composition of the scala media. However, current data support the hypothesis that EH is an epiphenomenon associated with a variety of inner-ear disorders (Merchant et al., 2005), and that genetics and environmental factors contribute to its development (Fig. 19.1). So, food or respiratory allergens, infectious agents, vascular events, or genetic factors could trigger an imbalance in inner-ear homeostasis. Several regulatory factors, such as the innate immune response, the endocrine system, or the autonomic nervous system, may also influence the development of the partial or complete phenotype observed in familial MD (Requena et al., 2014). The cumulative effect of one or several triggers and the individual response may explain the clinical heterogeneity observed in MD phenotype.

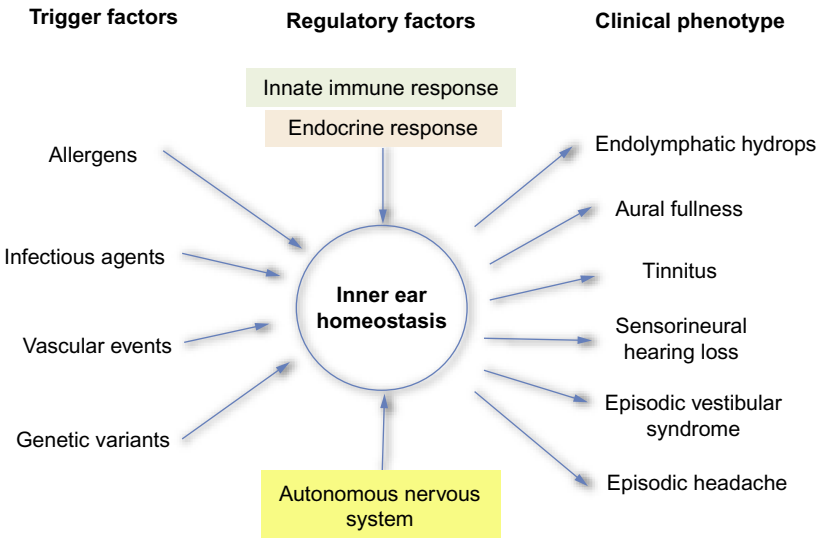

Fig. 19.1. Core hypotheses for Menière's disease. Multiple genetic or environmental factors could challenge inner-ear homeostasis and trigger a partial or a complete clinical phenotype, depending on the individual susceptibility, according to several regulatory factors such as the inmate immune response, the endocrine system, and the autonomic nervous system. (Modified after Merchant et al., 2005.)

Epidemiologic and genomic evidence supports each of the three major hypotheses regarding etiology of MD: allergy, autoimmunity, and genetic factors. Furthermore, one or more suspected environmental factors may trigger the disease.

Allergy

Among cross-sectional surveys, the prevalence of diagnosed allergy was three times higher in those with a history of MD compared with the general population (Derebery, 2000). Among patients with MD, 58% had a history of allergy and 41% had a positive skinprick test (Derebery, 2000), and 43% of patients had elevated levels of immunoglobulin E compared with controls (Keles et al., 2004). Derebery and Berliner (2010) proposed that allergic inflammation affects the endolymphatic sac in patients with MD. Although the evidence of a causal association between allergy and MD is not demonstrated, a food or seasonal allergy should be considered as a trigger of MD and treated (Weinreich and Agrawal, 2014).

Autoimmunity

Autoimmune inner-ear disease and MD may have an overlapping phenotype and several immune mechanisms are probably involved in the pathophysiology of MD. Some evidence supports this hypothesis, including the response to steroid therapy, the finding of elevated levels of autoantibodies or circulating immune complexes against inner-ear antigens in the serum of some patients with MD (Kim et al., 2014), and the association of allelic variants of MICA, TLR10, and NFKB1 genes with hearing loss progression in patients with MD (Gazquez et al., 2012; Requena et al., 2013; Cabrera et al., 2014).

Although preliminary candidate gene studies found that bilateral MD was associated with allelic variants of human leukocyte antigen (HLA) genes (Lopez-Escamez et al., 2002) or PTPN22 (Lopez-Escamez et al., 2010), these findings have not been formally replicated. Different studies suggest the role of innate immune response in the hearing outcome of autoimmune inner-ear disease (Pathak et al., 2011; Svrakic et al., 2012) and MD (Requena et al., 2013; Cabrera et al., 2014; Kim et al., 2014). Several mechanisms may explain the development of an immune-mediated inner-ear disease: (1) cross-reactions with a cross-reactive epitope (antibodies cause accidental inner-ear damage because the ear shares epitopes with a potentially harmful substance, virus, or bacterium) as suspected for some inflammatory diseases (Platt et al., 2013); (2) damage to the inner ear caused by proinflammatory cytokines such as interleukin-1β (Pathak et al., 2011; Zhao et al., 2013) or tumor necrosis factor (Svrakic et al., 2012), as in some autoimmune diseases; or (3) inappropriate immune response or intolerance to harmless unrecognized substances combined with genetic factors that modify the immune response as in allergies (Greco et al., 2012). These findings, together with the elevated prevalence of several autoimmune diseases, point to autoimmunity in MD (Gazquez et al., 2011; Tyrrell et al., 2014).

Genetic bases of MD

Several lines of evidence support a genetic susceptibility for MD. First, familial clustering was observed in MD in Finland and Spain, and the sibling recurrence risk ratio is 45 times higher compared to the general population (Hietikko et al., 2013; Requena et al., 2014). Although linkage studies were performed in several multicase families with MD (Klar et al., 2006; Gabriková et al., 2010; Arweiler-Harbeck et al., 2011) and a locus at 12p12.3 was defined in Swedish families (Gabriková et al., 2010), no single gene was associated with familial MD. Remarkably, Requena et al. (2015) have identified the first two disease-causing mutations in FAM136A and DTNA genes by whole-exome sequencing. These mutations segregated MD phenotype in a family with an autosomal-dominant inheritance pattern in three affected women in consecutive generations showing anticipation. Most cases of FMD have an autosomal-dominant pattern of inheritance, but genetic heterogeneity is observed with suspected mitochondrial and recessive pattern (Requena et al., 2014). A second line of evidence for a genetic predisposition to MD comes from candidate gene studies. Although no consistent association has been replicated (Gazquez and Lopez-Escamez, 2011; Hietikko et al., 2012), allelic variants in MICA (Gazquez et al., 2012), TLR10 (Requena et al., 2013), and NFKB1 genes (Cabrera et al., 2014) influence hearing loss progression in MD. Finally, the clear predilection of the disease for Caucasians over other ethnicities also supports a genetic component (Ohmen et al., 2013).

CLINICAL MANIFESTATIONS

Numerous factors have been alleged to precipitate an MD attack, including stress, sleep deprivation, some food, allergens, barometric pressure change, and hormonal changes (menses) (Andrews and Honrubia, 2010).

The occurrence of recurring episodes of spontaneous vertigo is the main feature of MD and it is present in 96.2% of patients (Paparella and Mancini, 1985). Vertigo is the most disabling symptom, commonly described as spinning, exacerbated by head movements, and accompanied by nausea, vomiting, and sweating. Spells of vertigo last several hours, and when they subside patients complain of unsteadiness for several days. These spells are often preceded by tinnitus, aural fullness, and a decrease in hearing in the affected ear. Some patients report sudden falls with no previous warning or provocative factor, and without vertigo, loss of consciousness, or other neurologic symptoms. These episodes are named otolithic crises of Tumarkin. The occurrence of these vestibular drop attacks is variable, although some series report up to 72% (Kentala et al., 2001; Morales-Angulo and Gallo-Terán, 2005; Pérez-Fernandez et al., 2010).

Hearing loss is associated with vertigo attacks in 77% of patients (Lopez-Escamez et al., 2014). It is fluctuating in the first years, in the sense that it is episodic and reversible after the crisis has subsided. Nevertheless, as the disease progresses, hearing worsens with each crisis and it does not return to the previous level. Eventually, deafness becomes permanent and no longer fluctuates. Lermoyez's syndrome is a rare phenomenon in some patients with MD. It consists of a transient improvement of hearing during the onset of a vertigo attack. Tinnitus may also improve.

Some patients report a previous history of hearing loss, often since childhood, preceding the onset of the episodes of vertigo. This variant is named delayed MD (Lopez-Escamez et al., 2015).

Tinnitus may be the initial symptom of MD, preceding the full picture by months. It is commonly described as low-pitched, as a harsh, roaring, machine-like sound or a hollow seashell sound. At the onset of the disease, tinnitus is intermittent and appears during the attacks in 83% of patients and disappears afterward (Lopez-Escamez et al., 2014). As the attacks recur, tinnitus also becomes permanent between episodes, although its intensity may increase or the tone may change before or during the episodes. Typically, patients mention that this change in their tinnitus warns them the attack is coming. At the late stages, when the episodes of vertigo have disappeared, tinnitus becomes a prominent symptom that may cause a significant impairment in quality of life.

Aural fullness is variable and more than 20% of patients never experience it (Levo et al., 2014; Lopez-Escamez et al., 2014). The sensation is described as a feeling of pressure in the ear similar to that observed when descending to land in an airplane. It commonly disappears as the disease progresses. Hyperacusis and diplacusis are also reported in patients with MD.

Brantberg and Baloh (2011) found that 68% of patients with MD described two or more of the three characteristic auditory symptoms (unilateral hearing loss, unilateral tinnitus, and unilateral aural fullness) during at least half of the vertigo spells.

Headache occurs in 41% of Menière's attacks and migraine-type headache occurs in 8% of patients during episodes of vertigo (Lopez-Escamez et al., 2014). However, headache is not considered a diagnostic criterion for MD.

Disease begins with the three classic symptoms in only 40% of patients (Belinchon et al., 2012). It is not uncommon that recurrent episodes of vertigo without auditory symptoms, or fluctuating hearing loss with or without tinnitus precede the characteristic triad of recurrent vertigo, hearing loss, and ipsilateral tinnitus by

months. The time delay between hearing loss and vertigo may be more than 5 years in 20% of MD patients (Pyykkö et al., 2013). However, most patients develop the full picture within the first year.

The number of episodes of vertigo decreases during follow-up, and about 70% of patients who do not present with an episode of vertigo for 1 year will continue to be free of episodes during the following year (Pérez-Garrigues et al., 2008). The frequency of episodes of vertigo shows a rapid decline over the first 8–9 years, and subsequently stabilizes over the following 10 years before declining gradually (Green et al., 1991; Stahle et al., 1991; Pérez-Garrigues et al., 2008).

The presence of vestibular abnormalities on bedside examination is well recognized in MD. Head-shaking nystagmus and vibration-induced nystagmus are common vestibular signs in patients with MD (Marques and Perez-Fernandez, 2012; Neff et al., 2012). Three or more beats of spontaneous nystagmus or the presence of nystagmus for at least 5 seconds after vigorous head shaking is considered as abnormal. Spontaneous nystagmus is often absent between relapses, although a horizontal-torsional nystagmus may be observed during an attack. Classically it has been described as a first irritating phase with nystagmus beating toward the affected ear, a second paretic phase with the nystagmus beating toward the opposite ear, and a final recovery phase in which again nystagmus beats toward the pathologic ear. Thus, nystagmus direction varies, beating either toward the affected ear or the healthy ear, so it cannot be considered a localizing finding. Positional nystagmus can be found either during or between attacks, although the frequency varies widely among different series (Hulshof and Baarsma, 1981; Dobie et al., 1982). The head impulse test (HIT) yields positive results in less than half of MD patients.

Vestibulospinal function tests are consistent with a peripheral vestibular syndrome: falling or deviation toward the side of the lesion is commonly observed in the Romberg test with eyes closed and during tandem walking.

DIAGNOSIS

The diagnosis of MD is based on clinical criteria, since there is no biologic marker. The traditional criteria were established by the Committee on Hearing and Equilibrium of the AAO-HNS (1995), and have been widely used for the last 20 years (Table 19.2). The current diagnostic criteria have been developed by consensus among the Bárány Society, the Japan Society for Equilibrium Research, the EAONO, the AAO-HNS, and the Korean Balance Society as part of the International Classification of Vestibular Disorders (Table 19.1).

Table 19.2

Menière's disease diagnostic scale

Certain Menière's disease
Definitive Menière's disease plus histopathologic confirmation
Definite Menière's disease
Two or more definitive spontaneous episodes of vertigo lasting 20 minutes or longer
Audiometrically documented hearing loss on at least one occasion
Tinnitus or aural fullness in the treated ear
Other causes excluded
Probable Menière's disease
One definitive episode of vertigo
Audiometrically documented hearing loss on at least one occasion
Tinnitus or aural fullness in the treated ear
Other causes excluded
Possible Menière's disease
Episodic vertigo of the Menière type without documented hearing loss, or sensorineural hearing loss fluctuating or fixed, with disequilibrium but without definitive episodes
Other causes excluded

Reproduced from Committee on Hearing and Equilibrium (1995).

The Bárány Society's criteria are more accurate, since they specify the duration of the episodes of vertigo (from 20 minutes to 12 hours) and the type of hearing loss (low- to medium-frequency SNHL) and require fluctuating auditory/aural symptoms. The previous 1995 AAO-HNS criteria set up four categories (certain, definite, probable, and possible), whereas the Bárány Society's criteria only consider two categories: definite and probable MD.

FUNCTIONAL TESTS

Audiologic evaluation

Pure-tone audiometry

The AAO-HNS established a hearing staging system, according to the pure-tone thresholds at 0.5, 1, 2, and 3 kHz obtained in the audiogram (Table 19.3). Audiometrically documented fluctuating low-tone unilateral SNHL is the key to the diagnosis of MD when facing patients with an episodic vestibular syndrome. With follow-up, it is easy to document fluctuation when recovery is appreciated, thus supporting the diagnosis of MD. A shift in pure-tone thresholds for bone conduction by at least 30 dB hearing level at each of two adjacent frequencies below 2000 Hz is required for unilateral MD. The low frequencies (250 and 500 Hz) are typically affected at the earlier stages. As disease progresses, all frequencies may be involved and the audiogram pattern flattened at a moderate or severe level (Belinchon et al., 2011).

Table 19.3

Staging of definite and certain Menière's disease

Stage	Pure-tone average (dB)
1	≤25
2	26–40
3	41–70
4	>70

Reproduced from Committee on Hearing and Equilibrium (1995). Staging is based on the four-tone average (arithmetic mean rounded to the nearest whole number) of the pure-tone thresholds at 0.5, 1, 2, and 3 kHz of the worst audiogram during the interval 6 months before treatment. This is the same audiogram that is used as the baseline evaluation to determine hearing outcome from treatment. Staging should be applied only to cases of definite or certain Menière's disease.

Electrocochleography (ECoG)

ECoG is a neurophysiologic technique in which an auditory evoked potential is obtained in response to brief sound stimuli and recorded by an intratympanic or extratympanic (noninvasive) electrode. The cochlear microphonic and the summating potential (SP) are generated by the hair cells of the organ of Corti, whereas the compound action potential (AP) of the auditory nerve represents the summed synchronized response of many individual nerve fibers. Testing parameters include latencies and amplitudes of SP and AP, and SP/AP amplitude ratio, and area under the curve of SP/AP ratio.

Changes in the SP response can reflect pressure differences between the scala media and the scala vestibuli, indicating excessive fluid pressure, thus deforming the basilar membrane toward the scala tympani, so that enhanced-amplitude SP is thought to reflect EH. SP/AP ratio is the most common parameter for diagnosis of EH. However, normal ECoG responses have also been reported in patients with EH.

Increases in SP amplitude with an enlarged SP/AP ratio and a prolonged AP latency shift have been observed in patients with MD (Ge and Shea, 2002; Ferraro and Durrant, 2006). Nevertheless, the sensitivity and specificity of SP/AP ratio for detecting MD are highly variable, with a low sensitivity and higher specificity (Lamounier et al., 2014). The use of tone bursts instead of clicks, and the combination of SP/AP ratio with the area under the curve SP/AP may increase the sensitivity of ECoG (Al-Momani et al., 2009; Claes et al., 2011). It has also been reported that the sensitivity of ECoG increases with the duration and severity of disease (Kim et al., 2005; Takeda and Kakigi, 2010). When hearing thresholds reach 60 dB, EcoG cannot be used. ECoG has been performed for determining hearing outcome (Moon et al., 2012) and to monitor the response to intratympanic steroid therapy (Martin-Sanz et al., 2013a).

Vestibular testing

Caloric tests

Bithermal caloric irrigation with computerized electronystagmography or videonystagmography has been the main laboratory test to evaluate vestibulo-ocular reflex (VOR) function. Caloric tests assess horizontal semicircular canal function, with the percentage of unilateral caloric weakness or canal paresis as the main outcome measure. Unilateral vestibular hypofunction on caloric testing is observed in up to 75% of unilateral MD patients (Wang et al., 2012), although it is worth noting that a normal bithermal caloric response has been reported in up to 50% of patients in some series. Unilateral canal paresis usually indicates the involved ear, but it has also been demonstrated in 19% of patients on the normal side (Proctor, 2000).

Video-head impulse test (vHIT)

This is a video-oculography device that allows assessment of the VOR at high frequencies during HIT. The system is becoming a bedside technique as it is noninvasive, fast, and more accessible than the scleral search coil (MacDougall et al., 2009). The vHIT not only records refixation saccades but also demonstrates early saccades, invisible to the human eye (covert saccades). The equipment may provide an objective measurement of VOR gain when head impulses are performed in the plane of each of the six semicircular canals.

It has been reported that 67% of patients with MD show a reduced VOR gain in at least one semicircular canal when the six canals are tested; the posterior semicircular canal of the affected ear is the most frequently involved canal (Zulueta-Santos et al., 2014).

Vestibular-evoked myogenic potentials (VEMPs)

These are otolith-mediated, middle-latency reflexes that are recorded from sternocleidomastoid (cVEMPs) or infraocular (oVEMPs) electromyography in response to high-intensity auditory stimuli (air conduction) or high-frequency vibratory stimulation (bone conduction). Air conduction is preferred for cVEMPs, while bone-conducted vibration is mostly used in oVEMPs. VEMPs show a biphasic waveform with a positive and a negative peak. The short-onset latency of the cVEMPs is generated by primary vestibular afferents projecting to the vestibular nuclei and hence via the ipsilateral medial vestibulospinal tract to the accessory nucleus. It is widely accepted that cVEMPs evaluate the integrity of the sacculus and the inferior vestibular nerve, whereas oVEMPs primarily evaluate contralateral utriculus and superior

vestibular nerve. The response parameters commonly used are latencies and interpeak amplitude of the response. VEMPs are currently a standardized technique and provide a quick and noninvasive method of assessing otolith function in patients with an episodic vestibular syndrome.

Patients with unilateral MD usually show abnormalities in VEMPs with reduced or absent responses, although at the initial stage an augmented response is sometimes registered (Young et al., 2002; Huang et al., 2011; Manzari et al., 2011; Murofushi et al., 2011; Taylor et al., 2011; Winters et al., 2011; Young, 2013; Jerin et al., 2014). It has also been reported that the asymmetry ratio of cVEMPs increases as the disease progresses (Young et al., 2003). Nevertheless, the sensitivity and specificity of VEMPs in diagnosing MD are as low as 50% and 49%, respectively.

Imaging techniques

Computed tomography (CT) images reveal that the vestibular aqueduct is significantly shorter and narrower and has a smaller external aperture on average in patients with MD, both in the affected and contralateral ear (Krombach et al., 2005; Miyashita et al., 2012). Although these findings can contribute to explain the pathogenesis of the disease, their diagnostic significance is limited.

Magnetic resonance imaging (MRI) obtained after intratympanic or intravenous administration of gadolinium has allowed not only in vivo visualization of the membranous labyrinth (Naganawa et al., 2006), but also the demonstration of EH in humans diagnosed of MD (Nakashima et al., 2007; Naganawa et al., 2008). Various authors have shown EH in 90% or more of patients with definite MD when specific inner-ear MRI protocols were performed (Fiorino et al., 2011; Pyykkö et al., 2013). Heavily T2-weighted three-dimensional fluid-attenuated inversion recovery sequences on 3-T scanner appear to offer the best images. In particular, as gadolinium reaches the perilymphatic space a signal void appears, corresponding to the distended endolympathic space.

Several studies have found a good correlation between cochlear hydrops on MRI and abnormal ECoG (Seo et al., 2013) or abnormal VEMP (Katayama et al., 2010; Fiorino et al., 2011). Nevertheless, the extent of EH visualized on MRI does not always correlate with the severity of cochleovestibular symptoms. MRI is emerging as a useful tool not only for diagnosis of EH, but also for early detection of contralateral involvement, to evaluate the permeability of the round and oval windows to intratympanic drugs and to document progression of the disease (Miller and Bykowski, 2014; Gu et al., 2015).

DIFFERENTIAL DIAGNOSIS

Table 19.4 includes the major causes of episodic vestibular syndromes. When facing a patient with recurrent vertigo and migraine, the biggest challenge is to distinguish between VM and MD (Espinosa-Sanchez et al., 2014b). Headache is a common complaint in 70% of patients with MD (Eklund, 1999), and migraine is a comorbidity in over 30% of MD patients (Parker, 1995; Shin et al., 2013). Further, it has also been reported that 45% of patients with MD experienced at least one migraine symptom during the vertigo episode (Radtke et al., 2002). During vertigo spells, patients with MD experienced headache in 41% and migraine-type headache in 8.4% (Lopez-Escamez et al., 2014).

Current criteria for MD and VM (Lempert et al., 2012; Lopez-Escamez et al., 2015) provide useful tools for establishing a diagnosis, but the clinical pictures of both diseases often overlap, especially at the beginning of the disease. These criteria require other causes to be excluded, although when patients have two different types of attacks, one fulfilling VM criteria and the other MD, both disorders should be diagnosed.

The association of unilateral auditory symptoms is the most useful clinical differential characteristic to distinguish between MD and VM (Brantberg and Baloh, 2011; Lopez-Escamez et al., 2014). Nevertheless, auditory symptoms in VM increase with follow-up, in such a way that hearing loss appears in 38% of patients with VM after a median follow-up of 9 years (Radtke et al., 2012).

SNHL is uncommon in VM; when it is present, audiometry usually demonstrates a low-frequency, mild to moderate, bilateral SNHL, usually episodic, and it

Table 19.4

Differential diagnosis of Menière's disease

Autosomal-dominant sensorineural hearing loss type 9 (DFNA9) caused by *COCH* gene
Autoimmune inner-ear disease
Cerebrovascular disease (transient ischemic attack/infarction/hemorrhage in the vertebrobasilar system)
Cogan's syndrome
Endolymphatic sac tumor
Meningiomas and other masses of the cerebellopontine angle
Neuroborreliosis
Otosyphilis
Susac syndrome
Third-window syndromes (perilymph fistula, canal dehiscence, enlarged vestibular aqueduct)
Vestibular migraine
Vestibular paroxysmia (neurovascular compression syndrome)
Vestibular schwannoma
Vogt–Koyanagi–Harada syndrome

progresses much more slowly than in MD. Fluctuating SNHL is not specific for MD, as it has also been observed in VM and other disorders such as autoimmune inner-ear disease, Cogan's syndrome, otosyphilis, and enlarged vestibular aqueduct syndrome.

Patients with MD show significantly more abnormal results than patients with VM using the head thrust test, head-shaking nystagmus, vibration-induced nystagmus, bithermal caloric tests, rotatory chair testing, and VEMPs (Neff et al., 2012; Wang et al., 2012; Blödow et al., 2014). Obtaining a CT scan is useful to rule out other causes of episodic vestibular symptoms mimicking MD, such as canal dehiscence or enlarged vestibular aqueduct. MRI is routinely requested to exclude a vestibular schwannoma.

PROGNOSIS

The clinical course of MD is variable, with episodes occurring at irregular intervals. Usually as the disease progresses, attacks decrease in frequency, and hearing loss becomes permanent, as does the tinnitus (Pérez-Garrigues et al., 2008).

Without treatment, 57% of patients had complete control of vertigo at 2 years, and 71% had complete control after an average of 8.3 years (Silverstein et al., 1989). Dizziness severity, bilateral SNHL, and comorbid migraine are associated with a decrease in health-related quality of life (Lopez-Escamez et al., 2009; Porter and Boothroyd, 2015). The functional scale developed by the AAO-HNS is useful to monitor the impact of MD on daily activities (Table 19.5).

Table 19.5

Functional level scale

Regarding your current state of overall functioning, not just during attacks, check the one that best applies:

1. My dizziness has no effect on my activities at all
2. When I am dizzy, I have to stop what I am doing for a while, but it soon passes and I can resume activities. I continue to work, drive and engage in any activity I choose without restriction. I have not changed any plans or activities to accommodate my dizziness
3. When I am dizzy, I have to stop what I am doing for a while, but it does pass and I can resume activities. I continue to work, drive, and engage in most activities I choose, but I have had to change some plans and make some allowance for my dizziness
4. I am able to work, drive, travel, take care of a family, or engage in most essential activities, but I must exert a great deal of effort to do so. I must constantly make adjustments in my activities and budget my energies. I am barely making it
5. I am unable to work, drive, or take care of a family. I am unable to do most of the active things that I used to. Even essential activities must be limited. I am disabled
6. I have been disabled for 1 year or longer and/or I receive compensation (money) because of my dizziness or balance problem

Reproduced from Committee on Hearing and Equilibrium (1995).

TREATMENT

There is no consensus about MD treatment (Sajjadi and Paparella, 2008; Harcourt et al., 2014). New guidelines for treatment of vestibular disorders, including MD, are being developed by the EAONO.

It is essential to provide information to patients about the natural history of the disease, discussing the therapeutic options and their potential adverse effects, and encouraging them to participate actively in making decisions that affect their lives. This approach maximizes treatment compliance. Treatment of MD can be categorized as either acute or preventive.

Acute treatment

Acute attacks of MD are self-limited and often subside in a few hours. Treatment of the acute episode is merely symptomatic, almost always with vestibular suppressants and antiemetics. Benzodiazepines are preferred as a vestibular suppressant while antidopaminergic agents are useful when nausea or vomiting appears. We recommend utilizing the minimum effective dosage of the drug; not to make use of vestibular suppressant for more than 5 days; and avoid the combination of two drugs with antidopaminergic effects.

Preventive treatment

The main goal of preventive treatment is to improve patients' quality of life. This may be achieved by reducing the frequency, duration, and severity of vertigo spells. Preventive treatment includes lifestyle and dietary modifications, pharmacologic therapy, and in some cases surgical procedures. Other treatment options, such as hearing aids, cochlear implants, and the Meniett device, are also discussed below.

Lifestyle and dietary modifications

Patients with MD are counseled to follow a regular daily routine, and avoid triggers such as stress, barometric pressure change, fatigue, or sleep deprivation. Alcohol, coffee, and tobacco are traditionally restricted, although the efficacy of these measures has not been demonstrated in randomized controlled trials (Luxford et al., 2013).

The most important dietary recommendation is a high water intake and a very lowsodium diet. Several evidences support that arginine vasopressin (AVP) regulates

water reabsorption in the inner ear by aquaporin 2 channels, including: (1) the elevated plasma levels of AVP in patients with MD; (2) the accumulation of endolymph in AVP-treated guinea pigs and rats; and (3) the downregulation of V2 receptors in the inner ear of AVP-treated rats (Egami et al., 2013).

Sodium restriction is supported by the hypothesis that an increase of endolymphatic pressure can lead to the rupture of membranes in the scala media. So, a high salt intake would increase sodium plasma levels and this in turn would raise endolymphatic levels of sodium causing enlargement of endolymphatic pressure. The EH would lead to distension and ruptures in Reissner membrane with extravasation of endolymph into perilymph.

Patients are advised to eliminate the use of salt at the table and limit its use during cooking and baking. Products with high-sodium content should be avoided. These recommendations are based on expert opinions but evidences are lacking.

An increase in water intake is presumed to reduce the severity of MD symptoms by decreasing the systemic AVP level (Naganuma et al., 2006). Thus, it seems reasonable to advise a high water intake to reduce Na^+ concentration in serum and endolymph. Since changes in endolymphatic osmolarity may facilitate the onset of vertigo, we recommend increased water intake with a low level of Na^+ and Ca^{2+} to prevent dehydration and reduce the number of vertigo spells. This recommendation is based on the finding of elevated plasma levels of AVP in patients with MD (Egami et al., 2013).

Since a food or inhalant allergy may provoke MD symptoms in some patients with a genetic predisposition, some authors recommend food allergen avoidance and even specific immunotherapy in those patients with allergy and MD (Derebery, 2011; Banks et al., 2012; Weinreich and Agrawal, 2014). Placebo-controlled trials are needed to confirm the benefits of these measures.

PHARMACOLOGIC THERAPY

Betahistine

This drug is broadly used worldwide, except for the USA, since it has not been approved by the US Food and Drug Administration. Betahistine is a structural analog of histamine that acts as a weak partial postsynaptic histamine H_1 receptor agonist and presynaptic H_3 receptor antagonist, with no effect on postsynaptic H_2 receptors (Gbahou et al., 2010). The mechanism of action of the drug appears to depend mainly on its action on H_3 receptors mediated by two metabolites, aminoethylpyridine and hydroxyethylpyridine (Bertlich et al., 2014).

Experimental studies in animals demonstrate that betahistine improves labyrinthine microcirculation by vasodilation of the arterioles of the stria vascularis, and also in the posterior semicircular canal ampulla. Thus, betahistine would reduce endolymphatic pressure by achieving a reduction in the production of, and an increment in the re-absorption of, endolymph (Dziadziola et al., 1999; Laurikainen et al., 2000; Ihler et al., 2012).

Furthermore, experimental data regarding betahistine also suggest a decrease in the sensory input from the vestibular receptors (Botta et al., 1998; Chávez et al., 2005; Desmadryl et al., 2012). On the other hand, there is growing evidence that betahistine acts also at various levels of the central nervous system. Animal and human studies indicate betahistine blocks the presynaptic histamine H_3 receptors on the histaminergic nerve terminals originating from the tuberomammillary nuclei of the posterior hypothalamus, thus increasing histamine turnover and release in the vestibular nuclei (Lacour, 2013). Likewise, betahistine may participate in the mechanisms of histaminergic modulation of glycine and gamma-aminobutyric acid (GABA) release in the vestibular nuclei that may contribute to rebalancing neural activity after a unilateral vestibular loss (Bergquist et al., 2006). These actions on the histaminergic system may promote and facilitate central vestibular compensation (Tighilet et al., 2007). Finally, experimental data suggest that the upregulation of the histamine caused by the betahistine would induce excitatory effects on the neuronal activity of cortical and subcortical structures. This arousal effect would facilitate sensorimotor and cognitive activity, necessary for recovery after vestibular function loss (Lin et al., 1990).

The effect of betahistine is dose- and duration-dependent (Tighilet et al., 2005; Ihler et al., 2012). The standard dosage is 48–96 mg/day, although a higher dosage between 288 and 480 mg/day is sometimes used (Strupp et al., 2008; Lezius et al., 2011). Adverse effects are rare, mild, and self-limiting. A cutaneous hypersensitivity reaction is the most frequently reported complaint. Nausea, vomiting, epigastric pain, and headache are occasionally reported, especially with higher doses (Jeck-Thole and Wagner, 2006; Benecke et al., 2010).

The clinical efficacy of betahistine has been evaluated in several trials and there is conflicting evidence. A Cochrane review concluded that there was not enough evidence to say whether betahistine has any effect on the frequency or duration of the episodes of vertigo MD (James and Burton, 2001). Subsequently, a meta-analysis has been performed supporting the therapeutic benefit of betahistine for both MD and vestibular vertigo (Nauta, 2014). Betahistine 144 mg/day yields similar vertigo control rate as intratympanic dexamethasone (Albu et al., 2015). However, a recent long-term, double-blind, randomized placebo-controlled clinical trial (BEMED study), using 48 or 114 mg/day betahistine, has shown

that betahistine has no beneficial effect in MD (Adrion et al., 2016). Further long-term randomized, placebo-controlled clinical trials with higher dosages of betahistine are warranted to confirm the findings of the BEMED trial. Clinical research should also focus on identifying biologic markers or clinical predictors for betahistine response in MD.

Diuretics

Diuretics are commonly used in MD patients, especially in the USA, where they are the primary mode of therapy. Diuretics act by diminishing sodium reabsorption at different sites in the nephron, thereby increasing urinary sodium and water loss. This reduction of extracellular volume is supposed to decrease endolymphatic pressure and volume, either by increased drainage of endolymph or a reduction in its production at the stria vascularis.

Thiazides, such as hydrochlorothiazide, are the most frequently used diuretics in patients with MD. The side-effects of diuretics are common. Thiazides produce hyponatremia, hypochloremia, hypokalemia, and metabolic alkalosis, whereas potassium-sparing diuretics cause hyperkalemia. Loop diuretics, e.g., furosemide, generate hypokalemia, hypovolemia, hypochloremic alkalosis, dilutional hyponatremia, and hyperuricemia. Significantly, loop diuretics can cause hearing loss, generally temporary, and it must be remembered that aminoglycosides act synergistically with loop diuretics to produce an unexpectedly high incidence of ototoxicity. Acetazolamide, a carbonic anhydrase inhibitor, gives rise to hypokalemia, hyperchloremic metabolic acidosis, and urinary lithiasis.

The effects of diuretics in patients with MD have been analyzed by the Cochrane Collaboration (Thirlwall and Kundu, 2006), concluding that the effect of diuretics in MD cannot be evaluated due to lack of properly conducted trials. Diuretics can be considered a second- or third-line drug that may be used alone or in combination with betahistine when this drug fails to reduce the frequency of vertigo spells.

Steroid therapy

The use of corticosteroids in autoimmune diseases, the beneficial effect of steroids in the treatment of sudden SNHL (Li et al., 2015), and the participation of inflammatory and immune mechanisms in the pathophysiology of MD have led to the consideration of corticosteroids as a treatment option in MD (Lopez-Escamez et al., 2007, 2010; Hamid and Trune, 2008; Hu and Parnes, 2009). The mechanism of action of corticosteroids in MD is not limited to their anti-inflammatory and immunosuppressive effects in the cochlea, including the stria vascularis. They can increase labyrinthine circulation and improve inner-ear function through ion or water transport mechanisms influencing cochlear fluid homeostasis (Fukushima et al., 2004; Alles et al., 2006; Otake et al., 2009; Nevoux et al., 2015).

Few studies have investigated the effect of oral steroids in MD (Morales-Luckie et al., 2005; Fisher et al., 2012), and there are no randomized clinical trials showing any benefit from oral steroids in MD in the long term. However, comorbid systemic autoimmune disorders, long-lasting recurrent episodes of vertigo, or a sudden drop in hearing thresholds are situations that could be managed with high doses of oral steroids during few weeks.

Animal studies demonstrate that intratympanic delivery results in significantly higher inner-ear levels of steroids as compared with systemic administration. Moreover, intratympanic delivery avoids the well-known adverse effects of systemic administration: osteoporosis, diabetes mellitus, hypertension, peptic ulcer, cataracts, and endocrine disorders. Compared with gentamicin therapy, the main advantage of intratympanic corticosteroids is the absence of risk of hearing loss. Furthermore, this is a low-cost and safe technique. Residual tympanic perforation is the main risk.

Experimental studies have demonstrated that, although after intratympanic injection, methylprednisolone reaches higher concentrations in endolymph and perilymph than dexamethasone, the latter drug may be more efficacious as it is absorbed more rapidly by endocytosis into the stria vascularis and surrounding tissues, where it acts intracellularly (Parnes et al., 1999; Hamid and Trune, 2008).

Clinical studies are heterogeneous and differ in drug delivery protocols, type, and concentration of steroids (Boleas-Aguirre et al., 2008; Herraiz et al., 2010; Martin-Sanz et al., 2013b; McRackan et al., 2014a). High-dose dexamethasone (16 mg/mL) appears to provide better outcome than a lower dosage (4 mg/mL) (Casani et al., 2012). The only prospective randomized double-blind trial considered for a Cochrane systematic review found 82% of complete control of vertigo over placebo (57%) (Garduño-Anaya et al., 2005). The authors of this review concluded that, although a single trial provided limited evidence, intratympanic corticosteroids have demonstrated a statistically and clinically significant improvement of the frequency and severity or vertigo (Phillips and Westerberg, 2011). Large prospective randomized controlled clinical trials are needed. At present, when first-line treatment fails to control vertigo, it is a common practice to administer intratympanic corticosteroids if the patient still has functional hearing.

Intratympanic gentamicin therapy (IGT)

The aminoglycoside antibiotics are used in the management of MD at low dosage to produce a partial vestibular

ablation. Initially, aminoglycosides were administered systemically in MD, but two major drawbacks appeared: hearing loss and bilateral vestibular hypofunction, with severe ataxia and oscillopsia.

The aim of IGT is to obtain a long-lasting, nonfluctuating, peripheral vestibular hypofunction capable of being centrally compensated. As compared with systemic administration, intratympanic therapy has many advantages: it is an office-based procedure that avoids toxicity in the contralateral ear or other organs and yields a higher concentration of drug in the inner ear.

The mechanism of vestibular toxicity of gentamicin is not well understood. Animal models suggest that ototoxicity is caused by hair cell apoptosis induced by overproduction of reactive oxygen species, including oxygen ions, free radicals, and peroxide (Choung et al., 2009). There is also increasing evidence that programmed cell death is a consequence of aminoglycoside interference with mitochondrial protein synthesis, stimulation of *N*-methyl-D-aspartate receptors, and activation of the caspase pathway.

Histologic studies show that, after IGT, there is atrophy of the neuroepithelium of the semicircular canal cristae ampullaris and fibrosis and edema of the stroma, whereas the utricular macula is relatively spared. IGT causes greater loss of type I than type II vestibular hair cells because they concentrate more aminoglycoside (Lyford-Pike et al., 2007). Damage to the vestibular dark cells also has been observed. With regard to the cochlea, the basal turn is the region most susceptible to permanent loss of hair cells and replacement by supporting cells. Outer hair cells are more damaged than inner hair cells, resulting in high-frequency hearing loss.

Gentamicin can be delivered to the inner ear using different application methods (Salt and Plontke, 2009; McCall et al., 2010; Miller and Agrawal, 2014). Usually, IGT is used, although new techniques are been developing to deliver drugs directly into the inner ear. Once the agent is in the middle-ear cavity it diffuses mainly through the round-window membrane, although it may also enter through the oval-window membrane (King et al., 2013). However, clearance via the eustachian tube leads to a variable amount of substance reaching inner-ear fluids.

Treatment schedules for IGT can be categorized as fixed-dose protocols, instillations on request, and titration techniques. The dose is preset in the fixed-dose protocols; these protocols differ depending on the amount of drug delivered and the frequency and number of doses; dosing may be daily, multiple daily, weekly, monthly, or continuous. When instillations are performed on request, a low dose is given, which is repeated only if vertigo spells persist or recur. In the titration technique, gentamicin is administered until a certain goal is achieved, such as the appearance of hearing loss or clinical signs of vestibular hypofunction, including spontaneous nystagmus, head-shaking nystagmus, or a positive head thrust test. For this purpose, vHIT has been shown to be a valuable tool in assessing vestibulo-ocular changes after IGT (Marques et al., 2015). Recent studies have shown that "on demand" low-dose protocols yield a lower risk of hearing loss and posttreatment instability with good long-term vertigo control (Manrique-Huarte et al., 2011; Casani et al., 2014; Quaglieri et al., 2014).

This variety of schedules and protocols makes it difficult to compare results among different studies (Cohen-Kerem et al., 2004). Based on the results of only two studies that fulfilled the methodologic inclusion criteria, a Cochrane review concluded that intratympanic gentamicin seems to be an effective treatment for vertigo complaints in MD, although it highlights the risk of hearing loss (Pullens and van Benthem, 2011). A meta-analysis pooling published data has demonstrated an 87.5% substantial vertigo control rate with significant tinnitus improvement, and minimal hearing deterioration (Huon et al., 2012). Recently, a retrospective study supports the use of intratympanic gentamicin in patients with Tumarkin attacks (Viana et al., 2014). Remarkably, IGT can achieve better control of vertigo than corticosteroid injection without significant differences in final hearing level (Casani et al., 2012; Gabra and Saliba, 2013). When IGT fails to control vertigo, a reasonable option is exploratory tympanotomy and direct application of gentamicin over the round window and the oval-window niches (Rah et al., 2015).

Other drugs

Vasodilators have been used frequently in the treatment of MD because they are supposed to improve microcirculation of the labyrinth, thus mitigating hypothetic ischemia. It also has been proposed that vasodilators work by reducing endolymphatic pressure or even by inhibiting vestibular nuclei activity (Smith et al., 2002; Düwel et al., 2003). Although their efficacy is questionable, and their mechanism of action is uncertain, calcium channel blockers are among the most widely prescribed drugs for the management of MD (Tapia-Toca et al., 2009).

Extract of ginkgo biloba is prescribed for a wide variety of disturbances, including tinnitus and dizziness. Several mechanisms of action have been proposed but there is no convincing evidence from trials of sufficient methodologic quality to support the use of ginkgo biloba extract for patients with MD (Espinosa-Sanchez et al., 2014a).

SURGICAL TREATMENT

Surgical management of MD is indicated in patients when medical and intratympanic therapies fail to control

vertigo, and represents less than 5% of patients. For several reasons, surgery should be carefully considered only in certain patients. First, although the natural history of MD is variable, as the disease progresses the frequency of vertigo spells usually decreases but hearing loss is further aggravated. Secondly, the risk of bilaterality ranges from 25% to 40% and these patients have chronic disequilibrium and severe bilateral SNHL. Since there is no biologic marker for bilateral involvement, patients should not undergo surgery within the first 10 years. This would limit surgery to a few cases with persistent vertigo after a very long follow-up. It is also remarkable that the benefits of surgery to control Tumarkin crisis have not been demonstrated.

Several procedures have been described for the surgical treatment of MD (Sismanis, 2010; Teufert and Doherty, 2010). The selection of a particular surgical technique depends on factors such as severity of disease, hearing status, and presence of unilateral versus bilateral disease; the status of hearing is the most important factor. With regard to preservation of hearing, surgical procedures for MD can be broadly classified as either destructive or nondestructive. Nondestructive procedures include endolymphatic sac surgery (ESS), either shunt or decompression, selective vestibular neurectomy, and semicircular canal occlusion.

Endolymphatic sac surgery

ESS has been a controversial subject that has generated a great amount of literature. It is thought that this procedure relieves a supposed high endolymphatic pressure by means of drainage into the mastoid or into the subarachnoid space. Although several case series report vertigo control between 60% and 80%, a Cochrane review has concluded that there is insufficient evidence for the beneficial effect of ESS in MD (Hu and Parnes, 2010; Pullens et al., 2013). A retrospective chart review has found no significant differences in vertigo control classes when IGT is compared with ESS (Paradis et al., 2013). It is also remarkable that a recent study suggests that ESS may prevent MD from developing in the contralateral ear (Kitahara et al., 2014).

Semicircular canal occlusion

Semicircular canal occlusion has also been utilized to control intractable vertigo in MD. Triple plugging or only horizontal semicircular canal occlusion has been described, with good vertigo control rates and hearing preservation (Yin et al., 2008; Charpiot et al., 2010).

Vestibular neurectomy

Vestibular nerve section can be accomplished through four approaches: middle fossa, translabyrinthine, retrolabyrinthine, and retrosigmoid approach. Translabyrinthine vestibular neurectomy sacrifices hearing whereas with the other three approaches it is possible to preserve hearing. The need for a craniotomy involves the risks of a cerebrospinal fluid leak, brain edema, meningitis, and intracranial bleeding. Middle fossa neurectomy presents a major risk of facial nerve damage compared with the posterior approach. When compared with intratympanic gentamicin, vestibular neurectomy achieves higher vertigo control rates (Hillman et al., 2004; Colletti et al., 2007).

Labyrinthectomy

This is a hearing-destructive procedure reserved for patients with nonfunctional hearing. Transmastoid labyrinthectomy allows a complete removal of all neuroepithelium with a 95–99% rate of vertigo control.

Cochlear implantation

Cochlear implantation (CI) has been shown to be beneficial in patients with MD who progress to bilateral severe to profound SNHL or unilateral MD with contralateral hearing loss from another cause (Fife et al., 2014; Vermeire et al., 2014; Samy et al., 2015). The hearing outcome seems similar to that in other patients who undergo CI, although those patients with inactive MD show worse speech recognition scores (McRackan et al., 2014b). Previous vestibular surgery, including labyrinthectomy and selective vestibular nerve section, does not contraindicate CI; furthermore, simultaneous labyrinthectomy and CI is an increasingly frequent option (Hansen et al., 2013; Martens et al., 2013; MacKeith et al., 2014; Pérez-Garrigues et al., 2015). Some studies point out that vestibular symptoms may improve after CI (McRackan et al., 2014b). CI is also an option for tinnitus relief in patients with bilateral SNHL and even single-sided deafness (Van Heyning et al., 2008; Vermeire and Van de Heyning, 2009; Ramos-Macías et al., 2015).

OTHER THERAPIES

Transtympanic ventilation tube insertion

Grommet insertion is a popular treatment option for MD in some countries (Smith et al., 2005; Park et al., 2009; Ogawa et al., 2015). However, the results are controversial and a placebo effect has been claimed as there are no randomized controlled clinical trials.

Meniett device

Therapy with the Meniett device (Medtronic Xomed, Jacksonville, FL, USA) is based on the hypothesis that

patients with MD experience changes in their symptoms depending on barometric pressure variations. The Meniett device is a portable system that applies positive low-pressure pulses to the external ear canal. A close-fitting ear cuff connects the device's tubing to the external ear canal; a long-term tympanostomy tube allows transmission of the pressure pulses from the ear canal to the inner-ear fluid system via the round- and oval-window membranes. The therapy consists of a 6-week trial period with three daily sessions for 5 minutes. Otorrhea associated with the tympanostomy tube is the most common adverse effect. Two recent meta-analyses show conflicting results (Ahsan et al., 2015; Syed et al., 2015).

Hearing aids

When hearing disability begins to affect quality of life, hearing aids should be advised. Fitting amplification to patients with MD involves several problems: fluctuating nature of hearing loss, low-frequency hearing loss, unilateral or asymmetric hearing loss, reduced dynamic range, and reduced word recognition scores (Valente et al., 2006; McNeill et al., 2008). Modern digital hearing aids can be specifically programmed to take these challenges into account. Tinnitus is a common complaint in advanced stages of MD when hearing loss no longer fluctuates and becomes permanent. In these patients, hearing aids provide not only better speech discrimination, but also sound enrichment that may facilitate the process of habituation to their tinnitus.

VESTIBULAR REHABILITATION

Commonly, the role of vestibular rehabilitation in MD has been limited in improving stability in patients with nonfluctuating complete unilateral vestibular loss after a vestibular neurectomy or labyrinthectomy, and in treating unsteadiness after IGT. A second indication is in individuals with unsteadiness and disequilibrium in which vertigo spells are controlled by oral medication or IGT or have ceased at a later stage (Gottshall et al., 2005).

Aside from these indications, the use of vestibular rehabilitation in patients with fluctuating vestibular loss is not well established (Gottshall et al., 2010). In addition, it is unclear in patients with bilateral MD.

EDUCATIONAL AND PSYCHOLOGIC ASPECTS

It is necessary to enquire into the concerns of patients and identify their fears, uncertainties, beliefs, and expectations. It is essential to inform patients about the natural history of MD, to clarify any aspect related to the disorder and its therapy (Kirby and Yardley, 2009; Arroll et al., 2012). We also discuss with the patient the therapeutic options and their potential adverse effects. Patients have to express their preferences and we encourage them to actively participate in making decisions that affect their lives.

MD has a high impact on health-related quality of life. The unexpected spells of vertigo and the communication problems related to poor speech discrimination are major factors that restrict daily routines (Yardley et al., 2003).

Anxiety and depression are common comorbidities in patients with MD (Söderman et al., 2002; van Cruijsen et al., 2006). The mental health impact of MD is inversely related to time once it has been diagnosed (Tyrrell et al., 2014). The majority of patients with MD report psychologic stress as one of the main triggers of their attacks (Kirby and Yardley, 2012). Validated questionnaires can be used to detect behavioral factors in vestibular patients (Staab, 2013). Relaxation techniques and cognitive behavioral therapy can help patients to cope with their symptoms (Yardley and Kirby, 2006). Self-help groups can also give patients the opportunity to support each other (Porter and Boothroyd, 2015).

GUIDELINE FOR CONSERVATIVE TREATMENT OF MD

Lifestyle modifications and medical therapy are able to control vestibular symptoms in most patients, although they have no effect on progression of hearing loss or tinnitus. We have developed a stepwise approach based on the number of episodes of vertigo and hearing level which can effectively control vertigo in most patients without surgery (Fig. 19.2). Conservative treatment includes the following steps:

1. low-sodium diet (around 1800 mg/day) and high water intake (2000 mL/day), considered as baseline therapy
2. betahistine 24 mg/8 hours for at least 6 months
3. prednisone 1 mg/kg for 15 days if multiple episodes of vertigo with longer duration are observed in consecutive weeks or a sudden drop in hearing level is found. If no response is observed, prednisone is stopped in 4 weeks
4. intratympanic gentamicin, if there are six episodes in the last 3 months. The most studied dosage is 0.3–0.5 mL gentamicin sulfate using a concentration of 26.4 mg/mL. It can be repeated up to four times. Gentamicin should not be used in patients with bilateral disease, since they can develop bilateral vestibular hypofunction and persistent vestibular ataxia.

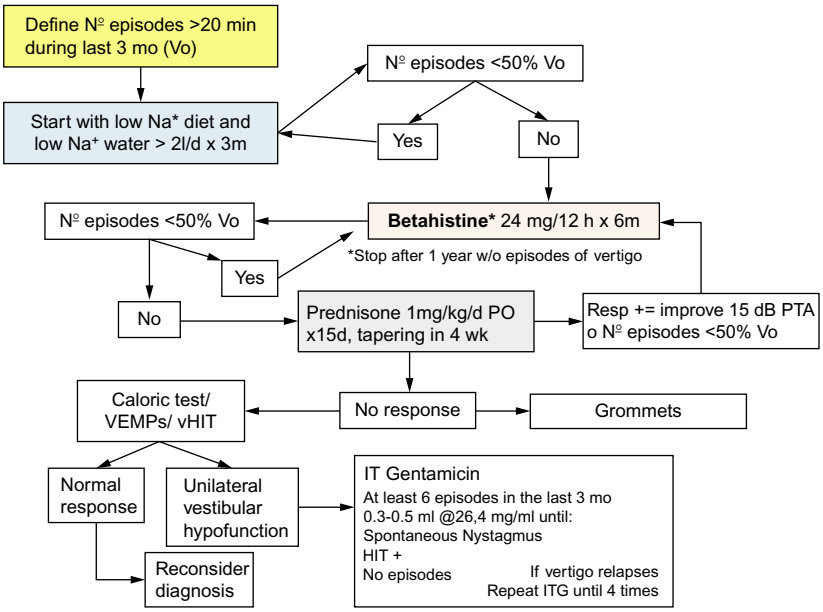

Fig. 19.2. Stepwise approach to conservative management of Menière's disease based on the number of episodes of vertigo and hearing thresholds. VEMPs, vestibular-evoked myogenic potentials; vHIT, video-head impulse test; IGT, intratympanic gentamicin therapy; PTA, pure-tone audiometry. (Modified after Lopez-Escamez and Espinosa-Sanchez, 2014.)

NEW PERSPECTIVES

New techniques for intratympanic delivery of drugs for inner-ear absorption have been developed (Lambert et al., 2012). These include hydrogel application and nanoparticles of poly-lactic/glycocolic acid; nanoparticles are useful when a sustained release is intended. To obviate the inherent problems associated with middle-ear application, newer procedures are been investigated to deliver medication directly to the inner ear. Cochlear implants, which are placed into the scala tympani, could be a method for drug delivery directly to the inner ear. In vitro and in vivo experiments in animals have achieved delivery of dexamethasone and neurotrophic factors (brain-derived neurotrophic factor, neurotrophin-3) by a modification of the electrode. Moreover, direct inner-ear delivery via an osmotic pump with a perfusion system has been developed in animal models. This last approach is based on microfluidics and miniaturization technologies and has the advantage of greater control and precision of the delivery process.

These new direct inner-ear delivery systems also have been investigated with the purpose of gene therapy, like RNA interference techniques to silence target genes, or gene edition to repair mutations. Another field of animal experimentation is stem cell therapy for hearing restoration, either promoting transdifferentiation of supporting cells of the organ of Corti into hair cells or using gene-edited induced pluripotent stem cells, which could be generated from peripheral blood mononuclear cells or skin fibroblasts of patients with MD (Almeida-Branco et al., 2015).

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Chapter 20

Otologic disorders causing dizziness, including surgery for vestibular disorders

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Abstract

This chapter will focus on vertigo/dizziness due to inner-ear malformations, labyrinthine fistula, otosclerosis, infectious processes, and autoimmune inner-ear disorders.

Inner-ear malformation due to dehiscence of the superior semicircular canal is the most recently described inner-ear malformation. Vertigo/dizziness is typically induced by sound and pressure stimuli and can be associated with auditory symptoms (conductive or mixed hearing loss).

Labyrinthine fistula, except after surgery for otosclerosis, in the context of trauma or chronic otitis media with cholesteatoma, still remains a challenging disorder due to multiple uncertainties regarding diagnostic and management strategies.

Otosclerosis typically manifests with auditory symptoms and conductive or mixed hearing loss on audiometry. Vertigo/dizziness is rare in nonoperated otosclerosis and should draw clinical attention to an inner-ear malformation. Computed tomography scan confirms otosclerosis in most cases and should rule out an inner-ear malformation, avoiding needless middle-ear surgical exploration.

Labyrinth involvement after an infectious process is unilateral when it complicates a middle-ear infection but can be bilateral after meningitis.

Labyrinth involvement due to an inflammatory disease is a challenging issue, particularly when restricted to the inner ear. The diagnosis relies on the bilateral and rapid aggravation of audiovestibular symptoms that will not respond to conventional therapy but to immunosuppressive drugs.

INTRODUCTION

This chapter will deal with vertigo/dizziness due to inner-ear malformations, labyrinthine fistula, otosclerosis, infectious processes, and autoimmune inner-ear disorders (AIEDs). For some items, such as inner-ear malformations, infectious processes, and AIEDs, etiologies are numerous and will be limited to those that are most relevant. It is also worth noting that vertigo/dizziness in the context of otologic disorders is often associated with audiologic symptoms, but literature reviews often focus on audiologic symptoms, which are easily quantified by audiometry, rather than on vestibular symptoms, which are more difficult to evaluate.

MALFORMATION OF THE INNER EAR

This chapter will focus on two inner-ear malformations, dehiscence of the superior semicircular canal (SSC) and enlarged vestibular aqueduct, which are frequent and regularly associated with vestibular symptoms.

Superior semicircular canal dehiscence

In 1998, Minor et al. described a new syndrome caused by dehiscence of the bone overlying the SSC at the level of the middle cranial fossa. This syndrome is presumed to be the result of a congenital or developmental defect. Other factors, such as head trauma, may trigger symptoms. It manifests in adulthood with vestibular or

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auditory symptoms, or both vestibular and auditory symptoms (Minor et al., 1998; Minor, 2000, 2005). Vestibular symptoms are typically induced by loud sound (Tullio phenomenon) and pressure stimuli (coughing, sneezing, straining, heavy weight lifting, or applying pressure to the tragus). However, other symptoms have been described, such as chronic disequilibrium, positional vertigo, recurrent vertigo, drop attacks, and oscillopsia synchronized to the pulse (Minor, 2000; Tilikete et al., 2004; Brantberg et al., 2005). Auditory dysfunction consists of aural fullness and autophony with conductive or mixed hearing loss. Interestingly, patients may display hypersensitivity to their own body sounds, such as heart beat, voice, and even eye movements (Albuquerque and Bronstein, 2004; Minor, 2005; Schmuziger et al., 2006).

The key to the identification of this syndrome is the analysis of the evoked eye movements during sound- and/or pressure-induced symptoms, as they align with the plane of the dehiscent SSC. Positive pressure in the external auditory canal, Vasalva maneuvers against pinched nostrils, and high-intensity sounds induce a nystagmus with a vertical slow-phase component directed upward and a torsional slow phase towards the healthy ear. This is in accordance with an excitation of the superior canal, i.e., ampullofugal deflection of the cupula. Eye movements are noted in the opposite direction for negative pressure in the external canal or maneuvers that increase intracranial pressure, such as Vasalva maneuvers against a closed glottis or jugular venous compression (Minor et al., 1998; Minor, 2000, 2005). On pure-tone audiometry, the presence of bone conduction thresholds better than normal and sometimes negative in the low frequencies associated with normal or elevated air conduction thresholds reveals a conductive or mixed hearing loss typical of the dehiscence syndrome (Fig. 20.1) (Merchant et al., 2007). Stapedial reflexes are present despite the conductive component, in accordance with "an inner conductive hearing loss" (Minor, 2005; Merchant et al., 2007). Cervical vestibular-evoked myogenic potentials (VEMPs) have abnormally low thresholds and high amplitude on the side of the dehiscence (Fig. 20.1) (Merchant et al., 2007). The diagnosis is confirmed by 0.5 mm collimated helical computed tomography (CT) scans with reformation of the images in the plane of the superior canal (Fig. 20.1) (Belden et al., 2003).

The explanation for the vestibular symptoms and hearing loss is a third mobile window due to dehiscence of the bone overlying the superior canal that will create a low-impedance pathway for sound and pressure energy, rendering the canal particularly sensitive to sound and pressure changes (Merchant et al., 2007). Indeed, resurfacing of the canal or surgical occlusion (plugging) can ameliorate both vestibular and auditory symptoms and signs (Minor, 2000, 2005). However, the surgical procedure is essentially indicated only for disabling vestibular symptoms due to the risk of sensorineural hearing loss as well as other risks that a middle fossa approach might carry (Minor, 2005). A transmastoid approach has been proposed in selected cases (Agrawal and Parnes, 2008; Deschenes et al., 2009).

Since the description of superior canal dehiscence syndrome, idiopathic horizontal- and posterior-canal dehiscence syndromes are emerging with similar symptoms, although the axis of nystagmus should match the anatomic axis of the involved semicircular canal during the pressure- or sound-induced vertigo, according to Ewald's first law (Zangh et al., 2010). Consequently, horizontal- and posterior-canal dehiscence should be considered in the differential diagnosis and searched for in patients presenting with symptoms known to be associated with superior canal dehiscence (Gopen et al., 2010; Russo et al., 2014; Zangh et al., 2010).

Enlarged vestibular aqueduct

Vestibular aqueduct enlargement, initially described by Valvassori and Clemis (1978), is the most common imaging abnormality in patients with congenital inner-ear defects (Irving and Jackler, 1997). The mechanism is an early arrest in the development of the endolymphatic canal and sac around the fifth to eighth weeks *in utero*, when the initial vesicle normally elongates and narrows to form the vestibular aqueduct (Fig. 20.2). It can be associated with other inner-ear malformations such as cystic dysplasia of the canals, enlargement of the vestibule, or various cochlear abnormalities (Irving and Jackler, 1997). This condition has been reported to be inherited in an autosomal-recessive manner and can be associated with syndromic hearing loss as in Pendred syndrome (Irving and Jackler, 1997; Stinckens et al., 2001). The anomaly is characterized by sensorineural and, more often, mixed hearing loss, which usually begins in early childhood (Nakashima et al., 2000). Hearing loss is typically bilateral and progressive, with stepwise rather than fluctuating hearing decrements often triggered by relatively minor head trauma. The stapedial reflex is usually present and VEMPs have abnormally low thresholds and high amplitude, as in the third mobile window mechanism (Sheykholeslami et al., 2004; Merchant and Rosowski, 2008). Vestibular symptoms are less frequent than hearing loss and commonly begin in childhood, but they may be delayed until adulthood (Oh et al., 2001; Faye et al., 2005).

Although sound- or pressure-induced vertigo has been reported, the vestibular symptoms are dominated by recurrent episodes of vertigo that can last hours and

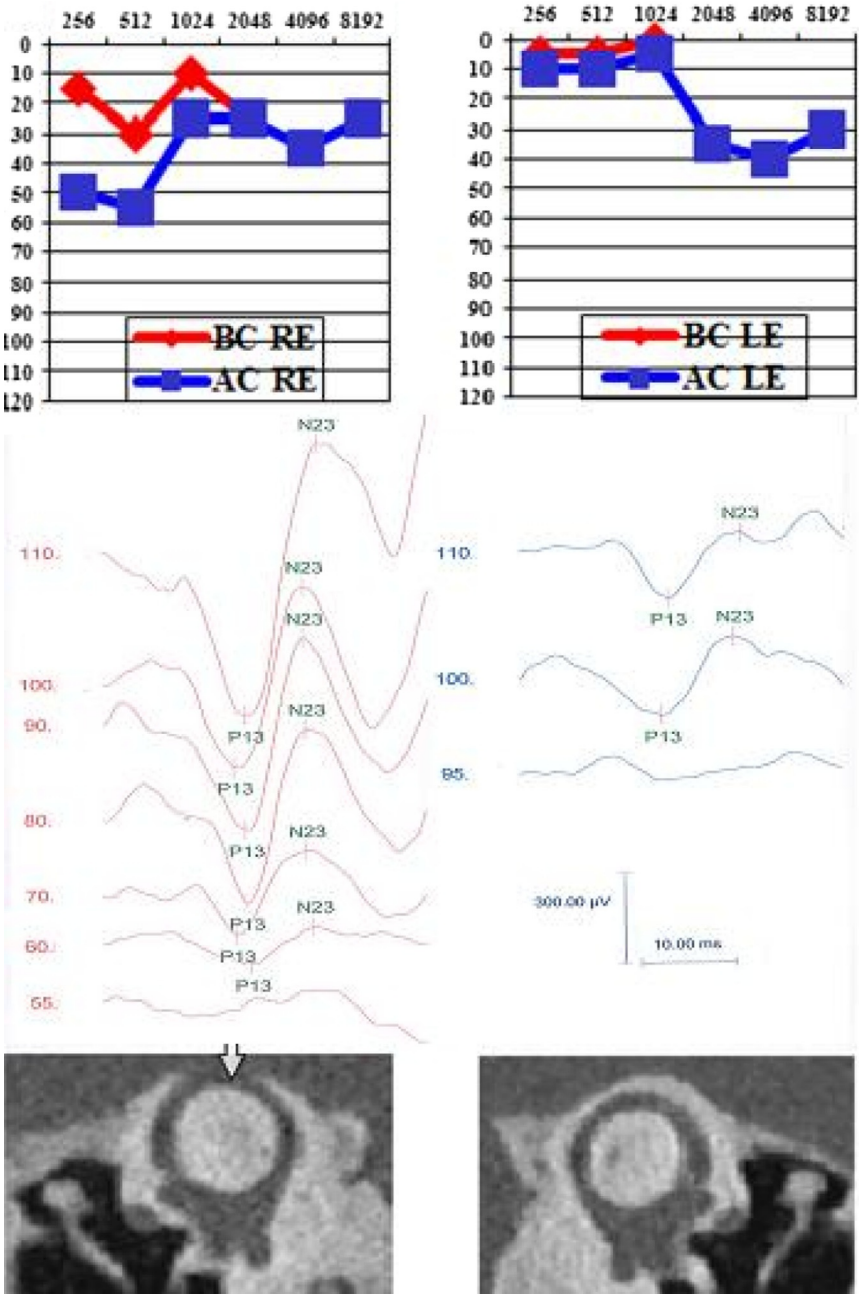

Fig. 20.1. Superior canal dehiscence. Pure-tone audiometry shows a mixed hearing loss on the right ear (RE) and a high-frequency sensorineural hearing loss on the left ear (LE). BC, bone conduction; AC, air conduction. Vestibular-evoked myogenic potentials demonstrate a lowered threshold on the right ear (60 dB) and a normal threshold on the left ear (100 dB). Computed tomography scan in the parasagittal plane (Pöschl's plane) shows a right superior canal bone dehiscence (arrow). There is no dehiscence on the left side.

mimic Menière's disease (Oh et al., 2001; Stinckens et al., 2001; Faye et al., 2005). Physical findings during one of these episodes have shown a peripheral vestibular syndrome consistent with unilateral irritation or deficit, as in patients with Menière's disease (Faye et al., 2005). Indeed, it is noteworthy that in typical Menière's disease, the endolymphatic sac and duct play a predominant role. However, the direct surgical treatment of the endolymphatic sac in enlarged vestibular aqueduct is controversial, as endolymphatic sac decompression, arachnoid bypass, or endolymphatic sac occlusion may worsen the hearing loss (Irving and Jackler, 1997). As section of the vestibular nerve carries an inherent risk, chemical labyrinthectomy (transtympanic gentamicin

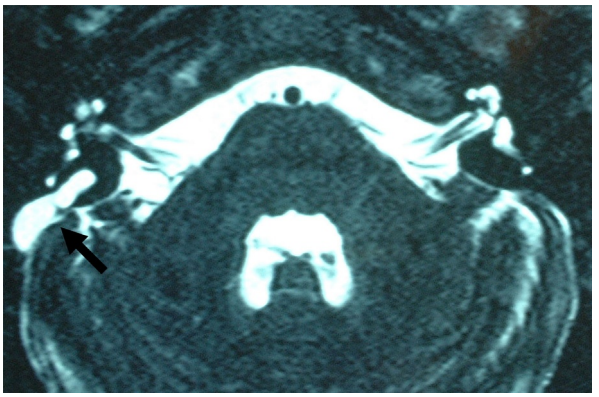

Fig. 20.2. Enlarged vestibular aqueduct. Axial magnetic resonance imaging scan with T2-weighted sequence demonstrates enlarged endolymphatic duct and sac on the right side (arrow). The endolymphatic duct and sac are not visualized on the left side as they are normally too small to be seen on a routine scan.

injection) can be the treatment of choice in patients with intractable vertigo associated with hearing loss (Yetiser et al., 1999; Faye et al., 2005).

LABYRINTHINE FISTULAS

Labyrinthine fistulas are caused by abnormal communications between the inner ear and surrounding structures, resulting in leakage of perilymph, leading to vestibular disturbances and/or hearing loss. The diagnosis of a labyrinthine fistula is difficult to establish but it can be made with certainty in three circumstances where the fistula has a preferential localization, and usually requires an exploratory tympanotomy to confirm the diagnosis (Minor, 2003).

The first circumstance is after stapedectomy, in which the prosthesis becomes dislodged from the oval window, allowing perilymph leakage into the middle ear (see section on otosclerosis below and Fig. 20.4C, below).

The second circumstance is after trauma that results in a temporal bone fracture or a membranous labyrinthine rupture (Fee, 1968). The trauma is obvious when related to head trauma or direct trauma to the inner ear (Fee, 1968; Seltzer and McCabe, 1986; Legent and Bordure, 1998). The trauma can also be due to changes in air or intracranial pressure that are transmitted to the inner ear. In 1971, Goodhill proposed that an implosive or explosive force can lead to membranous ruptures (oval and/or round windows) and a perilymphatic fistula (Goodhill, 1971, 1980). Implosive force is due to positive pressure in the middle ear transmitted via the eustachian tube during nose blowing or Vasalva maneuver. A similar mechanism occurs during increased pressure in the external ear, typically observed after a slap, that can damage the oval window via the ossicular chain. Explosive force is due to increased intracranial pressure transmitted to the labyrinth via the cochlear aqueduct or internal auditory canal during sneezing, coughing, or physical exertion such as weight lifting. Hughes et al. (1990) presented the results of a survey of 167 surgeons showing that the single most important feature of the history suggesting a perilymphatic fistula was previous barotrauma or head trauma. In this context, exploratory tympanotomy is justified by significant improvement of vestibular symptoms that can be long-lasting (months to years), because intermittent or constantly varying fluid leakage prevents complete vestibular compensation (Glasscock et al., 1992; Fitzgerald et al., 1997).

The third circumstance is after chronic otitis media, which is combined in most cases with the formation of a cholesteatoma that can result in erosion of the dense petrous bone surrounding the structures of the labyrinth (Busaba, 1999; Magliulo et al., 2008). Labyrinthine fistula is the most common complication of cholesteatoma, with an incidence of 5–10% (Sheehy and Brackmann, 1979; Gormley, 1986; Parisier et al., 1991; Ikeda et al., 2012). The fistula is located at the horizontal semicircular canal in approximately 90% of cases because of its anatomic proximity to the middle ear (Fig. 20.3) (Busaba, 1999). However, structures such as the oval window, the promontory, other canals, or the cochlea may be involved alone or in combination with the horizontal canal (Dornhoffer and Milewski, 1995; Busaba, 1999; Brantberg et al., 2006). Vestibular symptoms have been reported to occur preoperatively in approximately 60% of patients (Sheehy and Brackmann, 1979; Dornhoffer and Milewski, 1995; Busaba, 1999; Gersdorff et al., 2000; Ikeda et al., 2012). The fistula test, performed with the pneumatic otoscope, producing vertigo and nystagmus, was positive in only 32% of patients (Dornhoffer and Milewski, 1995). Thus, the presence of vertigo and/or a positive fistula test, as well as sensorineural hearing loss, should raise the suspicion for a fistula, but their absence does not guarantee an intact bony labyrinth (Dornhoffer and Milewski, 1995).

Because fistulas cannot be diagnosed accurately on clinical grounds before surgery, CT scanning has been increasingly used to detect fistula or other complications. Despite recent advances in imaging techniques, CT scan evidence for fistula can be found in only 83% of patients (Ikeda et al., 2012). Although a CT scan is the most reliable preoperative method for detection of labyrinthine fistula, the definitive diagnosis is only made intraoperatively (Ikeda et al., 2012). Surgical treatment depends on the localization, size, and depth (bony and/or membranous labyrinth) of the fistula as well as the condition of the other ear. Nowadays, there is a tendency toward complete removal of cholesteatoma with closure of the

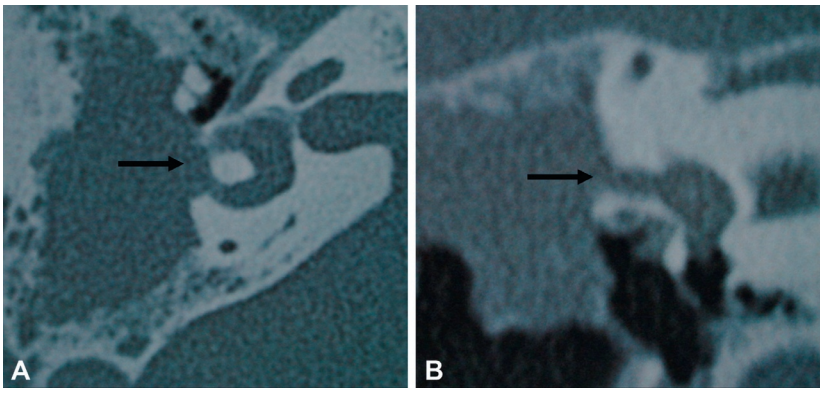

Fig. 20.3. Horizontal canal fistula due to cholesteatoma. Axial (**A**) and coronal (**B**) computed tomography scan demonstrates a fistula of the horizontal semicircular canal (arrow) due to an extensive cholesteatoma of the middle ear.

labyrinthine fistula (Magliulo et al., 2008). Simple resurfacing of the horizontal semicircular canal is a safe approach to retain normal vestibular function, whereas plugging leads to loss of canal function with a risk of hearing deterioration (Hirvonen et al., 2016).

Apart from the previous three circumstances, the diagnosis of a spontaneous perilymphatic fistula is challenging due to multiple uncertainties regarding diagnostic and management strategies (Minor, 2003). The association of both hearing loss and vestibular symptoms favors the diagnosis, as auditory or vestibular symptoms alone is rarely indicative of the diagnosis (Seltzer and McCabe, 1986). The vestibular symptoms are variable but vestibular symptoms induced by sound (Tullio phenomenon) and/or pressure stimuli, or mimicking Menière's disease may indicate a fistula (Seltzer and McCabe, 1986; Fitzgerald et al., 1997). There is no reliable sign and the fistula test (Hennebert or fistula sign), with recording for eye and/or posture deviation during positive and negative pressure in the external auditory canal, is neither sensitive nor specific (Fitzgerald et al., 1997). CT scans are often negative, although a pneumolabyrinth and/or unexplained fluid in the middle ear suggests the diagnosis. In children, a CT scan showing abnormalities of the middle ear, particularly of the stapes, or of the inner ear or both heightens the suspicion of perilymphatic fistula (Weissman et al., 1994).

Either a conservative approach, including bed rest, head elevation, and avoidance of straining, or a surgical strategy may be pursued. There is a tendency toward an initial conservative approach and then exploratory tympanotomy if the symptoms persist. When performed, surgical exploration is also challenging, as it is difficult to confirm leakage of perilymph and the use of a Western blot assay for beta-2 transferrin protein has a low sensitivity (Fitzgerald et al., 1997; Buchman et al., 1999). This usually leads to systematic patching of two sites, the oval window (which is the most common site of fistula) and the round window, with varied results (Seltzer and McCabe, 1986; Hughes et al., 1990; Glasscock et al., 1992; Fitzgerald et al., 1997). As a rule, the postoperative outcome is better for vestibular symptoms than for auditory symptoms (Seltzer and McCabe, 1986; Fitzgerald et al., 1997).

OTOSCLEROSIS

Otosclerosis typically manifests with auditory symptoms and a conductive or mixed hearing loss on pure-tone audiometry. The occurrence of vestibular symptoms in otosclerosis before surgery is a controversial issue. Vertigo or dizziness has been reported to occur in 10–20% of patients (Birch and Elbrond, 1985; Gros et al., 2003). However, a retrospective study involving 13 800 patients examined for balance disorders demonstrated that the proportion of patients with otosclerosis among those with balance disorders was low (0.7%), approaching the incidence of otosclerosis in the general population (Grayeli et al., 2009). The authors proposed a coincidence of otosclerosis and vestibular symptoms instead of a causal relationship (Grayeli et al., 2009). Thus, vestibular symptoms seem to be rare before surgery, probably essentially encountered in far-advanced and/or cochlear forms of otosclerosis (Shea et al., 1994; Gros et al., 2003; Hayashi et al., 2006).Thus, the presence of vestibular symptoms in the context of a conductive or mixed hearing loss should definitively draw clinical attention to an inner-ear malformation such as superior canal dehiscence or enlarged vestibular aqueduct rather than to otosclerosis (Halmagyi et al., 2003). It is here that stapedial reflexes can be of use, as patients with otosclerosis present with absent reflexes, while patients with superior canal dehiscence have normal reflexes. Additionally, VEMPs are either absent or present with elevated thresholds in otosclerosis, while they are present with lowered thresholds in superior canal dehiscence

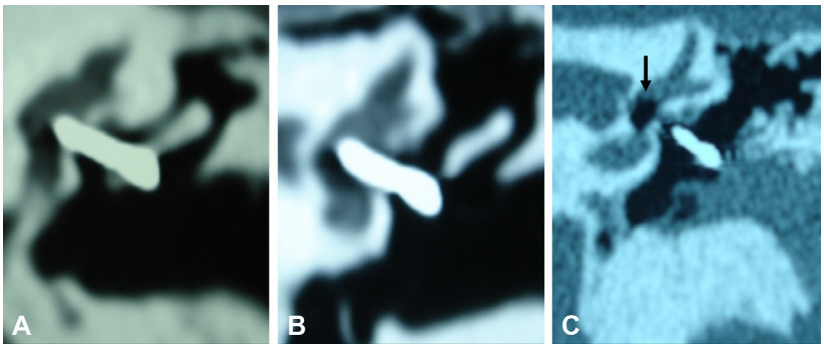

Fig. 20.4. Position of a stapes prosthesis in otosclerosis. Coronal computed tomography scan obtained at the level of the oval window demonstrates a stapes prosthesis for otosclerosis. (**A**) The prosthesis is in the normal position extending from the long process of the incus to the oval window. (**B**) The prosthesis is abnormally extending through the oval window into the vestibule. (**C**) The prosthesis is extruded with an air gap between the prosthesis and the oval window and a pneumolabyrinth (arrow) in the vestibule.

(Halmagyi et al., 2003; Merchant et al., 2007). Finally, a diagnosis of otosclerosis relies on CT imaging that shows demineralization in 90% of patients with otosclerosis and rules out an inner-ear malformation.

The treatment of otosclerosis consists of surgery or wearing a hearing aid. Surgery needs to open the inner ear (stapedectomy or stapedotomy with a small fenestration of the oval window) in order to put on a prosthesis (Fig. 20.4A). Consequently, approximately half of patients complain of mild, transient, and short-lasting (minutes to hours) postoperative vestibular symptoms, which are essentially a rotatory vertigo or floating sensation (Kujala et al., 2010; Hirvonen and Aalto, 2013). In other patients, vertigo can occur immediately after surgery and may last several days due to various proposed mechanisms. When it results from traumatic injury to the inner ear or perilymph aspiration (dry labyrinth), the vertigo usually resolves spontaneously within a few days. The mechanism can be due to a prosthesis that is extruded, i.e., moved away from the oval window, leading to perilymphatic fistula and audiovestibular symptoms that can mimic Menière's disease (Fig. 20.4C) (Harrison et al., 1967). Conversely, the prosthesis can enter the labyrinth (Fig. 20.4B). CT imaging can depict the position of the prosthesis and contribute to identifying those cases requiring revision surgery (Swartz et al., 1986; Stone et al., 2000).

Of note, the presence of a pneumolabyrinth is a regular finding during the early postoperative period but can be a sign of perilymphatic fistula if it persists after 1 week, as is the presence of a new, unexplained middle-ear effusion (Stone et al., 2000; Bajin et al., 2013). In approximately 1% of patients, vertigo can be disabling, long-lasting, and associated with total sensorineural hearing loss. The mechanism can be due to bleeding, infection, or inflammation, i.e., an intravestibular granuloma, in the inner ear. Magnetic resonance imaging (MRI) is complementary to CT imaging, as high signal intensity of the labyrinth on noncontrast T1-weighted images favors inner-ear bleeding, while enhancement after contrast administration of T1-weighted images is in keeping with infection or inflammation of the labyrinth (Rangheard et al., 2001). The prognosis is often severe with permanent sensorineural hearing loss. Benign paroxysmal positional vertigo is another cause of vertigo following surgery for otosclerosis (Collison and Kolberg, 1998; Atacan et al., 2001). The pathophysiology of benign paroxysmal positional vertigo after otosclerosis surgery may be related to trauma to the otolith organs, as the distance between the stapes footplate and the utricule is about 1 mm (Atacan et al., 2001).

Finally, delayed vertigo occurring 1 month to 7 years after surgery was reported in 0.5% of patients and may have been caused by perilymphatic fistula (Albera et al., 2004). The vertigo may be described as paroxysmal unsteadiness, recurrent vertigo due to endolymphatic hydrops by an *ex vacuo* mechanism, or chronic dizziness (Harrison et al., 1967; Shea et al., 1994; Albera et al., 2004).

INFECTIOUS DISEASE OF THE EAR

Middle-ear infection (otitis media) is common in children but can occur at any age and can be acute or chronic. Patients with acute middle-ear infection complain of otalgia and fever and examination usually reveals a bulging eardrum with a conductive hearing loss. Acute middle-ear infection can lead to persistent fluid in the middle ear, i.e., serous or chronic otitis media, which develops insidiously with slight conductive hearing loss but no pain or fever. This phenomenon can be favored by fluid extending to the air cells of the mastoid bone due to its honeycomb-like structure. However, there is rarely vertigo in acute and/or chronic middle-ear infection with

or without mastoiditis. The appearance of vertigo/dizziness is due to an extension of the previous infections to the inner ear typically observed in labyrinthitis.

Labyrinthitis

From both a theoretic and clinical point of view, it is conventional to distinguish suppurative labyrinthitis from serous or toxic labyrinthitis.

Suppurative labyrinthitis is caused by bacteria that invade the inner ear. The symptoms are acute and include vertigo, vomiting, and severe sensorineural hearing loss. The infection originates either in the middle ear, particularly when there is a congenital or acquired defect of the bony labyrinth, or in the cerebrospinal fluid (CSF), as there are anatomic connections between the subarachnoid space and the inner ear via the internal auditory canal and cochlear aqueduct.

When the infection originates in the middle ear (and/or mastoid), the symptoms are unilateral and the tympanic membrane is abnormal. Vertigo is severe, lasting for several days, with a typical peripheral vestibular syndrome. The responsible agent is sometimes identified by analysis of purulent secretions after wide myringotomy. Thanks to antibiotic therapy, bacterial labyrinthitis is rare nowadays and the prognosis has been ameliorated, although a risk of progression to meningitis still persists. The most common offending organisms for meningitis are *Streptococcus pneumoniae* and *Haemophilus influenzae,* with an incidence of meningitis after suppurative otolabyrinthitis inversely related to the prevalence of immunization to these bacteria in the population. In this situation, a congenital or acquired defect of the bony labyrinth should be searched for to prevent recurrence of meningitis (Kimitsuki et al., 2004; Urata et al., 2014).

When the infection originates in the CSF, i.e., bacterial meningitis, with a nonotologic cause, the symptoms of meningitis typically precede the audiovestibular manifestations. When the latter manifestations occur, they are usually bilateral and dominated by a disabling sensorineural hearing loss (Woolley et al., 1999). With simultaneous bilateral vestibular failure, patients may complain of disequilibrium rather than vertigo and vestibular impairment can be underestimated in the context of neurologic impairment and in the absence of routine vestibular testing. This is particularly true for children who tend to compensate quickly (Cushing et al., 2009). However, it has been well demonstrated in children before the age of independent walking that the occurrence of bilateral vestibular loss due to bacterial meningitis will definitely delay posture-motor development (Wiener-Vacher et al., 2012). Bacterial meningitis causing auditory and/or vestibular symptoms is usually due to *S. pneumoniae,* less frequently to *Neisseria meningitidis* or *H. influenzae*, with various degrees of involvement of the cochlear or vestibular part of the labyrinth (Woolley et al., 1999; Wellman et al., 2003; Douglas et al., 2008; Wiener-Vacher et al., 2012).

MRI is able to visualize a contrast enhancement of the cochleovestibular structures of the inner ear, with a correlation between MRI abnormalities and the extent of cochlear dysfunction (Dichgans et al., 1999). Suppurative labyrinthitis can evolve to labyrinthitis ossificans and lead to permanent hearing and vestibular loss (Fig. 20.5). This phenomenon can be bilateral after meningitis and may require placement of a cochlear implant before ossification of the cochlea occurs that will preclude insertion of the implant. This would be a theoretic indication for a vestibular implant, for which research is ongoing (Guyot et al., 2012). Effective vaccines are available for bacteria, such as *S. pneumoniae, N. meningitidis,* and *H. influenzae,* leading to a substantial decrease in the incidence of meningitis and to their prevalence as causes of cochleovestibular disorders.

Serous or toxic labyrinthitis is due to toxins or chemical products that invade the inner ear. The symptoms of serous or toxic labyrinthitis are less pronounced, often with only high-frequency hearing loss and mild to moderate vertigo, and the prognosis is usually favorable. Vestibular lesions will tend to recover rather than compensate.

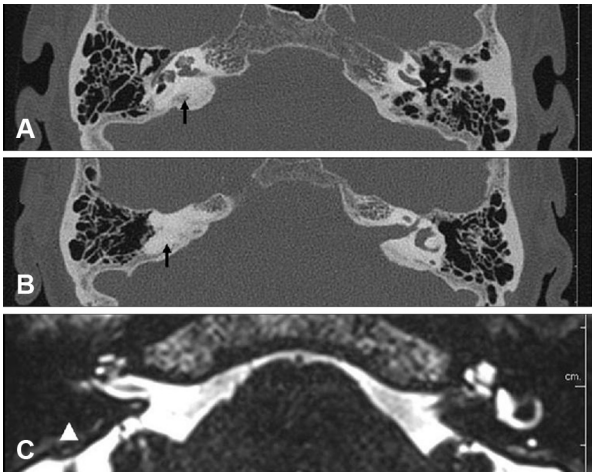

Fig. 20.5. Labyrinthine ossification after meningitis. Axial computed tomography (CT) scan (**A** and **B**) and magnetic resonance imaging (MRI) scan in T2-weighted sequences (**C**) in a patient with a history of bacterial meningitis and absent vestibular function on the right side. (**A** and **B**) CT scan demonstrates ossification of the vestibule, horizontal and posterior semicircular canals on the right side (arrow). (**C**) MRI scan in T2 weighted-sequences shows no fluid in the utricle and horizontal and posterior semicircular canals (arrowhead). Correlation of CT and MRI findings is helpful to confirm the mechanism of the lesion, i.e., right labyrinthitis ossificans.

From a purely vestibular point of view, it is difficult to distinguish between a unilateral labyrinthitis and vestibular neuritis, as both present with vertigo lasting a few days, vomiting, and a typical peripheral vestibular syndrome. However, in vestibular neuritis there may be preceding symptoms, such as an upper respiratory tract infection with no middle-ear infection, the vertigo is isolated, i.e., there is no associated hearing loss, and the tympanic membrane is normal.

Specific infection of the inner ear

Inner-ear infection can occur with specific agents, either viral or bacterial, in the context of a generalized infectious disease.

Viral infection of the inner ear

Two recent articles reviewed the viruses involved in inner-ear disorders, although they focus on audiologic rather than vestibular symptoms (Beyea et al., 2012; Cohen et al., 2014). Infection can be congenital, i.e., transmitted by the mother to the fetus during pregnancy, or acquired.

Congenital viral infection is usually due to cytomegalovirus (CMV) or rubella, which are both included in the acronym TORCHS for frequently occurring infectious teratogens (toxoplasmosis, rubella, CMV, herpes simplex, and syphilis), responsible for disabling neurologic disorders and hearing loss (Cohen et al., 2014). CMV is the leading nongenetic cause of childhood sensorineural hearing loss (Beyea et al., 2012; Cohen et al., 2014). The latter can be delayed and manifest months or years after birth. In early childhood, vestibular expression of CMV infection is a delayed acquisition of stance and gait instead of vertigo. This vestibular involvement is frequent and usually related to a deficiency of the peripheral vestibular system, as demonstrated by abnormal VEMPs, caloric tests, and rotational tests (Zagolski, 2008). Prevention of maternal infection with CMV and ganciclovir treatment of affected newborns with associated cerebral or other severe focal organ lesions are promising interventions (Beyea et al., 2012; Cohen et al., 2014). Currently, there is no effective CMV vaccine. Rubella is another infectious teratogen for which vaccination of women prior to reproductive age is extremely effective at prevention of congenital rubella in their offspring.

Acquired infection in childhood is usually due to mumps and measles, although these viral infections are becoming rarer since the implementation of vaccination. Mumps used to be the most common cause of unilateral acquired sensorineural deafness in children, usually sudden in onset, profound and permanent, sometimes associated with vertigo (Hyden et al., 1979, Mizushima and Murakami, 1986; Yanagita and Murahashi, 1986). It should be emphasized that the initial lesion of the inner ear caused by certain viruses like mumps and measles may lead, many years (1–74 years) later, to recurrent vertigo due to a secondary or delayed endolymphatic hydrops similar to the hydrops observed in Menière's disease (Schuknecht et al., 1990; Hyden, 1996; Kamei, 2004; Bovo et al., 2010). This delayed endolymphatic hydrops can be of the ipsilateral type, more rarely of the contralateral type (Kamei, 2004; Bovo et al., 2010). Interestingly, when endolymphatic hydrops is of the contralateral type, histopathology studies show changes in the deaf ear similar to those known to occur in mumps and measles labyrinthitis (viral labyrinthitis), whereas pathologic changes in the other ear resemble those known to occur in Menière's disease (Schuknecht et al., 1990; Kamei, 2004). Various mechanisms have been discussed, including, more recently, an autoimmune process (Bovo et al., 2010).

Finally, there is clear evidence that vestibular involvement is more common in subjects with human immunodeficiency virus (HIV) infection compared to a control group (Hausler et al., 1991; Teggi et al., 2008; Heinze et al., 2011). The mechanism is diverse, including the direct effect of HIV on the vestibular system, both peripherally and centrally, an increased susceptibility to opportunistic infections in the ear or brain, particularly for syphilis infection, as well as treatment with potentially ototoxic medications (Hausler et al., 1991; Pappas et al., 1995; Heinze et al., 2011; Mathews et al., 2012).

Bacterial infection of the inner ear

The rare occurrence of a tuberculosis infection or a spirochetal infection, i.e., syphilis or Lyme disease, should be kept in mind and searched for due to their specific management.

Tuberculosis is a rare cause of chronic otitis media, with eardrum perforation and persistent otorrhea, middle-ear granulation tissue, and/or polyps associated with ossicular erosion. The presence of a mastoid cutaneous fistula and/or an intraparotid lymphadenopathy is suggestive of the diagnosis. However, the diagnosis is often difficult to establish and delayed, as histologic and bacterial findings may remain negative (Dumas et al., 2012). Thus, the infectious process can evolve and be responsible for facial paralysis, vertigo, and sensorineural hearing loss in the context of labyrinthitis, and finally intracranial dissemination (Hwang et al., 2013).

Syphilis is a spirochetal infection due to *Treponema pallidum* that can be responsible for congenital (see TORCHS syndrome, above) and/or acquired inner-ear infection, known as luetic labyrinthitis or otosyphilis.

Otosyphilis is usually a presumptive diagnosis based on positive serology in patients with cochleovestibular symptoms with no other likely causes. It can manifest with sensorineural hearing loss, unilateral or bilateral, sudden or progressive, with or without vertigo, isolated or associated with neurologic symptoms in the context of meningoneurolabyrinthitis. Otosyphilis can simulate Menière's disease and share, on histologic examination, the same aspects of endolymphatic hydrops, although the mechanism of hydrops formation remains unclear (Miller et al., 2010).

Lyme disease is another spirochetal infection potentially responsible for acquired inner-ear infection. However, the link between Lyme disease and inner-ear dysfunction is more controversial than in syphilis (Gagnebin and Maire, 2002; Abuzeid and Ruckenstein, 2008). This link may depend on geographic consideration (North America versus Europe) and should be interpreted regarding the stage of the disease (Abuzeid and Ruckenstein, 2008; Bertholon, 2013). In the early disseminated stage of Lyme disease (stage 2), it is difficult to confirm that the occurrence of hearing loss, usually unilateral with or without vertigo, or the occurrence of vestibular neuritis is related to Lyme disease, as CSF analysis is often negative and the diagnosis essentially relies on Lyme serology, with controversies over the sensitivity and specificity of the tests (Hyden et al., 1995; Bertholon, 2013; Peeters et al., 2013). In late-stage Lyme disease, there are observations of bilateral progressive sensorineural hearing loss associated with gait disorders of central nervous system origin, such as paraparesis or cerebellar syndrome, that can be definitely related to Lyme disease with lymphocytic meningitis on CSF (Bertholon et al., 2000, 2012).

Labyrinthitis is not necessarily due to an infectious process and can be inflammatory in origin. Pure and predominant inflammatory processes are discussed below.

AUTOIMMUNE INNER-EAR DISORDER

AIED is assumed to be related to either antibodies or immune cells that cause damage to the inner ear. The damage to the inner ear results in hearing impairment, which has been extensively studied, as audiometry is a reliable clinical marker, and/or vertigo/dizziness, for which fewer studies are available. AIED is rare, probably accounting for less than 1% of all cases of hearing impairment or dizziness (Bovo et al., 2009, 2010). In general, AIED occurs more frequently in women than men, and less frequently in children and the elderly. AIED can be limited to the inner ear or may be part of a multisystem organ disorder. Some patients will move from a previously isolated inner-ear disorder to a multisystem organ disorder. We will first deal with AIED limited to the inner ear, the diagnosis of which is always difficult, and then consider AIED in the context of a multisystem organ disorder.

Isolated autoimmune inner-ear disorder

Isolated AIED was first described in 1979 and is difficult to diagnose, as the inner ear is the sole target of an inappropriate attack by the immune system and because, so far, there is no known biomarker heralding the presence of an underlying autoimmune disease (McCabe, 1979). The key to the identification of an autoimmune disorder is the bilateral and rapid aggravation of audiovestibular symptoms that will not respond to conventional therapy, but will respond to immunosuppressive drugs (McCabe, 1979).

Sensorineural hearing loss can occur simultaneously in both ears, although more often involvement of one ear is followed, within a short period of weeks or months, by involvement of the other ear. The hearing disorder is usually associated with vertigo/dizziness, although symptoms can be limited to the cochlear or vestibular system (McCabe, 1979; Zingler et al., 2007; Greco et al., 2014). It is the rapid aggravation of the symptoms, particularly the usually asymmetric hearing loss, that will draw attention to an AIED (McCabe, 1979). Vestibular symptoms range from vertigo that can be recurrent to progressive dizziness/disequilibrium aggravated in darkness with oscillopsia during head movement due to bilaterally absent vestibular function (McCabe, 1979; Sismanis et al., 1997).

Conventional therapy is not efficient in AIED. On the contrary, dramatic improvement with immunomodulatory treatment supports the diagnosis. There is general agreement to try steroids (1 mg/kg/day of prednisone or equivalent) for 2–4 weeks, gradually tapered over months (Alexander et al., 2009; Matsuoka and Harris, 2013). The ideal duration of treatment has not been determined and is often individualized according to treatment response and drug tolerance. After a period of amelioration or stabilization, the disease may progress despite the steroid treatment. Other immunosuppressive drugs have been tried, including aziathropine, methotrexate, and cyclophosphamide (McCabe, 1979; Sarcaydin et al, 1993; Sismanis et al., 1997). New biologic modifiers, i.e., rituximab and adalimumab intravenously or infliximab transtympanically, have been proposed (Van Wijk et al., 2006; Cohen et al., 2011; Matsuoka and Harris, 2013). Plasmapheresis is an alternative to immunosuppressive drug failure or intolerance (Luetje, 1989; Luetje and Berliner, 1997). However, the use of all these immunosuppressive drugs, with their risks of side-effects, is a difficult issue, as diagnosis relies on clinical findings, with no serologic marker that can confirm an

autoimmune disorder limited to the inner ear (Bovo et al., 2009, 2010; Lobo et al., 2014).

Autoimmune inner-ear disorder in the context of a multisystem organ disorder

In these patients, the immune system attacks the inner ear and some other organs, such as the eyes, the central nervous system, skin, and kidneys. From an audiovestibular point of view, the same criteria, i.e., bilaterality, rapid aggravation of the symptoms, and efficacy of immunosuppressive agents, point to an AIED. Vestibular symptoms range from vertigo, which can be recurrent and mimic Menière's disease, to progressive dizziness/disequilibrium aggravated in darkness. Indeed, the vestibular symptoms are diverse depending on several factors, such as the speed of occurrence of the vestibular loss, the degree of loss, the unilaterality or bilaterality of the lesion, and whether the damage has triggered a fluctuating dysfunction (endolymphatic hydrops due to an immune reaction similar to the one observed in Menière's disease). In the context of multisystem organ disorder, the diagnosis is often easier to establish due to the lesion of other targets and the possible abnormalities of biologic markers. Consequently, the use of cytotoxic agents is broader.

Herein, we will only discuss diseases where vestibular and/or audiovestibular symptoms are a regular finding. The diseases include Cogan syndrome, relapsing polychondritis, Vogt–Koyanagi–Harada syndrome, Susac syndrome, and Wegener disease. We will not discuss diseases for which vestibular symptoms have been rarely described, may be purely coincidental, or are predominantly due to central nervous system involvement.

Cogan syndrome

Cogan syndrome predominantly affects young adults between the ages of 20 and 40 years, but can occur in a pediatric population (Cogan, 1945; Pagnini et al., 2012). Typical Cogan syndrome is defined by nonsyphilitic interstitial keratitis associated with audiovestibular symptoms (Cogan, 1945). Patients complain of disabling vertigo that can be recurrent and mimic Menière's disease at the beginning (Cogan, 1945; Haynes et al., 1981). However, the sensorineural hearing loss is usually bilateral and progresses to complete deafness within 2 years, which is unusual in Menière's disease (Cogan, 1945; Haynes et al., 1980). Corticosteroid therapy usually leads to improvement and should be started early in the disease in order to ameliorate the overall prognosis and preserve hearing (Haynes et al., 1981; Pagnini et al., 2012). Refractory cases of hearing loss can be treated by other immunosuppressive drugs and/or cochlear implantation (Pagnini et al., 2012; Bacciu et al., 2015). In many cases, symptomatology is not restricted to the eyes and ears, with cardiovascular (valve insufficiency), musculoskeletal, neurologic, gastrointestinal, and cutaneous symptoms also present (Pagnini et al., 2012).

Relapsing polychondritis

Relapsing polychondritis is a rare disease in which recurrent attacks of inflammation affect cartilaginous and connective tissue structures, including the ear, nose, larynx, tracheobronchial tree, eyes, joints, skin, heart valves, and aorta (Fig. 20.6). The disease is easily misdiagnosed in patients who present with multiorgan damage, including joints, eyes, and audiovestibular manifestations of unknown origin. It is the development of chondritis of the ears (Fig. 20.6B), occurring in 90% of patients, and/or nose, that provides the diagnosis. Inner-ear involvement, with hearing loss and vertigo, is not rare and has even been reported as the initial symptom of the disease (Kimura et al., 1996; Kumakiri et al., 2005). Hearing loss can be bilateral and severe, leading to cochlear implantation (Seo et al., 2012).

Vogt–Koyanagi–Harada syndrome

Vogt–Koyanagi–Harada syndrome is a rare syndrome characterized by inflammatory ocular disease as well as skin, ear, and meningeal manifestations (uveomeningitis). The symptoms are dominated by bilateral panuveitis (anterior and posterior segment). Skin lesions include alopecia, poliosis, and vitiligo. Inner-ear involvement manifests as bilateral sensorineural hearing loss, sometimes vertigo. Vertigo is typically of a peripheral type, with canal paresis on caloric examination, and is usually not recurrent (Yoshimoto, 1995; Dousary, 2011). Vertigo/dizziness due to central impairment of the cerebellar type is rare (Yoshimoto, 1995). Meningeal manifestations consist of headache and fever. CSF analysis often demonstrates nonspecific inflammation with predominantly lymphocytic pleocytosis.

Susac syndrome (retinocochleocerebral vasculopathy)

Susac syndrome is also called SICRET syndrome (small infarctions of cochlear, retinal, and encephalic tissue) or RED-M (microangiopathy with retinopathy, encephalopathy, and deafness) (Schwitter et al., 1992; Susac, 1994). Susac syndrome is caused by occlusions of microvessels, presumed to be mediated by an autoimmune response, leading to a characteristic clinical triad of central nervous system dysfunction, visual symptoms, and sensorineural hearing impairment, with or without vertigo (Susac, 1994). At clinical onset, the most common

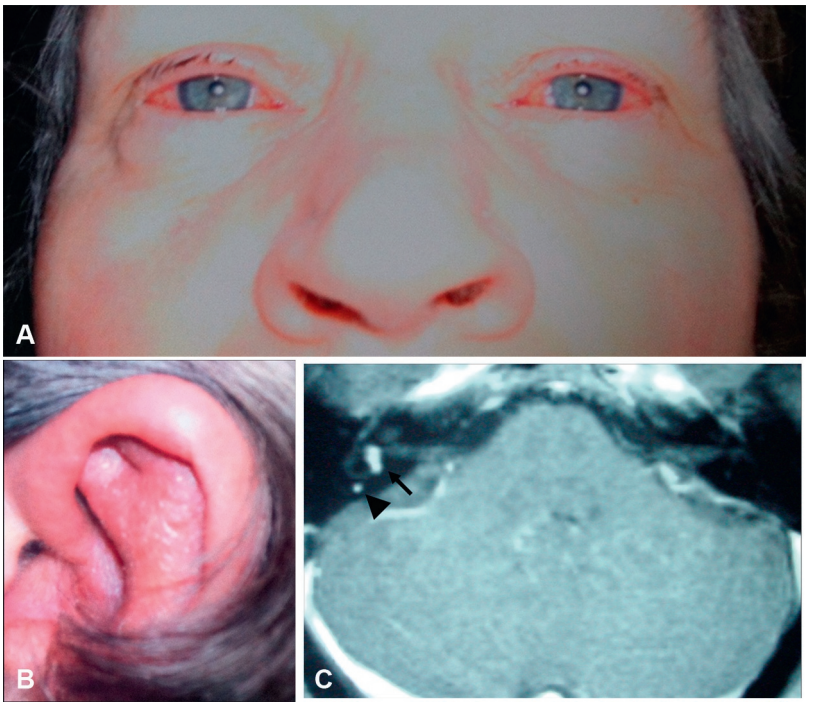

Fig. 20.6. Relapsing polychondritis. Typical bilateral eye (**A**) and ear (**B**) inflammation in relapsing polychondritis. Axial magnetic resonance imaging (MRI) scan (**C**) in another patient suffering from relapsing polychondritis who complained of a right sudden deafness and vertigo with a right peripheral vestibular deficit. Axial MRI scan (**C**) shows enhancement of the right vestibule (arrow) and posterior canal (arrowhead) after gadolinium administration in keeping with labyrinthitis in the context of relapsing polychondritis. The alternative diagnosis was an intralabyrinthine schwanomma that can be excluded by the development of a right labyrinth ossification on imaging follow-up.

manifestation is central nervous system dysfunction, followed by visual symptoms and audiovestibular disturbances. The audiogram shows unilateral or bilateral sensorineural hearing loss that can predominate over low to medium frequencies (Monteiro et al., 1985; Schwitter et al., 1992; Susac, 1994; Ayache et al., 2000). The latter can be compatible with damage to the apical portions of the cochlea, which are supplied by end arterioles in the inner ear (Monteiro et al., 1985; Roeser et al., 2009). Vertigo is less frequent than hearing loss but can mimic Menière's disease when associated with a predominantly low- to medium-frequency hearing loss (Roeser et al., 2009; Mateen et al., 2012). Gait impairment is frequent and caused by lesions of various organs as the syndrome involves the ears, brain, and eyes. Ophthalmoscopy and fluorescein angiography confirm bilateral occlusions of retinal artery branches. Brain MRI shows multiple and bilateral lesions of white- and gray-matter nuclei with prominent involvement of the corpus callosum. CSF analysis demonstrates nonspecific abnormalities such as elevated protein levels and pleocytosis. Based on the hypothesis of an autoimmune disease, treatment should be immunosuppressive. In addition, anticoagulant or antiplatelet agents should be considered. Long-term follow-up shows that most patients can return to work without severe impairment (Aubert-Cohen et al., 2007).

Wegener disease

Wegener granulomatosis is a systemic immune disease with necrotizing granulomatous vasculitis of the upper and lower pulmonary tracts and glomerulonephritis. Otologic involvement can be the first and only sign of the disease, i.e., without pulmonary and kidney involvement (Wierzbicka et al., 2011). The most common manifestations are facial paralysis, postauricular pain, and otitis media with effusion. The latter can be complicated by mixed or sensorineural hearing loss and vertigo (Illum and Thorling, 1982; Takagi et al., 2002). Vertigo and/or disequilibrium is rarely reported in Wegener's disease, but this may be underestimated, as vestibular compensation may minimize the complaints of noncharacteristic vertigo (Takagi et al., 2002; Schmerber and Karkas, 2013). Differential diagnosis will include chronic infections such as tuberculosis and syphilis as well as sarcoidosis. However, cytoplasmic-antineutrophil cytoplasm antibodies (c-ANCA) assay is the basic diagnostic test

and marker of Wegener's disease activity (Wierzbicka et al., 2011). Biopsy specimens, preferentially from the nose or paranasal sinus rather than from the middle ear, are helpful in atypical cases (Takagi et al., 2002). Early diagnosis and appropriate treatment, usually combining steroids and cytotoxic drugs, are important to prevent irreversible changes.

In conclusion, the suspicion of an AIED based on clinical grounds, such as a rapidly progressive bilateral inner-ear disorder, deserves more extensive clinical and biologic examination. The extent of this examination depends on whether the AIED is isolated or integrated in a multisystem organ disorder. As a rule, an ocular examination is worthwhile, as well as blood tests to search for kidney involvement and nonspecific general inflammation with erythrocyte sedimentation rate, C-reactive protein, complement detection (C1q, C3, C4, CH50), and immunoglobulins. Laboratory tests of more specific inflammation include c-ANCA for Wegener disease, antinuclear autoantibody for lupus, and rheumatoid factor for rheumatoid arthritis. Additionally, serologic testing for infectious diseases such as syphilis or Lyme disease, which may mimic AIED and require specific treatment, should be performed. Based on clinical features and the results of the previous biologic tests, more extensive examinations may be required, including CSF analysis and a positron emission tomography scan. Of note, blood tests for specific markers of inner-ear disorders are not performed on a routine basis due to their lack of sensitivity and specificity (Matsuoka and Harris, 2013).

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Chapter 21

Posttraumatic dizziness and vertigo

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Abstract

Traumatic brain injury is an increasingly common public health issue, with the mild variant most clinically relevant for this chapter. Common causes of mild traumatic brain injury (mTBI) include motor vehicle accidents, athletics, and military training/deployment. Despite a range of clinically available testing platforms, diagnosis of mTBI remains challenging. Symptoms are primarily neurosensory, and include dizziness, hearing problems, headaches, cognitive, and sleep disturbances. Dizziness is nearly universally present in all mTBI patients, and is the easiest symptom to objectify for diagnosis. Aside from a thorough history and physical exam, in the near future specialized vestibular function tests will be key to mTBI diagnosis. A battery of oculomotor (antisaccade, predictive saccade) and vestibular tasks (head impulse test) has been demonstrated to sensitively and specifically identify individuals with acute mTBI. Vestibular therapy and rehabilitation have shown improvements for mTBI patients in cognitive function, ability to return to activities of daily living, and ability to return to work. Dizziness, as a contributor to short- and long-term disability following mTBI, is ultimately crucial not only for diagnosis but also for treatment.

INTRODUCTION

An 18-year-old patient presents to you after a collision in a soccer game. The individual reports feeling "off," has a headache, and complains of feeling dizzy. This is a common symptom complex seen after a sports-related mild traumatic brain injury (mTBI). Traumatic brain injury (TBI) is an increasingly common public health issue (Okie, 2005; Warden, 2006; Hoge et al., 2008; Schneiderman et al., 2008; Terrio et al., 2009; Faul et al., 2010; Lew et al., 2011; Coronado et al., 2012; Hendricks et al., 2013; DoD Worldwide Numbers for TBI, 2014). Every year over 3.8 million individuals in the USA are diagnosed with TBI. Common causes include motor vehicle accidents, sports, and work-related accidents. The situation is even more serious in the military, where 25% of all individuals who have been deployed to Southwest Asia suffer at least one head injury. Head trauma can be divided into several different classes, including mild, moderate, and severe TBI. Moderate and severe TBI typically involve significant brain injury and often a lengthy hospitalization. These complex neurologic disorders include dizziness as one of many multifactorial disorders, making diagnosis and treatment more difficult by the host of comorbid conditions. As a result, this chapter will focus on mTBI and the dizziness associated with this disorder.

THE ROLE OF DIZZINESS IN THE DIAGNOSIS OF MTBI

The diagnosis of mTBI is difficult. Despite a host of sideline and site-of-injury test platforms that have been introduced, diagnosis of mTBI remains challenging (Harmon et al., 2013; Putukian et al., 2013; Choe and Giza, 2015). The symptoms of mTBI are primarily neurosensory (Hoffer et al., 2010, 2013, 2016), and generally include dizziness, hearing problems, headaches, cognitive

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difficulties, and sleep disturbances. Many of these symptoms prove difficult to evaluate, particularly headache and sleep disorders, which rely on self-report and are inherently inaccurate in this group of patients. Cognitive difficulties can be measured objectively, but tests are not necessarily efficient and test results can be difficult to interpret. Hearing disorders can be easily diagnosed if the abnormality is a simple hearing loss, but often the symptoms present as a central auditory-processing abnormality, which is more difficult to assess, or tinnitus, which relies on self-report. Therefore, dizziness, which is almost universally present (Hoffer et al., 2010) in this population, is the easiest and most objective symptom to measure in mTBI.

SYMPTOMS

Posttraumatic dizziness can present in a wide variety of manifestations. These symptoms vary depending on a number of factors, including the type and force of the impact. Additionally, beyond the actual initial impact, there are a number of other elements to consider. These include the number of previous head traumas experienced by the individual, undefined genetic factors, and a more complex phenomenon that can be best characterized as the "forces at work." A complete discussion of this last concept is beyond the scope of this chapter. In brief, the "forces at work" encompass the direction of the impact and any secondary force that occurs as a result of the impact (Chavko et al., 2007; Moore et al., 2009; Wang et al., 2014). In some instances, the secondary force is obviously relevant to the head injury. For example, after a blast exposure (initial force), which itself can cause head injury, a person is thrown and hits the head on a blunt object (secondary force). In other cases, these secondary forces are less obvious such as neck trauma (i.e., neck movement after a head impact), or other injuries occurring at the time of a head injury (Stuhmiller et al., 1990; Johnson et al., 2014; Shah et al., 2014).

Symptoms of posttraumatic dizziness can be divided into several categories, to include vertigo (illusory sensation of the surrounding environment or the individual moving/rotating), head motion-induced vertigo, dizziness (sensation of disturbed or impaired spatial orientation without a false or distorted sense of motion), head motion-induced dizziness, unsteadiness (sensation of being off balance or feeling clumsy without directional preference), and visual lag (sensation of the surrounding environment following behind head movement with a delay) (Gottshall et al., 2003; Bisdorff et al., 2009; Akin and Murnane, 2011; Grubenhoff et al., 2011; Scherer et al., 2011; Suarez et al., 2011; Hoffer, 2015). We have characterized the acute and subacute dizziness complexes seen after head trauma (Table 21.1).

Head trauma can result in benign paroxysmal positional vertigo (BPPV), in which individuals have the brief sensation of vertigo on assuming various head positions. Traumatic BPPV does not differ significantly from idiopathic BPPV, except that there may be a slightly higher incidence of individuals with traumatic BPPV presenting with lateral canal findings. Nevertheless, in both cases the posterior semicircular canal is the most common canal to be affected by the stray otoliths. Exertional dizziness is dizziness (usually unsteadiness but occasionally vertigo) that occurs at the conclusion or near the very end of a period of exercise or exertion.

Vestibular migraine shares many of the same features as posttraumatic vestibular migraine (Headache Classification Committee of the International Headache Society, 2013). In this disorder, individuals report episodic vertigo with periods of unsteadiness and corresponding migraine headaches at least 50% of the time (Lempert et al., 2012).

Table 21.1

Vestibular disorders seen after traumatic brain injury

Entity	History	Physical exam
Benign paroxysmal positional vertigo (BPPV)	Positional vertigo	Nystagmus on Dix–Hallpike test or modified Dix–Hallpike test
Exertional-induced dizziness	Dizziness at the conclusion of exercise	Abnormalities in challenged gait test during exertion
Vestibular migraine	Episodic vertigo lasting 5 minutes to 72 hours with periods of unsteadiness Headache lasting 4–72 hours	Abnormalities in challenged gait ± Abnormalities on head impulse testing Normal static posture tests
Spatial disorientation	Constant feeling of unsteadiness worsened by standing but still present when sitting or lying down Drifting to one side while walking Shifting weight when standing still ± Vertigo and headache	Abnormalities in challenged gait ± Abnormalities on head impulse Abnormalities with static posture

The most difficult and likely most common balance disorder seen after head injury is spatial disorientation, in which an individual feels continuously unsteady (Hoffer et al., 2004). This sensation of unsteadiness is worsened by standing still or moving quickly. Slow movements tend to lessen the severity of this disorder. We, and others, have postulated that this may be due to a posttraumatic loss of the body's ability to sense the gravitoinertial vector used by the body to determine true upright. Therefore, during slow motion, the added inputs from moving help to rectify this vector, whereas inputs when standing still or inputs that are changing quickly (fast motion) are less useful (Hoffer et al., 2015).

SPECIFIC POSTTRAUMATIC VESTIBULAR DISORDERS

As opposed to the above discussion, there are specific, identifiable etiologies of dizziness secondary to head trauma, such as perilymphatic fistula (PLF), superior semicircular canal dehiscence (SSCD), and temporal bone fracture. These generally occur concurrently with moderate to severe TBI and thus will only be discussed in brief.

PLF is a disorder caused by an abnormal opening (most commonly at the round or oval window) or rupture of the fluid-filled membranous labyrinth (Goodhill, 1980; Glasscock et al., 1992). This allows for fluid leakage from the inner ear to middle ear cavity. Injury occurs from barotrauma as a result of the head trauma and may also result from an explosive blast wave or rapid scuba diving depressurization. These individuals will typically present with difficult-to-diagnose dizziness in the form of vertigo at the time of the injury, along with sensorineural hearing loss and tinnitus.

SSCD is a condition where the bone over the superior semicircular canal is cracked or congenitally absent, which causes a protrusion of the membranous superior semicircular canal. This protrusion creates a "third mobile window" in the bone that enables aberrant communication from the inner ear, causing vestibular and/or auditory symptoms (Spasic, 2015). In classic presentations, these individuals have unsteadiness or vertigo which is intensified by loud noises (Tullio phenomenon) or pressure changes (Hennebert sign). Auditory symptoms may include an intensified sound of the patient's own voice (autophony) and conductive hearing loss. Unlike PLF, SSCD can develop more slowly, as the crack (caused by damage to the bony covering of the canal) widens over time. "Third mobile window" syndromes may be associated with different patterns of performance on verbal memory, visual memory, and attention components of the Wide Range Assessment of Learning and Memory test battery, with different postoperative recovery outcomes (Wackym et al., 2016).

Severe head trauma may cause unilateral vestibular loss by the mechanism of temporal bone fracture. The majority of temporal bone fractures (80%) are longitudinal (in the axis of the petrous bone) rather than transverse (Cannon and Jahrsdoerfer, 1983). Longitudinal temporal bone fractures are more likely to involve the inner ear, while transverse fractures are more likely to transect the vestibulocochlear nerve or involve the otic capsule and inner ear (Fife and Giza, 2013). Vestibular loss may be seen after head trauma, even without temporal bone fracture as a result of traction or injury-induced demyelination of the vestibulocochlear nerve, trauma-related bleeding or microischemic changes, or direct injury to the labyrinth (Agrup et al., 2007).

TESTING ABNORMALITIES IN DIZZINESS WITH MTBI

The most important information obtained from a patient with suspected posttraumatic dizziness or vertigo is through a thorough medical history and a standard vestibular physical exam. Examiners should pay particular attention to postural stability (Romberg and tandem Romberg tests), gait with horizontal and vertical head turning (museum gait), spontaneous nystagmus, smooth pursuit, and head impulse testing (HIT). Beyond these physical exam maneuvers, the most important measures are specialized vestibular function tests that can be conducted with infrared goggles and assorted visual stimuli (Cifu et al., 2014). These tests can be separated into oculomotor tasks (vertical and horizontal smooth pursuit, vertical and horizontal saccades, antisaccade, predictive saccade, optokinetic response, saccade reaction time test) and vestibular tasks (HIT, subjective visual vertical and horizontal).

Work in our lab currently under review for publication has demonstrated that a battery of antisaccade (increased error rate percentage), predictive saccade (decreased absolute number), and HIT tasks (increased absolute gain symmetry, decreased average gain) can sensitively and specifically (88% and 97% respectively) identify individuals with acute mTBI (Thiagarajan and Ciuffreda, 2014; Balaban et al., 2015, 2016; Kiderman et al., 2015). These tasks reflect underlying pathophysiologic differences in those with acute mTBI compared to controls. The increased antisaccade error rate suggests impaired inhibitory contributions of frontal cortical regions and GABAergic output from various brain regions (Munoz and Everling, 2004). The abnormal HIT results are presumed to be a result of disruption to neuroanatomic pathways involving the vestibular nuclei, related cerebellar connections, and direction projections from the oculomotor, trochlear, and oculomotor nuclei.

As such, we believe that vestibular testing is the most efficient, effective, and objective way to determine the presence or absence of mTBI. Vestibular testing can be performed as early as immediately after the head trauma or later in the injury time course, with nearly equal accuracy.

TREATMENT

The treatment of dizziness associated with head injury requires the efforts of a multidisciplinary team. For the three specific posttraumatic vestibular disorders discussed above (PLF, SSCD, temporal bone fracture), surgery is the mainstay of treatment. Therapy for most individuals with other causes of posttraumatic dizziness is vestibular rehabilitation. Gottshall and colleagues (2003) have demonstrated that cognitive function, ability to return to activities of daily living, and ability to return to work all improve with vestibular rehabilitation. This work was confirmed by a study from Alsalaheen et al. (2010), which showed shorter disability time and improved outcomes in this population after vestibular rehabilitation. In individuals with blast-induced mTBI, Gottshall and Hoffer (2010) employed a battery of vestibular, visual, and cognitive tests to demonstrate that target-following and dynamic visual acuity tasks returned to normative values after 8 weeks of vestibular therapy. Other groups have used ocular therapy and cervical therapy to result in improvements (reduction in horizontal fixational error, increased horizontal and vertical saccadic gain, reduced saccade ratio for simulated reading, and reduced time to medical clearance for return to athletics in youths) for treated individuals compared to those exposed to the placebo (Schneider et al., 2014; Thiagarajan and Ciuffreda, 2014). This idea was further confirmed by a large study that demonstrated the effectiveness of eye, head, and postural therapy (Alsalaheen et al., 2013).

In our experience, vestibular therapy is most effective when combined with a regimen that controls related symptoms, particularly headache. Individuals have better outcomes when their headache (a frequent complaint after head injury) is controlled. Moreover, despite the successes of vestibular therapy, individual patient factors (particularly young age) and less severe associated symptoms are independent predictors of a successful outcome (Jacobs et al., 2010).

CONCLUSION

Dizziness is one of the most common symptoms seen after head injury and is a significant contributor to short- and long-term disability from this disorder. As discussed in this chapter, recent advances have made dizziness easier to assess with objective outcomes. These developments suggest that vestibular testing is one of the most effective and efficient methods for diagnosis of mTBI. Balance disorders from head injury can be treated, and this treatment typically consists of vestibular rehabilitation therapy. Vestibular rehabilitation therapy can result in improvement in the dizziness as well as other neurosensory symptoms.

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Chapter 22

Vestibular migraine

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Abstract

During the last decades a new vestibular syndrome has emerged that is now termed vestibular migraine (VM). The main body of evidence for VM is provided by epidemiologic data demonstrating a strong association between migraine and vestibular symptoms. Today, VM is recognized as one of the most common causes of episodic vertigo. The clinical presentation of VM is heterogeneous in terms of vestibular symptoms, duration of episodes, and association with migrainous accompaniments. Similar to migraine, there is no clinical or laboratory confirmation for VM and the diagnosis relies on the history and the exclusion of other disorders. Recently, diagnostic criteria for VM have been elaborated jointly by the International Headache Society and the Bárány Society. Clinical examination of patients with acute VM has clarified that the vast majority of patients with VM suffer from central vestibular dysfunction. Findings in the interval may yield mild signs of damage to both the central vestibular and ocular motor system and to the inner ear. These interictal clinical signs are not specific to VM but can be also observed in migraineurs without a history of vestibular symptoms. How migraine affects the vestibular system is still a matter of speculation. In the absence of high-quality therapeutic trials, treatment is targeted at the underlying migraine.

During the last three decades several new vestibular syndromes have emerged on the basis of clinical, epidemiologic, and pathophysiologic findings, such as vestibular migraine (VM), superior canal dehiscence syndrome, and vestibular paroxysmia. VM is by far the most common of these new disorders, gaining increasing recognition by clinicians and scientists. A PubMed search in 2015 yielded that 80% of papers on the association between migraine and vestibular symptoms have been published since the turn of the millennium.

Vertigo as a presentation of migraine was already recognized from the early days of neurology (Liveing, 1873; Escat, 1904; Boenheim, 1917), but systematic studies on the association between vertigo and migraine started only a hundred years later. Beginning with Slater's (1979) and Kayan and Hood's (1984) classic papers, the clinical features of VM have been well elucidated in several large case series (Cutrer and Baloh, 1992; Cass et al., 1997; Johnson, 1998; Dieterich and Brandt, 1999; Neuhauser et al., 2001; Reploeg and Goebel, 2002). To date, most dizziness clinic experts rank VM as one of the most common causes for episodic vertigo. Numerous synonyms have been used to designate vertigo caused by a migraine mechanism, including benign recurrent vertigo, migrainous vertigo, migraine-associated vertigo, migraine-associated dizziness, and migraine-related vestibulopathy. VM has been convincingly advocated as a term that stresses the particular vestibular manifestation of migraine and thus best avoids confounding with nonvestibular dizziness associated with migraine (Brandt and Strupp, 2006). Although there is still some debate on VM as an entity (Phillips et al., 2010; von Brevern et al., 2011), it is expected that the dissemination of recently developed diagnostic criteria for

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VM by the Bárány Society and the International Headache Society (Lempert et al., 2012) will enhance research and improve the quality of clinical care of patients with VM.

EPIDEMIOLOGY

The scientific basis for our current understanding of VM is provided mainly by epidemiologic studies. However, the interrelations between vertigo and migraine are complex. First, both migraine and vertigo are common complaints in the general population and may coexist in a patient just by coincidence. Second, some vertigo syndromes have been shown to be epidemiologically associated with migraine. According to our current understanding, these disorders are linked to, but not caused by, migraine. They include Menière's disease, benign paroxysmal positional vertigo (BPPV), motion sickness, rare cerebellar disorders, and several psychiatric syndromes that may manifest with vertigo and dizziness (Lempert and Neuhauser, 2009). Finally, there is VM that is conceptualized as migraine manifesting predominantly with episodic vertigo.

Epidemiologic association of migraine and vertigo

As both vertigo and migraine rank among the most common complaints in medicine, it is crucial to ask for the evidence supporting a specific link between vestibular symptoms and migraine beyond a chance concurrence. In several studies, the prevalence of migraine in unselected dizziness clinic patients has been found to be higher than expected (Aragones et al., 1993; Savundra et al., 1997). Furthermore, all case-control studies published to date indicate a more than chance association of migraine with vertigo. The prevalence of migraine was 1.6 times higher in 200 dizziness clinic patients than in 200 age- and sex-matched controls (Neuhauser et al., 2001). Conversely, in migraineurs, the prevalence of vertigo is higher as compared to nonmigraineurs. In a seminal study by Kayan and Hood (1984), 27% of unselected migraine patients reported vertigo, compared with 8% of patients with tension-type headache. Similarly, several other case-control studies found an increased prevalence of vertigo and dizziness in migraineurs (Kuritzky et al., 1981; Vukovic et al., 2007; Akdal et al., 2013).

Even more striking is the preponderance of migraine in patients with recurrent spontaneous vertigo, not fulfilling diagnostic criteria for Menière's disease. Cha et al. (2009) found that 87% of 208 patients with "benign recurrent vertigo" met the criteria for migraine and that 70% of these fulfilled diagnostic criteria for VM. In 72 patients with recurrent vertigo of unknown cause, the prevalence of migraine was six times higher as compared to an age- and sex-matched control group (61% vs. 10%) (Lee et al., 2002). Likewise, in patients with recurrent vertigo of unknown cause, Rassekh and Harker (1992) found a prevalence of migraine of 81% as compared to 22% in patients with Menière's disease.

The intersection of vertigo and migraine has also been examined on the population level. Assuming a lifetime prevalence of migraine of 14% (Jensen and Stovner, 2008) and a lifetime prevalence of vertigo of 7.4% (Neuhauser et al., 2005), a chance coincidence of 1% can be calculated. Notably, a large epidemiologic study of the general population found that three times more adults have a history of both vertigo and migraine than would be expected by chance alone (Neuhauser et al., 2006).

Epidemiology of vestibular migraine

In specialized dizziness clinics, VM is the most common cause of spontaneous recurrent vertigo, accounting for about 10% of diagnoses (Brandt, 1999; Neuhauser et al., 2001; van Omberg et al., 2015). VM is still widely underdiagnosed, as shown by a study from a dizziness clinic in Switzerland, where VM accounted for 20.2% of the diagnoses in young patients, but was suspected by the referring doctors in only 1.8% (Geser and Straumann, 2012). In a large two-stage population-based study with screening interviews followed by expert telephone interviews, the lifetime prevalence of VM in the general population has been estimated at 0.98% (Neuhauser et al., 2006). In a community-based sample of middle-aged women in Taiwan, VM was identified in 5% of the whole group and in 30% of those with migraine (Hsu et al., 2011).

VM may occur at any age (Cutrer and Baloh, 1992; Cass et al., 1997), although rarely after the sixth decade of life (Dieterich and Brandt, 1999). In most patients, migraine begins earlier in life than VM (Dieterich and Brandt, 1999; Neuhauser et al., 2001). Similar to migraine, VM has a female preponderance, with a female-to-male ratio between 1.5 and 4.5 to 1 (Dieterich and Brandt, 1999; Neuhauser et al., 2006). Familial occurrence has been reported in some patients, indicating an autosomal-dominant pattern of inheritance with decreased penetrance in men (Oh et al., 2001). Some migraineurs have been free from migraine attacks for years when VM first manifests itself (Dieterich and Brandt, 1999). Often, migraine headaches are replaced by vertigo attacks in women around menopause (Park and Viirre, 2010).

Diagnostic criteria for vestibular migraine

During the last three decades the International Classification of Headache Disorders (ICHD) has been developed by the International Headache Society as a widely used framework to define operational diagnostic criteria for

Table 22.1

Diagnostic criteria for migraine without aura

A. At least five attacks fulfilling criteria B–D
B. Headache attacks lasting 4–72 hours
C. Headache has at least two of the following characteristics:
   1. Unilateral localization
   2. Pulsating quality
   3. Moderate or severe pain intensity
   4. Aggravation by or causing avoidance of routine physical activity
D. During headache at least one of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia
E. Not attributable to another disorder

Reproduced from Headache Classification Subcommittee of the International Headache Society (2013).

headache disorders such as migraine (Table 22.1). In the previous ICHD (ICHD-2), vertigo was not included as a migraine symptom in adults, except for basilar-type migraine (now termed migraine with brainstem aura), which presents with vertigo in more than 60% of patients (Sturzenegger and Meienberg, 1985; Kirchmann et al., 2006). As a symptom of migraine with brainstem aura, vertigo should last between 5 and 60 minutes and should be accompanied or followed by migraine headache. In addition, at least one more aura symptom originating from the brainstem is required. Fewer than 10% of patients with VM fulfilled the criteria for basilar-type migraine/migraine with brainstem aura (Cass et al., 1997; Johnson, 1998; Dieterich and Brandt, 1999), which makes this diagnosis an inappropriate category for most of these patients.

Neuhauser and coworkers (2001) proposed diagnostic criteria for VM that have been widely used for clinical and research purposes. These criteria have a high positive predictive value. A re-evaluation of 75 patients 105 ± 16 months after the initial diagnosis of VM confirmed this diagnosis in 84%, whereas a competing diagnosis was considered in 16% (Radtke et al., 2011).

Recently, the Bárány Society, which represents the international community of basic scientists, otolaryngologists, and neurologists committed to vestibular research, and the International Headache Society have jointly refined these diagnostic criteria, defining VM and probable VM (Lempert et al., 2012). These criteria have been included in the third edition of the ICHD (ICHD-3), published in 2013. VM appears in the appendix of the ICHD-3 for new disorders that need further research for validation. In addition, the classification of VM is part of the evolving International Classification of Vestibular Disorders (ICVD) of the Bárány Society. The new ICHD-3 includes only VM, while the ICVD also contains probable VM (Table 22.2). The recent classification of VM is a major step forward and should allow for broader acceptance of the disorder and more accurate recognition.

SYMPTOMS

Types of vertigo

Patients with VM typically report episodic spontaneous or positional vertigo. Some experience a sequence of spontaneous vertigo transforming into positional vertigo after several hours or days. Altogether, 40–70% of patients experience positional vertigo in the course of the disease, but not necessarily with every attack. This positional vertigo is distinct from BPPV with regard to duration of individual attacks (often as long as the head position is maintained in VM versus only seconds in BPPV), duration of symptomatic episodes (minutes to days in VM versus weeks in BPPV), and nystagmus findings (von Brevern et al., 2004). A frequent additional symptom is head motion-induced dizziness, i.e., imbalance, illusory motion, and nausea aggravated or provoked by head movements (Kuritzky et al., 1981; Cass et al., 1997). Visually induced vertigo, i.e., vertigo provoked by moving visual scenes such as traffic or movies, can be another prominent feature of VM (Cass et al., 1997; Waterston, 2004; Radtke et al., 2012). The combination of different types of vertigo distinguishes VM from other neurotologic disorders such as BPPV or Menière's disease, which typically present with monosymptomatic vertigo. The duration of symptomatic episodes ranges from minutes to hours and several days, sometimes even in the same patient (Kayan and Hood, 1984; Cutrer and Baloh, 1992; Dieterich and Brandt, 1999; Neuhauser et al., 2001). Although the core attack with objective clinical signs rarely exceeds 72 hours, for some patients it may take considerably longer to fully recover from an episode.

Often patients with VM report episodic vestibular symptoms as well as persistent dizziness and imbalance (Neff et al., 2012). In many patients this latter symptom can be attributed to secondary psychiatric morbidity (Furman et al., 2005a; Eckhardt-Henn et al., 2008; Boldingh et al., 2011; Neff et al., 2012). About 50% of patients with VM have a psychiatric comorbidity, most commonly anxiety, phobic and somatoform disorders (Lahmann et al., 2015). In addition, patients with VM are often affected by motion sensitivity even between attacks (Jeong et al., 2010), which may also lead to a chronic type of dizziness. These two components of interictal dizziness, psychogenic dizziness, and motion sensitivity, may not be easily discriminated in individual patients (Furman et al., 2005a).

Table 22.2

Diagnostic criteria for vestibular migraine

1. Vestibular migraine
   A. At least five episodes with vestibular symptoms[1] of moderate or severe intensity,[2] lasting 5 minutes to 72 hours[3]
   B. Current or previous history of migraine with or without aura according to the *International Classification of Headache Disorders* (ICHD)[4]
   C. One or more migraine features with at least 50% of the vestibular episodes[5]:
      - Headache with at least two of the following characteristics: one-sided location, pulsating quality, moderate or severe pain intensity, aggravation by routine physical activity
      - Photophobia and phonophobia[6]
      - Visual aura[7]
   D. Not better accounted for by another vestibular or ICHD diagnosis[8]
2. Probable vestibular migraine
   A. At least five episodes with vestibular symptoms[1] of moderate or severe intensity,[2] lasting 5 minutes to 72 hours[3]
   B. Only one of the criteria B and C for vestibular migraine is fulfilled (migraine history or migraine features during the episode)
   C. Not better accounted for by another vestibular or ICHD diagnosis[8]

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[1]Vestibular symptoms, as defined by the Bárány Society's Classification of Vestibular Symptoms and qualifying for a diagnosis of vestibular migraine, include:

- Spontaneous vertigo including:
  - Internal vertigo, a false sensation of self-motion, and
  - External vertigo, a false sensation that the visual surround is spinning or flowing
- Positional vertigo, occurring after a change of head position
- Visually induced vertigo, triggered by a complex or large moving visual stimulus
- Head motion-induced vertigo, occurring during head motion
- Head motion-induced dizziness with nausea. Dizziness is characterized by a sensation of disturbed spatial orientation. Other forms of dizziness are currently not included in the classification of vestibular migraine.

[2]Vestibular symptoms are rated "moderate" when they interfere with, but do not prohibit, daily activities and "severe" if daily activities cannot be continued.

[3]Duration of episodes is highly variable: about 30% of patients have episodes lasting minutes, 30% have attacks for hours, and another 30% have attacks over several days. The remaining 10% have attacks lasting seconds only, which tend to occur repeatedly during head motion, visual stimulation, or after changes of head position. In these patients, episode duration is defined as the total period during which short attacks recur. At the other end of the spectrum, there are patients who may take 4 weeks to fully recover from an episode. However, the core episode rarely exceeds 72 hours.

[4]Migraine categories 1.1 and 1.2 of the ICDH-2.

[5]One symptom is sufficient during a single episode. Different symptoms may occur during different episodes. Associated symptoms may occur before, during, or after the vestibular symptoms.

[6]Phonophobia is defined as sound-induced discomfort. It is a transient and bilateral phenomenon that must be differentiated from recruitment, which is often unilateral and persistent. Recruitment leads to an enhanced perception and often distortion of loud sounds in an ear with decreased hearing.

[7]Visual auras are characterized by bright scintillating lights or zigzag lines, often with a scotoma that interferes with reading. Visual auras typically expand over 5–20 minutes and last for less than 60 minutes. They are often, but not always, restricted to one hemifield. Other types of migraine aura, e.g., somatosensory or dysphasic aura, are not included as diagnostic criteria because their phenomenology is less specific and most patients also have visual auras.

[8]History and physical examinations do not suggest another vestibular disorder or such a disorder is considered but ruled out by appropriate investigations or such disorder is present as a comorbid or independent condition, but episodes can be clearly differentiated. Migraine attacks may be induced by vestibular stimulation. Therefore, the differential diagnosis should include other vestibular disorders complicated by superimposed migraine attacks.

Relation to headaches

VM often misses not only the duration criterion for a migraine aura as defined by the ICHD, but also the temporal relationship to migraine headaches: vertigo can precede headache as would be typical for an aura, may begin with headache, or may appear late in the headache phase. Most patients experience attacks both with and without headache (Cutrer and Baloh, 1992; Johnson, 1998; Dieterich and Brandt, 1999). Quite frequently, patients have an attenuated headache with their vertigo as compared to their usual migraine (Behan and Carlin, 1982; Johnson, 1998). Often patients develop VM after the intensity of their migraine headaches has

Table 22.3

Diagnostic criteria for benign paroxysmal vertigo of childhood

A.	At least five attacks fulfilling criterion B
B.	Multiple episodes of severe vertigo, occurring without warning and resolving spontaneously after minutes to hours
C.	Normal neurologic examination, audiometric and vestibular functions between attacks
D.	Normal electroencephalogram

Reproduced from Headache Classification Subcommittee of the International Headache Society (2013).

declined during their lifetime. Thus, the dominant clinical feature of VM is usually vertigo, not headache. In some patients, vertigo and headache never arise together (Cutrer and Baloh, 1992; Johnson, 1998; Neuhauser et al., 2001). Misdiagnosis of VM as "cervical vertigo" may occur when accompanying pain is mainly localized in the neck, which is quite common in patients with migraine (Yacovino and Hain, 2013).

Other symptoms

Autonomic symptoms with nausea and vomiting are frequent but nonspecific accompaniments of acute VM (von Brevern et al., 2005; Polensek and Tusa, 2010). Along with the vertigo, patients may experience photophobia, phonophobia, osmophobia, and visual or other auras. These phenomena are of diagnostic importance, since they may represent the only clinical connection of vertigo and migraine. Patients need to be asked specifically about these migraine symptoms since they often do not volunteer them. A dizziness diary can be useful for prospective recording of associated features.

Auditory symptoms, including hearing loss, tinnitus, and aural pressure, have been reported in up to 38% patients with VM (Kayan and Hood, 1984; Parker, 1991; Cass et al., 1997; Johnson, 1998; Neff et al., 2012). Hearing loss is usually mild and transient, without or with only minor progression in the course of the disease (Johnson, 1998). About 20% develop mild bilateral downsloping hearing loss over the years (Radtke et al., 2012). In contrast, unilateral moderate to severe hearing loss starting in the low-frequency range would rather favor a diagnosis of Menière's disease.

Precipitating factors

Asking for migraine-specific precipitants of vertigo attacks may provide valuable diagnostic information, e.g., provocation by deficient sleep, excessive stress, skipped meals, lack of fluid and exposure to sensory stimuli, such as bright or scintillating lights, intense smells or noise. In women, VM can be precipitated by hormonal changes, appearing just before menses, similar to migraine headaches. The influence of specific foods and weather conditions is probably overestimated. Sometimes, migraine accompaniments and typical precipitants may be missing, but VM is still considered the most likely diagnosis after other potential causes have been investigated and appear unlikely. In this case a favorable response to antimigraine drugs may support the suspicion of an underlying migraine mechanism. However, apparent efficacy of a drug should not be regarded as a definite confirmation of the diagnosis, since spontaneous improvement, placebo response, and additional drug effects (e.g., anxiolytic or antidepressant) have to be taken into account.

VESTIBULAR MIGRAINE IN CHILDHOOD

Migraine-related vestibular syndromes are the most common cause of episodic vertigo in children. About 30–50% of children and adolescents with vestibular symptoms report headache associated with their vertigo and a migraine mechanism has been suspected in about a third of children suffering from dizziness and vertigo (Riina et al., 2005; Szirmai, 2010; Jahn et al., 2011; Langhagen et al., 2015). The clinical presentation of VM is similar in children and adults, although difficulties describing their symptoms and a shorter medical history may hamper establishing the diagnosis (Langhagen et al., 2015). Motion sickness and a family history of migraine have been reported in about 50% of affected children (Jahn et al., 2011).

Benign paroxysmal vertigo of childhood is a migraine-related vestibular syndrome manifesting before puberty that is recognized by the International Headache Society as a precursor of migraine (Table 22.3). It has been estimated that 2.6% of children between the ages of 6 and 12 years are affected by benign paroxysmal vertigo of childhood (Abu-Arafeh and Russell, 1995), although this diagnosis seems to be less common in children than VM (Langhagen et al., 2015). Benign paroxysmal vertigo of childhood is characterized by sudden brief attacks of vertigo with imbalance, occurring without warning and lasting minutes, rarely hours, in otherwise healthy children (Basser, 1964). The attacks may be accompanied by nausea, vomiting, pallor, sweating, and nystagmus, but headache and other migrainous symptoms are lacking. Thus, the diagnosis is less specific than VM and rests mainly on the exclusion of other disorders. The ictal ocular motor findings of benign paroxysmal vertigo of childhood have not been well documented. The interictal clinical examination is typically normal (Langhagen et al., 2015). Usually the condition ceases spontaneously after a few years. Many of

these children have a family history of migraine and later develop migraine headache, often years after vertigo attacks have ceased (Krams et al., 2011).

CLINICAL AND LABORATORY TESTING

There is no specific testing abnormality in VM, either in the acute episode or in the interictal interval. However, laboratory testing can be useful to exclude other diseases and to reassure the patient. It is important to bear in mind that minor signs of peripheral and central vestibular dysfunction are not uncommon in patients with VM in the symptom-free interval. Many older studies on laboratory findings in patients with VM are limited by the fact that they lack specific diagnostic criteria for VM, control groups, and normative data, but studies overcoming these limitations have been published recently. In the following, findings during the acute episode and in the symptom-free interval are summarized.

Findings during the episode

Examination during an episode of VM usually yields pathologic nystagmus, indicating central vestibular dysfunction in most patients. A prospective study of 20 patients during the acute phase of VM recorded pathologic nystagmus in 70% of patients by means of three-dimensional video-oculography (von Brevern et al., 2005). A peripheral type of spontaneous nystagmus with a unilateral deficit of the horizontal vestibulo-ocular reflex (VOR) was observed in 3 patients, a central type of spontaneous nystagmus in 3, a central positional nystagmus in 5, and a combined central spontaneous and positional nystagmus in 4 patients during the acute episode of VM (Fig. 22.1). Hearing was not affected in any patient during the episode. Saccadic pursuit was noted in 5 patients during the attack and in 3 of them also in the interval. Overall, findings pointed to central vestibular dysfunction in 10 patients (50%), to peripheral vestibular dysfunction in 3 patients (15%), and were

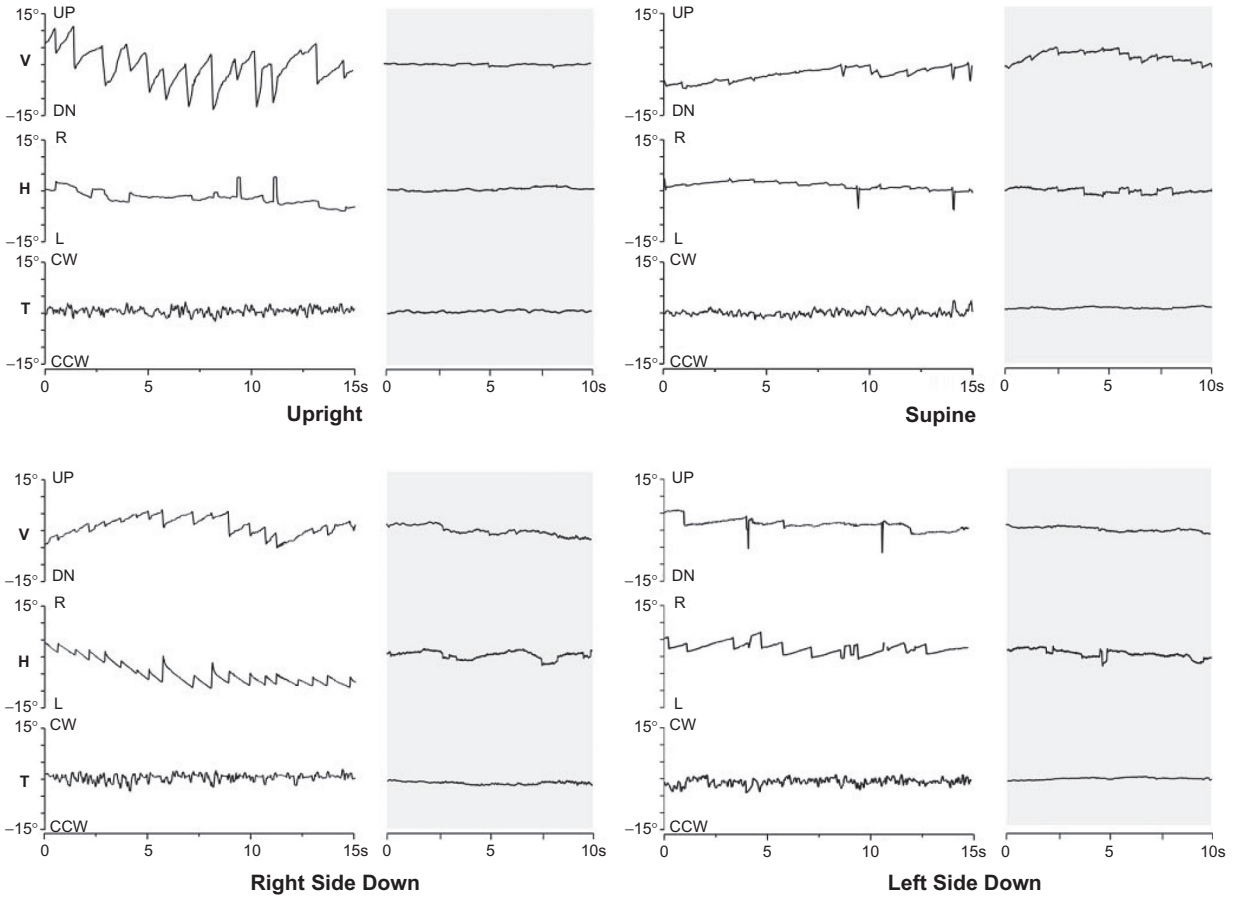

Fig. 22.1. Video-oculographic recording of spontaneous and persistent positional nystagmus in a patient during acute vestibular migraine and during the symptom-free interval (gray shading). Vertical (V), horizontal (H), and torsional (T) eye movement components are shown. Note the downbeating nystagmus in the upright position, which ceases in the supine position. In the lateral positions a predominantly horizontal, geotropic nystagmus appears. (Reproduced from von Brevern et al., 2005.)

inconclusive with regard to the involved structure in 35%. On follow-up vestibular and ocular motor abnormalities had disappeared in almost all patients.

A retrospective study reported on findings in 26 patients presenting with pathologic nystagmus during acute VM (Polensek and Tusa, 2010). All patients had positional nystagmus, mostly of a horizontal, direction-changing type. Furthermore, 19% of patients presented with spontaneous nystagmus and 35% with head-shaking-induced nystagmus, always beating in the horizontal plane. As the intensity of the nystagmus was weak, it could only be observed with fixation blocked. In the interval, nystagmus had dissipated in all patients. Caloric testing was normal in all patients. The authors concluded that findings pointed to a central vestibular dysfunction in all patients. Another retrospective study described transient spontaneous nystagmus in 8 patients with VM examined in the attack, 3 of whom also had severe vertical positional nystagmus (Dieterich and Brandt, 1999).

Findings in the interval

Saccadic pursuit has been reported in 3% (Cass et al., 1997) to 57% (Neugebauer et al., 2013) of adult patients and in 24% of children (Langhagen et al., 2015) with VM. No other ocular motor finding has been reported with such a wide variance in VM, which may be due to the fact that the vast majority of studies assessed smooth pursuit clinically without eye movement recording. Furthermore, assessment of smooth pursuit is problematic as it relies on attention and cooperation of the patient. In most studies, saccadic pursuit has been described in about 10–20% of patients with VM in the interval (Table 22.4). Two case series that described saccadic horizontal smooth pursuit in about half of patients with VM found impaired fixation suppression of the VOR in only 3% of these patients (Dieterich and Brandt, 1999; Neugebauer et al., 2013). These are conflicting findings, as cancellation of the VOR is typically impaired when smooth pursuit is saccadic (Radtke et al., 2012).

Spontaneous nystagmus is rare in the interval, with a prevalence of well below 10% in most case series (Table 22.4). In contrast, positional nystagmus of a central type is not uncommon and has been described in about 10–20% of patients (Table 22.4). Gaze-evoked nystagmus occurred in less than 5% of patients in several case series (Çelebisoy et al., 2007; Casani et al., 2009; Jeong et al., 2010; Radtke et al., 2012; Boldingh et al., 2013), and only Dieterich and Brandt (1999) observed gaze-evoked nystagmus in a large proportion of patients (27%) with VM. Head-shaking nystagmus has been described in 15–50% of patients (Jeong et al., 2010; Radtke et al., 2012; Boldingh et al., 2013; Shin et al., 2013) and can be horizontal or downbeating (Jeong et al., 2010). Vibration-induced nystagmus, typically indicating peripheral vestibular hypofunction (Hamann and Schuster, 1999), has been observed in 32% of patients with VM (Shin et al., 2013).

The most consistent laboratory finding in VM is a unilaterally reduced caloric response. In most studies, about 10–20% of patients with VM showed a unilateral canal paresis (Table 22.4). The magnitude of caloric asymmetry has been specified in almost none of these studies. Thus, it is unclear whether a complete or almost complete

Table 22.4

Prevalence of ocular motor and vestibular dysfunction in patients with vestibular migraine in the symptom-free interval

Reference	*n*	Spontaneous nystagmus	Central positional nystagmus	Saccadic pursuit	Central ocular motor disorder	Unilateral caloric paresis
Cutrer and Baloh, 1992	91	7%	7%	n.r.	n.r.	21%
Cass et al., 1997	100	7%	13%	3%	n.r.	18%
Dieterich and Brandt, 1999	90	11%	11%	48%	66%	8%
Bir et al., 2003	53	0%	n.r.	24%	n.r.	12%
Çelebisoy et al., 2007	35	0%	n.r.	9%	12%	20%
Wang et al., 2009	62	26%	n.r.	21%	n.r.	21%
Teggi et al., 2009	30	3%	10%	9%	23%	20%
Casani et al., 2009	22	n.r.	9%	14%	18%	18%
Radtke et al., 2012	61	2%	18%	8%	28%	16%
Neugebauer et al., 2013	30	3%	n.r.	57%	63%	7%
Boldingh et al., 2013	38	5%	19%	13%	54%	16%

Reproduced from von Brevern (2014).
n.r., not reported.

canal paresis is compatible with a diagnosis of VM. In two studies, about 25% of patients with a canal paresis had an asymmetry of more than 50% (Radtke et al., 2012; Blödow et al., 2014). The presence of a caloric asymmetry seems to be independent of the stage of the disease (Blödow et al., 2014). Pathologic caloric testing has also been reported in about 20% of children with VM (Marcelli et al., 2010; Langhagen et al., 2015).

Bilateral caloric hyporesponsiveness has been reported in up to 11% (Kayan and Hood, 1984; Olsson, 1991; Maione, 2006), and an isolated directional preponderance of caloric responses in about 10% of patients with VM (Kayan and Hood, 1984; Dieterich and Brandt, 1999; Vitkovic et al., 2008). Interestingly, patients with VM are four times more likely to have an emetic response to caloric stimulation than patients with a vestibular disorder coexisting with migraine (Vitkovic et al., 2008).

A pathologic head impulse test as assessed by bedside testing has been reported in up to 26% of patients with VM (Boldingh et al., 2013), but in most studies it occurred only exceptionally (Neff et al., 2012; Radtke et al., 2012; Mahringer and Rambold, 2014). Video head impulse testing yielded a mildly reduced unilateral gain in 9–11% of patients with VM (Blödow et al., 2014; Mahringer and Rambold, 2014). The video head impulse test seems to be less sensitive for detection of a vestibular deficit in VM than caloric irrigation (Blödow et al., 2014).

Rotatory chair testing revealed an isolated directional preponderance in about 20% of patients (Cass et al., 1997; Dieterich and Brandt, 1999). Some authors reported a reduced gain of the horizontal VOR during rotatory chair testing (Dimitri et al., 2001; Furman et al., 2005b), but this finding was present in only 1% of patients in a large case series (Cass et al., 1997).

Assessment of cervical and ocular vestibular-evoked myogenic potentials (cVEMPs and oVEMPs) in patients with VM has yielded conflicting results. Some studies have described either unilaterally or bilaterally reduced amplitudes as compared to healthy controls in about two-thirds of patients with VM, indicating saccular and utricular dysfunction (Baier and Dieterich, 2009; Zuniga et al., 2012). Another study found a high prevalence of absent cVEMPs (43%) in patients with VM (Boldingh et al., 2011). Cervical recorded VEMPs were also absent in 35% of 20 patients with basilar-type migraine, most of them experiencing vertigo (Liao and Young, 2004). Another study found no differences in cVEMP parameters between patients with VM and controls, but the rate of absent oVEMPs was higher in patients with VM as compared to controls (Zaleski et al., 2015). The latencies of the response were only rarely prolonged in patients with VM (Murofushi et al., 2009), or entirely normal in other studies (Baier and Dieterich, 2009; Boldingh et al., 2011; Zuniga et al., 2012). VEMPs do not seem to be helpful for the differentiation of VM from Menière's disease, where similar results can be found (Baier and Dieterich, 2009). One study elicited VEMPs applying tone bursts of various frequencies and concluded that this method may help to separate VM from Menière's disease, but these results await replication (Taylor et al., 2012).

A large case series of patients with VM yielded normal results of posturography in 74% of patients (Cass et al., 1997). Group analysis of posturography demonstrated excessive reliance on somatosensory cues (Çelebisoy et al., 2007) or on visual cues (Casani et al., 2009; Teggi et al., 2009) in patients with VM as compared to controls.

It is important to notice that these clinical and laboratory findings are not specific to patients with VM but can also be found in migraine patients without a history of vestibular symptoms. Of note, unilateral caloric hyporesponsiveness occurs with similar frequency in migraine patients with and without a history of vestibular symptoms (Dash et al., 2008; Casani et al., 2009; Marcelli et al., 2010; Boldingh et al., 2013). A unilateral canal paresis has been described in up to 35% of migraine patients without vertigo (Toglia et al., 1981; Casani et al., 2009; Boldingh et al., 2013). Likewise, a study comparing cVEMPs between groups of migraineurs with and without vertigo found no difference in amplitudes (Roceanu et al., 2008). While a high frequency of pathologic oculographic findings has been reported by several authors in migraine (Toglia et al., 1981; Ansink et al., 1985; Bir et al., 2003; Harno et al., 2003; Casani et al., 2009), other studies failed to find significant ocular motor abnormalities (Schlake et al., 1989; Wilkinson et al., 2006). Several studies examined the prevalence of vestibular dysfunction in patients with VM as compared to migraine patients without vertigo. In two studies the prevalence of peripheral and central vestibular dysfunction did not differ between both groups (Bir et al., 2003; Casani et al., 2009), whereas another study reported a higher prevalence of central and peripheral vestibular dysfunction in patients with VM (70%) than in migraine patients (38%) (Boldingh et al., 2013). Saccadic pursuit seems to be more frequent in VM as compared to migraine without vertigo (Casani et al., 2009; Boldingh et al., 2013). Clinical examination yielded head-shaking nystagmus in 9–25% of migraine patients without vertigo (Jeong et al., 2010; Boldingh et al., 2013). Central positional nystagmus has been described by means of video-oculography in 28% of patients with migraine without a history of vestibular symptoms (Harno et al., 2003).

Two studies examined the evolution of interictal vestibular and ocular motor dysfunction in patients with VM over time. In a group of 61 patients with VM the prevalence of at least one ocular motor abnormality increased from 15% at initial presentation to 41% after a median follow-up time of 9 years (Radtke et al., 2012). The most frequent abnormalities were positional nystagmus and head-shaking nystagmus (Table 22.5). Positional nystagmus clearly attributable to central vestibular dysfunction was present at follow-up in 18% of patients. Another 8-year-long observational study with 30 patients found that the prevalence of central ocular motor deficits increased from 20% to 63% in VM (Neugebauer et al., 2013). The most common finding in the latter study was saccadic pursuit.

In general, signs of central ocular motor and vestibular dysfunction remain subtle throughout the course (Radtke et al., 2012; Neugebauer et al., 2013). Interestingly, interictal ocular motor abnormalities may show some variation over time and in some patients eye movements may even return to normal at follow-up (Dieterich and Brandt, 1999; Radtke et al., 2012). Ocular motor abnormalities observed in the symptom-free interval may partly reflect delayed recovery of vestibular dysfunction after an acute vertigo attack.

Audiometry revealed sensorineural hearing loss not attributable to any cause in up to 20% of patients (Maione, 2006). A review of audiometric findings in VM summarized results of nine studies and found an average prevalence of unexplained hearing loss of 7.5% (Battista, 2004). Thus, hearing loss is rather unusual, and low-frequency, progressive, or fluctuating hearing loss, typical for Menière's disease, is a rare finding in VM. In a case series of 61 patients with VM, 18% of patients had developed mild bilateral symmetric sensorineural hearing loss with a downsloping pattern involving the low-frequency range to a minor degree after a median of 9 years after initial presentation (Radtke et al., 2012).

In summary, patients with VM may show mild signs of peripheral and central vestibular dysfunction in the symptom-free interval. Although the prevalence of ocular motor abnormalities tends to increase with time, findings in individual patients may fluctuate. These clinical signs and testing results are not specific to VM and may also be found in patients with migraine without vestibular symptoms. Gross ocular motor abnormalities are found infrequently in VM and should raise the suspicion of another disease.

Table 22.5

Interictal ocular motor abnormalities in 61 patients with definite vestibular migraine at initial presentation and after a median follow-up time of 9 years

	Initial presentation	Follow-up
At least one ocular motor abnormality	15%	41%
Positional nystagmus	12%	28%
Head-shaking nystagmus	2%	15%
Gaze-evoked nystagmus	0%	4%
Spontaneous nystagmus	2%	2%
Saccadic pursuit	0%	8%
Deficit of visual vestibulo-ocular reflex suppression	2%	8%
Pathologic saccades	0%	0%
Unilateral deficit on head impulse test	2%	3%

Modified from Radtke et al. (2012).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of VM includes other disorders causing episodes of spontaneous and positional vertigo. Again, history taking provides more valuable clues than technical procedures, which rather serve to provide further evidence for or against a clinical working diagnosis.

Menière's disease

The most challenging differential diagnosis of VM is Menière's disease, particularly in the early course, when permanent hearing loss may not yet be detectable in the latter. Both disorders present similarly in terms of severity and duration of vertigo episodes (Brantberg and Baloh, 2011). Vestibular testing with caloric irrigation, head impulse test, and VEMPs do not reliably discriminate between VM and Menière's disease. Usually, the distinction can be made based on hearing loss, which is only occasional and mild in VM, while it is a typical and more severe accompaniment of Menière's disease. Furthermore, when hearing loss develops in VM, it is often bilateral (Battista, 2004; Radtke et al., 2011), whereas involvement of both ears from the onset has been described in only 2% of Menière patients (Huppert et al., 2010). Tinnitus and aural fullness may also occur during vertigo attacks in VM (Lopez-Escamez et al., 2014). Again, in contrast to Menière's disease, in which these symptoms are typically unilateral, these symptoms are usually bilateral in VM (Cass et al., 1997; Brantberg and Baloh, 2011). Nonetheless, there is a diagnostic overlap between VM and Menière's disease, not only in the early stage (Neff et al., 2012). After a mean follow-up of 9 years in 75 patients with the initial diagnosis of VM, 10% of patients fulfilled diagnostic criteria for both Menière's disease and VM. Yet, these patients had clinical features atypical of

classical Menière's disease, such as symmetric and mostly mild hearing loss and often long duration of vertigo episodes, raising doubts that Menière's disease was the more appropriate diagnosis (Radtke et al., 2011). These findings can be interpreted in two ways: either current diagnostic criteria for Menière's disease and VM are not sufficiently discriminative or both disorders share an underlying mechanism. A genetic link between VM and Menière's disease is supported by familial clustering of migraine, episodic vertigo, and Menière's disease, but this constellation is rather rare (Cha et al., 2007; Hietikko et al., 2011). Alternatively, migraine could damage the inner ear, leading to endolymphatic hydrops (Gürkov et al., 2014). Endolymphatic hydrops has been identified in a minority of patients with VM by means of magnetic resonance imaging (MRI), but most of them also fulfilled criteria for Menière's disease (Gürkov et al., 2014; Nakada et al., 2014). To complicate matters further, migrainous symptoms such as headache and photophobia are also frequent accompaniments in attacks of Menière's disease (Radtke et al., 2002; Brantberg and Baloh, 2011; Shin et al., 2013; Lopez-Escamez et al., 2014). For practical purposes, when patients present with early unilateral hearing loss and vertigo attacks lasting at least 20 minutes and not longer than 12 hours, Menière's disease should be diagnosed, even when migraine symptoms occur during vertigo episodes. In those patients with only minor hearing symptoms and a history compatible with both VM and Menière's disease, medical treatment with a trial of migraine prophylaxis is advisable. Failure of this approach should prompt consideration of treatment for Menière's disease but invasive procedures should be avoided. Only patients who have two different types of attacks, one fulfilling the criteria for VM and the other for Menière's disease, should be diagnosed with the two disorders. A future classification of VM may include a VM/Menière's disease overlap syndrome (Neff et al., 2012).

Benign recurrent vertigo

The term "benign recurrent vertigo" was coined in 1979 by Slater for patients with recurrent attacks of spontaneous vertigo that cannot be explained by other known peripheral or central vestibular disorders. Other authors have used "recurrent vestibulopathy" for similar patients (Leliever and Barber, 1981). To date, this syndrome is ill defined, as some authors include patients with VM (Cha et al., 2009), whereas others exclude patients with a migraine history (van Leeuven and Bruintjes, 2010). There is a large overlap between benign recurrent vertigo and VM. Notably, Slater (1979) speculated that benign recurrent vertigo may be a migraine equivalent. Several large case series endorse the association between benign recurrent vertigo and migraine (Lee et al., 2002; Cha et al., 2009; Brantberg and Baloh, 2011). Besides the increased prevalence of migraine, there are several clinical similarities between benign recurrent vertigo and VM: (1) female preponderance (Cha et al., 2009); (2) family occurrence suggestive of an autosomal-dominant inheritance, with reduced penetrance in some patients (Lee et al., 2006); (3) precipitation by lack of sleep and emotional stress (Slater, 1979); and (4) transition from spontaneous to positional vertigo during an episode (Slater, 1979). As the majority of patients with benign recurrent vertigo can be classified as VM or probable VM, the term benign recurrent vertigo (or recurrent vestibulopathy) should be restricted to patients with episodic spontaneous vertigo of unknown cause and without a history of migraine. The clinical presentation of benign recurrent vertigo is similar to VM and Menière's disease with respect to duration and severity of vertigo (Brantberg and Baloh, 2011). Although cochlear symptoms during episodes of vertigo are not rare, the rate of conversion to Menière's disease is low, ranging between 1% and 7% 3 years after initial diagnosis (Leliever and Barber, 1981; van Leeuven and Bruintjes, 2010).

Benign paroxysmal positional vertigo

VM may present with purely positional vertigo, thus mimicking BPPV. Direct nystagmus observation during the acute phase may be required for differentiation. In VM, positional nystagmus is usually persistent and of a central type, i.e., not aligned with a single semicircular canal (von Brevern et al., 2005; Polensek and Tusa, 2010). Symptomatic episodes tend to be shorter with VM (minutes to days rather than weeks) and more frequent (several times per year with VM rather than once every few years with BPPV) (von Brevern et al., 2004). There is epidemiologic evidence for an association between migraine and BPPV. Migraine is three times more common in patients presenting with idiopathic BPPV compared to patients with BPPV secondary to trauma or surgical procedures (Ishiyama et al., 2000). Similarly, the prevalence of migraine was two times higher in patients with idiopathic BPPV compared to age- and sex-matched controls (Lempert et al., 2000). Genetic factors and vascular damage to the labyrinth have been proposed as potential mechanisms linking the two disorders (Ishiyama et al., 2000).

Transient ischemic attacks

Isolated vertigo is the most common manifestation of vertebrobasilar transient ischemic attacks (Paul et al., 2013) and this differential diagnosis should be considered, particularly in elderly patients. Suggestive features include vascular risk factors, coronary or peripheral

atherosclerosis, sudden onset of symptoms, duration of episodes of less than 1 hour, total history of attacks of less than a few months, and angiographic or Doppler ultrasound evidence for vascular pathology of the vertebral or proximal basilar artery (Fife et al., 1994).

Vestibular paroxysmia

Vestibular paroxysmia is a controversial disorder, presumably caused by vascular compression of the vestibular nerve (Hüfner et al., 2008). The presenting feature is brief attacks of vertigo, typically lasting several seconds, which recur many times per day. Successful prevention of attacks with carbamazepine supports the diagnosis.

Episodic ataxia

VM shares some clinical features with episodic ataxia type 2 (EA2). In both disorders, a history of migraine and a positive family history for episodic vertigo are often present. EA2 is a rare autosomal-dominant inherited paroxysmal disorder of early onset characterized by episodes of incoordination and truncal ataxia. Presentation after the age of 20 is exceptional. The attacks are commonly triggered by physical and emotional stress and typically last hours. In about half of the patients at least one of the following can be found: vestibular symptoms with vertigo, nausea, and vomiting during attacks, generalized weakness during attacks, gradually progressive baseline ataxia, and a history of migraine (Jen et al., 2004). Between attacks, the vast majority of patients present with gaze-evoked nystagmus and a third with spontaneous or positional downbeat nystagmus. These interictal ocular motor signs are an important key to differentiate VM from EA2, as they are absent or subtle in the former and prominent in the latter. Other features that may help to distinguish VM from EA2 are the age at onset, triggers, and the striking response to treatment with acetazolamide in EA2. Genetic testing is commercially available for EA2 and identifies a mutation in the CACNA1A gene in about 60% of patients.

Psychiatric dizziness syndromes

There is a complex relationship between vertigo and dizziness, migraine, and some psychiatric disorders. Both panic disorders and major depression are bidirectionally associated with migraine (Breslau et al., 2000, 2001). As with all vestibular disorders, patients with VM are at highest risk of developing comorbid psychiatric disorders, particularly anxiety disorders and depression (Eckhardt-Henn et al., 2008). Because of the frequent association of dizziness, migraine, and anxiety, Furman and coworkers (2005a) have proposed "migraine/anxiety-related dizziness" as a new syndrome on the basis of neuroanatomic links on the brainstem level between the vestibular system and neuronal pathways involved in emotional processing. Besides vestibular episodes, about one-third of patients with VM exhibit chronic subjective dizziness (Neff et al., 2012). Anxiety-related dizziness is characterized by situational worsening, intense autonomic activation, catastrophic thinking, and avoidance behavior, and is not accompanied by severe nausea, vomiting, external vertigo (seeing the world move), and falls. However, in individual patients with co-occurrence of VM and psychogenic dizziness, the differentiation of their relative contribution can be problematic.

PATHOPHYSIOLOGY

The pathophysiology of VM is still a matter of speculation. The vestibular origin has been ascertained by the observation of pathologic nystagmus in the acute phase of VM, indicating central vestibular dysfunction in most patients (von Brevern et al., 2005; Polensek and Tusa, 2010). As the clinical presentation of VM is heterogeneous in terms of duration, type of vestibular symptoms, and nystagmus during the attack, it is likely that migraine interacts with the vestibular system at various levels. Beside central vestibular structures, the labyrinth also seems to be affected, as indicated by an increased prevalence of inner-ear disorders (BPPV and Menière's disease) and unilateral reduced caloric response in patients with migraine.

It remains unclear how migraine affects the vestibular system. Several hypotheses have been proposed; all of them are derived from the presumed pathophysiology of migraine (Furman et al., 2013). Migraine is currently conceptualized as a neurogenic disorder in genetically susceptible individuals that starts in the brain and probably results from dysfunction of brainstem and diencephalic nuclei that activate sensory nerve endings around the extracranial and intracranial arteries of the head (Akerman et al., 2011).

Migraine aura has been associated with a transient and reversible cortical event, spreading depression. Spreading depression is characterized by a short-lasting neuronal depolarization spreading over adjacent areas of the cortex, followed by a longer-lasting inhibition of neuronal activity (Ferrari et al., 2015). This mechanism could lead to vestibular symptoms when the multisensory cortical areas processing vestibular information become involved; these are mainly located in the temporoparietal junction. Alternatively, a spreading depression affecting the brainstem has been proposed to account for short-lasting episodes of VM (Dieterich and Brandt, 1999). Of note, vertigo is the most common aura manifestation in basilar-type migraine/migraine with brainstem aura

(Kirchmann et al., 2006). However, several features of VM, such as the longer duration of most episodes, complex nystagmus pattern, and interictal peripheral vestibular dysfunction, cannot be explained by spreading depression.

Vasospasm of the internal auditory artery has been proposed to cause peripheral vestibular and cochlear dysfunction in migraine with and without vertigo (Baloh, 1997). However, vasospasm can hardly account for episodes lasting hours or days. Furthermore, central vestibular and ocular motor dysfunction in patients with migraine points to another mechanism unrelated to labyrinthine ischemia.

Neuroanatomic studies in animals point to a connection between the vestibular system and nociceptive brainstem structures, such as the noradrenergic locus ceruleus and the serotonergic dorsal raphe nuclei (Schuerger and Balaban, 1999; Halberstadt and Balaban, 2003; Furman et al., 2013). Calcitonin gene-related peptide is another neurotransmitter essential in the cascade leading to a migraine attack and may also modulate the activity of central and peripheral vestibular neurons (Cutrer and Baloh, 1992). When these neurotransmitters are released unilaterally, static vestibular tone imbalance may result, presenting clinically with spontaneous or positional vertigo; when they are released bilaterally, vestibular signal processing in response to head motion may become distorted, presenting with head motion-induced vertigo and dizziness. Reciprocal connections between the vestibular nuclei and the trigeminal system (Buisseret-Delmas et al., 1999) may be the pathophysiologic basis of the observation that vestibular stimulation can trigger migraine headache (Murdin et al., 2009).

Activation of the trigeminovascular reflex during migraine leads to a sterile inflammatory response of intracranial vessels and was shown to affect also the inner ear in animal experiments (Vass et al., 2001; Koo and Balaban, 2006). Electric stimulation of the trigeminal nerve causes plasma extravasation in the murine inner ear (Vass et al., 2001). This mechanism may well explain vestibular and cochlear symptoms due to dysfunction of the inner ear in migraine. This hypothesis is supported by the observation that painful trigeminal stimulation can evoke nystagmus in migraineurs, but not in subjects without a history of migraine (Marano et al., 2005).

Finally, a dysfunction of ion channels expressed in the inner ear or in central vestibular structures could account for vestibular symptoms in VM. This last hypothesis is the only one that was systematically tested thus far. It appears to be promising, since other paroxysmal disorders presenting with migraine and vertigo, such as familial hemiplegic migraine and EA2, have been found to result from dysfunction of the PQ-calcium channel encoded by the CACNA1A gene. However, searching for mutations in this and other candidate genes was negative in patients with VM (Kim et al., 1998; von Brevern et al., 2006).

Recently, cerebral imaging studies have been performed in patients with VM. Fluorodeoxyglucose positron emission tomography examination of 2 patients with VM during an attack has shown increased metabolism of temporoparietoinsular areas and of both thalami, indicating activation of vestibulothalamocortical pathways (Shin et al., 2014). Voxel-based morphometry has shown gray-matter volume reduction in multisensory vestibular processing areas similar to brain changes reported in central vestibular compensation following peripheral vestibular loss (Obermann et al., 2014). Functional imaging with functional MRI during caloric irrigation of the vestibular organ has shown increased thalamic activation in patients with VM as compared to patients with migraine without aura and healthy subjects (Russo et al., 2014). Although these findings may indicate an activation of the central vestibular system in VM, the origin of vestibular dysfunction remains to be elucidated.

TREATMENT

Treatment of VM starts with effective counseling. A thorough explanation of the migrainous origin of the episodes is essential to relieve unnecessary fears of a serious disorder and prepares for adherence to lifestyle changes and medications. At first, many patients are surprised when the diagnosis is explained to them, particularly when the presenting symptom is vertigo and not headache. Nonpharmaceutical approaches to the prophylactic treatment of VM can be as effective as medication. Avoidance of identified triggers, regular sleep and meals, and physical exercise have a firm place in migraine prophylaxis. In migraine headaches, relaxation techniques and biofeedback are as effective as pharmacologic prophylaxis (Holroyd and Penzien, 1990).

Symptomatic treatment during episodes of VM lasting longer than 1 hour can be achieved with vestibular suppressants such as dimenhydrinate. There is anecdotal evidence that triptans may be effective for VM. The only controlled trial on the efficacy of triptans in VM remained inconclusive due to its limited power (Neuhauser et al., 2003). A retrospective study found that the effect of triptans on vertigo was related to its effect on headache (Bikhazi et al., 1997). Interestingly, triptans seem also to reduce motion sickness in migraineurs, possibly by influencing serotonergic vestibuloautonomic projections (Furman et al., 2011). Intravenous methylprednisolone (1000 mg/day for 1–3 days) effectively terminated prolonged attacks or exacerbations with daily recurrences in 4 patients (Prakash and Shah, 2009). In patients with severe nausea or vomiting, the

route of administration of acute medication should be parenteral (i.e., by suppositories, nasal spray, or subcutaneous injection).

In many patients, episodes of VM are severe, long, and frequent enough to warrant prophylactic medication. Unfortunately, there is a lack of solid data derived from placebo-controlled trials. Thus far, there is only one randomized controlled trial of prophylactic treatment of VM, comparing the efficacy of flunarizine over 12 weeks to no prophylactic medical treatment. The frequency and severity of vertiginous episodes decreased with flunarizine, but the study can be criticized for lack of both blinding and application of placebo in the control group (Lepcha et al., 2014). Several retrospective and observational analyses have reported a reduction of intensity and frequency of attacks of VM with prophylactic migraine drugs such as metoprolol, propranolol, flunarizine, topiramate, lamotrigine, valproate, and amitriptyline (Baier et al., 2009; Fotuhi et al., 2009; van Omberg et al., 2015). Furthermore, response to the carbonic anhydrase inhibitor acetazolamide, which is usually not used for migraine prophylaxis, has been reported (Baloh et al., 1996). These results have to be regarded with caution as the clinical course is variable and spontaneous remission is common (Reploeg and Goebel, 2002; Neuhauser et al., 2003; Baier et al., 2009). However, most experts agree that prophylactic drug treatment can be effective in VM. In the absence of evidence for the most effective medication, comorbid conditions and side-effects should be taken into consideration for the choice of drug. In patients with hypertension a beta-blocker is usually the first option. For several drugs, such as flunarizine, valproate, and amitriptyline, weight gain can be a cause for concern. Sedation and other side-effects can be greatly reduced with slow titration of dosage. Treatment efficacy should be evaluated after 3 months on the basis of a diary of events. A realistic goal is a reduction in attack frequency of about 50–70%. Similar to migraine headache, the frequency of episodes of VM varies over time. Thus, the need for prophylactic medical treatment is often only transient.

In patients with constant dizziness, visual dependence, and unsteadiness in addition to episodes of VM, vestibular rehabilitation can be effective (Whitney et al., 2000; Vitkovic et al., 2013). Psychiatric illness often significantly adds to reduction of quality of life and patients with coexisting anxiety disorders or depression may be treated with antidepressants and psychotherapy.

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Chapter 23

Ischemic syndromes causing dizziness and vertigo

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Abstract

Dizziness/vertigo and imbalance are the most common symptoms of vertebrobasilar ischemia. Even though dizziness/vertigo usually accompanies other neurologic symptoms and signs in cerebrovascular disorders, a diagnosis of isolated vascular vertigo is increasing markedly by virtue of recent developments in clinical neurotology and neuroimaging. It is important to differentiate isolated vertigo of a vascular cause from more benign disorders involving the inner ear, since therapeutic strategies and prognosis differ between these two conditions. Over the last decade, we have achieved a marked development in the understanding and diagnosis of vascular dizziness/vertigo. Introduction of diffusion-weighted magnetic resonance imaging (MRI) has greatly enhanced detection of infarctions in patients with vascular dizziness/vertigo, especially in the posterior-circulation territories. However, well-organized bedside neurotologic evaluation is even more sensitive than MRI in detecting acute infarction as a cause of spontaneous prolonged vertigo. Furthermore, detailed evaluation of strategic infarctions has elucidated the function of various vestibular structures of the brainstem and cerebellum. In contrast, diagnosis of isolated labyrinthine infarction still remains a challenge. This diagnostic difficulty also applies to isolated transient dizziness/vertigo of vascular origin. Regarding the common nonlacunar mechanisms in the acute vestibular syndrome from small infarctions, individual strategies may be indicated to prevent recurrences of stroke in patients with vascular vertigo.

INTRODUCTION

Dizziness/vertigo and imbalance are the most common symptoms of vertebrobasilar ischemia, that comprises about 20% of all ischemic strokes (Savitz and Caplan, 2005; Paul et al., 2013). Recent prospective studies using a large database reported dizziness as a presenting symptom in 47–75% of patients with posterior-circulation stroke (Akhtar et al., 2009; Searls et al., 2012). Even though dizziness/vertigo is usually accompanied by other neurologic symptoms and signs in cerebrovascular disorders, the diagnosis of isolated vascular vertigo is increasing markedly by virtue of recent developments in clinical neurotology and neuroimaging (Kim et al., 2015). It is important to differentiate isolated vertigo of a vascular cause from more benign disorders involving the inner ear, since therapeutic strategies and prognosis differ between these two conditions. Misdiagnosis of an acute stroke may result in significant morbidity and mortality, while overdiagnosis of vascular vertigo would lead to unnecessary costly work-ups and medication (Choi et al., 2013b).

Over the last decade, our anatomic and pathophysiologic understanding of vascular dizziness/vertigo has markedly expanded (Baloh et al., 2012). Introduction

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of diffusion-weighted magnetic resonance imaging (MRI) has greatly enhanced the detection of infarctions in patients with vascular dizziness/vertigo, especially due to impaired posterior circulation (Lee et al., 2006). However, well-organized bedside neurotologic evaluation is even more sensitive than MRI, including diffusion-weighted imaging, in detecting acute infarction as a cause of spontaneous vertigo lasting more than 24 hours, especially during the first 48 hours (Kattah et al., 2009; Newman-Toker et al., 2013a; Saber Tehrani et al., 2014). Furthermore, detailed evaluation of patients with strategic infarctions restricted to specific anatomic sites has enabled us to better understand the function of vestibular structures and define various ischemic vestibular syndromes in humans (Kim et al., 2015).

However, diagnosis of isolated labyrinthine infarction remains a challenge, since no confirmatory tool other than a postmortem study is currently available (Kim et al., 1999). We still lack the technology to image infarctions restricted to the labyrinth. A similar diagnostic difficulty applies to isolated transient dizziness/vertigo of vascular origin, which is a common variant of vertebrobasilar ischemia (Grad and Baloh, 1989; Hoshino et al., 2013; Paul et al., 2013). Furthermore, the current diagnostic criteria of transient ischemic attacks do not readily include dizziness/vertigo as a focal symptom (Furie et al., 2011). Since nonlacunar mechanisms are more common (47%) than previously thought in the acute vestibular syndrome (AVS) from small infarctions, customized therapies may be indicated to prevent recurrences of stroke in patients with vascular vertigo (Jackson and Sudlow, 2005; Saber Tehrani et al., 2014).

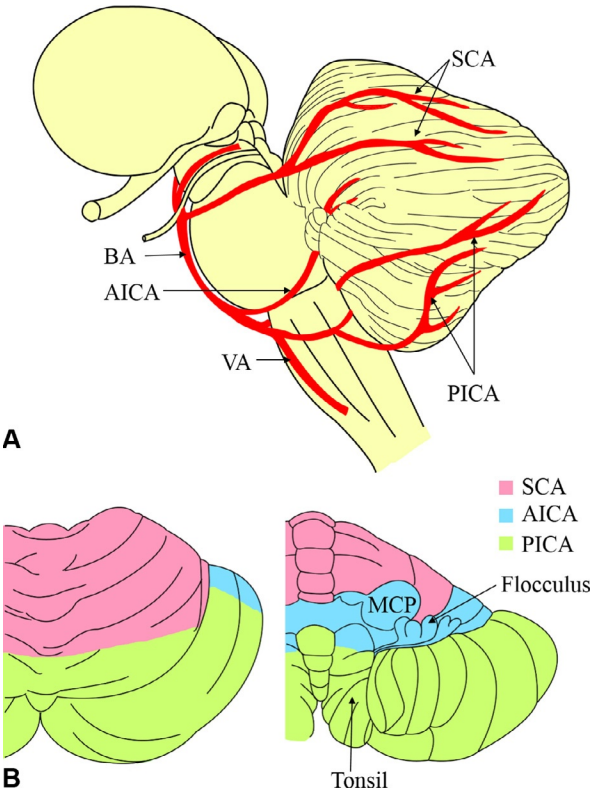

Fig. 23.1. The vascular anatomy of the posterior circulation (**A**) and vascular territory of the cerebellum (**B**). The cerebellum receives its blood supply from three paired arteries. The posterior inferior cerebellar artery (PICA) usually derives from the distal vertebral artery (VA). The anterior inferior cerebellar artery (AICA) usually branches from the proximal or midbasilar artery (BA), and the superior cerebellar artery (SCA) usually stems from the distal BA. In general, the shorter, proximal branches from all three of the cerebellar arteries supply portions of the brainstem, whereas the longer circumferential branches supply the cerebellum. Variations are common. MCP, middle cerebellar peduncle. From Lee and Kim (2005).

CEREBELLAR INFARCTION

The cerebellum is supplied by the posterior inferior (PICA), anterior inferior (AICA), and superior (SCA) cerebellar arteries (Fig. 23.1). Cerebellar ischemic stroke probably ranks first among central vascular vertigo syndromes. A prospective study showed that about 11% (25/240) of patients with isolated cerebellar infarctions present with vertigo as a sole symptom and most of them (24/25: 96%) had an infarction in the territory of the medial branch of the PICA, including the nodulus (Lee et al., 2006). Correct identification of cerebellar stroke is important for proper management, especially during the acute phase (Savitz et al., 2007). Patients with cerebellar infarction should undergo evaluation for embolism from the heart or great vessels to prevent recurrence (Amarenco et al., 1994). Cerebellar infarction may develop a mass effect in 10–25% of patients and PICA territory infarcts are more likely to produce a mass effect than those involving the SCA territory (Macdonell et al., 1987; Amarenco, 1991). Large cerebellar infarction can cause brainstem compression, leading to hydrocephalus, cardiorespiratory complications, coma, and death (Koh et al., 2000). Characteristics of cerebellar infarctions involving each arterial territory are summarized in Table 23.1.

PICA infarction

Patients with PICA territory cerebellar infarction mostly present with dizziness/vertigo and imbalance, since the vestibulocerebellar structures such as the nodulus, uvula, and tonsil (paraflocculus) are supplied by the PICA (Fig. 23.2) (Tatu et al., 1996). Due to the usual absence of prominent cerebellar signs such as dysarthria and limb dysmetria, detailed neurotologic evaluation is warranted to diagnose infarctions involving the PICA territory,

Table 23.1

Characteristics of cerebellar infarctions involving each vascular territory

	Posterior inferior cerebellar artery (PICA)	Anterior inferior cerebellar artery (AICA)	Superior cerebellar artery (SCA)
Vascular origin	Vertebral artery	Proximal or mid-basilar artery	Distal basilar artery
Major branches	Medial and lateral	Cerebellar and internal auditory	Medial and lateral
Key brainstem structures supplied by proximal branches	Posterolateral medulla: cranial nerve nuclei (V, VIII (vestibular), IX, X) and fascicles (IX, X) Sympathetic tract Spinothalamic tract Inferior cerebellar peduncle	Posterolateral pons: cranial nerve nuclei (V, VII, VIII (vestibular, cochlear)) and fascicles (VII, VIII) Sympathetic tract Spinothalamic tract Middle cerebellar peduncle	Posterolateral midbrain (and upper lateral pons): cranial nerve nuclei (IV, V) and fascicle (IV) Sympathetic tract Spinothalamic tract Medial lemniscus Superior cerebellar peduncle
Cerebellar and peripheral structures supplied by major branches	Posteroinferior cerebellum, including: inferior vermis (including uvula, nodulus) Paraflocculus	Anteroinferior cerebellum including flocculus. Inner ear: vestibular labyrinth; cochlea	Superior cerebellum, including: superior vermis Dentate and fastigial nuclei
Core cerebellar syndrome	Isolated acute vestibular syndrome without auditory symptoms (pseudovestibular neuritis)	Isolated acute vestibular syndrome with auditory symptoms (pseudolabyrinthitis)	Acute gait or trunk instability with associated dysarthria (pseudointoxication) Nausea or vomiting (pseudogastroenteritis)
Indicative neurologic signs	Lateral medullary syndrome: hemifacial analgesia; unilateral absent gag reflex; palatal palsy; vocal cord palsy; Horner's syndrome; body-dissociated hemianalgesia; limb hemiataxia; dysmetria	Lateral pontine syndrome: hemifacial sensory loss; facial palsy (lower motor neuron type); Horner's syndrome; body hemianalgesia; limb hemiataxia; dysmetria	Lateral midbrain syndrome: fourth-nerve palsy; hemifacial sensory loss; Horner's syndrome; body hemisensory loss; limb hemiataxia; dysmetria
	Vertebral artery syndrome: 12th nerve palsy; body hemisensory loss; hemiplegia or quadriplegia	Mid-basilar syndrome: impaired arousal or coma; sixth-nerve palsy or internuclear ophthalmoplegia; horizontal gaze palsy; body hemisensory loss; hemiplegia or quadriplegia	Top of the basilar syndrome: impaired memory or attention; stupor; visual field cut; ptosis; third-nerve palsy; vertical gaze palsy; hemiplegia or quadriplegia

especially the medial PICA (Lee et al., 2006). Indeed, about 17% of patients with PICA territory infarction imitated acute peripheral vestibulopathy (Lee et al., 2006). In a study of 72 patients with cerebellar infarction, mostly in the PICA territory, spontaneous nystagmus was observed in 39%, and was mostly ipsilesional in unilateral infarctions (Huh and Kim, 2011). Even though severe imbalance and direction-changing gaze-evoked nystagmus (GEN) have been reported to occur in 71% and 54% of patients with PICA infarctions (Lee et al., 2006), the sensitivity and specificity of these signs are unsatisfactory in diagnosing cerebellar infarctions in the territory of PICA. Similarly, perverted head shaking (mostly downbeat after horizontal head shaking) and positional downbeat nystagmus, the signs of central vestibular dysfunction, are found in only half of patients with cerebellar infarction (Huh and Kim, 2011). Thus, a negative head impulse test (HIT) is most useful in differentiating PICA-territory cerebellar infarctions from inner-ear disorders as a cause of acute spontaneous vertigo syndrome (Newman-Toker et al., 2008, 2013b; Chen et al., 2014). Bedside HIT is invariably negative in patients with isolated vertigo from PICA infarction (Lee et al., 2006).

Unidirectional GEN was found in 33% of patients with acute unilateral cerebellar stroke and the nystagmus

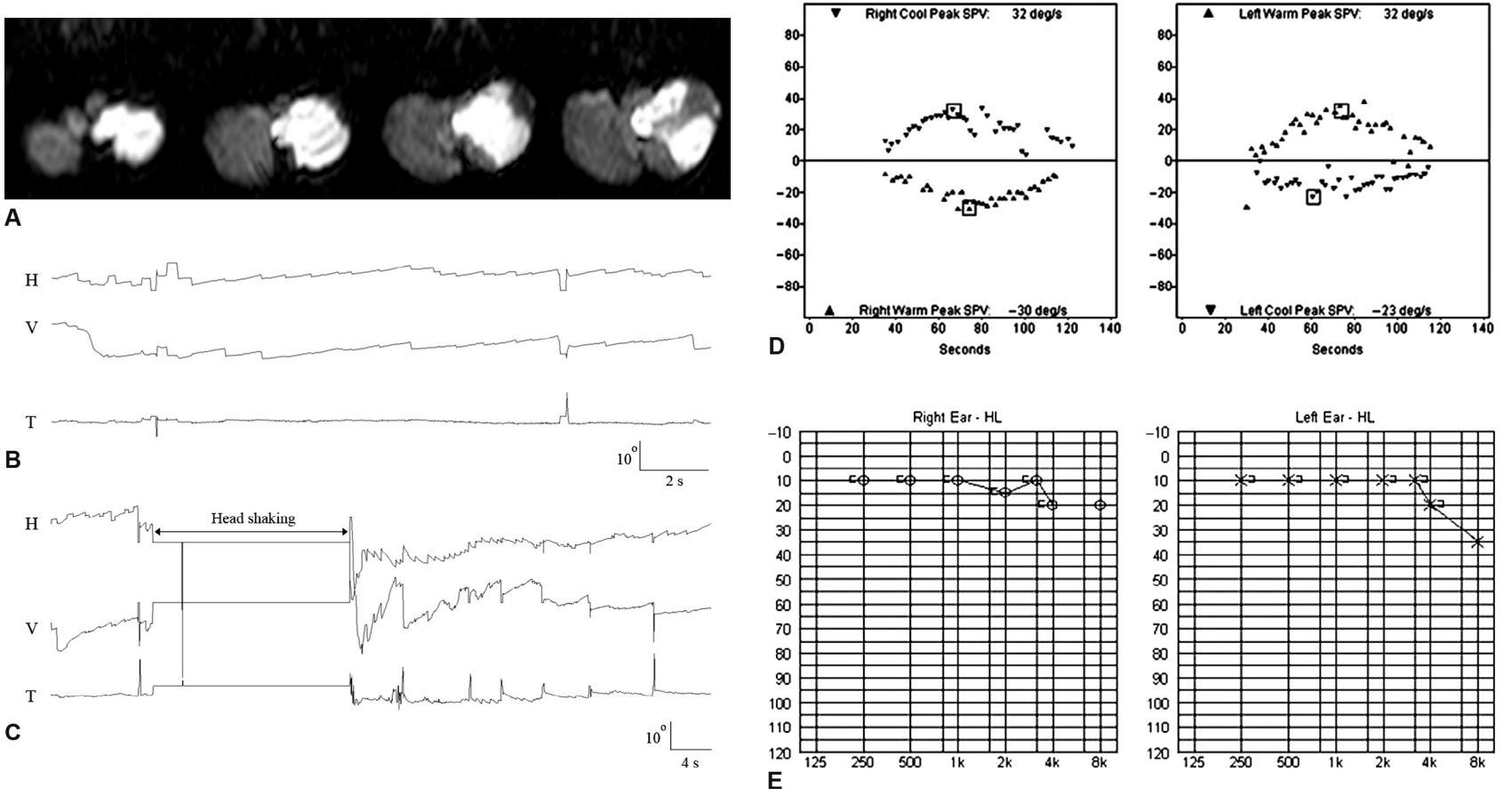

Fig. 23.2. Neurotologic findings in a patient with infarction in the territory of posterior inferior cerebellar artery (**A**). The patient shows ipsilesional spontaneous nystagmus (**B**), head-shaking nystagmus beating to the lesion side and downward (perverted, **C**) in the presence of normal caloric responses (**D**) and intact hearing (**E**).

was directed either toward or away from the lesion side (Baier and Dieterich, 2011). The structures responsible for unidirectional GEN included the pyramid, uvula, tonsil, and parts of the biventer and inferior semilunar lobules (Baier and Dieterich, 2011). Thus, GEN may be a sign indicating damage to the midline and lower cerebellar structures. Another study found head-shaking nystagmus (HSN) in 51% of patients (37/72) with isolated cerebellar infarction, and the horizontal component of HSN was consistently ipsilesional (Huh and Kim, 2011). Furthermore, perverted HSN was observed in 62% (23/37, 62%) of patients with HSN and was mostly downbeat (22/23, 96%) (Huh and Kim, 2011). Lesion subtraction analyses revealed that damage to the uvula, nodulus, and inferior tonsil was mostly responsible for generation of HSN in patients with unilateral PICA-territory infarction (Huh and Kim, 2011).

Cerebellar contributions to vestibular-evoked myogenic potentials (VEMPs) remain controversial. A study reported normal cervical VEMPs (cVEMPs) in cerebellar infarctions involving non-AICA territories (Pollak et al., 2006). However, a recent study showed frequent abnormalities of cVEMPs (11/27, 41%) and ocular VEMPs (oVEMPs, 9/27, 33%) in patients with isolated unilateral cerebellar infarction, mostly in the PICA territory (Choi et al., 2014b). Furthermore, the patients with ocular tilt reaction (OTR) showed abnormal VEMPs more frequently than those without (11/15 vs. 3/12, $p = 0.021$) (Choi et al., 2014b).

Isolated nodular infarction presents with isolated vertigo along with ipsilesional nystagmus and falling to the contralesional side, which mimicks peripheral vestibulopathy (Moon et al., 2009). However, severe imbalance, negative HIT, and normal caloric responses are important discriminants between nodular infarctions and peripheral vestibular dysfunction. Other findings of nodular infarctions include periodic alternating nystagmus, perverted HSN, paroxysmal positional nystagmus, and impaired tilt suppression of postrotatory nystagmus (Moon et al., 2009; Huh and Kim, 2011; Choi et al., 2015a; Kim et al., 2015).

A patient with vertigo from isolated unilateral infarction of the cerebellar tonsil showed a small ipsilesional spontaneous nystagmus only without fixation, horizontal gaze-evoked and rebound nystagmus, small contraversive tilt of the subjective visual vertical (SVV), and profound loss of smooth pursuit, more pronounced to the lesion side, but a normal vestibulo-ocular reflex (VOR) (Lee et al., 2014b). These findings contrast with impaired VOR during head impulses in unilateral floccular infarction (Park et al., 2013), suggesting that the tonsil has a critical role in the control of smooth pursuit and the flocculus has a critical role in the control of the VOR.

AICA infarction

The AICA supplies both peripheral and central vestibular structures; the inner ear, lateral pons, middle cerebellar peduncle, and anterior inferior cerebellum, including the flocculus (Amarenco and Hauw, 1990a). Thus, AICA infarction usually results in combined peripheral and central vestibulopathy (Lee et al., 2009; Choi et al., 2014a). Patients with AICA infarction mostly show dizziness/vertigo, nystagmus, hearing loss, facial weakness, limb and facial sensory loss, ataxia, and cerebellar dysmetria in various combinations (Fig. 23.3). Eight subtypes of AICA infarction were proposed according to the pattern of neurotologic presentations, and combined loss of auditory and vestibular function was the most common type (Lee et al., 2009). Diagnosis of an AICA infarction, however, remains a challenge, especially when signs and symptoms other than those from an inner-ear infarction are absent or inconspicuous (Kim et al., 2009).

In AICA infarction, spontaneous nystagmus is predominantly horizontal and mostly beats away from the lesion side (Lee et al., 2009). Asymmetric bidirectional GEN, frequently mimicking Bruns' nystagmus, is found in 43% of patients (Lee et al., 2009). HSN is also common with both peripheral and central patterns. The HINTS (negative HIT, direction-changing nystagmus, and skew deviation), the most useful bedside tool to detect central vestibulopathy, may not be sufficiently robust to detect central lesions in AICA infarction, since the HIT is mostly positive in this disorder (Huh et al., 2013; Newman-Toker et al., 2013b; Choi et al., 2014a). Indeed, the HINTS failed to detect central lesions in 5 of 18 patients with AICA infarction (Huh et al., 2013). Therefore, detection of central lesions may require additional tests, such as horizontal head shaking, which detected central patterns of HSN in 3 of the 5 patients with AICA infarction and negative HINTS (Huh et al., 2013). Thus, careful evaluation of HSN may provide clues for diagnosis of AICA infarction in patients with acute audiovestibular loss (Huh et al., 2013).

The hearing loss and caloric paresis detected during the acute phase of AICA infarction usually recover over time (Lee et al., 2011b; Kim et al., 2014a). However, multiple risk factors for stroke and profound hearing loss predicted a poor outcome for recovery of hearing loss (Kim et al., 2014a). AICA infarctions usually cause ipsiversive OTR and tilt of the SVV (Lee et al., 2005, 2008). Since patients with AICA infarction and normal caloric responses produce contralesional ocular torsion only (Lee et al., 2008), damage to peripheral vestibular structures appears to play a crucial role in determining the direction of the OTR and SVV tilt in AICA infarctions (Lee et al., 2008). About half of patients with AICA

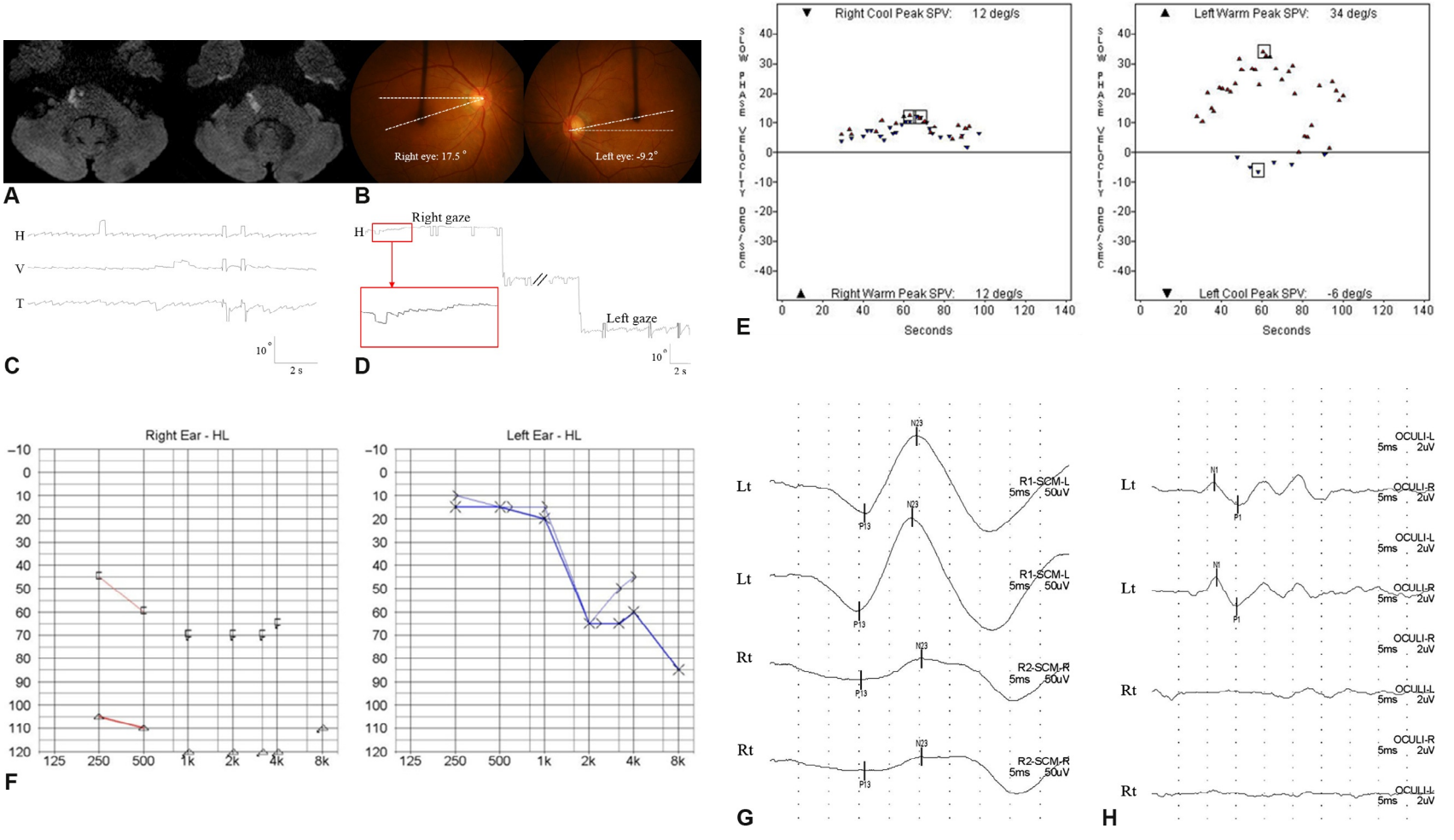

Fig. 23.3. A patient with infarction in the territory of right anterior inferior cerebellar artery (**A**) shows ipsiversive ocular torsion (**B**), contralesional spontaneous nystagmus (**C**), gaze-evoked nystagmus (**D**), ipsilesional caloric paresis (**E**), ipsilesional hearing loss (**F**), decreased amplitude of the ipsilesional cervical vestibular-evoked myogenic potentials (VEMPs, **G**), and absent responses of ocular VEMPs during ipsilesional ear stimulation (**H**). From Choi, Park, Kim et al. (2015b), with permission from Springer Science and Business Media.

infarctions show abnormal cVEMPs in response to click stimulation of the ipsilesional ear (Ahn et al., 2011). Patients with abnormal cVEMPs are more likely to have caloric paresis or sensorineural hearing loss compared with those with normal cVEMPs. These findings suggest that the peripheral vestibular structures play a crucial role in producing abnormal cVEMPs in AICA infarction (Ahn et al., 2011).

Isolated unilateral floccular infarction may cause sudden vertigo and imbalance along with ipsilesional spontaneous nystagmus and a contraversive ocular torsion and SVV tilt (Park et al., 2013). Of interest, recording of the HIT documented a bilaterally decreased horizontal VOR gain during the high-velocity, high-acceleration stimulation while bithermal caloric tests were normal and recording of the VOR using the rotatory chair showed an increased gain during low-frequency horizontal stimulations. These findings suggest that the flocculus modulates the VOR by inhibiting the horizontal VOR during low-frequency stimulation and facilitating it during high-frequency stimulation.

Audiovestibular loss may occur in isolation before pontocerebellar infarction of the AICA territory (Lee et al., 2009; Lee, 2012), probably due to relative ischemic vulnerability of the inner ear or the vestibular structures in the brainstem, especially when patients have basilar artery occlusive disease, presumably close to the origin of the AICA on brain MRA, even if initially other central signs are absent and MRI does not demonstrate acute infarction (Lee et al., 2009; Lee, 2012).

SCA infarction

Ipsilateral trochlear palsy, Horner's syndrome, and contralateral ataxia may be observed in SCA territory infarctions, since the SCA supplies the posterior aspect of the caudal midbrain and the superior cerebellum. However, midbrain involvement is rare in SCA infarction, and the classic syndrome of SCA infarction (ipsilateral trochlear palsy, Horner's syndrome, and contralateral ataxia) is rarely encountered (Kase et al., 1985; Amarenco and Hauw, 1990b). Cerebellar infarctions in the SCA territory have been known to rarely cause vertigo, since the superior cerebellum supplied by the SCA does not have significant vestibular connections (Kase et al., 1985; Amarenco and Hauw, 1990b). However, a recent study (Lee and Kim, 2013) showed that approximately half (19/41) of patients with isolated SCA infarction experience true vertigo and 27% show mainly ipsilesional spontaneous nystagmus or GEN (Fig. 23.4). Thus, the vertigo and nystagmus in SCA infarctions are more common than previously thought. A unilateral medial SCA infarction can cause contrapulsion of saccades (hypermetria of contralesional saccades and hypometria of ipsilesional saccades) and ipsilesional limb dysmetria (Ranalli and Sharpe, 1986). Saccadic contrapulsion in medial SCA infarction may be explained by imbalanced cerebellar outflow due to blockage of fastigial output in the superior cerebellar peduncle (Ranalli and Sharpe, 1986). However, a patient with isolated infarction involving the superior cerebellar peduncle showed ipsiversive ocular torsion, mild dysarthria, ipsilesional limb ataxia, and severe truncal ipsipulsion, but no saccadic contrapulsion (Lee et al., 2015).

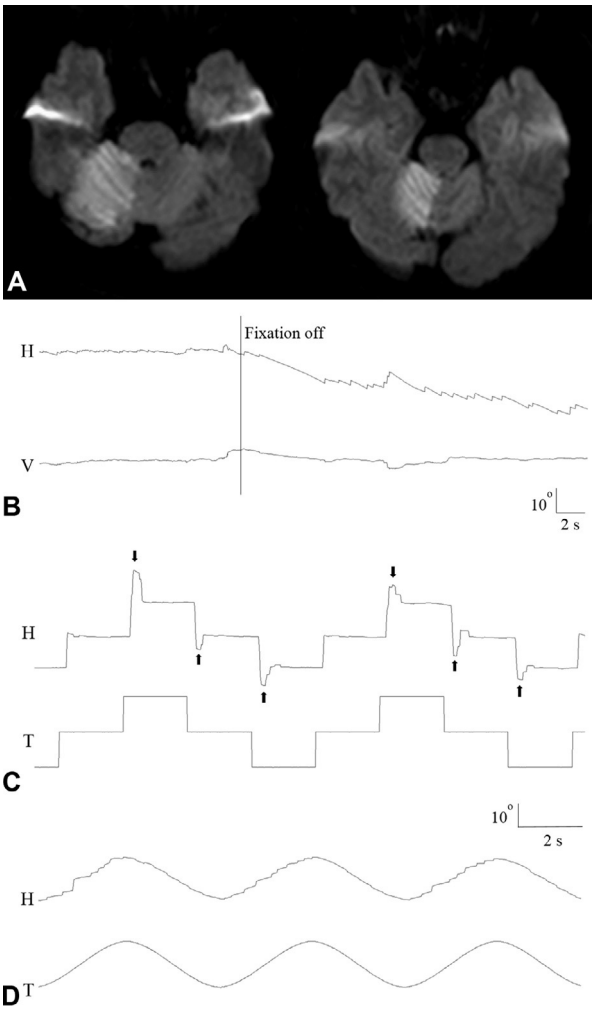

Fig. 23.4. A patient with right rostral cerebellar infarction in the territory of the superior cerebellar artery (**A**) shows ipsilesional spontaneous nystagmus without visual fixation (**B**), saccadic hypermetria in both horizontal directions (**C**), and impaired ipsilesional smooth pursuit (**D**).

BRAINSTEM INFARCTION

Since the neural structures subserving ocular motor and postural control are mostly located in the tegmentum and tectum of the brainstem, dorsal brainstem infarctions

frequently present with dizziness/vertigo and imbalance (Kumral et al., 2002b; Choi et al., 2005). Those structures are usually supplied by the perforators of the vertebral artery in the medulla and by the long circumferential arteries branching from the basilar artery in the pons and midbrain (Kumral et al., 2002b). Vertigo from brainstem infarctions is typically accompanied by the characteristic symptoms and signs from neighboring structures, which allow clinical recognition of the affected vascular territory (Savitz and Caplan, 2005).

Medullary infarction

Medullary infarctions are usually divided into lateral and medial. Lateral medullary infarction (LMI: Wallenberg syndrome) has been regarded as a prototype of central vestibular syndromes due to its involvement of the vestibular nuclei (Baloh et al., 1981; Waespe and Wichmann, 1990; Rambold and Helmchen, 2005; Choi et al., 2007). In contrast, the vestibular and ocular motor findings of medial medullary infarction (MMI) have been recognized only recently (Choi et al., 2005). Neurotologic findings of lateral and medial medullary infarctions are compared in Table 23.2.

Lateral medullary infarction

Infarctions involving the dorsolateral medulla (Wallenberg syndrome) commonly involve the inferior and medial vestibular nuclei, and typically present with nausea/vomiting, dizziness/vertigo, and imbalance. Other findings of LMI include ipsilateral Horner's syndrome, impaired pain and temperature sensation in the ipsilateral face and contralateral body and extremities, dysphagia, ataxia, and hoarseness (Sacco et al., 1993; Kim, 2003). LMI is usually caused by occlusion of the ipsilateral vertebral artery just proximal to the origin of PICA and occasionally the PICA is selectively occluded (Fisher et al., 1961; Fisher and Tapia, 1987; Kim, 2003; Kameda et al., 2004). In younger patients, especially in patients with a history of head trauma or neck manipulation or with posterior neck pain or occipital headache, traumatic dissection of the distal vertebral artery should be considered (Frumkin and Baloh, 1990).

In LMI, spontaneous nystagmus is usually horizontal or mixed horizontal-torsional with a small vertical component (Baloh et al., 1981). Typically, the horizontal nystagmus beats away from the lesion side while it may beat toward the lesion side during ipsilesional gaze (Fig. 23.5). The vertical component is usually upbeating, and torsional nystagmus may be ipsi- or contralesional (Morrow and Sharpe, 1988; Rambold and Helmchen, 2005). The spontaneous nystagmus may change directions during the follow-up (Choi et al., 2007). GEN is observed in almost all patients and is mostly horizontal (Dieterich and Brandt, 1992). Positional nystagmus is rare and may beat torsionally (Dieterich and Brandt, 1992). HSN is frequently observed, with the horizontal component beating ipsilesionally in most patients (Choi et al., 2007; Choi and Kim, 2009). Even in patients with contralesional spontaneous nystagmus, horizontal HSN beats in the opposite direction of spontaneous nystagmus. Some patients show unusually strong HSN. However, the preserved suppression of HSN with visual fixation necessitates removal of fixation (e.g., Frenzel goggles) for proper observation of HSN (Choi et al., 2007).

Patients with LMI invariably show ocular ipsipulsion that comprises a steady-state ocular deviation to the lesion side, hypermetric ipsilesional saccades, hypometric contralesional saccades, and oblique ipsilesional misdirection of vertical saccades (Kommerell and Hoyt, 1973; Baloh et al., 1981). Ocular lateropulsion may occur in lesions involving the neural pathways connecting the inferior olivary nucleus (ION), cerebellar Purkinje cells, fastigial nucleus, and paramedian pontine reticular formation (PPRF) (Helmchen et al., 1994). Ocular ipsipulsion in LMI has been ascribed to damage to the climbing fibers from the contralesional ION to the dorsal vermis (Waespe and Wichmann, 1990). Damage to the climbing fibers in the inferior cerebellar peduncle after decussation from the ION would increase the Purkinje cell activity in the dorsal vermis and result in increased inhibition of the ipsilateral fastigial nucleus and

Table 23.2

Neuro-otologic features of lateral and medial medullary infarctions

	Lateral medullary infarction	Medial medullary infarction
Spontaneous nystagmus	Mixed horizontal-torsional-vertical (contralesional > ipsilesional, upbeat >> downbeat)	Ipsilesional horizontal Upbeat Hemi-seesaw
Gaze-evoked nystagmus	Mostly horizontal	Horizontal (ipsilesional > contralesional)
Ocular lateropulsion	Ipsilesional	Contralesional
Ocular tilt reaction	Mostly ipsiversive	Mostly contraversive

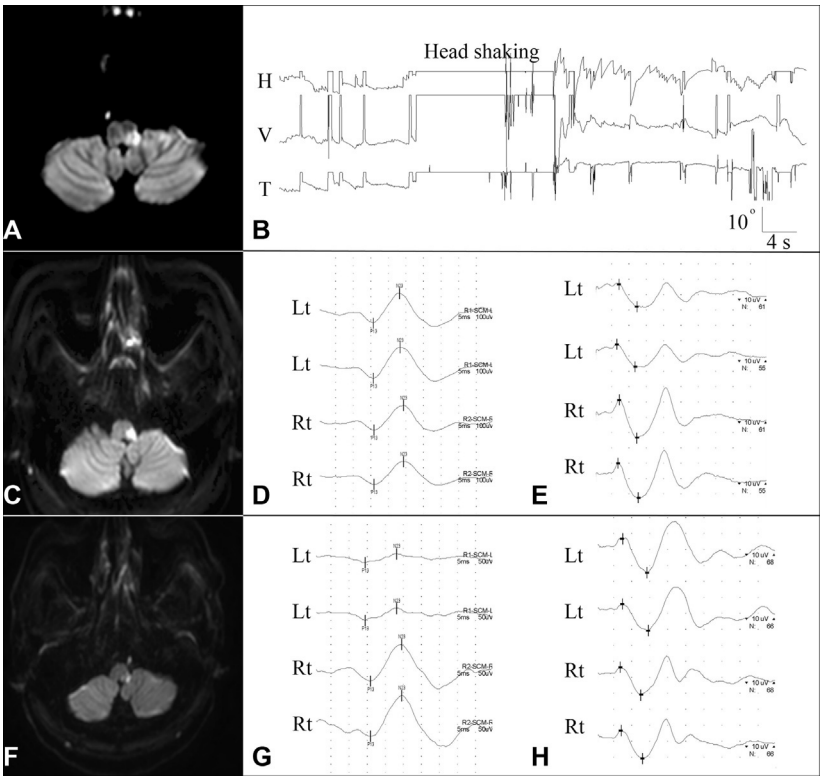

Fig. 23.5. Patients with left lateral medullary infarction show contralesional spontaneous nystagmus that changes to left beating after horizontal head shaking (**A**, **B**), normal cervical vestibular-evoked myogenic potentials (cVEMPs) but decreased amplitude of ocular VEMPs (oVEMPs) during ipsilesional ear stimulation (**C**–E), and decreased amplitude of ipsilesional cVEMPs in the presence of normal oVEMPs (**F**–H). From Oh, Kim, Kim et al. (2016), with permission from Springer Science and Business Media.

contralateral PPRF. Thus, the relative activation of the ipsilateral PPRF would create a bias toward ipsilateral saccades.

LMI causes prominent imbalance, with falling to the lesion side as if being pulled by a strong external force. Body lateropulsion correlates with SVV tilt, i.e., the more pronounced the lateropulsion, the greater the SVV tilt (Dieterich and Brandt, 1992). Some patients show body lateropulsion as a sole manifestation of LMI (Kim et al., 2004b; Thomke et al., 2005). Body lateropulsion in LMI may be attributed to disruption of the ascending dorsal spinocerebellar tract or descending lateral vestibulospinal tracts (Kim et al., 2004b; Thomke et al., 2005).

Unilateral damage to the graviceptive projections from the vestibular nuclei to the contralateral interstitial nucleus of Cajal (INC) may cause OTR and SVV tilt (Brandt and Dieterich, 1987). Brainstem lesions caudal to the pons, including LMI, cause ipsiversive OTR and SVV tilt (Dieterich and Brandt, 1992), whereas more rostral lesions affecting the medial longitudinal fasciculus (MLF) or INC lead to contraversive OTR and SVV tilt. Cervical and ocular VEMPs can be abnormal in LMI due to damage to the descending sacculocolic and ascending utriculo-ocular pathways (Kim et al., 2011b; Oh et al., 2013).

Most patients with isolated vestibular nuclear infarction present with features of both peripheral and central vestibulopathies (Choi et al., 2014a), which include contralesional spontaneous nystagmus, direction-changing GEN, positive HITs to the lesion side or in both directions, and ipsilesional caloric paresis (Fig. 23.6) (Kim et al., 2014c).

Medial medullary infarction

MMI is characterized by a triad of contralateral hemiparesis sparing the face, contralateral loss of deep sensation, and ipsilateral hypoglossal paralysis (Bassetti et al., 1997). MMI, however, also generates distinct patterns of ocular motor and vestibular abnormalities, especially when the lesions are extended into the tegmentum in the rostral medulla, including the ascending efferent fibers from the vestibular nuclei, the MLF, the perihypoglossal nuclear complex, including the nucleus prepositus hypoglossi (NPH), nucleus of Roller, and nucleus intercalatus, the climbing fibers emanating from the ION, and the cell groups of the paramedian tracts (PMT), which are all involved in the control of eye movements (Choi et al., 2005). MMI is usually caused by thrombosis of the

anterior spinal artery or distal intracranial vertebral artery and is frequently bilateral.

Horizontal nystagmus usually beats ipsilesionally, probably due to involvement of the NPH (Fig. 23.7) (Kaneko, 1997; Choi et al., 2005). Upbeat nystagmus is an occasional finding and may be ascribed to damage to the nucleus of Roller or intercalatus (Pierrot-Deseilligny and Milea, 2005). However, the evolution of upbeat into hemi-seesaw nystagmus in patients with MMI suggests an involvement of the VOR pathways from both anterior semicircular canals as a mechanism of upbeat nystagmus (Choi et al., 2004; Lee et al.,

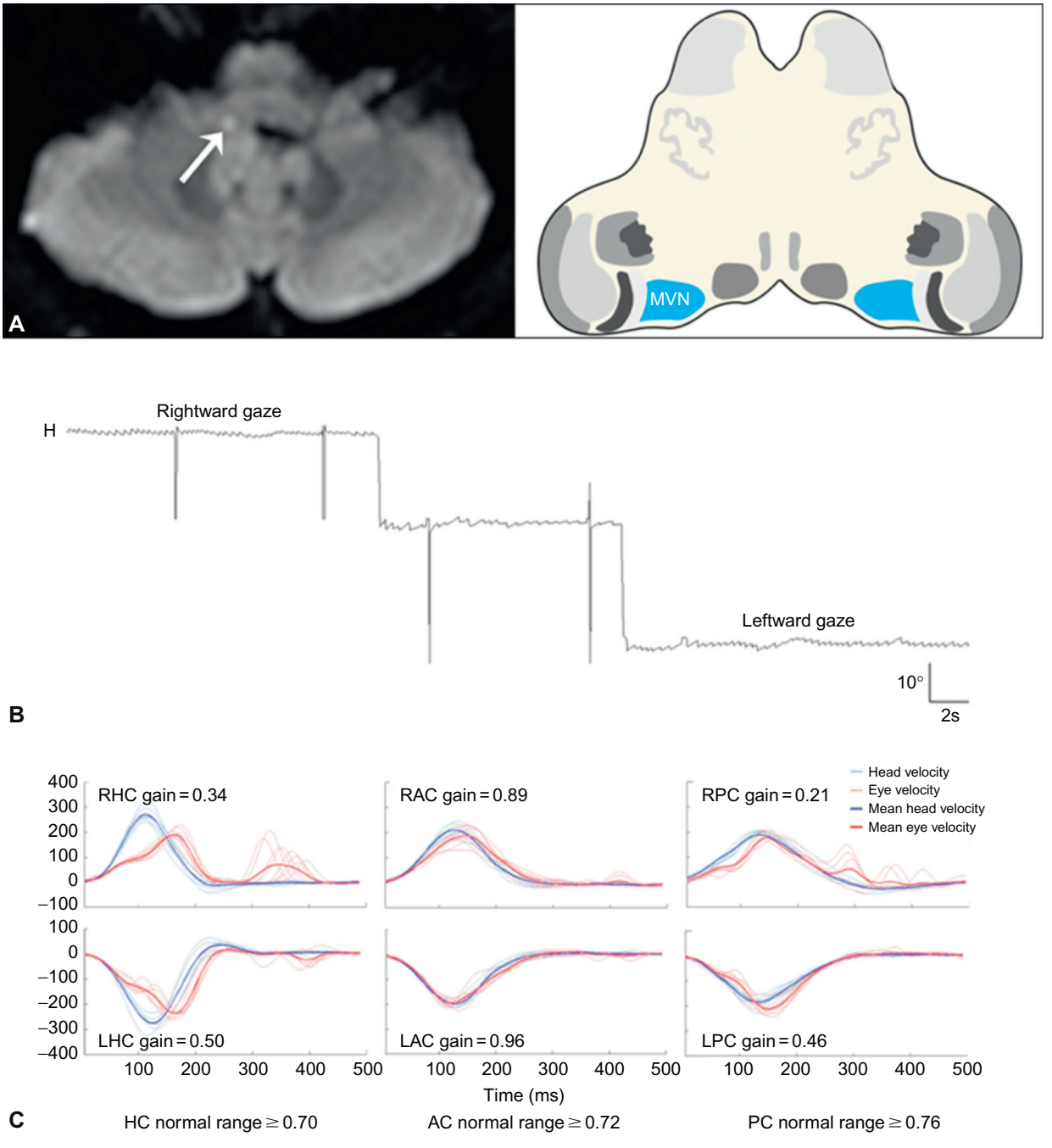

Fig. 23.6. A patient with infarction restricted to right medial vestibular nucleus (**A**: MVN) shows gaze-evoked nystagmus (**B**), decreased gain of the vestibulo-ocular reflex during head impulse tests (**C**),

(Continued)

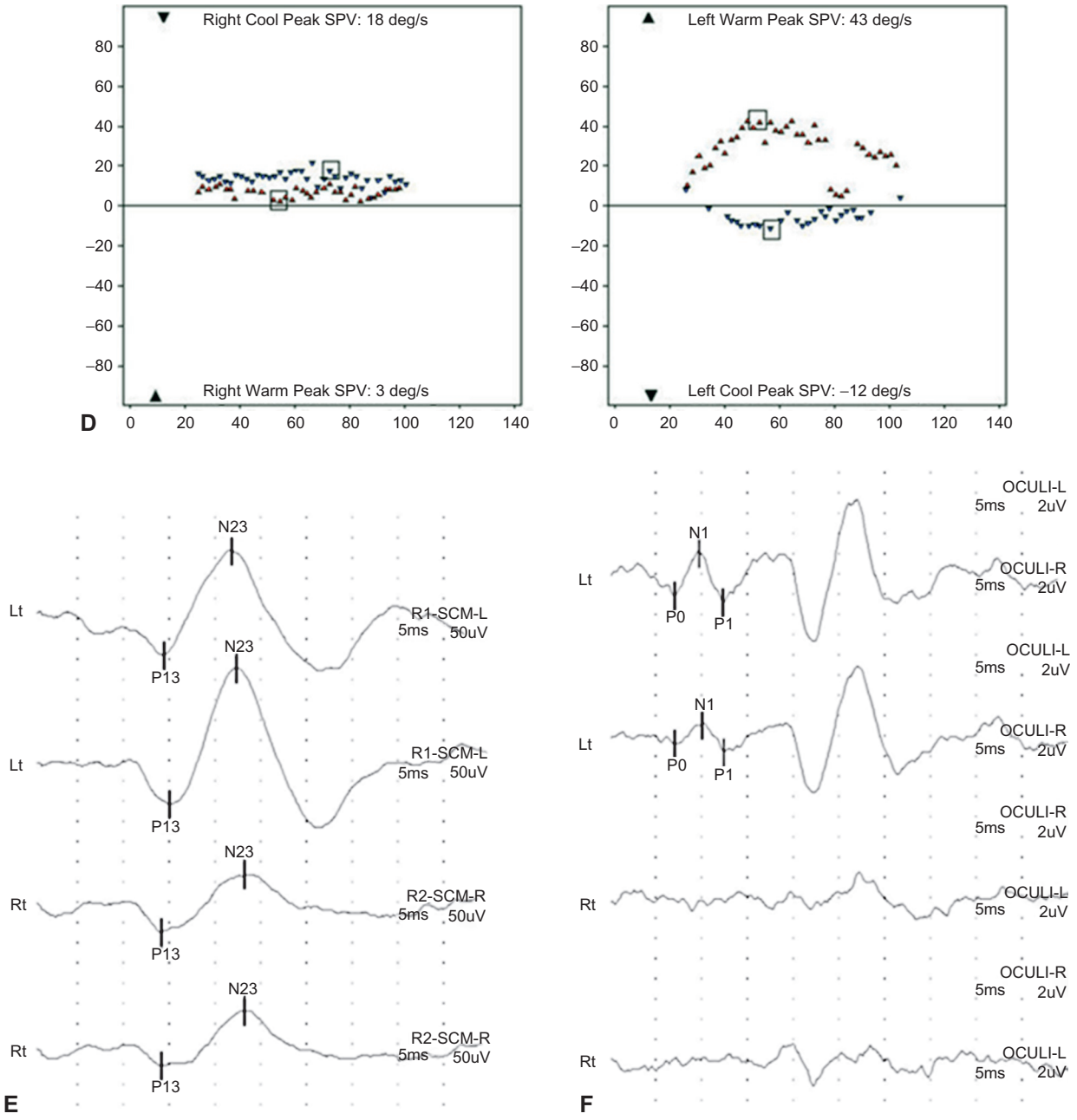

Fig. 23.6—cont'd ipsilesional caloric paresis (**D**), and decreased or absent responses of cervical and ocular vestibular-evoked myogenic potentials during ipsilesional ear stimulation (E–F). From Kim, Lee, Park et al. (2014c), with permission from Springer Science and Business Media.

2014c). In the caudal medulla, the nucleus of Roller and the caudal subgroup of the PMT cells are involved in processing of vertical eye position through their projections to the cerebellar flocculus and may be the neural substrates for upbeat nystagmus (Tilikete et al., 2002; Pierrot-Deseilligny et al., 2005; Choi et al., 2011). GEN is common and mostly more intense when looking to the lesion side (Choi et al., 2005). Damage to the climbing fibers before decussation may cause ocular contrapulsion (Kim et al., 2004a).

MMI may show contraversive OTR and SVV tilt, which indicates damage to the graviceptive brainstem pathways from the vestibular nuclei after decussation (Choi et al., 2005). Ipsilesional cVEMPs are impaired in about a half of the patients with MMI, especially when the lesions extend to the dorsal tegmentum, where the MLF is located (Fig. 23.7) (Kim et al., 2010). These findings indicate that cVEMPs are mediated by the inhibitory medial vestibulospinal tract that descends within the MLF.

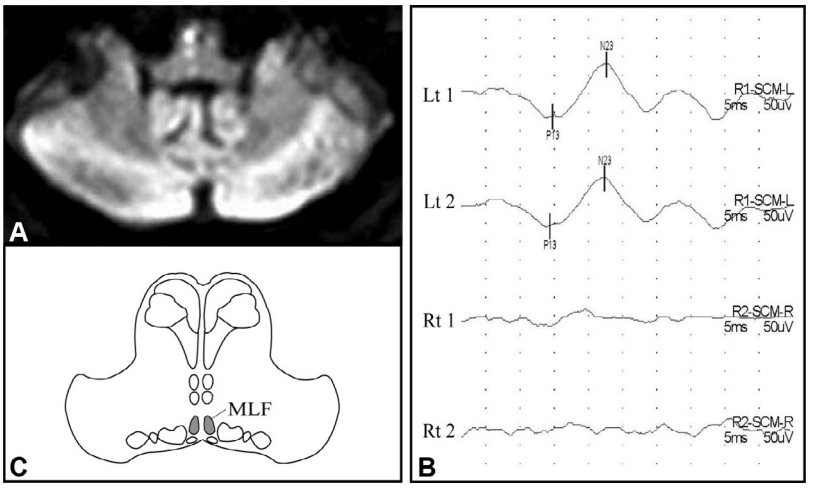

Fig. 23.7. A patient with right medial medullary infarction (**A**) shows absent formation of ipsilesional cervical vestibular-evoked myogenic potentials (**B**). The lesion on diffusion-weighted magnetic resonance imaging extends dorsally to involve the medullary tegmentum where the medial longitudinal fasciculus (MLF) is located (**C**).

Pontine infarction

Pontine infarctions may be classified according to the vascular territories involved into: (1) anteromedial; (2) anterolateral; (3) tegmental; and (4) bilateral (Bassetti et al., 1996). Vestibular and ocular motor findings are mostly observed in infarctions involving the pontine tegmentum that is mainly supplied by the anterior medial pontine arteries, AICA (lower pons), and SCA (upper pons) (Lopez et al., 1996; Felicio et al., 2009). Anteromedial pontine infarction usually causes a motor deficit with dysarthria and ataxia, but tegmental symptoms and signs, including vertigo, nystagmus, Horner's syndrome, and horizontal gaze palsy, occur in one-third of patients (Kataoka et al., 1997). Likewise, tegmental symptoms and signs also occur in more than a half of patients with anterolateral infarctions. Lateral pontine infarction is usually due to occlusion of the AICA or SCA, and is commonly associated with cerebellar infarction. A small infarction in the tegmental area just ventral to the fourth ventricle may cause body lateropulsion, probably from damage to the graviceptive pathway ascending through the paramedian pontine tegmentum (Kumral et al., 2002b).

Nystagmus and involuntary eye movements

In pontine tegmental lesions, upbeat nystagmus may occur due to bilateral damage to the ventral tegmental tracts (Pierrot-Deseilligny et al., 2005) or the MLFs, which are known to carry a signal for the upward VOR (Kim et al., 2006; Lee et al., 2013). However, exponentially decreasing slow phases and disobedience of upbeat nystagmus to Alexander's law in a patient with bilateral INO also suggest an unstable as well as a leaky neural integrator for vertical gaze, possibly due to damage to the MLFs themselves or to the cell groups of the PMT (Choi et al., 2012). Occasionally, downbeat nystagmus may occur in midline pontine lesions, and may be attributed to damage of the PMT neurons, which provide the cerebellum with vestibular and eye velocity signals that are essential for the velocity-to-position integration (Wagner et al., 2009; Nakamagoe et al., 2012; Helmchen et al., 2013). Acquired pendular nystagmus is commonly encountered in brainstem strokes as the syndrome of oculopalatal tremor (Kim et al., 2007b; Tilikete et al., 2011). This condition usually develops several weeks or months after brainstem or cerebellar strokes. Interruption of the dentate-olivary tract and resultant pseudohypertrophic degeneration of the ION are the underlying pathology of this phenomenon (Shaikh et al., 2010). Ocular bobbing, i.e., an intermittent downward jerk of the eyes followed by a slow return to the primary position, can be observed in comatose patients with extensive infarctions involving the pontine base and tegmentum (Fisher, 1964).

Ophthalmoplegia

Since the neural structures responsible for horizontal gaze are located in the pontine tegmentum, infarctions involving the pontine tegmentum may give rise to varied combinations of horizontal gaze palsy from isolated abducens palsy to total gaze palsy (Kataoka et al., 1997; Leigh and Zee, 2006).

Internuclear ophthalmoplegia (INO)

Since the MLF contains the fibers carrying a command for conjugate horizontal gaze from the abducens interneurons to the medial rectus subdivision of the contralateral oculomotor nucleus, lesions affecting the MLF cause

INO that is characterized by a paresis of adduction in the ipsilesional eye and dissociated abducting nystagmus of the contralesional eye during the gaze away from the lesion side (Cogan et al., 1950; Christoff et al., 1960). Some patients with bilateral INO may show impaired fixation and sporadic bursts of monocular abducting saccades in either eye (Herishanu and Sharpe, 1983). Exotropia of the contralesional eye or both eyes is common in unilateral (wall-eyed monocular INO: WEMINO) or bilateral (wall-eye bilateral INO: WEBINO) INO (Gonyea, 1974). Convergence may be normal or impaired (Cogan, 1970). INO may occur as an isolated or predominant symptom of dorsal brainstem infarction and has an excellent prognosis (Kim, 2004).

INO plus

Since the MLF also carries the fibers originating from the vertical semicircular canals and utricle, INO is usually accompanied by vertical-torsional nystagmus (Dehaene et al., 1996; Oh et al., 2005; Jeong et al., 2011), contraversive OTR and SVV tilt (Zwergal et al., 2008), and impaired vertical VOR (Fig. 23.8) (Ranalli and Sharpe, 1988; Cremer et al., 1999). Three distinctive patterns of vertical-torsional nystagmus have been described in INO, probably depending on the vertical VOR pathways involved (Oh et al., 2005; Jeong et al., 2011). Predominant impairment of the vertical VOR originating from the contralateral posterior semicircular canal was demonstrated in INO with HIT (Ranalli and Sharpe, 1988; Cremer et al., 1999). The relatively preserved anterior canal function suggests an extra route for the ascending VOR pathway (Buttner-Ennever and Buttner, 1978) from the anterior canal, possibly the ventral tegmental tract. Patients with INO frequently show impaired formation of ipsilesional oVEMPs in response to forehead tapping (Kim et al., 2014b). This suggests that the MLF contains the fibers for the otolith-ocular reflex from the contralateral ear. The occasional abnormality and decreased amplitude of ipsilesional cVEMPs also suggest a descending modulatory pathway for the sacculocolic reflex in the MLF (Kim et al., 2014b). In bilateral INO, vertical smooth pursuit, vertical optokinetic nystagmus and after-nystagmus, and vertical gaze holding are also impaired (Ranalli and Sharpe, 1988).

Conjugate horizontal gaze palsy

Since the PPRF contains the burst neurons for ipsilateral saccades (Horn et al., 1996), selective damage to the burst neurons in the PPRF would result in contralesional conjugate deviation of the eyes and isolated ipsilesional saccadic palsy in the whole field (Hanson et al., 1986; Johnston and Sharpe, 1989). However, vestibular and smooth-pursuit eye movements are commonly impaired in PPRF lesions due to concomitant damage to the fibers of passage for these eye movements (Leigh and Zee, 2006). In contrast, lesions involving the abducens nucleus invariably lead to ipsilesional palsy of saccades, smooth pursuit, and VOR, mostly in the ipsilateral hemifield (Muri et al., 1996). Infarctions restricted to the abducens nucleus are extremely rare, however, and nuclear infarctions usually involve adjacent tegmental structures, especially the MLF, PPRF, and the genu portion of the facial nerve fascicle. Pontine lesions that affect the dorsolateral pontine nuclei may disrupt ipsilateral pursuit (Thier et al., 1991). Lesions affecting the nucleus reticularis tegmenti pontis (NRTP) may impair vergence eye movements (Rambold et al., 2004, 2005a, b).

One-and-a-half syndrome

Unilateral lesions involving the abducens nucleus or PPRF in association with damage to the MLF cause ipsilesional horizontal gaze palsy and INO on attempted gaze to the contralesional side (Leigh and Zee, 2006). Consequently, the only remaining eye movement is abduction of the contralesional eye ("a half-gaze palsy"). The term paralytic pontine exotropia was coined for patients who showed an exotropia of the contralesional eye along with one-and-a-half syndrome (Sharpe et al., 1974).

Abducens palsy

Abducens palsy from brainstem lesions is mostly caused by disruption of the abducens fascicle (Bronstein et al., 1990). Fascicular abducens nerve palsy may be isolated (Donaldson and Rosenberg, 1988; Paik et al., 2004), but usually accompanies ipsilateral gaze palsy, ipsilateral peripheral facial palsy, or contralateral hemiparesis.

Midbrain infarction

The midbrain contains the structures important for control of vertical and torsional eye movements. Midbrain infarctions frequently cause ataxia and ocular motor abnormalities, including third cranial nerve palsy, INO, and vertical gaze palsy (Kumral et al., 2002a; Sharpe and Kim, 2002; Kim and Kim, 2005). The midbrain is irrigated by the branches arising from the posterior cerebral artery, upper basilar artery, and the SCA. Pure midbrain infarction is relatively rare and is mostly caused by either large- or small-vessel disease (Kumral et al., 2002a; Kim and Kim, 2005). In contrast, embolism from the heart or from the proximal vessels to the posterior territory often causes the top of the basilar syndrome, with multiple infarctions involving the thalamus, occipitotemporal lobes, and cerebellum as well as the midbrain (Caplan, 1980).

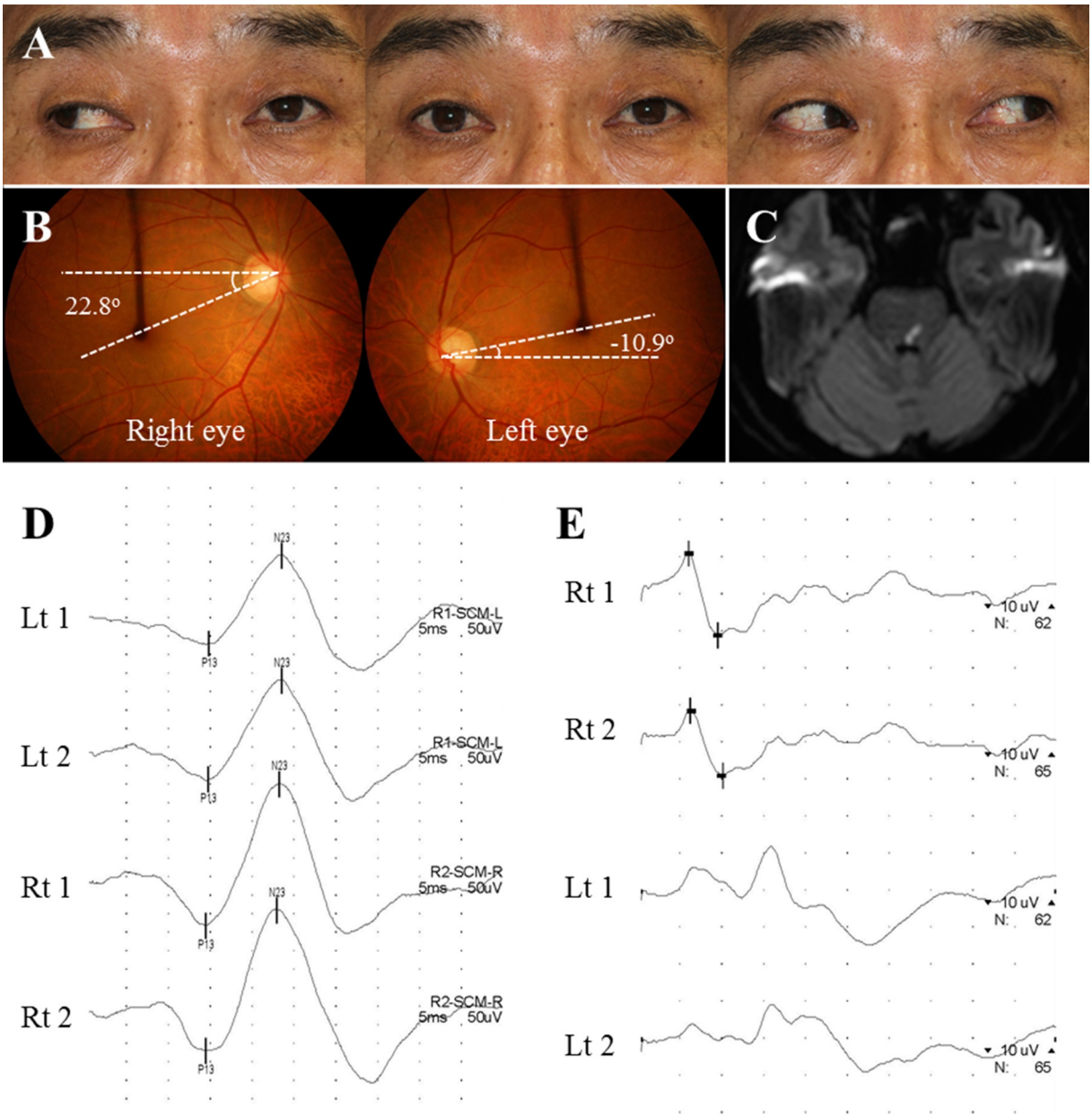

Fig. 23.8. A patient with left internuclear ophthalmoplegia shows diminished adduction of the left eye on rightward gaze (**A**), clockwise (from the patient's perspective) ocular torsion (**B**), acute pontine infarction in the area of left medial longitudinal fasciculus on diffusion-weighted magnetic resonance imaging (**C**), normal cervical vestibular-evoked myogenic potentials (VEMPs) (**D**), and absent reponses of ocular VEMPs recorded below the left eye (right-ear stimulation, **E**). From Kim, Lee, and Kim (2014d).

Top of the basilar syndrome

Occlusion of the rostral tip of the basilar artery gives rise to a characteristic combination of ocular motor abnormalities (pretectal syndrome) by damaging the pretectum that contains the rostral interstitial nucleus of the MLF (riMLF), the INC, the rostral portion of the mesencephalic reticular formation (MRF), and the posterior commissure (PC), which are involved in the premotor control of vertical and torsional eye movements (Wall et al., 1986; Keane, 1990). The pretectum is usually supplied by the posterior thalamosubthalamic paramedian artery (Ranalli et al., 1988). The riMLF lies dorsomedial to the rostral pole of the red nucleus and contains the medium lead burst neurons that generate vertical and ipsiversive torsional saccades (Buttner-Ennever and Buttner, 1978; King and Fuchs, 1979). Each riMLF projects bilaterally to motoneurons for the elevator muscles (superior rectus and inferior oblique). An ipsilateral projection reaches the motoneurons for the depressor muscles (inferior rectus and superior

oblique) (Moschovakis et al., 1991a, b). Thus, unilateral lesions of the riMLF result in a mild and variable defect of downward saccades, contralesional ocular torsion with torsional nystagmus beating contralesionally, and loss of ipsitorsional quick phases (Ranalli et al., 1988; Leigh et al., 1993). Bilateral lesions of the riMLF cause a more profound defect of vertical saccades, but vertical gaze holding, the VOR and smooth pursuit, and horizontal saccades are preserved (Leigh and Zee, 2006).

The INC is an element of the neural integrator for vertical and torsional eye motion (Crawford et al., 1991; Helmchen et al., 1996). The INC appears to project exclusively to the ocular motoneurons via the posterior commissure. Unilateral lesions of INC produce impaired gaze holding in the vertical and torsional planes, contraversive OTR, and torsional nystagmus that has ipsilesional quick phases (Halmagyi et al., 1990; Helmchen et al., 1998), while bilateral lesions reduce the range of all vertical eye movements without saccadic slowing, and impaired gaze holding after all vertical and torsional movements (Leigh and Zee, 2006). The PC contains axons from INC projecting to the contralateral oculomotor and trochlear nuclei, and to the INC. The PC also contains axons from the nucleus of the PC projecting to the contralateral riMLF and INC, which may be important for upgaze, and to the "M" group of neurons that may be relevant for coordination of vertical eye and lid movements (Kokkoroyannis et al., 1996). Accordingly, varied combinations of vertical gaze palsy may occur depending on the structures involved, e.g., upgaze palsy, downgaze palsy, vertical one-and-a-half syndrome (bilateral conjugate upgaze palsy with unilateral depression palsy, or bilateral conjugate downgaze palsy with unilateral elevation palsy), and complete vertical gaze palsy (Sharpe and Kim, 2002). Dissociated vertical nystagmus may occur in the pretectal syndrome (Marshall et al., 1991; Halmagyi et al., 1994). The neurons specifically involved in vergence control are located 1–2 mm dorsal and dorsolateral to the oculomotor nucleus (Judge and Cumming, 1986; Mays et al., 1986). Pretectal syndrome may cause various ocular motor disorders related to vergence, which include convergence insufficiency, convergence spasm, and convergence nystagmus. Convergence spasm results in limitation of abduction on voluntary lateral gaze, which resembles sixth cranial nerve palsy (pseudo-abducens palsy) (Caplan, 1980). The pretectal syndrome also may be associated with bilateral ptosis or lid retraction (Collier's sign) (Keane, 1990).

Other ocular motor abnormalities

Third cranial nerve palsy

Anteromedial and anterolateral midbrain infarctions frequently give rise to third cranial nerve palsy by damaging the oculomotor nuclei or fascicles (Biller et al., 1984). Varied patterns of third cranial nerve palsy may occur depending on the subnuclei or fascicles involved (Castro et al., 1990; Ksiazek et al., 1994). However, fascicular third nerve palsies frequently accompany contralateral hemiplegia (Weber's syndrome), cerebellar signs (Claude's syndrome), or involuntary movements (Benedikt's syndrome) (Liu et al., 1992).

Trochlear palsy

The trochlear nucleus is located in the central gray matter of the midbrain, close to the midline, near the MLF and the decussating fibers of the superior cerebellar peduncle. Fibers emerging from the trochlear nucleus pass laterally and posteriorly around the central gray matter, decussate in the superior medullary velum, and leave the midbrain below the inferior colliculus. Hence the innervation of the superior oblique muscle is crossed. The trochlear nucleus is supplied by the paramedian branches from the basilar artery bifurcation that are susceptible to shear injury due to trauma (Burgerman et al., 1989). Thus, trochlear palsy alone or with upbeat nystagmus may occur in brainstem strokes involving the trochlear nucleus or fascicle (Galetta and Balcer, 1998; Makki and Newman, 2005; Lee et al., 2010).

Internuclear ophthalmoplegia

INO in association with cerebellar signs (limb and gait ataxia) may occur in caudal paramedian midbrain infarction, which damages the decussation of the brachium conjunctivum and the MLF (Okuda et al., 1993; Krespi et al., 2001; Mossuto-Agatiello, 2006).

Hearing loss

Central hearing loss is uncommon owing to the characteristic organization of the central auditory pathways, which consist of many nuclei with extensive interconnections (Huang et al., 1993). Midbrain infarction rarely involves the collicular areas. Unilateral or bilateral damage to the inferior colliculus may impair hearing (Kimiskidis et al., 2004; Musiek et al., 2004) or cause tinnitus (Choi et al., 2010), though this may not be evident on electrophysiologic testing of cochlear function (Vitte et al., 2002).

LABYRINTHINE INFARCTION

Since the internal auditory artery (IAA), usually a branch of the AICA, supplies the inner ear, vertebrobasilar ischemic strokes may present with vertigo and hearing loss due to labyrinthine infarction. The labyrinth appears to be vulnerable to ischemia because the IAA is an end artery with minimal collaterals from the otic capsule (Grad and Baloh, 1989; Oas and Baloh, 1992). IAA infarction mostly occurs due to thrombotic narrowing

of the AICA itself, or in the basilar artery at the orifice of the AICA (Amarenco et al., 1993). As isolated labyrinthine damage may precede pontocerebellar involvement in AICA infarction, audiovestibular loss may serve as a window to prevent the progression into more widespread infarction involving the posterior circulation, mainly in the AICA territory (Kim et al., 2009; Lee, 2012).

Labyrinthine infarction should be considered in older patients with acute vertigo and unilateral hearing loss, particularly when there is a history of strokes or known vascular risk factors. Since labyrinthine infarction is hardly visualized with current imaging techniques, a definite diagnosis of isolated labyrinthine infarction is not possible without a pathologic confirmation (Kim et al., 1999). Thus, clinicians should consider all the clinical features and laboratory findings available when attempting to determine the cause of acute vertigo and hearing loss, since normal brain imaging does not exclude vascular etiologies as the mechanism of acute audiovestibular loss (Kim et al., 2007a).

HEMISPHERIC AND THALAMIC INFARCTION

Hemispheric infarction

Cortical areas including the primary and premotor cortices and parietal multisensory cortex give off projections to the vestibular nucleus and modulate the vestibulomotor reflex arcs. In addition, they participate in the vestibular control of balance and in ocular motor control (Akbarian et al., 1994). Patients with hemispheric infarctions may show impaired vestibular control of balance, probably by disrupting corticobulbar modulation of brainstem balance centers, which was demonstrated using galvanic vestibular stimulation (Marsden et al., 2005). Damage to the parietal multisensory cortex also results in imbalance and impaired perception of verticality (Perennou et al., 2000; Yelnik et al., 2002). Lesions of the posterior insula cause pathologic tilts of the SVV, mostly contraversive, but without skew deviation or ocular torsion (Grusser et al., 1990). Rotatory vertigo and imbalance have been described in supratentorial infarctions involving the parietoinsular vestibular cortex, putamen, and posterior limb of the internal capsule (Brandt et al., 1995; Urasaki and Yokota, 2003; Anagnostou et al., 2010; Nakajima et al., 2012; Park et al., 2014a; von Brevern et al., 2014).

Thalamic infarction

The thalamus is mostly supplied by the tuberothalamic, thalamoperforating (thalamic-subthalamic), thalamogeniculate, and posterior choroidal arteries (Schmahmann, 2003). The thalamoperforating arteries, branches of the basilar communicating artery segment of the posterior cerebral artery, usually supply the riMLF and INC, and give rise to vertical gaze palsy, OTR, and torsional nystagmus when compromised (Dieterich and Brandt, 1993; Halmagyi et al., 1994; Sharpe and Kim, 2002). Thalamic esotropia occurring with caudal thalamic lesions may be marked, and is not always associated with downward eye deviation (Gomez et al., 1988; Hertle and Bienfang, 1990). This type of esotropia reflects a disturbance of vergence inputs to the oculomotor nuclei. Patients with posterolateral thalamic infarction may have disturbances of the SVV (either ipsilesional or contralesional) (Dieterich and Brandt, 1993). However, OTR is not present unless the rostral midbrain is also involved. Unilateral thalamic infarctions may cause contralesional falling or astasia (Masdeu and Gorelick, 1988). Thalamic astasia is the postural consequence of perceptual tilt. It is usually caused by involvement of the superolateral portion of the ventrolateral thalamic nucleus (Masdeu and Gorelick, 1988).

TRANSIENT DIZZINESS/VERTIGO AND IMBALANCE OF VASCULAR ORIGIN

Transient isolated vascular vertigo typically occurs abruptly, and usually lasts several minutes (Fisher, 1967). According to a report, 62% of patients with vertigo due to vertebrobasilar ischemia had a history of at least one isolated episode of vertigo, and 19% reported vertigo as the initial symptom (Grad and Baloh, 1989). Patients with AICA infarction may have isolated recurrent vertigo, fluctuating hearing loss, and/or tinnitus, similar to Menière's disease, as the initial symptoms 1–10 days prior to permanent infarction (Lee and Cho, 2003). Another study found that patients who visited the emergency department with dizziness/vertigo had a twofold (95% confidence interval (CI), 1.35–2.96, $p < 0.001$) higher risk for strokes or cardiovascular events than those without dizziness/vertigo during a follow-up of 3 years (Lee et al., 2011a). The authors also demonstrated that patients hospitalized with isolated vertigo had a three-times (95% CI, 2.20–4.11; $p < 0.001$) higher risk for stroke than the general population during a 4-year follow-up period (Lee et al., 2011a). Furthermore, patients with vertigo and three or more vascular risk factors have a 5.5-fold higher risk for strokes (95% CI, 3.10–9.79; $p < 0.001$) than those without risk factors (Lee et al., 2011a).

Another study adopted the ABCD2 score (Johnston et al., 2007), a clinical prediction tool to assess the risk of strokes after a transient ischemic attack, to predict cerebrovascular events in emergency department patients with dizziness (Navi et al., 2012). The authors found that only 1.0% of dizzy patients with a score of 3 or less had a cerebrovascular event, compared to 8.1% of patients with a score of 4 or more (Navi et al., 2012). Of note, 27% of the patients with a score of 6

or 7 suffered from subsequent cerebrovascular episodes (Navi et al., 2012). Thus, the ABCD2 score may predict cerebrovascular attacks in patients with transient vertigo.

All of these data suggest that isolated episodic vertigo with or without auditory symptoms may be the only manifestation of transient ischemia within the vertebrobasilar circulation. Thus, patients with suspected episodes of vascular vertigo should have a prompt assessment of the cerebral vasculature, especially when vertigo lasting several minutes occurs in the elderly or in patients with vascular risk factors (Choi et al., 2013b; Kim and Lee, 2013). Perfusion imaging may help determine the presence and extent of hypoperfusion, especially when routine MRI, including diffusion-weighted imaging, is normal (Kim et al., 2011a). However, the exact role of perfusion imaging needs to be validated in isolated vertigo of vascular origin.

Rotational vertebral artery syndrome (RVAS) refers to recurrent attacks of paroxysmal vertigo, nystagmus, and syncope due to compression of the vertebral artery during horizontal head rotation (Choi et al., 2013a). Most patients with RVAS exhibit a stenosis or anomaly, e.g., hypoplasia or termination in the PICA, of the vertebral artery on one side, and compression of the dominant vertebral artery at the C1–2 level during contraversive head rotation, which compromises the blood flow in the vertebrobasilar artery territory (Fig. 23.9). RVAS is confirmed when angiography documents compression of the vertebral artery during attacks of vertigo induced by head rotation (Choi et al., 2013a), but may be diagnosed by demonstrating head rotation-induced decrease of blood flow in the posterior circulation using transcranial Doppler (Sakaguchi et al., 2003).

Subclavian steal refers to stenosis of the subclavian artery proximal to the origin of the vertebral artery that leads to reversed vertebral artery flow (Fisher, 1961; Reivich et al., 1961). Even though subclavian steal syndrome is usually asymptomatic and often an incidental finding, symptoms of vertebrobasilar ischemia may occur, especially during exercise of the arm on the affected side. Subclavian steal occurs three times more often on the left side, and atherosclerosis is the most common cause of subclavian artery stenosis. Antithrombotic medical treatments should be the mainstay, and surgical corrections are reserved for refractory symptomatic cases.

LESION SITES RESPONSIBLE FOR ISOLATED VASCULAR VERTIGO

There are several lesion sites that may cause isolated vascular vertigo (Table 23.3) (Kim et al., 2015). Even though any infarction or ischemia restricted to the peripheral or central vestibular structures may cause isolated vascular vertigo, the inner ear is a strong candidate due to its requirement for high-energy metabolism and absence of collateral circulation (Grad and Baloh, 1989; Oas and Baloh, 1992). By contrast, the retrocochlear vestibulocochlear nerve has an abundant collateral blood supply arising from the lateral medullary artery, arteries supplying adjacent dura matter and petrous bone, and the inferior lateral pontine artery (Mazzoni, 1990). However, diagnosis of labyrinthine infarction would remain presumptive without a pathologic study until developments in imaging techniques permit reliable detection of infarction limited to the inner ear (Kim et al., 1999).

Recent studies also suggest that the inferior cerebellum can be responsible for transient isolated vascular vertigo. A patient with multiple vascular risk factors and isolated recurrent vertigo lasting several seconds to minutes showed a severe focal stenosis of the PICA

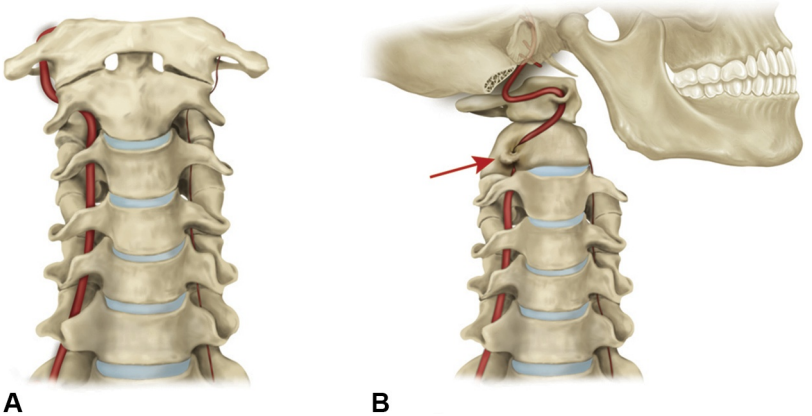

Fig. 23.9. (**A**, **B**). Mechanism of rotational vertebral artery syndrome (RVAS). A typical pattern of RVAS is induced by compression of the dominant vertebral artery at the C1–2 level during contraversive head rotation. From Choi, Choi, Kim et al. (2013a), with permission from the American Heart Association.

Table 23.3

Comparison of ocular motor findings among the six syndromes of isolated central vestibulopathy

	Vestibular nucleus	NPH	Flocculus	Tonsil	Nodulus	ICP
Spontaneous nystagmus	Contralesional, strong	Ipsilesional, weak	Ipsilesional, strong	Ipsilesional, weak	PAN, or ipsilesional	Ipsilesional, weak
Gaze-evoked nystagmus	Strong, contralesional > ipsilesional	Strong, ipsilesional > contralesional	Weak, ipsilesional > contralesional	Strong, ipsilesional > contralesional	None	None
Downbeat nystagmus	None	None	None	None	None	None
Rebound nystagmus	None	None	None	Yes	None	None
Ocular tilt reaction	Ipsiversive	Contraversive	Contraversive	None	Contraversive	Contraversive
Body lateropulsion	Ipsilesional	Contralesional	None	None	Contralesional	Ipsilesional
SVV tilt	Ipsiversive	?	Contraversive	Contraversive	Contraversive	Contraversive
Smooth pursuit	Impaired, ipsilesional	Impaired, ipsilesional	Superimposed on spontaneous nystagmus	Markedly impaired, ipsilesional > contralesional	Normal	Impaired, ipsilesional
VOR gain						
Caloric test	Ipsilesional paresis	Normal	Normal	Normal	Normal	Normal
Rotatory chair test	Normal	?	Increased	Minimally decreased	Loss of tilt suppression	Not done
Bedside HIT	Impaired, ipsilesional	Normal	Impaired, ipsilesional	Normal	Normal	Normal
HIT using MSC	Impaired, bilateral	?	Impaired, bilateral	Normal	Normal	Normal
Saccades	Normal	Normal	Normal	Normal	Normal	Normal

NPH, nucleus prepositus hypoglossi; ICP, inferior cerebellar peduncle; PAN, periodic alternating nystagmus; SVV, subjective visual vertical; VOR, vestibulo-ocular reflex; HIT, head impulse test; MSC, magnetic search coil.

along with impaired perfusion in the caudal cerebellum (Kim et al., 2011a). Another patient also developed RVAS due to compression of a vertebral artery terminating as PICA (Noh et al., 2011). Since the circulation through the basilar artery from the contralateral vertebral artery remained intact during the attack, the vertigo was ascribed to transient ischemia of the inferior cerebellum or lateral medulla. However, the different patterns of nystagmus in RVAS suggest various mechanisms for vascular vertigo (Strupp et al., 2000; Choi et al., 2005, 2013a; Park et al., 2014b).

In the brainstem, earlier reports have described several neural structures responsible for isolated vestibular syndromes (Kim and Lee, 2012; Saber Tehrani et al., 2014; Kim et al., 2015), which include the vestibular nucleus (Kim et al., 2014b) and root entry zone of the eighth nerve in the pontomedullary junction (Francis et al., 1992; Thomke and Hopf, 1999), rostral dorsolateral or caudal lateral medulla (Kim, 2000; Thomke et al., 2005), paramedian pontine or midbrain tegmentum (Felice et al., 1990; Yi et al., 2007), and inferior cerebellar peduncles (Bertholon et al., 1996). In a recent study of patients with AVS and at least one stroke risk factor (Saber Tehrani et al., 2014), approximately 15% (15/105) of the patients with a stroke had isolated AVS from a small ($\leq$10 mm) infarction, and 11 of them (11/15, 73%) showed a lesion involving the inferior cerebellar peduncle, mostly in the lateral medulla (9/11, 82%). Of interest, only 1 patient showed an isolated small infarction in the cerebellum (Saber Tehrani et al., 2014), which is known as one of the most common sites causing AVS when involved (Lee et al., 2006). Since the medial vestibular nucleus is more vulnerable to ischemia than other structures in the brainstem or cerebellum, according to a recent animal study (Lee et al., 2014a), ischemia of the dorsolateral medulla where the vestibular nuclei are located may be a mechanism of isolated vascular vertigo. Indeed, several studies described isolated vertigo from infarctions restricted to the vestibular nuclei (Kim et al., 2014c). Rarely, hemispheric infarctions involving the vestibular cortices can cause isolated vertigo with spontaneous nystagmus and SVV tilt (Brandt et al., 1995; Ahn et al., 2010; von Brevern et al., 2014).

Occasionally, serial evaluation is required to confirm stroke because initial diffusion-weighted MRI may be falsely negative in 12–20% of stroke patients within the first 48 hours (Kattah et al., 2009; Tarnutzer et al., 2011), particularly when isolated labyrinthine infarction progresses to involve portions of the brainstem and cerebellum due to AICA occlusion (Kim et al., 2009). The HINTS plus hearing test identifies these patients with a greater accuracy than early diffusion MRIs (Newman-Toker et al., 2013a; Saber Tehrani et al., 2014).

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Chapter 24

Functional and psychiatric vestibular disorders

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Abstract

Behavioral factors have long been recognized as affecting spatial orientation and balance function. Neuroanatomic and neurophysiologic studies conducted worldwide over the last 30 years have substantially advanced our knowledge about the inherently strong connectivity among threat/anxiety, vestibular, visual, and somatosensory systems in the brain. Clinical investigations have shed greater light on the nature of functional and psychiatric disorders that manifest or magnify vestibular morbidity. Concepts of these syndromes have changed over 150 years. Even their nomenclature has had different meanings in different eras. This chapter will review functional and psychiatric vestibular disorders. Terminology will follow the *International Classification of Diseases*, 11th edition, beta draft and the *International Classification of Vestibular Disorders*.

Anxiety plays a central role in behavioral vestibular morbidity. Anxiety, traumatic stress, obsessive, and depressive disorders may be primary causes of episodic and chronic vestibular symptoms or secondary complications of other vestibular disorders. These psychiatric illnesses affect 30–50% of patients who consult neurologists or otologists for vestibular symptoms. Coexisting psychiatric disorders adversely affect treatment for patients with structural vestibular diseases, especially when unrecognized. Persistent postural-perceptual dizziness is the leading cause of long-term vestibular disability. Fortunately, pharmacologic, psychotherapeutic, and rehabilitative treatments of these illnesses have improved in recent years.

INTRODUCTION

Safe and secure locomotion requires continuous threat assessment. In animals and humans, this is accomplished by close connections between threat/anxiety pathways and networks that process space and motion information in the brain (see Staab et al., 2013 for review). Animal studies have identified reciprocal connections between vestibular nuclei and the parabrachial nucleus, and between the parabrachial nucleus and the central nucleus of the amygdala (Balaban, 2004). These pathways send context-specific information about body rotation and position to areas that instinctively evaluate threat. Connections from the superior colliculi and thalamus to the amygdala subserve similar purposes for visual and somatosensory inputs, respectively (Tamietto and de Gelder, 2010). Space–motion inputs and threat assessment also converge in the hippocampus (Burgess, 2008) and multimodal vestibular cortex located at the junction of the parietal lobe and posterior insula (Dieterich and Brandt, 2008). Both of these areas connect to the anterior insula, anterior cingulate, and dorsolateral prefrontal cortex. Thus, spatial working memory and cortical integration of vestibular, visual, and somatosensory information are linked to cortical areas that regulate emotional responses. Implications of these connections were identified in a recent functional magnetic resonance imaging study in normal humans (Indovina et al., 2014). Activity and connectivity in vestibular and anxiety regions correlated with the anxiety-related personality traits of neuroticism and introversion in response to sound-evoked vestibular stimulation. Individuals with higher levels of neuroticism had greater activation of brainstem, cerebellar, and parastriate regions and greater connectivity between vestibular and anxiety systems in

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cortical and subcortical areas than those with lower levels of neuroticism. Individuals with higher levels of introversion had greater activation of the amygdala and lesser connectivity between the amygdala and inferior frontal gyrus (i.e., higher amygdalar activity with lower cortical modulation).

Numerous physiologic studies have demonstrated the ubiquity of the influence of threat and anxiety on postural control in health and disease. Normal human subjects walked slower and took shorter strides on a raised catwalk compared to a floor-level walkway of similar dimensions (Brown et al., 2002), an effect that was magnified when performing cognitive tasks (Adkin et al., 2002). Normal subjects rose to tiptoes more slowly on a high versus low platform and rose more slowly still when positioned on the edge of the raised platform versus the middle (Gage et al., 2003). When standing at height, normal humans restricted the range of motion of their center of mass by reflexively co-contracting tibialis anterior, soleus, and gastrocnemius muscles. This decreased movement at the ankles produced a stiffer stance, with lower-amplitude, higher-frequency sway (Cleworth et al., 2012). These adjustments to gait and posture coincided with autonomic activation, increased anxiety about falling, reduced confidence in balance, and greater sensations of unsteadiness (Adkin et al., 2002; Cleworth et al., 2012). In a separate study, individuals with moderate levels of anxiety-related personality traits adopted a stiffer postural control strategy at lower levels of threat than people with low trait anxiety (Hainaut et al., 2011).

Similar changes in stance and gait also have been identified in patients with functional and anxiety-related vestibular disorders, where they may be more pronounced than in normal individuals or employed unnecessarily in situations of minimal threat. For example, individuals with visual height intolerance (i.e., moderate uneasiness with heights) or acrophobia (fear of heights) stiffened their stance and slowed their gait on a 15-meter-high balcony (Schniepp et al., 2014a; Brandt et al., 2015). Patients with phobic postural vertigo had stiffened postural control, slow gait, and short strides even in nonthreatening situations of walking across a floor (Schniepp et al., 2014b). In patients with acrophobia and phobic postural vertigo, their stiffened postural control was associated with co-contraction of lower-leg muscles and a low threshold for engaging closed-loop sensory feedback processes that are more typically utilized in more demanding situations (Wuehr et al., 2013, 2014).

Patients with anxiety disorders also appear to be more susceptible to the destabilizing effects of visual motion stimuli and may alter their gaze control as a result. Subjects with anxiety disorders (Redfern et al., 2007) and phobic postural vertigo (Querner et al., 2002) had more sway than normal individuals on a posture platform when exposed to moving visual stimuli. Three studies showed that patients with anxiety disorders had visual or somatosensory preference patterns on the Sensory Organization Test (Cevette et al., 1995; Jacob et al., 1997, 2009). Another investigation found that patients with long-term persistent dizziness after acute vestibular neuritis (an anxiety-mediated phenomenon) had higher levels of visual dependence on the Rod and Disk Test than patients who recovered with minimal or no residual symptoms (Cousins et al., 2014). Patients with visual height intolerance and acrophobia restricted their gaze range to avoid looking down from the edge when standing or walking on a balcony (Kugler et al., 2014; Brandt et al., 2015).

Adverse effects of anxiety disorders on balance and locomotion have been observed in children. Erez et al. (2004) found that children with anxiety disorders reported more sensitivity to challenging balance situations in the natural environment than children without anxiety disorders. Children with anxiety disorders also performed more slowly and made more mistakes on laboratory balance tasks than their normal peers, even though they had no neurotologic deficits.

Lepicard and colleagues (Lepicard et al., 2000, 2003; Venault et al., 2001) showed that animals from a strain of mice bred for highly anxious behaviors had more difficulty traversing a raised, rotating beam than mice from a nonanxious strain. They slipped and paused on the beam more often than their nonanxious counterparts. Treatment of anxious mice with fluoxetine, paroxetine, or diazepam improved their balance performance, whereas administration of an anxiogenic agent to normal mice caused their balance function to deteriorate. In a human parallel, paroxetine treatment of 15 patients with panic disorder normalized their instability on static posturography (Perna et al., 2003).

Given these extensive data about tight anatomic connections between threat/anxiety and visual-vestibular-somatosensory systems in the brain as well as physiologic evidence of resulting behaviors, it should not be surprising that anxiety and depression affect clinical presentations and treatment outcomes for patients with structural vestibular conditions. Several prospective studies have found that elevated anxiety and worries about outcomes, not the state of peripheral or central vestibular deficits, are the strongest predictors of persistent symptoms (Godemann et al., 2005; Heinrichs et al., 2007; Best et al., 2009) and disability (Yardley et al., 2001) in patients who have experienced acute vestibular syndromes. This is not a rare occurrence, as 30–50% of patients who experience such illnesses develop clinically significant anxiety or depressive symptoms in their aftermath (Eagger et al., 1992; Clark et al., 1994; Eckhardt

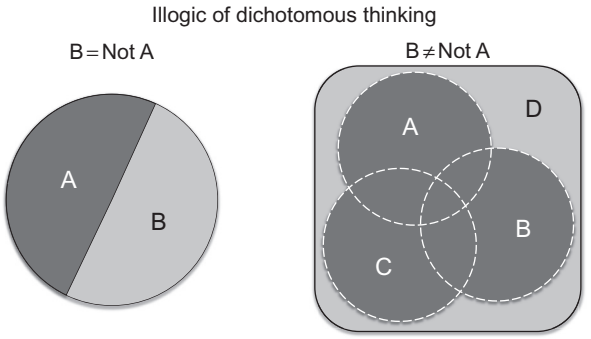

Fig. 24.1. The illogical nature of dichotomous thinking in medical diagnostics. Left: The only situation in which B = not A occurs when all of A is known, all of B is known, they are mutually exclusive, and there are no other possibilities. None of these assumptions holds in the differential diagnosis of vestibular symptoms. Right: Structural (A), functional (B), and psychiatric (C) disorders have indistinct and overlapping boundaries. Unknown diagnostic entities (D) likely exist. In this real-world situation, it is impossible to define any condition solely by what it is not. It is also impossible to make any diagnosis solely by attempting to eliminate the others.

et al., 1996; Savastano et al., 1996; Celestino et al., 2003; Eckhardt-Henn et al., 2003; Grunfeld et al., 2003; Persoons et al., 2003; Staab and Ruckenstein, 2003; Kammerlind et al., 2005).

Anxiety may adversely affect the outcomes of medical and surgical interventions, even when performed with great proficiency. For example, Boleas-Aguirre et al. (2007) followed 105 patients for an average of 5 years after treatment of Menière's disease with transtympanic gentamicin. Their data showed that high scores on the anxiety/autonomic subscale of the Vertigo Symptom Scale were more closely linked to disability before and after treatment than scores on the physical symptom subscale and that pretreatment anxiety/disability was associated with persistent nonvertiginous dizziness, even though gentamicin treatment produced excellent control of vertigo attacks. Fortunately, two sets of studies have offered a hint that early or even anticipatory behavioral interventions can improve outcomes. Edelman et al. (2012) used just three cognitive therapy sessions to treat patients with unremitting dizziness and high anxiety after acute vestibular syndromes. Treatment applied within 8 weeks of the acute illness substantially reduced both physical and psychologic symptoms, a positive benefit that was sustained at 6-month follow-up (Mahoney et al., 2013). Magnusson et al. (2009) employed a "prehab" strategy of vestibular exercises in advance of transtympanic gentamicin treatment of Menière's disease or surgical resection of cerebellopontine angle tumors to enhance postoperative recovery.

These advances in basic neuroscience and physiologic research have not made sufficient inroads into routine clinical practice, at least in part because neurotologic evaluations have not changed to accommodate them. In neurologic and otologic settings, physicians and other clinicians have been trained for decades to think dichotomously about behavioral morbidity (Staab, 2013). The clinical history, physical examination, and laboratory testing focus almost exclusively on identifying medical or surgical diagnoses. If none of these are present, then patients' symptoms are assumed to have a psychologic cause or, worse, are dismissed as "not real." This approach is fundamentally illogical. As illustrated in Figure 24.1 (left side), the only circumstance in which one may infer the presence of an entity solely by eliminating its counterparts is when all possibilities are fully known, and the boundaries between them are firm and nonoverlapping. Neurotologic diagnoses do not fit this pattern (Fig. 24.1, right side). Structural, functional, and psychiatric conditions do indeed overlap. Diagnostic boundaries are indistinct, and all possibilities are not known. Under these circumstances, a dichotomous approach is far too likely to produce incomplete assessments (missing functional and psychiatric morbidity) or false attributions (functional and psychiatric diagnoses assumed by the absence of structural ones).

Fortunately, anatomic and physiologic research has been accompanied by clinical investigations that have defined functional and psychiatric vestibular disorders in a practical way for nonpsychiatric specialists and identified simple diagnostic screening tools that are easy to use in routine neurologic, otologic, and primary care practices (see Staab, 2013, for review). Treatment research also has advanced, making functional and psychiatric vestibular disorders some of the most treatable causes of vestibular symptoms (see Staab, 2013, for review). Taken together, these improvements make the effort to identify behavioral morbidity worthwhile for patients and clinicians.

DIAGNOSTIC CLASSIFICATION OF FUNCTIONAL AND PSYCHIATRIC VESTIBULAR DISORDERS

Table 24.1 organizes functional and psychiatric vestibular disorders according to the structure of the *International Classification of Vestibular Disorders* (ICVD) (Bisdorff et al., 2015). Functional and psychiatric vestibular disorders, like structural diseases, are grouped by the temporal profile of the vestibular symptoms that they cause. In keeping with integrated concepts that embody the ICVD, functional and psychiatric disorders are as much a part of the differential diagnosis of acute, episodic, and chronic vestibular syndromes as are structural diseases. They are not classified separately.

Table 24.1

Diagnostic classification of functional and psychiatric vestibular disorders

	Acute vestibular syndromes	Episodic vestibular syndromes	Chronic vestibular syndromes
Primary causes of vestibular symptoms	Isolated panic attack Functional vestibular symptoms	Panic attacks • Panic disorder • Social phobia • Posttraumatic stress disorder • Obsessive compulsive disorder Specific phobias • Fear of falling • Acrophobia Functional vestibular symptoms	Generalized anxiety • Generalized anxiety disorder • Agoraphobia • Social phobia • Posttraumatic stress disorder • Obsessive compulsive disorder Specific phobias • Fear of falling • Acrophobia Major depressive disorder Functional vestibular symptoms
Secondary causes of vestibular symptoms	Isolated panic attack Specific phobias • Fear of falling • Acrophobia Functional vestibular symptoms	Panic attacks • Panic disorder • Social phobia • Posttraumatic stress disorder Specific phobias • Fear of falling • Acrophobia Functional vestibular symptoms	Generalized anxiety • Generalized anxiety disorder • Agoraphobia • Posttraumatic stress disorder Specific phobias • Fear of falling • Acrophobia Major depressive disorder Persistent postural-perceptual dizziness Functional vestibular symptoms
Coexisting conditions	All of the functional and psychiatric disorders listed above may coexist with acute, episodic, or chronic vestibular syndromes due to structural illness		

Anxiety disorders

Anxiety disorders are the primary diagnoses for 8–10% of all patients who have a chief complaint of vestibular symptoms (Staab, 2013). They are far and away the most common psychiatric causes of vestibular symptoms, manifesting in panic attacks, generalized anxiety, and phobic behaviors. Panic attacks are acute episodes of physical and psychologic symptoms that may occur spontaneously or in response to feared triggers. They have a sudden onset, peak within 10–15 minutes, and then fade, though lingering effects may persist for hours (American Psychiatric Association, 2013; World Health Organization, 2015). Vestibular symptoms of nonvertiginous dizziness, lightheadedness, and unsteadiness are the second most common physical manifestations of panic attacks after cardiopulmonary symptoms such as chest pain, palpitations, and dyspnea (Sklare et al., 1990). Other physical symptoms may include diaphoresis, trembling or shaking, nausea, hot or cold flushes, and numbing or tingling paresthesias. Vertigo may occur infrequently during panic attacks, but is usually less intense than the spinning or tilting sensations caused by structural illnesses affecting the labyrinth or brainstem.

Panic attacks also include psychologic symptoms of intense anxiety, fear of dying or losing control, and depersonalization or derealization. Isolated panic attacks may affect up to 10% of the population and are not considered a psychiatric illness (American Psychiatric Association, 2013), though they may be important in neurotologic practice because acute anxiety in the setting of an acute vestibular illness is a harbinger of poor symptomatic recovery (Godemann et al., 2005; Heinrichs et al., 2007; Best et al., 2009). Recurrent panic attacks that include vestibular symptoms may be caused by primary panic disorder, social phobia, posttraumatic stress disorder, and obsessive compulsive disorder. Other vestibular syndromes may trigger secondary panic disorder,

social phobia (due to fear of appearing intoxicated or disabled from vestibular symptoms), or posttraumatic stress disorder (if vestibular crises occur with a threat to life or limb). Vestibular syndromes may exacerbate pre-existing obsessive compulsive disorder, but are not likely to trigger this disorder *de novo*.

Generalized anxiety often causes chronic dizziness, lightheadedness, and unsteadiness, but not vertigo. Its key diagnostic feature is chronic worry that is out of proportion to life circumstances (American Psychiatric Association, 2013; World Health Organization, 2015). Patients and others who know them well consider them to be worrywarts, but the level of worry must be consistently distressing or functionally impairing to reach the threshold for a psychiatric diagnosis. Chronic worry and psychosomatic symptoms of anxiety may be caused by generalized anxiety disorder, agoraphobia, social phobia, posttraumatic stress disorder, and obsessive compulsive disorder. Acute and episodic vestibular syndromes have a propensity to trigger or exacerbate these disorders, and they in turn increase the likelihood that short-lived vestibular symptoms will become chronic (Best et al., 2009).

Two specific phobias are of particular importance in neurotology: fear of falling and acrophobia (fear of heights). Both may be lifelong primary problems or develop secondarily after exposures to falls, near falls, or anxiety-provoking heights. Fear of falling is especially debilitating in the elderly, in whom it may paradoxically increase the risk of actual falls because stiffened postural control strategies and restricted gaze range reduce needed postural flexibility when negotiating obstacles or recovering from unexpected postural challenges (Nagai et al., 2012; Young et al., 2012). Loss of balance confidence may be severe enough to prompt affected individuals to become excessively sedentary or to use canes, walkers, or wheelchairs that are not needed physically, leading to deconditioning that may exacerbate their handicap (Julius et al., 2012). Many patients with fear of heights simply avoid provocative environments, but that may limit occupational and recreational endeavors and reduce quality of life (Schäffler et al., 2014).

Primary and secondary anxiety disorders may confound vestibular laboratory testing. Studies from the 1990s reported that patients with anxiety disorders were more likely than normal individuals to have at least one parameter in the abnormal range in tests of basic vestibular and oculomotor reflexes, such as caloric, positional, and positioning tests, and smooth pursuit (Sklare et al., 1990; Swinson et al., 1993; Hoffman et al., 1994; Jacob et al., 1996, 1997). However, most of these were minor isolated abnormalities. No clear pattern of clinically meaningful test results was ever identified. This line of research offers a warning against overzealously interpreting subtle vestibular laboratory test results as evidence of structural deficits in patients with anxiety disorders, especially when results do not correlate well with clinical history.

Anxiety disorders are more likely to affect performance on tests of integrated balance function, such as posturographic assessments, including the Sensory Organization Test, than tests of basic vestibular or ocular reflexes, such as caloric examination. A widely cited study by Cevette et al. (1995) used a mathematic equation to identify an "aphysiologic pattern" of relatively poor performance on the simpler (lower-numbered) conditions of the test. It should be noted that the "aphysiologic" group was comprised of individuals with known functional and psychiatric causes of their vestibular symptoms. Jacob et al. (2009) found similar posturographic patterns in patients with anxiety disorders. Criteria set forth by Mallinson and Longridge (2005) suggested that the Sensory Organization Test could be used to identify malingering, but those authors did not consider functional or psychiatric disorders in their work. Recent investigations have begun to re-examine these posturographic parameters in patients with functional and psychiatric disorders using up-to-date diagnostic criteria (Sohsten et al., 2016). Emerging results suggest that the "aphysiologic" patterns may prove to be manifestations of the high-risk postural and gaze control strategies reviewed above. Thus, they may reflect the very real physiologic effects of anxiety on posture and gaze.

Depressive disorders

Major and minor depressive disorders are not as likely as anxiety disorders to cause vestibular symptoms. However, the prevalence of depression in patients with episodic or chronic vestibular syndromes exceeds that of the general population by a factor of at least two (Staab, 2013). Furthermore, a prospective study of young to middle-aged adults in Japan found that dizziness was a harbinger of incident depression within 1 year (Nakao and Yano, 2006). In that study, the rate of new depression among patients with dizziness was higher than any other somatic symptom, including ones long associated with depression, such as chronic back pain. Vertigo, when defined strictly as in the ICVD as a false sensation of rotation or translation when no motion is present (Bisdorff et al., 2009), has a fairly ubiquitous connotation the world over. Dizziness, defined as a sensation of impaired spatial orientation without motion (Bisdorff et al., 2009), is a less distinct experience that may have greater regional or cultural variability. Diagnostic schemes must accommodate these differences; hence the acknowledgment of a clinically observed association

between dizziness and depression, even though investigations of physiologic mechanisms are lacking.

Functional vestibular disorders

The late 20th century and early 21st century have seen greater interest in describing functional syndromes by positive diagnostic criteria (i.e., defining them for what they are rather than what they are not). This is accompanied by a growing recognition that illness may result not only from structural or cellular defects in organs and tissues, but from abnormal functioning of physiologic systems that are structurally intact, including networks in the brain (hence renewed use of the term "functional"). The field of gastroenterology is furthest along in this endeavor with its Rome III Criteria for Functional Gastrointestinal Disorders (Drossman, 2006). That includes more than 40 disorders defined solely by their symptoms. Diagnostic signs and test results are absent. Headache neurology (Headache Classification Committee of the International Headache Society, 2013) and psychiatry (American Psychiatric Association, 2013) also have officially sanctioned manuals of disorders defined by symptom-based diagnostic criteria, though neither field uses the term functional for its illnesses. Importantly, studies using these sets of diagnostic criteria have generated large quantities of data on potential pathophysiologic mechanisms, including results that have informed the development of approved pharmaceuticals, multiple off-label medication options, and effective nonpharmacologic interventions.

In neurotology, one functional vestibular syndrome has been formally defined, namely persistent postural-perceptual dizziness (PPPD), which is supported by 30 years of clinical and physiologic research (ICD-11 beta draft: World Health Organization, 2015). A second functional vestibular syndrome has been suggested on the basis of clinical observations of atypical and invariant vestibular symptoms (e.g., kaleidoscopic motion in multiple directions, chronic unchanging vertigo), but this has not yet gelled into a formal definition (Dieterich et al., 2016). PPPD is included in the beta draft version of the *International Classification of Diseases*, 11th edition (ICD-11 beta draft: World Health Organization, 2015) under the category of chronic vestibular syndromes. It was defined by the Behavioral Subcommittee of the Committee for the Classification of Vestibular Disorders of the Bárány Society and vetted through the ICD-11 Neurology Workgroup before being added to the ICD-11 beta draft. The origins of PPPD can be traced to the first description of phobic postural vertigo in 1986 (Brandt and Dieterich, 1986), through investigations of space–motion discomfort (Jacob et al., 1993) and visual vertigo (Bronstein, 1995) in the 1990s, to chronic subjective dizziness (Staab and Ruckenstein, 2007) in the 2000s. The evolution of PPPD and reviews of possible treatments are detailed elsewhere (Staab, 2013; Dieterich et al., 2016). The ICD-11 beta draft definition (World Health Organization, 2015) of PPPD is:

> *persistent non-vertiginous dizziness, unsteadiness, or both lasting three months or more. Symptoms are present most days, often increasing throughout the day, but may wax and wane. Momentary flares may occur spontaneously or with sudden movement. Affected individuals feel worst when upright, exposed to moving or complex visual stimuli, and during active or passive head motion. These situations may not be equally provocative. Typically, the disorder follows occurrences of acute or episodic vestibular or balance-related problems. Symptoms may begin intermittently, and then consolidate. Gradual onset is uncommon.*

PPPD is the most common cause of chronic vestibular symptoms. Incidence and prevalence estimates derived from research on phobic postural vertigo (Brandt and Dieterich, 1986), chronic subjective dizziness (Staab and Ruckenstein, 2007), and long-term outcomes of acute vestibular syndromes suggest that it is the second most common diagnosis (after benign paroxysmal positional vertigo) encountered among patients who present to tertiary neurotology centers for evaluation of dizziness. It is the most common diagnosis in middle-aged patients. PPPD may develop in as many as 25% of individuals who experience acute or episodic vestibular syndromes, even if they compensate well for their initial illnesses. Historically, patients with persistent dizziness following acute vestibular events have been diagnosed with "chronic vestibulopathy" or "psychogenic dizziness." Neither designation is accurate, precise, or supported by research data. Both are so outmoded that they should be abandoned. In contrast, PPPD has a clear definition and offers the potential for symptomatic recovery through treatment options described below.

A second functional vestibular disorder has not been formally defined, but the Behavioral Subcommittee of the Bárány Society's classification project (Staab et al., 2014) and others (Dieterich et al., 2016) have considered a collection of symptoms that are unique, not associated with other structural, functional, or psychiatric conditions, and capable of causing significant distress and disability. One such symptom is vertigo, unsteadiness, or dizziness that is present constantly and chronically without variability in response to changes in posture, position, activity level, or exposure to external motion stimuli. Another is vertigo that involves sensations of

simultaneous motion in multiple planes or about multiple rotational axes or full-field swirling or kaleidoscopic motion of the visual surround. Clinical observations in the absence of formal studies of these phenomena suggest that they are often present in patients with multiple other somatic symptoms, especially chronic pain and fatigue. They may, therefore, be vestibular presentations of psychiatric illnesses that manifest primarily with somatic symptom burden. These are designated bodily distress disorder in the ICD-11 beta draft (World Health Organization, 2015) and somatic symptom disorder in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5: American Psychiatric Association, 2013). A third functional vestibular presentation is voluntary nystagmus. All three of these are much less common than other psychiatric vestibular disorders or PPPD. They await better elucidation in the future.

IDENTIFYING FUNCTIONAL AND PSYCHIATRIC VESTIBULAR DISORDERS

The key to detecting functional and psychiatric vestibular disorders is the patient's clinical history, because these diagnoses are based on symptoms alone. The role of physical examinations and laboratory testing in patients who meet criteria for any of the disorders listed in Table 24.1 is to evaluate for conditions that may coexist or overlap with these illnesses or better explain patients' presentations. For example, a patient with a history suggesting both Menière's disease and agoraphobia may experience episodic attacks of vertigo, fluctuating hearing, and tinnitus, plus widespread avoidance of multiple activities due to catastrophic worries about the consequences of anticipated vertigo attacks. Physical examination, audiometric assessment, and vestibular laboratory testing would be undertaken to evaluate the state of the labyrinth. Clinical history would outline the extent of fears and avoidance behaviors, which should not be dismissed as an understandable complication of Menière's disease. Another patient may have chronic unsteadiness and difficulties negotiating motion-rich environments that superficially suggest PPPD, but also a history of increasingly frequent falls or near falls, which are not part of PPPD, plus physical exam findings of downbeat nystagmus and truncal ataxia that identify a cerebellar disorder as a more accurate diagnosis than PPPD.

Several short patient self-reports are available to screen for anxiety and depressive disorders. These are easy to use and worth incorporating into consultations with new patients. They are excellent tools for detecting psychiatric morbidity that may adversely affect medical or surgical management. The Patient Health Questionnaire (PHQ-9), a nine-item inventory of depressive symptoms, and the Generalized Anxiety Disorders Scale (GAD-7), a seven-item inventory of anxiety symptoms, are available in multiple languages and may be downloaded free of charge without copyright restriction from the website www.phqscreeners.com. An even briefer screener, the PHQ-4, is available from the same site. It includes just the first two questions of the PHQ-9 and GAD-7, and has nearly the same sensitivity and specificity as the longer questionnaires.

TREATMENT OF FUNCTIONAL AND PSYCHIATRIC VESTIBULAR DISORDERS

No large-scale, randomized, controlled trials of treatments for functional or psychiatric vestibular disorders have yet been done. However, an increasing number of uncontrolled medication trials and several modest-sized controlled investigations of rehabilitative and psychotherapeutic interventions have been completed in the last 15 years. There is no *a priori* reason to believe that established therapies for primary anxiety or depressive disorders should be any more or less effective when these illnesses manifest vestibular symptoms versus other complaints. The greatest concern during the early pharmacotherapy trials was that serotonergic antidepressants would exacerbate vestibular symptoms because dizziness was listed as a common side-effect of all serotonin reuptake inhibitors. That proved not to be a problem. Similarly, psychotherapeutic interventions, particularly cognitive behavioral therapy, and vestibular rehabilitation were found to be adaptable to patients with functional and psychiatric vestibular disorders.

One large case series (Staab et al., 2002) and four open-label prospective trials (Staab et al., 2004; Horii et al., 2004, 2007; Simon et al., 2005) of selective serotonin reuptake inhibitors (SSRIs) have been completed in the USA and Japan. These studies included a total of 190 patients with chronic unsteadiness and dizziness with or without comorbid anxiety or depressive symptoms. Most patients in these studies would have met diagnostic criteria for a chronic vestibular syndrome due to an anxiety disorder or PPPD. All six SSRIs that are commercially available in the USA were included in at least one of these studies. One prospective trial ($n = 20$) specifically enrolled subjects with chronic subjective dizziness, so it is most applicable to PPPD. Taking the results of these investigations together, the following general conclusions may be made:

1. SSRIs were tolerated well by patients with prominent vestibular symptoms. Dropout rates due to adverse medication effects (<20%) were no greater than observed in trials of these medications for other disorders.

2. Approximately two-thirds of patients who began treatment and five of six who completed treatment experienced at least a 50% reduction in vestibular symptoms. This corresponded to an average drop in symptom severity from moderate (partially impairing) to mild (not impairing), and applied equally to patients with chronic vestibular syndromes due to anxiety disorders versus chronic subjective dizziness.
3. Chronic dizziness and unsteadiness improved in concert with anxiety and depression in patients with affective comorbidity.
4. It took 8–12 weeks of treatment to achieve significant reductions in vestibular symptoms.
5. Mean and modal doses were in the lower half of the approved dose ranges for all medications.
6. No SSRI proved more or less effective than the others. The only discrepancy among these studies was that US patients without clinically significant anxiety or depressive symptoms enjoyed the same reductions in chronic dizziness as patients with affective problems, whereas Japanese patients without mood or anxiety symptoms did not improve. The reason for this difference is not known.

One case series of venlafaxine ($n = 32$) (Staab, 2011a) and one open-label trial of milnacipran ($n = 40$) (Horii et al., 2008) examined the effects of these serotonin norepinephrine reuptake inhibitors (SNRIs). The venlafaxine study included patients with chronic subjective dizziness and vestibular migraine (Staab, 2011a). Those with coexisting anxiety disorders were more likely to experience improvements in all symptoms (dizziness, headache, anxiety) than those without anxiety disorders. Results of the milnacipran study were comparable to the SSRI trials. All published evidence on pharmacologic treatment of vestibular symptoms with serotonergic antidepressants should be considered preliminary until conformed in randomized controlled trials of sufficient power.

Two sets of randomized controlled trials of cognitive behavioral therapy, one for phobic postural vertigo (Holmberg et al., 2006, 2007) and the other for chronic subjective dizziness (Edelman et al., 2012; Mahoney et al., 2013), have been completed. The studies of phobic postural vertigo included 31 patients randomized to self-directed exposure exercises versus 12 weeks of cognitive behavioral therapy. Patients who received therapy had greater symptom improvements at the end of active treatment (Holmberg et al., 2006), but benefits were not sustained at 12-month follow-up (Holmberg et al., 2007). The studies of chronic subjective dizziness included 44 patients randomly assigned to three sessions of therapy or a wait-list control condition. Patients who received active treatment had large reductions in dizziness and dizziness-related handicaps (Edelman et al., 2012), improvements that were retained at 6-month follow-up (Mahoney et al., 2013). The most important difference between these studies was that patients with phobic postural vertigo had chronic illness, whereas those with chronic subjective dizziness were enrolled within 8 weeks of illness onset, capturing them as the disorder was still developing. These results, which should be applicable to PPPD, suggest that early intervention with short-term cognitive behavioral therapy may prevent long-term morbidity. In contrast, psychotherapeutic treatment of long-standing PPPD symptoms may offer less benefit.

Several controlled studies of vestibular rehabilitation have established this intervention as an effective treatment for acute and chronic vestibular symptoms. Most of those studies enrolled patients without regard to the specific causes of their symptoms and without fully characterizing their behavioral morbidity. Therefore, they cannot offer information about the effects of vestibular rehabilitation on functional or psychiatric vestibular disorders (Staab, 2011b). Two studies are exceptions. Meli et al. (2007) demonstrated that vestibular rehabilitation significantly reduced anxiety and depressive symptoms in 40 treated patients with chronic dizziness versus 40 untreated control subjects. Thompson et al. (2015) found that most patients with PPPD found physical therapy consultation to be helpful and a majority experienced clinically significant improvements in symptoms with home-based exercises, though benefits for symptoms related to self-motion were greater than for those related to visual motion in the environment.

CONCLUSIONS

Thirty years of anatomic and physiologic research have demonstrated a tight integration of threat/anxiety, spatial orientation, and locomotor control processes in the brain. Clinical investigations of patients with acute, episodic, and chronic vestibular syndromes have outlined a differential diagnostic scheme that includes primary and secondary anxiety and depressive disorders as common causes and consequences of vestibular symptoms. One major functional vestibular disorder, PPPD, has been included in the draft of the forthcoming update of the ICD-11 (ICD-11 beta draft). These advances offer a better understanding of the neural mechanisms of stance, gait, and spatial perception. To improve patient outcomes, however, the decades-old dichotomous approach to identifying functional and psychiatric vestibular morbidity has to give way to an integrated method that matches the structure and function of the brain.

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Chapter 25

Vertigo and dizziness in children

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Abstract

Vertigo and dizziness of at least moderate severity occur in >5% of school-aged children and cause considerable restrictions in participation in school and leisure activity. More than 50% of dizzy children also have headache. Vestibular migraine and benign paroxysmal vertigo as a migraine precursor are the most common diagnoses in dizziness clinics for children and adolescents. They account for 30–60% of diagnoses. Other common causes are somatoform, orthostatic, or posttraumatic dizziness. All other disorders that are known to cause vertigo and dizziness in adults also occur in children, but incidence rates are usually lower.

The vestibular and balance systems are largely developed after 1 year of age. Therefore, clinical and laboratory testing is reliable. Brain magnetic resonance imaging to exclude severe conditions, such as a brainstem tumor, is necessary only if clinical – in particular, ocular motor – testing is abnormal.

Most conditions causing vertigo and dizziness in childhood and adolescence are treatable. Nonpharmacologic prophylaxis should always be recommended in vestibular migraine. Behavioral support is useful in somatization. Evidence for the effectiveness of drug therapy is largely based on experience in adult populations. High-quality controlled studies in childhood cohorts are sparse. It is important to make a correct diagnosis early on, as counseling and appropriate treatment may avoid chronic illness.

INTRODUCTION

Vertigo and dizziness occur with considerable frequency in childhood and adolescence (Jahn et al., 2015). The general pediatrician, neuropediatrician, and neuro-otologist should be aware of the full spectrum of disorders to reach a correct diagnosis, leading to prompt and effective treatment. Vestibular deficits, vertigo, and dizziness in childhood may result in delayed postural control and lack of coordination (Inoue et al., 2013). It is sometimes difficult to make the correct diagnosis because children are often unable to describe their complaints (Miyahara et al., 2009). They may also find it hard to say how long attacks last and what provokes or accompanies them. A correct diagnosis, however, not only obviates unnecessary investigations and alleviates parental worries; it is the prerequisite for successful therapy. Posterior fossa intracranial tumors are often considered in the differential diagnosis, but such serious causes are fortunately rare, accounting for less than 1% of diagnoses, even in specialized centers (Jahn et al., 2015). Careful clinical examination of oculomotor and vestibular function is the key step on the way to diagnosis. All disorders that are known in adults also occur in childhood, but the epidemiology differs and presentation is often atypical.

EPIDEMIOLOGY

It is often assumed that vertigo and dizziness seldom occur in childhood, despite the high prevalence rates reported in epidemiologic studies (Jahn and Dieterich, 2011). Depending on the question asked and the age group investigated, the 1-year prevalence for one or more

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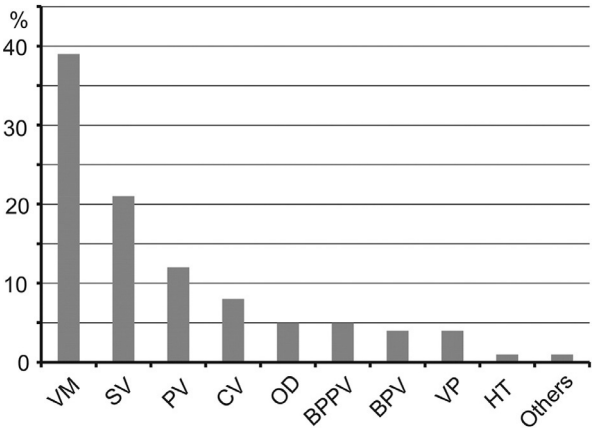

Fig. 25.1. Diagnoses in dizzy children in a tertiary care center (German Center of Vertigo and Balance Disorders). Relative frequency of diagnoses in 400 consecutive children aged 1–18 years of age. The most frequent diagnosis is vestibular migraine. VM, vestibular migraine; SV, somatoform vertigo/dizziness; PV, peripheral vestibular vertigo (uni- and bilateral failure); CV, central vertigo; OD, orthostatic dizziness; BPPV, benign paroxysmal positional vertigo; BPV, benign paroxysmal vertigo; VP, vestibular paroxysmia; HT, head trauma.

attacks of moderate to severe vertigo is between 5% and 25% (Abu-Arafeh and Russell, 1995; Humphriss and Hall, 2011). The diagnostic spectrum of causes of dizziness in children is known to differ from those in adults. A recent meta-analysis of nine studies (including approximately 800 subjects seen in hospital pediatric departments in specialized clinics) on the prevalence and diagnosis of vestibular disorders in children affirmed that benign paroxysmal vertigo (BPV) of childhood (18.7%) and vestibular migraine (17.6%) are the most frequent diagnoses (Gioacchini et al., 2014). Both are related to migraine. This proportion of about 40% of migraine-related syndromes in a population of dizzy children and adolescents fits well with the experience of tertiary referral centres (Langhagen et al., 2013). The next most common causes of vertigo in children, according to a meta-analysis including more than 3000 children, are peripheral vestibular syndromes (13%) and head trauma (10%) (Jahn et al., 2015) (Fig. 25.1).

PATIENT HISTORY

History taking remains essential, even in young patients. It should focus on the points summarized in Table 25.1. As in adults, it is important to differentiate between rotatory and swaying vertigo, as well as episodic and sustained forms. In particular, rotatory vertigo is associated with vestibular lesions. Relevant provoking factors include change of body and/or head position, coughing, sneezing, sleep deprivation, and psychosocial stress. Patients should be asked about headache and cochlear symptoms, such as hearing loss or tinnitus (Wiener-Vacher, 2008).

Bedside and laboratory examination

Clinical examination of peripheral and central vestibular function in children includes ocular motor testing, head impulses, and balance tests (Jahn et al., 2011). As peripheral vestibular nystagmus is suppressed by visual fixation, it is mandatory to prevent fixation (e.g., using Frenzel goggles) when searching for spontaneous nystagmus (Brandt, 1999). Neuronal circuits for oculomotor and vestibular function develop within the first year of life and can be reliably tested, even in toddlers (Fife et al., 2000). Clinical tests can be used accurately to identify children with vestibular hypofunction (Christy et al., 2014). Emerging new methods of vestibular testing in adults include: (1) the video head impulse test (vHIT) for quantifying vestibulo-ocular reflex (VOR) function (Bartl et al., 2009; MacDougall et al., 2009); and (2) the vestibular-evoked myogenic potential (VEMP) for testing utricular and saccular function (Colebatch, 2001; Papathanasiou et al., 2014). Further, body sway can be quantified using force plates or accelerometers as an objective measure for postural imbalance (Jahn et al., 2011). Brain magnetic resonance imaging (MRI) should be considered in all patients presenting with

Table 25.1

History taking in dizzy children

Ask for	Comments
• Type of vertigo/ dizziness • Duration of symptoms • Provoking factors • Additional symptoms	Rotatory vertigo, imbalance, gait instability, lightheadedness Attacks lasting: • Seconds, e.g., vestibular paroxysmal benign paroxysmal positional vertigo (BPPV) • Minutes, e.g., Menière's • Hours, e.g., vestibular migraine • Days, e.g., labyrinthitis • Months and years, e.g., cerebellar ataxia Change of head position, e.g., BPPV Coughing, sneezing, e.g., perilymph fistula Specific foods, e.g., vestibular migraine Hearing loss or pressure in the ear, e.g., Menière's disease Headache, e.g., vestibular migraine

central vestibular signs to exclude brain tumors, encephalitis, malformations, and other pathologies (Jahn et al., 2015).

Head impulse test

The head impulse test for VOR function is easily performed at the bedside. Video-oculography systems with inertial sensors for synchronized recording of head and eye velocity allow quantification of VOR gains and are usually well tolerated (Lehnen et al., 2013). While this vHIT is now widely used in adults (Heuberger et al., 2014; Mahringer and Rambold, 2014), it has not yet been validated in children. Instead, caloric irrigation of the ears is usually applied. In contrast to head impulses, this test may induce unpleasant vertigo and nausea and is consequently not always tolerated by children (Jahn et al., 2015). In addition, it is more time consuming and requires equipment that is not suitable at the bedside. In contrast, vHIT can be performed everywhere, and the frequency of head impulses corresponds to the physiologic range (>1 Hz compared to 0.003 Hz with calorics) (Jahn and Schneider, 2012). Preliminary evidence shows that vHIT can be applied to children (>2 years) and that it is able to detect even mild deficits of semicircular canal function (Lehnen et al., 2013). Calorics and rotational chair testing remain valuable alternatives and provide complementary information about VOR function.

Caloric and rotational testing

Caloric and rotational testing has been validated in normal, dizzy, and hearing-impaired children (Fife et al., 2008). Reponses to caloric irrigation of the ears have been successfully recorded in normal children as young as 1 year of age. Rotational testing has some advantages over caloric testing, if the primary goal is to determine the presence or absence of vestibular function. Calorics are superior for quantification of the deficit. Small children can sit on an adult's lap during rotational chair testing. The examiner observes nystagmus during rotation that is combined vestibular and optokinetic. Evaluation of vestibular function works best when visual fixation is prevented (by darkness and infrared oculography or by using Frenzel goggles). The vestibular response of the horizontal semicircular canal is best observed when the chair is stopped after 5–10 rotations at constant velocity (usually 180°/s) (Jahn, 2011). The quick phases of the vestibular nystagmus beat opposite to the direction of rotation (e.g., to the left after stopping a chair rotation to the right). The nystagmus duration should be symmetric for left and right rotations.

Vestibular-evoked myogenic potentials

VEMPs involve muscle reflexes evoked by stimulating the vestibular end organs with sound, electric current, or bone-conducted vibration. Two methods have been described: the cervical (c) VEMP recorded from the sternocleidomastoid muscles and the ocular (o) VEMP recorded from extraocular muscles. In simple terms, cVEMP is a test for saccular (inferior vestibular nerve) and oVEMP for utricular (superior vestibular nerve) otolith functions (Rosengren and Kingma, 2013). Besides vHIT and calorics for semicircular canal testing, VEMP has also been established in most vestibular laboratories as a standard test. There is an increasing number of reports on the use of VEMP testing in children (Zhou et al., 2014) to search for vestibular involvement in hearing-impaired children (Maes et al., 2014), to identify young patients with dislocated cochlear implants (Cushing et al., 2013; Psillas et al., 2014; Robard et al., 2014), and to detect causes of impaired motor development (Inoue et al., 2013), as well as other specific deficits, like congenital torticollis (Hallberg et al., 2013). An interesting recent study showed that, unlike calorics and cVEMP, oVEMP is not present in newborns, but it can be recorded in children older than 2 years of age who are able to walk without support (Wang et al., 2013). This finding has been discussed in the context of balance control during locomotion, but it may also be relevant for determining susceptibility to motion sickness, which is usually absent in small children under 2 years of age.

PERIPHERAL VESTIBULAR DISORDERS

Benign paroxysmal positional vertigo (BPPV)

BPPV is a common cause of vertigo in adults (>20% in specialized clinics). It accounts for about 5% of children presenting to vertigo clinics (Jahn et al., 2015). Risk factors are head trauma and a peripheral vestibular lesion in the past (e.g., vestibular neuritis). The pathophysiologic basis of the disorder is the presence of particles of calcium carbonate crystals (otoconia) within the semicircular canals (canalolithiasis) (Hall et al., 1979; Parnes and McClure, 1992; Brandt et al., 1994b). The posterior canal is affected in about 90%. Patients describe having attacks of rotatory vertigo when changing the position of the head relative to gravity (e.g., lying down, turning over in bed, looking up). Attacks last for seconds only. The essential diagnostic test is the positioning maneuver in the plane of the affected canal (e.g., the Dix–Hallpike maneuver). If BPPV is present, a nystagmus occurs with a short latency; it beats rotatory to the undermost ear

and vertically to the forehead and has a crescendo–decrescendo character. At the same time the patient experiences rotatory vertigo. BPPV cannot be excluded, however, if nystagmus is not elicited at the time of presentation. A patient with a typical history should be told to repeat the diagnostic maneuver at home in the morning to test if vertigo can be provoked.

Effective therapy consists of specific liberatory maneuvers (Semont et al., 1988; Epley, 1992) that can be provided by a physical therapist or by family members; some patients may perform them effectively as "self-treatment" at home. Both maneuvers are equally effective. It has to be kept in mind that all studies on therapeutic maneuvers have been conducted in adults, not in children. The horizontal canal is less frequently affected. For a detailed description of the various diagnostic and therapeutic maneuvers, see Chapter 18.

Acute unilateral vestibular failure

Any acute imbalance between the left and right vestibular periphery presents with a vestibular syndrome characterized by rotatory vertigo lasting for days, postural imbalance with falls to the affected side, oscillopsia (apparent movement of the environment due to involuntary eye movements), nausea, and vomiting. These symptoms can occur in inflammatory conditions, like viral labyrinthitis, as well as after inner-ear trauma or in the acute symptomatic stage of Menière's disease.

Vestibular neuritis/labyrinthitis

In children viral labyrinthitis is often associated with hearing loss. Hearing impairment does not occur in typical vestibular neuritis, which is supposedly caused by reactivated herpesvirus infection (Arbusow et al., 2001, 2010). Both forms may occur in children. Patients present with spontaneous nystagmus beating to the unaffected side, pathologic head impulses to the affected side, and reduced responsiveness to caloric irrigation of the affected ear. Treatment depends on the etiology. In the acute stage, vestibular suppressants are useful (dimenhydrinate 1–2 mg/kg); however, they should not be given for more than 3 days (Jahn et al., 2011). Mobilization should start as soon as possible in order to support recalibration of the vestibular system by mechanisms of central compensation (adaptation of cerebellar and brainstem circuits) (Brandt, 1999; Halmagyi et al., 2010). Labyrinthitis in acute otitis media is treated by antibiotics if bacterial infection is present. In vestibular neuritis unrelated to an acute infection steroids can improve vestibular recovery (Table 25.2) (Strupp et al., 2004). With steroids, a recovery of peripheral vestibular function is achieved in 60%, whereas without steroids recovery takes place approximately 40% of affected ears. However, it has not been shown that steroid treatment improves quality of life in the long term. Most symptoms in unilateral vestibular failure improve independently of the recovery of the peripheral deficit. The healthy side can compensate for all static deficits (e.g., gaze and postural stability). Physical therapy helps to improve balance (Hillier and McDonnell, 2011). Discrete dynamic deficits often persist, e.g., blurred vision during quick head turns to the affected side.

Traumatic unilateral vestibular loss

Acute unilateral vestibular deficits may result from concussion of the inner ear, particularly with temporal bone fractures (Gioacchini et al., 2014). The symptoms are similar to acute unilateral vestibular failure in the context of any other origin. Treatment includes vestibular suppressants for up to 3 days to improve nausea and vomiting (Table 25.2). Early mobilization and balance training are important to promote central vestibular compensation of the deficit. One should keep in mind that the most common type of vertigo occurring after head trauma is BPPV (see above).

Menière's disease

Patients with Menière's disease present with recurrent attacks of rotatory vertigo, nausea, vomiting, and accompanying cochlear symptoms, like pressure in the ear, hearing loss, and/or tinnitus. Typical attacks last for 20 minutes to a few hours. The supposed etiology is disturbed endolymph secretion and resorption with increase of pressure in the endolymphatic space (vestibular and cochlear labyrinth), which in children is more often secondary, e.g., occurring after viral labyrinthitis. Overall, Menière's disease is rare in children (<10% of the incidence in adults) (Choung et al., 2006). Prophylactic treatment with betahistine dihydrochloride (1–2 mg/kg/day) – based on extrapolation of the limited evidence in adults – has not been systematically studied in children.

Vestibular paroxysmia

Patients present with short attacks of rotatory, rocking, or tilting vertigo (seconds), sometimes provoked by head movements (Brandt and Dieterich, 1994a). Attacks can be elicited by hyperventilation in some patients. As in trigeminal neuralgia and hemifacial spasm, the pathophysiologic basis of the disease is a nerve-vessel compression, in this case of the vestibulocochlear nerve, at

Table 25.2

Therapy of peripheral vestibular vertigo and dizziness in childhood

Clinical syndrome	Therapeutic options
Benign paroxysmal positional vertigo (BPPV) • Posterior canal (up to 90%) • Horizontal canal (about 10%) • Anterior canal (<1%)	Specific release maneuvers
Acute unilateral vestibular failure Labyrinthitis • Viral • Bacterial (in meningitis) • Serous (otitis) • Autoimmune (e.g., Cogan's syndrome) Traumatic Vestibular neuritis	General measures Days 1–3: symptomatic treatment with vestibular suppressants (e.g., dimenhydrinate) Early mobilization to support central compensation Therapy based on the specific cause: • Viral: in herpes zoster oticus: acyclovir 3 × 5 mg/kg/day • Bacterial: antibiotics • Serous: treatment of otitis (antibiotics) • Autoimmune: prednisolone, 1 mg/kg/day, dose reduction depends on response • Vestibular neuritis: prednisolone, 1 mg/kg/day, reduction by 20% every third day
Vestibular paroxysmia	Carbamazepine, 2–6 mg/kg/day Oxcarbazepine, 4–8 mg/kg/day
Perilymph fistula • From middle to inner ear (posttraumatic, postinfectious, cholesteatoma) • From inner ear to the middle cranial fossa (superior canal dehiscence)	• Therapy of underlying disease • Conservative therapy with avoidance of provocation • Surgery infrequently necessary
Bilateral vestibulopathy • Congenital • Postinfectious (meningitis) • Toxic (aminoglycosides) • Malnutrition (vitamin B_{12}, folic acid) • Autoimmune • Degenerative (spinocerebellar ataxia) • Neoplastic (e.g., bilateral vestibular schwannoma) • Idiopathic	• Balance training to support sensory substitution by visual and somatosensory systems • Treatment of the specific cause

the root entry zone to the brainstem. MRI can reveal the pathologic nerve contact; however, the response to treatment seems to be a more specific criterion for the diagnosis (Brandt and Dieterich, 1994c; Hufner et al., 2008; Best et al., 2013). The inclusion of treatment response into the diagnostic criteria makes it impossible to determine response rates. Experience in specialized clinics and expert opinion suggest a high rate of patients responding to low-dose treatment with carbamazepine (Table 25.2). Therapy can be reduced once the patient has been free of attacks for 4 weeks, but relapses are common (Hufner et al., 2008).

Vestibular paroxysmia has been recently described in children and should be considered in those who present with brief, frequent vertiginous spells (Lehnen et al., 2015). Spells in a child population also occur at rest and with certain head positions, and respond to treatment with low-dose sodium channel-blocking antiepileptics such as carbamazepine (2–4 mg/kg) (Brandt and Dieterich, 1994a; Hufner et al., 2008; Lehnen et al. 2015). This disabling disorder accounts for about 4% of all diagnoses in vertiginous children presenting in the setting of a tertiary referral center for vertigo and balance disorders. This frequency is similar to that in adults (Jahn et al., 2015). BPV of childhood should be considered as a differential diagnosis in younger children. In contrast to vestibular paroxysmia, BPV usually disappears spontaneously after the child's sixth birthday. Furthermore, auditory symptoms are rare in BPV but often occur with vestibular paroxysmia. When attacks occur frequently a treatment test with carbamazepine for a few days might be justified, even if BPV cannot be fully excluded.

Perilymph fistula

Patients present with short attacks of vertigo provoked by coughing, pressure in the ear canal, sneezing, lifting heavy weights, or loud noises. Typical attacks last for seconds. A fistula to the middle ear (e.g., outer fistula after otitis media) is more common in children than in adults (Wiener-Vacher, 2008; Jahn et al., 2011). For diagnostic purposes attacks can be provoked by Valsalva maneuvers or pressure to the tragus. Outer fistula occurs if the round or oval window in the middle ear ruptures; inner fistula occurs if the bone layer separating the anterior canal from the middle cranial fossa becomes dehiscent (either spontaneously or posttraumatically) (Minor, 2000). High-resolution computed tomography of the temporal bone can reveal labyrinth dysplasia and anterior canal dehiscence. In most cases the avoidance of provoking factors is sufficient, while surgery is rarely necessary (Agrawal et al., 2012).

Bilateral vestibular failure

Patients with bilateral vestibular failure present with gait disturbance in darkness and on uneven ground (Brandt, 1999). Oscillopsia commonly occurs when walking due to the loss of the VOR. Head impulses are pathologic on both sides. Caloric irrigation and rotation show no or only minimal eye movement responses to vestibular stimulation. Etiologic factors include hereditary vestibular areflexia, ototoxic medication (e.g., gentamicin), and postmeningitic vestibular failure (Baloh et al., 1994; Zingler et al., 2007). Treatment depends on etiology. All patients with bilateral vestibular failure should receive balance training with postural and gait components, although not all patients improve (Herdman et al., 2015), and the evidence for the benefit is only moderate (Porciuncula et al., 2012). Characteristics and treatment principles for the most common peripheral vestibular syndromes are summarized in Table 25.2.

Hereditary vertigo syndromes and malformations

A number of congenital syndromes are associated with vestibular dysfunction (Verhagen et al., 1987). Malformations of the labyrinth occur after embryopathic infections (rubella, cytomegalovirus). Mondini dysplasia and CHARGE association (coloboma, heart malformation, choanal atresia, retardation, genital hypoplasia, ear abnormality) cause dysplasia of inner-ear structures (Murofushi et al., 1997; Abadie et al., 2000; Delahaye et al., 2007). Affected patients often present with bilateral vestibular failure. Rare syndromes with specific vestibular deficits include familial vestibular areflexia and familial vestibulopathy (Verhagen et al., 1987; Baloh et al., 1994). In neurofibromatosis type 2, vestibular symptoms are caused by vestibular schwannoma. In Usher syndrome (type 1), progressive loss of hearing and vision goes along with vestibular deficits (Kremer et al., 2006). Friedreich's ataxia, mitochondrial syndromes, and metabolic disorders (Refsum disease) can affect vestibular function (Jahn et al., 2011). Therapy depends on the specific disorder and is usually symptomatic.

CENTRAL VESTIBULAR DISORDERS

Vertigo syndromes related to migraine

There is no doubt that migraine-related vertigo syndromes are very common in children and adolescents (Langhagen et al., 2014). More than 50% of children who suffer from vertigo or dizziness also have headaches (Cavestro et al., 2014; Jahn et al., 2015). The differentiation of vestibular migraine and BPV of childhood is still a matter of debate, despite the fact that both are defined in the new edition of the classification of the International Headache Society (http://ihs-classification.org/_downloads/mixed/International-Headache-Classification-III-ICHD-III-2013-Beta.pdf), which was developed jointly with the Bárány Society (Lempert et al., 2012; Winner, 2013).

Benign paroxysmal vertigo of childhood

BPV is one of the episodic syndromes that may be associated with migraine and is often regarded as a precursor of migraine (Batuecas-Caletrio et al., 2013; Gelfand, 2013; Prasad, 2014). This is the most common cause of episodic vertigo in children between 2 and 8 years of age (Jahn et al., 2011; Langhagen et al., 2014). The current migraine classification, however, does not contain any age criterion. The major difference between BPV of childhood and vestibular migraine is the lack of a migraine history in affected patients. BPV is characterized by recurrent brief attacks of vertigo (seconds to minutes), occurring without warning and resolving spontaneously in otherwise healthy children. Attacks are often associated with nystagmus and postural imbalance. In some patients headache, nausea, and vomiting accompany the attack. Cochlear symptoms (hearing loss or tinnitus) are not typical. Children do not show any signs of vestibular dysfunction between attacks. The frequency of attacks can vary widely (Headache Classification Committee of the International Headache Society (IHS), 2013). Typical BPV attacks begin in small children before the age of 4 and disappear spontaneously at the age of 8–10 years (Basser, 1964; Jahn et al., 2011). Later in life, typical migraine may develop; there is often a family history of migraine with aura. Paroxysmal torticollis and periodic vomiting (other migraine

equivalents) may also present with vertigo and dizziness, thus mimicking BPV. Due to the brevity of the attacks and the benign course of these disorders, pharmacologic therapy is rarely necessary (Langhagen et al., 2014).

Vestibular migraine

Vestibular migraine can affect all age groups. The diagnosis requires a history of migraine with or without aura. Vestibular symptoms can last from 5 minutes to 72 hours (Headache Classification Committee of the International Headache Society (IHS), 2013). Many epidemiologic series on dizziness in children have shown that the separation of BPV and vestibular migraine is quite arbitrary. Some authors see migraine equivalents (like BPV) as part of the migraine syndrome (Tarantino et al., 2014); others apply two diagnoses to the same patient, e.g., BPV and migraine without aura (Pacheva and Ivanov, 2013; Marcelli et al., 2014; Teixeira et al., 2014). All patients with episodic vertigo that occurs together with headache, autonomic signs, and increased sensitivity to light and sound should be diagnosed as having vestibular migraine (Jahn et al., 2015). In several clinical series, more than 50% of dizzy children also have headache regardless of the final diagnosis (Jahn, 2009; Langhagen et al., 2013). Typical for vestibular migraine are episodic attacks of rotatory or swaying vertigo lasting minutes to hours, followed by or accompanied by headache and sensitivity to light and noise. However, even in adults, only 70% of vestibular migraine patients present with headache. In children, the presentation of vestibular migraine varies and might be atypical, particularly in those younger than 10 years of age. Similar to adults, discrete central ocular motor signs (e.g., saccadic pursuit) are commonly observed between attacks also in children (Langhagen et al., 2014). Prospective studies on ocular motor function in children with vestibular migraine are lacking.

In contrast to headache, the vertigo component of vestibular migraine does not respond well to acute therapy with nonsteroidal analgesics or triptans (appropriate studies have not been conducted). Prophylactic treatment may be indicated for frequent ($\geq$3 per month) or severe (vomiting, unable to get up and go to school) attacks. Our experience with magnesium aspartate (200–400 mg/day) has been good in some cases. In our personal experience about 50% respond to magnesium (at least 50% reduction in the number of attacks), but due to the lack of any controlled studies, other factors such as spontaneous fluctuations, placebo effects, and incomplete follow-up might interfere. Topiramate has also been shown to prevent attacks of vestibular migraine in children (Lewis and Paradiso, 2007). Anecdotal evidence, as well as inference from treatment in adults, suggests that propranolol, metoprolol, valproic acid, amitriptyline, and flunarizine may be effective therapies (Table 25.3) (Winner, 2013; Jahn et al., 2015).

Motion sickness

Motion sickness is another common disorder in dizziness clinics for children. A population-based cross-sectional study of 831 children aged 7–12 years found that the prevalence of motion sickness in this age group was >40% when traveling by car or bus, but only 7% when riding on a carousel (Henriques et al., 2014). Children under 2 years of age are fairly resistant to motion sickness; in contrast, children between 4 and 10 years are more susceptible than adults (Brandt, 1999). There is still an ongoing debate on the causes of the high prevalence of motion sickness in children. A sensory mismatch between otolith and semicircular canal signals is likely to be at least as relevant as a vestibular–visual mismatch, because exposure to otolith stimulation (e.g., road bumps) in combination with semicircular canal stimulation (e.g., head turns) is a typical trigger of motion sickness. The high susceptibility of subjects between the ages of 5 and 10 may be due to the different times of maturation of these systems. In this context it is interesting that, unlike calorics and cVEMP, oVEMP is not present in newborns, but can be recorded in children older than 2 years of age who are able to walk without support (Wang et al., 2013). This finding has been discussed in the context of balance control during locomotion, but it might also be relevant for determining susceptibility to motion sickness, which is usually absent in small children under 2 years of age (Jahn et al., 2015). Most likely a combination of factors, including exposure to stimuli and expectation, contributes to the symptoms. Vegetative symptoms such as nausea and vomiting are part of the syndrome and are most likely provoked by low-frequency vertical oscillations (0.2 Hz) (Jahn, 2011). Head movements and lack of visual control worsen the symptoms. Motion sickness can be prevented by controlling visual stimuli, such as looking out of the car and avoidance of head movements (Gahlinger, 1999). Drug prophylaxis is indicated in severe cases, for example, using dimenhydrinate (1–2 mg/kg) 1 hour before exposure to such situations. This dosage can be repeated every 6 hours (Table 25.3) (Huppert et al., 2011; Jahn et al., 2011).

Structural central vestibular lesions

Central vestibular disturbances are due to lesions in the brainstem (vestibular nuclei, ocular motor nuclei, medial longitudinal fasciculus, reticular formation, midbrain tegmentum) and in the cerebellum (flocculus and nodulus) (Brandt and Dieterich, 1994b). Supratentorial lesions (thalamus, cortex) rarely cause rotatory vertigo, but affected patients can present with dizziness and

Table 25.3

Treatment of central vestibular vertigo and dizziness in childhood

Clinical syndrome	Therapeutic options
Central lesion	
Neoplastic (e.g., cerebellar/brainstem tumor)	Therapy based on the etiology
Degenerative/hereditary (e.g., spinocerebellar ataxia, episodic ataxia)	**Episodic ataxia type II** Acetazolamide, 5–10 mg/kg/day 4-Aminopyridine, 5 mg (qd, bid, tid, experience in children based on single cases)
Inflammatory (e.g., brainstem encephalitis)	
Vascular (e.g., malformation)	**Downbeat/upbeat nystagmus**
Traumatic (e.g., brainstem concussion)	4-Aminopyridine (see above)
Epileptic (e.g., vestibular aura)	
Migraine-related	
Benign paroxysmal vertigo of childhood	Drug prophylaxis rarely necessary because of the benign course; prophylaxis in cases with frequent or severe attacks (falls) possible (see below)
Vestibular migraine Basilar-type migraine (migraine with brainstem aura)	Avoidance of provoking factors (alimentary, stress, lack of sleep); relaxation techniques; sufficient physical activity (sports); sufficient fluid intake Drug prophylaxis recommended with frequent (≥3/month) and/or severe attacks (>72 hours) • Magnesium aspartate, 200–400 mg/day • Propranolol, 1–2 mg/kg/day • Metoprolol succinate, 0.5–1 mg/kg/day • Topiramate, 1–2 mg/kg/day • Amitriptyline, 0.5–1 mg/kg/day • Valproic acid, 10–20 mg/kg/day • Levetiracetam, 20–30 mg/kg/day
Motion sickness	Behavioral prophylaxis by visual control (looking out of the car), avoidance of heavy meals before traveling,sufficient fresh air, distraction Drug prophylaxis • Dimenhydrinate, 1–2 mg/kg, every 6 hours

qd, every day; bid, twice a day; tid, three times a day.

deviation of the subjective vertical (Brandt and Dieterich, 1999, 2015). Clinical examination of ocular motor deficits allows the topographic diagnosis of central vestibular syndromes. Tumors of the brainstem and the cerebellum can cause vertigo in children. MRI should be performed if the clinical examination reveals central ocular motor signs. Therapy is aimed at the underlying etiology (e.g., vascular, inflammatory, degenerative, neoplastic). Sometimes, symptomatic treatment is useful to reduce oscillopsia and postural imbalance (e.g., aminopyridines in downbeat nystagmus syndrome) (Strupp et al., 2008). Physical therapy with posture and gait training is generally recommended, but evidence for this therapy is sparse.

Episodic ataxia type 2

This is a rare autosomal-dominant inherited disorder with mutation in the CACNA1A gene, coding for a subunit of the P/Q calcium channel. The mutation causes Purkinje cell dysfunction in the cerebellum (Strupp et al., 2007). Patients present with attacks of gait imbalance, dysarthria, and vertigo provoked by physical exertion. Attacks last for minutes to hours. Between attacks clinical examination shows a cerebellar syndrome with ocular motor signs (e.g., downbeat nystagmus) and gait ataxia. The syndrome usually manifests in childhood. Therapy includes medical prophylaxis by either acetazolamide or 4-aminopyridine (Table 25.3) (Strupp et al., 2007, 2011).

NON-VESTIBULAR DIZZINESS

Functional dizziness

Functional (somatoform) dizziness is common in adolescence (Fig. 25.1). The terms phobic postural vertigo, psychiatric/psychogenic dizziness, and chronic subjective dizziness have been used synonymously. However, systematic studies on functional dizziness in childhood and adolescence are lacking (Jahn et al., 2015). In young adults, “phobic postural vertigo” was the most common diagnosis made in a tertiary outpatient clinic for dizzy

patients (Strupp et al., 2003). Patients with somatoform syndromes often present with chronic dizziness and normal findings on clinical examination and vestibular testing (Lahmann et al., 2015). Usually, the symptoms worsen in certain situations (e.g., at school, in department stores) (Brandt et al., 1994a). Management consists of: (1) appropriate diagnostic work-up; (2) providing information on the illness to both patients and parents; (3) desensitization to visual and self-motion by vestibular rehabilitation, regular walks, and sports; and (4) behavioral therapy. In adults, more than 75% improve with treatment (Huppert et al., 2005). The literature largely neglects psychiatric comorbidity and somatization when evaluating the child with vertigo and dizziness. It is known that almost half of adult patients with vertigo/dizziness who present to a tertiary care unit have had a psychiatric comorbidity (Lahmann et al., 2015). About 40% of children with migraine also fulfill criteria of somatoform vertigo when presenting at a specialized dizziness unit ($n = 168$). Somatoform vertigo in combination with migraine was the most frequent diagnosis in adolescent girls with dizziness (Langhagen et al., 2013). A study from South Korea showed a similarly high prevalence of psychiatric comorbidity in children with vertigo and dizziness in a tertiary care setting ($n = 105$). The authors reported that about half of the children had high levels of distress requiring psychiatric consultation (Lee et al., 2014). As psychiatric comorbidity adversely impacts treatment outcome, further research on its recognition and specific treatment is needed.

Orthostatic dizziness

Orthostatic dizziness accounts for 5% of diagnoses in specialized dizziness clinics (German Center for Vertigo and Balance Disorders in Munich, Germany; Fig. 25.1), but it is much more common in general pediatric practice. A recent survey in German grammar schools ($n = 1661$) revealed a period prevalence (3 months) of 52% (95% confidence interval, 49.5–54.4%) (Langhagen et al., 2015). Orthostatic dizziness was by far the most frequent complaint in this cohort. It was more common in girls than in boys and had limited impact on social activities. The key to the diagnosis is the history of dizziness after getting up from a supine or sitting position or during prolonged standing. An important diagnostic test is the assessment of blood pressure in supine and upright positions (orthostatic test). Where there is concomitant syncope and relevant impairment, a cardiologic work-up is recommended. For most patients counseling on behavioral measures, including sufficient fluid intake, activation of muscle pump (leg movements) before getting up, avoidance of fast rises and avoidance of prolonged standing without leg activity is the appropriate treatment.

CONCLUSION

Migraine-related syndromes account for about 40% of diagnoses in children with vertigo and dizziness. Somatoform vertigo (functional dizziness) is also a common condition, particularly in adolescence. Central vestibular syndromes related to serious causes (e.g., tumor of the posterior intracranial fossa) are rare and can be detected by careful clinical examination. The vast majority of vertigo and dizziness syndromes in childhood are benign. Healthcare professionals for dizzy children and adolescents must be aware of the differential diagnosis of episodic as well as persistent syndromes. Although the prognosis of episodic forms is usually benign (BPV, vestibular migraine, vestibular paroxysmia), the correct diagnosis is a prerequisite for targeted treatment. Functional dizziness, sensory disorders such as bilateral peripheral vestibular loss, and central vertigo/dizziness can be recognized by persistent complaints and their specific clinical presentation. High-quality treatment trials for pediatric dizziness syndromes are lacking.

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Chapter 26

The conundrum of cervicogenic dizziness

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Abstract

Cervicogenic or cervical dizziness is debated as an entity. However, there exists both a physiologic basis and a multitude of clinical data to make such a disease concept at least possible and worth considering. In addition, the interaction of proprioceptive and vestibular mechanisms may amplify dizziness of other origin.

Cervical pain and dizziness are both common symptoms and may coincide, and neck pain or obvious dysfunction does not necessarily cause dizziness or balance disturbances. So far, there is also the lack of a proper diagnostic test for cervicogenic dizziness. On the other hand, there is growing evidence that cervical proprioceptive input is important for balance and postural control not only in animals but also in humans, and that intervention in disorders affecting the human cervical segment may relieve dizziness in some patients.

It is advocated that the diagnosis should be used with care and that there is a need for better diagnostic tests. In the absence of such a test, one has to rely on preliminary criteria and a diagnosis *ex juvantibus*. A possible approach would require patients to present with neck pain before or in close temporal relation with dizziness; that other causes should be made at least unlikely; and that treatment of a cervical dysfunction reduces also dizziness or balance disturbance.

BACKGROUND

Cervical dizziness or vertigo is a longstanding concept, which has been repeatedly challenged and which has remained controversial. Already Claude Bernard in 1865 described how dissecting neck muscles can cause balance instability in dogs. The early report of Barré–Lieou syndrome (Hain, 2015) postulated that impingement of vertebral arteries during neck torsion impairs blood flow in the vertebral arteries and causes secondary balance disturbances.

One may approach the concept of cervical dizziness in at least two ways. The first is from a clinical point of view. A clinician will observe a number of patients with neck pain who simultaneously report imbalance, dizziness, or even vertigo. The simultaneous presence of the two symptoms will then lead to the likely assumption of an etiologic rather than a coincidental relationship. The second approach would focus on the well-described influence of cervical proprioceptive information on orientation and balance control in both animals and humans and the confluence of vestibular and cervical proprioceptive afferents in the vestibular nuclei. From this, one may deduce that a disturbance of structures involved in these proprioceptive mechanisms should be of importance for perceived balance control and hence, through sensory conflict, a potential cause of dizziness.

PAIN AND DIZZINESS

Although the relationship between cervical pain, cervical dysfunction, and dizziness has often been challenged, an impaired sensorimotor control is assumed in patients with cervical pain (Hellstrom et al., 2005). Simultaneously

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there are a number of reports demonstrating various impairments in proprioceptive or other somatosensory functions in patients simultaneously suffering from cervical pain and dizziness. For example, muscle spindle sensitivity may change (Thunberg et al., 2001; Matre et al., 2002; Hellstrom et al., 2005), as may coordinated muscle activation (Johansson and Sojka, 1991; Passatore and Roatta, 2006). Recently, Malmström et al. (2013) demonstrated that injecting hyperosmotic saline in deep cervical muscles in volunteers, which induces a strong and radiating cervical pain, causes disturbed orientation, described as an impaired ability to sense head-on-trunk movements (Malmström et al., 2013). Furthermore, it has been demonstrated that subjects who seek advice because of cervical pain and dizziness may show disturbed postural control (Karlberg et al., 1996a) and that treating the cause of the neck pain, with physiotherapy focusing on musculoskeletal findings, or with surgery in case of a cervical disc prolapse, may also improve the performance in postural control (Karlberg et al., 1995, 1996a; Persson et al., 1996). Hence, there is some evidence for a causal relationship, and not just a coincidence of neck pain on the one hand and disturbed balance and the experience of dizziness on the other.

PHYSIOLOGIC BASIS

Consider the freedom of movement of the head, with its vestibular organ orientating us with precision in space, together with information from vision and proprioception. For optimal head orientation there is also a need to perceive the head movements in relation to the lower-body segments in order to interpret the information from the vestibular organs. The high amount of proprioceptive receptors in the muscles and ligaments of the cervical segments (Voss, 1971; Richmond and Bakker, 1982; Kulkarni et al., 2001; Boyd-Clark et al., 2002), together with the feature of the vestibular organs to encode active and passive movements equally (Cullen and Roy, 2004), indicates that cervical information acts as a reference in order to process vestibular information appropriately. One might even regard the head as a "giant otolith."

It is obvious, both from control theory and for purely mechanical reasons, that cervical information, i.e., proprioception, plays an important role in upholding balance in both humans and animals. Humans and most mammals depend on vestibular and visual information in both feedback and feed-forward mode. Since these sensors are situated in the base of the skull they will signal movements and gravitation effects affecting the head of the individual. Additional information of the position of the head relative to the rest of the body is required to control and balance movements and posture. A mismatch of sensations might cause dizziness and imbalance, and particularly distorted proprioception from the cervical segment would be likely to create a mismatch with visual and vestibular sensations. Alternatively, one may speculate that a cervical proprioceptive error may cause an uncertainty about body control, triggering enhanced awareness of motion and thereby a type of somatoform dizziness. Of course, both of these mechanisms may act in parallel and interact with each other.

The anatomic and physiologic support for the importance of cervical sensation in balance control is strong in animal-based research and evident also in humans (Hain, 2015). As stated above, already Claude Bernard in 1865 reported loss of balance in dogs after deep cervical muscles were transected. The perception of head orientation in space and in relation to the trunk is dependent on integration of several sensory pathways, including information from the vestibular organs, proprioceptors, mechanoceptors, and vision (Falla, 2004; Hain, 2015). The sensorimotor control of head and body depends on proprioception, central nervous processing, and integration of vestibular and visual cues, and comparison with volition and cognition in a continuous feedback with feed-forward action and subsequent motor responses (Gurfinkel et al., 1988; Wolpert et al., 1995; Falla, 2004). Furthermore, Sadeghi et al. (2012) demonstrated that cervical proprioception may substitute for loss of vestibular information after labyrinthectomy in alert monkeys even on the single neuronal level of the vestibulo-ocular reflex arc. Furthermore, subjects with bilateral vestibular loss seem to be able to perform head movements at their own pace with equal precision as healthy controls. It was also shown that neurons of the vestibular cerebellum which process either vestibular input or combined vestibular and proprioceptive input can discriminate between active and passive head movements and also distinguish body movements under the stationary head from head movements on the body (Brooks and Cullen, 2013). Considering these findings and the fact that induced deep cervical pain (Malmström et al., 2013) as well as muscular fatigue has an impact on orientation of the head, it seems at least possible that cervical mechanisms can cause dizziness.

The argument that few patients with different forms of torticollis report dizziness does not contradict such an assumption. Both neuropathic and myopathic torticollis are stationary conditions where head-on-trunk movements will be restricted. Also in traumatic torticollis the head is generally fixed relative to the trunk. It is feasible to assume that in such conditions there is no longer very much of a vivid dynamic sensory input from the cervical segment, and, as we assume, no need for a resting discharge from peripheral intramuscular or segmental receptors, the substrate for a sensory mismatch is less,

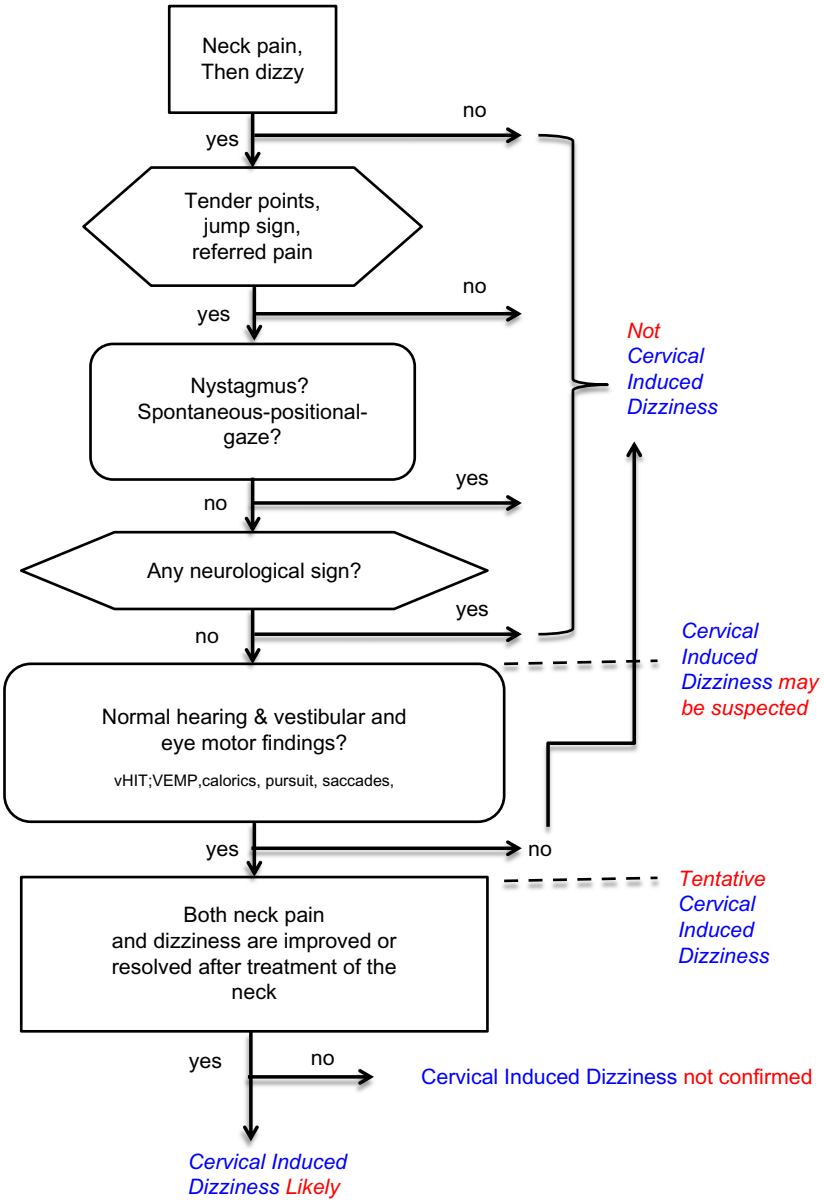

Fig. 26.1. Flow chart suggesting a possible approach to decide upon the likelihood of cervicogenic dizziness. vHIT, video head impulse test; VEMP, vestibular-evoked myogenic potential.

at least after some time. In a dynamic situation, however, torticollis have been associated with imbalance or reflexive eye motor asymmetries (Diamond et al., 1988; Hallberg et al., 2013). Hence, there seems to be at least a physiologic substrate for the possibility of cervicogenic dizziness.

DIAGNOSIS

At present, there is no real diagnostic tool for cervical dizziness. As argued above, the demonstration of a distorted cervical proprioception would be a way to make the diagnosis more likely. However, one would have to measure the extent of such disturbances and their relationship with symptoms. The smooth-pursuit neck torsion test was suggested to correspond to disturbed proprioception or even whiplash injuries (Tjell and Rosenhall, 1998; Treleaven et al., 2005; Treleaven, 2008). This has been challenged by demonstrating that there is an effect of neck pain as such and that head turning has only a small effect on voluntary eye movements. In addition, test performance appears to deteriorate in patients with neck pain of both traumatic and other origin (Kongsted et al., 2007; Janssen et al., 2015).

Posturography may be impaired in patients with cervical complaints and dizziness and discriminates between

groups with cervical problems, vestibular problems, and no complaints (Karlberg et al., 1996a, b). Using elaborate mathematic models of human postural control measurements, a discrimination on an individual level can be done but will still only to refer a subject to one of a pre-decided set of groups. Thus, posturography has not reached the level of discrimination on the individual level to be clinically conclusive (Karlberg et al., 1996a, b).

A possible approach could be to consider a patient with neck pain and dizziness, having cervical dizziness only if other causes have been made less likely, and if he or she responds to manual or other therapies of the cervical segments, with prompt reduction of cervical pain and dizziness. At present and in the absence of proper diagnostic tools, such an approach is necessary (Karlberg et al., 1996a; Malmström et al., 2007; Hansson et al., 2013). Although unsatisfying, this situation is not unique in medicine. For example, migraine and several neuropsychiatric disorders are defined in a similar way. Until a test or set of criteria, or both, is developed and validated, we will have to diagnose cervical dizziness as suggested above, i.e., as a diagnosis *ex juvantibus*. When a patient presents with longstanding neck pain, say more than 2–3 months, and when dizziness has emerged after the onset of pain, an approach as suggested in Figure 26.1 may be useful to decide on the likelihood of cervical dizziness.

The possibility must be acknowledged that cervical dizziness may be secondary to any other ailment causing dizziness, vertigo, or disturbed balance or any other disturbances leading to asymmetric or impaired sensory motor control. However, even if the dizziness is a result of another condition, one may still consider cervical dysfunction as a contributing factor. This would have implications for the suggested treatment. Both the initiating disorder and the cervical distress would have to be addressed in parallel.

CONCLUSION

Cervicogenic dizziness remains controversial. The lack of a diagnostic test or generally accepted criteria makes the entity even more problematic. Both anatomic–physiologic considerations and epidemiologic data suggest a relationship of neck pain and dizziness. Furthermore, there is emerging evidence that therapeutic interventions for cervical complaints may have an effect on dizziness and even on balance tests. At present, however, the diagnosis of cervicogenic or cervical dizziness is based on taking a history and trying to exclude other causes carefully. The best evidence for the diagnosis, and perhaps a starting point for further studies, may be patients who recover from both dizziness and neck pain after treatment of their cervical problems.

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Chapter 27

Motion sickness

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Abstract

Over 2000 years ago the Greek physician Hippocrates wrote, "sailing on the sea proves that motion disorders the body." Indeed, the word "nausea" derives from the Greek root word *naus*, hence "nautical," meaning a ship. The primary signs and symptoms of motion sickness are nausea and vomiting. Motion sickness can be provoked by a wide variety of transport environments, including land, sea, air, and space. The recent introduction of new visual technologies may expose more of the population to visually induced motion sickness. This chapter describes the signs and symptoms of motion sickness and different types of provocative stimuli. The "how" of motion sickness (i.e., the mechanism) is generally accepted to involve sensory conflict, for which the evidence is reviewed. New observations concern the identification of putative "sensory conflict" neurons and the underlying brain mechanisms. But what reason or purpose does motion sickness serve, if any? This is the "why" of motion sickness, which is analyzed from both evolutionary and nonfunctional maladaptive theoretic perspectives. Individual differences in susceptibility are great in the normal population and predictors are reviewed. Motion sickness susceptibility also varies dramatically between special groups of patients, including those with different types of vestibular disease and in migraineurs. Finally, the efficacy and relative advantages and disadvantages of various behavioral and pharmacologic countermeasures are evaluated.

SIGNS AND SYMPTOMS

The primary signs and symptoms of motion sickness are nausea and vomiting. The aversive nature of nausea and vomiting due to motion sickness was exploited in historic times both as an unusual form of punishment (Reason and Brand, 1975) and also as a strange type of therapy (Harsch, 2006). Other related symptoms include stomach awareness, sweating and facial pallor (sometimes called "cold sweating"), increased salivation, sensations of bodily warmth, dizziness, drowsiness (also denoted as the "sopite syndrome"), sometimes headache, and unsurprisingly, loss of appetite and increased sensitivity to odors. The importance and negative impact on performance of "sopite" are often underestimated (Lackner, 2014). Yawning has been shown to be a behavioral marker for the sopite syndrome and consequent reduced task performance (Matsangas and McCauley, 2014).

A typical motion sickness questionnaire is shown in Table 27.1, which lists the more frequent symptoms, excluding vomiting and facial pallor. This is an adaptation of the simulator sickness questionnaire (Kennedy and Fowlkes, 1992). The occurrence of oculomotor symptoms (such as eye strain, difficulty focusing, also headache) is relatively higher in situations where visual mismatches may be the provoking stimulus, such as in simulators and virtual-reality systems, as opposed to motion sickness due to whole-body accelerative stimuli such as during ship motion. Headache is provoked more by visual than real motion, even when the real motion is twice as provocative as visual motion in terms of nauseogenicity (Bijveld et al., 2008). For a more rapid assessment, the following global sickness rating scale has proved reliable and useful: 1 = no symptoms; 2 = initial symptoms of motion sickness but no nausea; 3 = mild nausea; 4 = moderate nausea; 5 = severe nausea and/or retching; 6 = vomiting (Golding et al., 2003).

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Table 27.1

Symptom questionnaire for motion sickness (excludes facial pallor and vomiting)

Do you have any of the following symptoms right now? (tick boxes)				
	0	1	2	3
	None	Slight	Moderate	Severe
General discomfort				
Fatigue				
Headache				
Eye strain				
Difficulty focusing				
Increased salivation				
Sweating				
Nausea				
Difficulty concentrating				
Fullness of head				
Blurred vision				
Dizziness (eyes open)*				
Dizziness (eyes closed)*				
Vertigo				
Stomach awareness				
Burping				

*Illusory feelings of motion.

Physiologic responses associated with motion sickness may vary between individuals. These include autonomic changes such as sweating and vasoconstriction of the skin causing pallor (less commonly, skin vasodilation and flushing in some individuals), with the simultaneous opposite effect of vasodilation and increased blood flow of deeper blood vessels, changes in heart rate which are often an initial increase followed by a rebound decrease, and inconsistent changes in blood pressure (Benson, 2002). Gastric stasis occurs for the stomach and increased frequency and reduced amplitude of the normal electogastric rhythm (Stern et al., 1985; Koch, 2014). The drop in stomach fundus and sphincter pressure correlates with the nausea of motion sickness (Schaub et al., 2014). A host of hormones are released, mimicking a generalized stress response, amongst which vasopressin is thought to be most closely associated with the time course of motion sickness (Eversmann et al., 1978). The observation of cold sweating suggests that motion sickness may disrupt

aspects of temperature regulation (Golding, 1992). This notion is also consistent with the observation that motion sickness reduces core body temperature during cold-water immersion, accelerating onset of hypothermia (Cheung et al., 2011).

Although motion sickness is unpleasant in its own right, under some circumstances it may have adverse consequences for performance and even for survival. Motion sickness preferentially causes decrements on performance of tasks that are complex, require sustained attention, and offer the opportunity of the person to control the pace of effort (Hettinger et al., 1990). Simple tasks and overlearned tasks are less susceptible to performance decrements caused by motion sickness, whereas novel tasks and cognitive tasks involving spatial orientation processing are particularly vulnerable (Gresty and Golding, 2009). For pilots and aircrew, motion sickness can slow training in the air and in simulators and even cause a minority to fail training (Benson, 2002). Approximately 70% of novice astronauts will suffer some degree of space sickness in the first 24 hours of flight. Although vomiting in space is doubtless unpleasant, the possibility of vomiting while in a spacesuit in weightlessness is potentially life-threatening, consequently precluding extravehicular activity for at least the first 24 hours of spaceflight (Heer and Paloski, 2006). For survival at sea, such as in in liferafts, sea sickness can reduce survival chances by a variety of mechanisms, including reduced morale and the "will to live," failure to consistently perform routine survival tasks, dehydration due to loss of fluids through vomiting (Benson, 2002), and possibly due to the increased risk of hypothermia (Cheung et al., 2011).

PROVOCATIVE CIRCUMSTANCES

There is a potential for motion sickness to be caused in a wide range of situations – in cars, tilting trains, funfair rides, aircraft, weightlessness in outer space, virtual reality and simulators (Table 27.2). The classic provocative environment is at sea, as observed by the Greek physician Hippocrates over 2000 years ago, "sailing on the sea proves that motion disorders the body." Indeed, the word nausea derives from the Greek root word *naus*, hence nautical, meaning a ship. The general term motion sickness embraces sickness provoked by a wide variety of environments, car sickness, air sickness, space sickness, sea sickness, cinerama sickness, simulator sickness. Interestingly, sound cues can be added to this list, since vection (illusory self-motion) can be induced using moving (rotating) auditory cues in the laboratory. However, auditory-induced vection is much weaker than equivalent visually induced vection and, unlike visual motion, auditory cues for implied motion are unlikely to produce significant sickness, except for the most susceptible individuals (Keshavarz et al., 2014).

Estimates for incidence rates of motion sickness vary widely, partly due to individual differences in susceptibility and also because superficially similar transport environments can vary dramatically in terms of their motions and consequent nauseogenicity. For example, although air travel in small planes that can encounter low-altitude air turbulence can provoke motion sickness in about 25% of passengers, flights in large airliners have incidence rates of less than 1% (Murdin et al., 2011). Long-distance coach journeys can cause some symptoms of motion sickness in over

Table 27.2

Provocative stimuli for motion sickness

Context	Examples of provocative stimuli for motion sickness
Land	Cars, coaches, tilting trains, skiing, riding camels, elephants, funfair rides
Sea	Boats, ferries, survival rafts, divers' lines undersea
Air	Transport planes, small aircraft, hovercraft, helicopters, parabolic flight
Space	Shuttle, spacelab
Optokinetic*	Wide-screen cinemas, microfiche-readers, "haunted swing," simulators, virtual reality (head mounted display, HMD), rotating visual drums or spheres, pseudo-Coriolis, reversing prism spectacles
Laboratory†	Cross-coupled (Coriolis) stimuli. Low-frequency translational oscillation (vertical or horizontal), off-vertical axis rotation (OVAR), counterrotation, **g** excess in human centrifuges, auditory vection (a very weak stimulus)
Associated‡ stimuli	Emetic toxins, chemotherapy, postoperative nausea and vomiting (PONV), extreme arousal (fear increases/fight decreases)

*Optokinetic stimuli are classed separately since they do not need additional physical transportation of the person under all definitions, although some might be also classed under Laboratory.

†Laboratory stimuli evoking motion sickness are simply refined elements of those provocative stimuli found in the outside world.

‡Associated stimuli are included to indicate the basic evolutionary functions served by nausea and vomiting.

a third of passengers (Turner and Griffin, 1999b) and a quarter of co-drivers became motion sick in rally cars (Perrin et al., 2013). In an extensive survey of cruise ships, motion sickness was the most common reason for physician consultations; the incidence was 4.2 per 1000 person/days, being higher than for infections or injuries (Schutz et al., 2014). Incidences can be much higher in small boats and rough seas. In liferafts, incidence rates of over 50% vomiting have been observed after 1 hour of moderate sea motion (Benson, 1999).

Cinerama sickness has long been known to affect a small percentage of the population, with less than 6% having any symptoms at all (Golding, 2006a), but the widespread introduction of new visual technologies may pose more of a problem. Technologies such as virtual reality and three-dimensional (3-D) stereoscopic video films may provoke more motion sickness than 2-D films. Although one study found only low levels of sickness, with no clear differences between viewing 2-D versus 3-D video (Pölönen et al., 2013), the majority of studies suggest that the new 3-D visual technologies are more provocative of motion sickness and pose a problem for some viewers (Bos et al., 2013; Naqvi et al., 2013; Solimini, 2013).

MECHANISMS AND THEORIES FOR MOTION SICKNESS

Mechanisms

The generally accepted explanation of the "how" or mechanism of motion sickness is based on some form of sensory conflict or sensory mismatch between actual versus expected invariant patterns of vestibular, visual, and kinesthetic inputs, as predicted by an "internal model." A key observation leading to the understanding of this concept is that the physical intensity of the stimulus is not necessarily related to the degree of nauseogenicity (Golding, 2006b). For example, with optokinetic stimuli, the motion is implied, but not real. A person sitting at the front in a wide-screen cinema experiences self-vection and cinerama sickness, but there is no physical motion of the body in the real world. The vestibular and somatosensory systems are signaling that the person is sitting still, but the visual system is signaling illusory movement or self-vection. Consequently, the generally accepted explanation of the "how" of motion sickness is based on some form of sensory conflict or sensory mismatch.

Sensory conflict or sensory mismatch is between actual versus expected invariant patterns of vestibular, visual, and kinesthetic inputs (Claremont, 1931; Reason and Brand, 1975). These also include intravestibular conflicts between rotational accelerations sensed by the semicircular canals and linear-translational accelerations (including gravitational), sensed by the otolith organs. A variety of detailed hypotheses have been developed to explain the exact nature of sensory conflict or sensory mismatch (e.g., Oman, 1990; Benson, 1999). Benson (2002) categorized neural mismatch into two main types: (1) conflict between visual and vestibular inputs or (2) mismatch between the canals and the otoliths. An even more simplified model was proposed by Bos and Bles (1998). They postulated that there is only one conflict: between the subjective expected vertical and the sensed vertical. However, despite this simplification, their underlying model is necessarily complex and finds difficulty in accounting for the observation that motion sickness can be induced by types of optokinetic stimuli which pose no conflict concerning the earth-vertical (Bubka et al., 2006). Most models of motion sickness also incorporate integrator and decay systems in which the rate of accumulation of "sensory conflict" is processed by leaky integrators with different time constants (Oman, 1990). This process can be below conscious experience until a threshold is reached signaling the onset of overt symptoms and the awareness of the beginning of motion sickness (Golding and Stott, 1997a).

The "rule of thumb" model originally advanced by Stott (1986) is not the most elegant in theoretic terms, but arguably is still the most practical. This model proposes a set of simple rules, which, if broken, will lead to motion sickness:

1. Visual-vestibular: motion of the head in one direction must result in motion of the external visual scene in the opposite direction.
2. Canal-otolith: rotation of the head, other than in the horizontal plane, must be accompanied by appropriate angular change in the direction of the gravity vector.
3. Utricle-saccule: any sustained linear acceleration is due to gravity, has an intensity of 1 **g**, and defines "downwards."

In other words, the visual world should remain space-stable, and the sustained force vector is gravity, which should always point down and average over a few seconds to 1 **g**.

In some environments there may be only one provocative stimulus. At sea it is the low-frequency "heave" motion of the vessel that provokes sea sickness. However in many environments multiple stimuli and conflicts may be involved. For example, air sickness in a pilot produced by the flight of an agile military aircraft may be due to up to five sources (Golding, 2006b). Flying through air turbulence produces low-frequency translational oscillation of the aircraft, which may cause air sickness. In addition, during aircraft turns there may be provocation from the four following sources: visual-vestibular mismatches as the pilot senses "down" to remain through the axis of the body but the external visual world to be tilted;

sustained changes in the scalar magnitude of gravitoinertial force (GIF) due to centripetal acceleration; cross-coupling (Coriolis) due to head movements during rotation of the aircraft if the turn is tight enough; and also the **g**-excess illusion if the pilot tilts the head during increased GIF.

In virtual-reality systems and simulators, self-vection, retinal slip, and poor eye collimation may be an important provocative stimulus, but phase lag between real motion and the corresponding update of the visual display may be equally or more important. Compensatory vestibulo-ocular reflexes (VORs) to head movements are as fast as 10 ms; consequently, visual update lag disparities not much longer than this may be easily detectable by subjects. If visual display update lags are much longer than this, they may provoke sickness, since it has been shown that virtual-reality sickness has been induced with update lags as short as 48 ms (Golding, 2006b).

Low-frequency translational motion is a major source of motion sickness in land vehicles, ships, and aircraft, and has been sufficiently well described to provide engineering design parameters (exposure time, acceleration, frequency) for standards regulated by the International Standards Organization (ISO 2631, 1997). The frequency weighting function is of theoretic as well as applied interest. Laboratory experiments (O'Hanlon and McCauley, 1974; Golding et al., 2001) and ship motion surveys (Lawther and Griffin, 1988) have shown that nauseogenicity increases as a function of exposure time and acceleration intensity, as might be expected, but, more unusually, that nauseogenicity peaks at the low-frequency motion of around 0.2 Hz. Such low-frequency motions are present in transportation in ships, coaches, aircraft flying through air turbulence, and on camels and elephants, all of which can provoke motion sickness.

This frequency relationship also explains why some forms of transport are not provocative; for example people do not experience horse sickness. During horse riding, walking, running, and riding off-road trail bikes, the frequencies are higher than 1 Hz. Consequently, although these motions can be quite severe (capable of bruising the person), they are not nauseogenic (Golding, 2006b). Hypotheses for the frequency dependence of nauseogenicity of translational oscillation are a phase error in signaling motion between canal-otolith and somatosensory systems (Von Gierke and Parker, 1994; Benson, 1999), or a frequency-dependent phase error between the sensed vertical and the subjective or expected vertical (Bos and Bles, 1998). It has also been proposed that a zone of perceptuomotor ambiguity around 0.2 Hz triggers sickness, since at higher frequencies imposed accelerations are usually interpreted as translation of self through space, whereas at lower frequencies imposed accelerations are usually interpreted as a shift in the main force vector, i.e., tilt of self with respect to the assumed gravity vertical (Golding et al., 2003; Golding and Gresty, 2005). The region of 0.2 Hz would be a cross-over between these two interpretations and, thus, a frequency region of maximal uncertainty concerning the correct frame of reference for spatial orientation. More recently, Gresty et al. (2011) proposed a related ecologic explanation, that this frequency tuning of motion sickness is related to mechanical limitations on human body motion. This proposes that a cause of motion sickness may be difficulty in selecting appropriate tactics to maintain body stability at vehicle motion *ca.* 0.2 Hz, between whole-body GIF alignment seen at lower frequencies versus lateropulsion seen at higher frequencies.

Although the physiologic mechanisms are still not fully known, understanding of the brain mechanisms which underpin sensory conflict and motion sickness has progressed greatly. In a series of elegant experiments, Oman and Cullen (2014) have identified brainstem and cerebellar neurons whose activity corresponds to what might be expected of putative sensory conflict neurons. The pathways that integrate vestibular and emetic gastrointestinal signals that produce nausea and vomiting are being elucidated (Yates et al., 2014). The concept of a discrete brainstem area postrema "vomiting center" has been superseded by the picture of a network of nuclei, including the nucleus tractus solitarius (NTS) and the medullary reticular formation. It seems that the same brainstem areas mediate vomiting and nausea irrespective of the triggering mechanism, whether motion or toxins. These brainstem areas not only include the NTS but also the dorsolateral reticular formation of the caudal medulla (lateral tegmental field), and the parabrachial nucleus, which act together to integrate signals that lead to nausea and vomiting (Yates et al., 2014). The NTS is the terminus of many visceral afferents and it also receives efferent projections from the area postrema. The NTS is now known to relay signals to the emesis pattern generator. In addition, neurons in the vestibular cerebellum, including the fastigial nucleus, are influenced by visceral afferents. Galvanic vestibular stimulation in the cat has been shown to produce patterns of neural activation revealed by c-fos labeling, some of which correlate with overt signs of motion sickness, others of which show no such relationship but may relate to covert affective aspects such as nausea (Balaban et al., 2014). The onset of visually induced nausea in humans has been studied with functional magnetic resonance imaging (fMRI) (Napadow et al., 2013a). Increased activity preceding nausea was found in the amygdala, putamen, and dorsal pons/locus coeruleus, whereas, with onset

of nausea, activity was observed in a broader network, including insular, anterior cingulate, orbitofrontal, somatosensory, and prefrontal cortices. Strong nausea was associated with sustained anterior insula and midcingulate activation, suggesting a closer linkage between these specific regions within the brain circuitry subserving nausea perception (Napadow et al., 2013a).

Why does motion sickness exist?

By contrast with the "how" of motion sickness, (i.e., the mechanisms), for which there is some consensus concerning sensory conflict, there are widely differing opinions concerning the "why" of motion sickness, or even if it is a useful question to ask. The primary functions of the vestibular system are spatial orientation, maintenance of balance, and stabilizing of vision through VORs. Additional vestibular functions have been proposed to explain the "why" of motion sickness. These hypotheses can be classified broadly into: poison detector; vestibular cardiovascular/autonomic reflex; disorientation/motor warning; and nonfunctional evolutionary maladaptation.

The poison or toxin detector hypothesis states that the vestibular system can act as a toxin detector. Thus, the evolutionary purpose of what we call motion sickness is postulated to be the same as for any emetic response, which is to protect the organism from the toxic effects of potentially harmful substances that it may have ingested (Treisman, 1977). The toxin detector hypothesis proposes that the brain has evolved to recognize any derangement of expected patterns of vestibular, visual, and kinesthetic information as evidence of central nervous system malfunction and to initiate vomiting as a defense against a possible ingested neurotoxin. In other words, it provides a backup to the main toxin detector system of chemoreceptors of the afferent vagal nerves and the chemoreceptor trigger zone of the brainstem.

To summarize this hypothesis, motion sickness in pedestrian humans or other animals is simply the inadvertent activation of this ancient defense reflex by the sensory conflicts induced by the novel altered visual and force environments of sea, air, land transport, space, and virtual reality (Golding, 2006b). This evolutionary-based hypothesis is consistent with the observation that motion sickness is evolutionarily well preserved, from humans down to the level of the fish (ironically, fish can become sea sick during aquarium transport) (Reason and Brand, 1975). It is also consistent with the observation that people who are more susceptible to motion sickness are also more susceptible to toxins, chemotherapy, and postoperative nausea and vomiting (PONV) (Morrow, 1985; Golding, 1998). There have also been further attempts to test the toxin detector hypothesis by seeing whether individual differences in bitter taste sensitivity and aversion, which reflects activity of one part of the primary toxin detector system, correlates with motion sickness susceptibility, thought to reflect activity in the hypothetical backup toxin detector system. However, unlike the well-proven associations of motion sickness susceptibility with chemotherapy sickness or PONV, these bitter-taste studies have provided contradictory results. Positive correlations (Sharma et al., 2008), negative correlations (Benson et al., 2012), or no significant correlations (Golding and Tayyaba, 2014) for bitter-taste sensitivity with motion sickness susceptibility have been reported. Finally, perhaps the most convincing evidence is that the toxin detector hypothesis has been experimentally tested in animals. This demonstrated that emetic responses to challenges from emetogenic toxins were significantly reduced after bilateral vestibular ablation (Money and Cheung, 1983).

The vestibular cardiovascular/autonomic reflex hypothesis is based on the observation that tilt stimulation of the otolith organs, which transduce linear accelerations, provokes a pressor response (increased blood pressure and cardiac output) mediated via vestibular-cardiovascular projections (Yates et al., 1998). It has been proposed that motion sickness is caused by the inappropriate activation of such vestibular-cardiovascular reflexes. The general concept is that the vestibular and visual systems influence autonomic control for the purpose of maintaining homeostasis during movement and changes in posture. Thus, motion sickness arises from an aberrant activation of neural pathways that serve to maintain a stable internal environment (Yates et al., 1998).

A somewhat similar, but nonfunctional, explanation has been proposed by Balaban (1999): that motion sickness might be regarded as referred visceral discomfort after activation of vestibular autonomic reflexes due to the convergence of vestibular and autonomic afferent information in the brainstem and cerebellum. The vestibular-cardiovascular reflex hypothesis has a good historic pedigree in the 19th-century concept of "cerebral anemia" as the cause of motion sickness (Nunn, 1881). Although some support is provided by the observation that cerebral hypoperfusion preceded nausea during GIF variation induced by centrifugation (Serrador et al., 2005), the situation is unclear, since there is considerable overlap between sick and nonsick individuals' pressor responses to motion sickness induced by the GIF variation of parabolic flight (Schlegel et al., 2001).

The importance of the vestibular-cardiovascular reflexes in maintaining blood pressure may be limited, at least in humans. Bilateral labyrinthectomized patients' pressor responses to rapid tilts are only minimally slower than normal subjects (<500 ms) (Radtke et al., 2003), and these patients do not appear to be fainting frequently

as they adjust their posture during everyday activity as they walk around, lie down, and stand up. Moreover, although not a formal disproof, this hypothesis does not predict the relative nauseogenicity of the various gravity-referenced and body-referenced directions of motions that would be expected to alter blood pressure (Golding et al., 1995, 2003).

The disorientation/motor warning hypothesis postulates that motion sickness is a punishment system which has evolved to discourage development of perceptual-motor programs that are inefficient or cause spatial disorientation (Guedry et al., 1998). In other words, this system has evolved to discourage self-exposure to circumstances causing disorientation or motor instability. An extension of this hypothesis is that prostration caused by motion sickness reduces the likelihood of injury or vulnerability to predators (Bowins, 2010). Recent variants of this last idea postulate that motion sickness evolved to discourage risky activity in ancestral fish that were suffering vestibular malfunction (Thornton and Bonato, 2013), or that proto-hominids would avoid looking for food in swaying trees that might threaten security; thus tending to survive (Knox, 2014). However an unanswered difficulty with all disorientation/motor warning hypotheses is: why would evolution select such slow-onset negative reinforcers such as nausea and vomiting, rather than the readily available rapid warning systems of fear and pain?

The most reductionist approach is the evolutionary maladaptation hypothesis (Oman, 2012). Evolution is not perfect: an example of evolutionary maladaptation is the co-location of the entries to the respiratory airways and the esophagus in many land animals, which makes them susceptible to death by choking. From the perspective of the evolutionary maladaptation hypothesis, motion sickness is just an unfortunate consequence of the physical proximity of the motion detector (vestibular) and vomiting circuitry in the brainstem. It is just bad luck. Oman (2012) has stated that adaptive hypotheses for motion sickness such as the toxin detector hypothesis are "naïve 'just-so' stories" (Oman, 2012, p. 125), the reference being to the children's stories by the author Rudyard Kipling providing amusing and fanciful explanations for differing animal characteristics, for example, such as how the elephant got its trunk, the leopard its spots. Oman (2012), to support his critique, notes: (1) that every symptom of motion sickness does not exactly match up with those evoked by food poisoning; and (2) that bilateral vestibular ablation does not totally prevent vomiting to all toxins, as observed by Money and Cheung (1983). However, these two criticisms, although valid, are not decisive. Criticism 1, about patterns of symptoms, is limited, since it is known that, apart from nausea and vomiting, there is no exact profile of symptoms. Symptoms vary considerably for many reasons, among different individuals, among different types of poisoning, and among different types of provocative motion stimuli. Criticism 2, that bilateral vestibular ablation does not abolish vomiting to all emetogenic poisons, misses the point that the toxin detector hypothesis for motion sickness does not claim this. The toxin detector hypothesis only postulates that the vestibular system provides a useful backup to the main toxin detector system of chemoreceptors of the afferent vagal nerves and the chemoreceptor trigger zone of the brainstem.

To summarize, all of the above hypotheses remain in contention to provide explanations for the "why" of motion sickness. If motion sickness is just a random and complicated evolutionary maladaptation, then it has been remarkably well preserved across species, from fishes to humans, and, by implication, over many millions of years. At present, the balance of evidence would seem to favor either the functional explanation of the toxin detector hypothesis or the "bad luck" evolutionary maladaptation hypothesis.

PREDICTORS OF MOTION SICKNESS SUSCEPTIBILITY

Concept of motion sickness susceptibility

Any concept of individual differences in motion sickness susceptibility must acknowledge the multifactorial nature of motion sickness susceptibility itself. At least three processes are thought to be at work: initial sensitivity to motion, rate of natural adaptation, and the ability to retain protective adaptation in the longer term (Reason and Brand, 1975). Moreover, correlations among various types of motion challenges are not high (Lentz, 1984), implying differential sensitivity in individuals to different types of motion. For example, the correlation between individual susceptibility to translational versus cross-coupled (Coriolis) motion can sometimes be very low (Golding, 2006b). Factor analysis of self-report questionnaires, designed to assess susceptibility to motion sickness, suggests the existence of independent latent susceptibilities to different types of provocative environments, usually forming factors that might be termed transportation by land, air, sea, or funfair rides (Golding, 1998). This might seem to contradict the notion of a general motion susceptibility dimension. Nevertheless, these apparently contradictory views can be argued to both be true, i.e., general motion susceptibility factors and specific factors both exist. Other limitations are imposed by the test–retest reliability of response to a motion challenge, which may be estimated from repeated exposures in the laboratory to be around $r = 0.8–0.9$ (Golding, 2006b).

Motion Sickness Susceptibility Questionnaires (MSSQs: sometimes called Motion History Questionnaires) enable a rapid estimate to be made of an individual's susceptibility. A typical questionnaire is shown in Table 27.3, and this has been validated to predict motion sickness to motion stimuli in the laboratory and in transport environments (Golding, 2006a). An overall indicator of susceptibility may be calculated as the MSSQ score = (total sickness score) × (18) / (18 – number of types not experienced). This formula corrects for differing extent of exposure to different motion stimuli in individuals. For the normal young adult population, the median MSSQ score is 11.3, where higher scores indicate greater susceptibility, and vice versa. More details are given in the original reference (Golding, 2006a).

Genetics

Individuals vary widely in their susceptibility, but nearly all people can be made motion-sick given a sufficiently provocative stimulus. Lackner (2014) has suggested that susceptibility in the general population varies by a vast range: about 10 000–1. There is a large genetic contribution to the individual differences in susceptibility. Monozygotic and dizygotic twin studies indicate that the heritability of motion sickness is high, at around 70%, in childhood and declines through puberty and the early adult years to around 55% (Reavley et al., 2006). This decline of heritability with age may be due to differing experiences between each individual twin of a pair of twins to provocative environments as they grow older and to the consequent differential habituation. In shrews, selective breeding for high versus low motion sickness susceptibility strains has shown the importance of genetic determinants for motion sickness and that this extends to anesthesia-induced emesis, indicating some common mechanisms under genetic control (Horn et al., 2014). Multiple genes are probably involved. But the nature of the genes involved is not yet clear. One example is the observation that a single-nucleotide polymorphism of the alpha2-adrenergic receptor increases autonomic responses to stress in humans and also contributes to individual differences in autonomic responsiveness to provocative motion (Finley et al., 2004). However, it is unclear whether this is a marker for motion sickness susceptibility or simply a general marker for autonomic reactivity. There is evidence for Chinese hypersusceptibility to motion sickness, and this may provide some indirect evidence for a genetic contribution to such differences (Stern et al., 1993; Klosterhalfen et al., 2005).

A recent large-scale genome study has isolated 35 single-nucleotide polymorphisms (SNPs) associated with motion sickness (Hromatka et al., 2015). Genetic variants associated with motion sickness pointed to roles for inner-ear development, neurologic processes, and (more surprisingly) glucose homeostasis. Several of these SNPs displayed sex-specific effects, with up to three times stronger effects in women. This study also suggested that PONV and migraines may share underlying genetic factors with motion sickness. The latter finding is of course consistent with the known comorbidities of motion sickness.

General predictors

Sex and age are the two main predictors of individual susceptibility in the general population. Surveys of transportation by sea, land, and air indicate that women are more susceptible to motion sickness than men, although it must be emphasized that this sex difference is an overall trend with considerable overlap. Women show higher incidences of vomiting and a higher incidence of symptoms such as nausea (Kennedy et al., 1995). Large-scale surveys of passengers at sea indicate a 5:3 female-to-male risk ratio for vomiting (Lawther and Griffin, 1988). This difference in vomiting suggests that the increased susceptibility in women is likely to be objective and not due to differential subjective reporting of symptoms. The elevated susceptibility in women does not seem related to extra habituation to greater ranges of motion environments experienced by risk-taking males (Dobie et al., 2001), nor to gender-biased differential self-selection between males and females, e.g., when volunteering for laboratory motion sickness experiments (Flanagan et al., 2005). Moreover, this sex difference is not exclusive to humans because, in animals, such as *Suncus murinus*, females show significantly more emetic episodes and shorter latencies to emesis in experimental exposures to motion (Javid and Naylor, 1999).

The cause of greater motion sickness susceptibility in women has been suggested to involve the female hormonal cycle. Susceptibility varies over the menstrual cycle, peaking around menstruation. But this cannot fully account for the greater susceptibility in females, because the magnitude of fluctuation in susceptibility across the menstrual cycle is only around one-third of the overall difference between male and female susceptibility (Golding et al., 2005). The elevated susceptibility of females to motion sickness or, indeed, to PONV or chemotherapy-induced nausea and vomiting (Morrow, 1985; Golding, 1998), may serve an evolutionary function. Thus, more sensitive sickness thresholds in females may serve to prevent exposure of the fetus to harmful toxins during pregnancy, or subsequently through milk. Elevated susceptibility in females may be "hard-wired," but capable of upregulation, albeit variably, by hormonal influences during the menstrual cycle and even further during pregnancy.

Table 27.3

Motion Sickness Susceptibility Questionnaire Short-form (MSSQ-Short)

This questionnaire is designed to find out how susceptible to motion sickness you are, and what sorts of motion are most effective in causing that sickness. Sickness here means feeling queasy or nauseated or actually vomiting.

Your childhood experience only (before 12 years of age): for each of the following types of transport or entertainment, please indicate:

1. As a child (before age 12), how often you felt sick or nauseated (tick boxes):

	Not applicable – never traveled	Never felt sick	Rarely felt sick	Sometimes felt sick	Frequently felt sick
Cars					
Buses or coaches					
Trains					
Aircraft					
Small boats					
Ships, e.g., Channel ferries					
Swings in playgrounds					
Roundabouts in playgrounds					
Big dippers, funfair rides					
	t	0	1	2	3

Your experience over the last 10 years (approximately): for each of the following types of transport or entertainment, please indicate:

2. Over the last 10 years, how often you felt sick or nauseated (tick boxes):

	Not applicable – never traveled	Never felt sick	Rarely felt sick	Sometimes felt sick	Frequently felt sick
Cars					
Buses or coaches					
Trains					
Aircraft					
Small boats					
Ships, e.g., Channel ferries					
Swings in playgrounds					
Roundabouts in playgrounds					
Big dippers, funfair rides					
	t	0	1	2	3

Adapted from Golding (2006a).

Infants and very young children 2 than two years old are immune to motion sickness. However, they have no difficulty vomiting. Motion sickness susceptibility usually begins from perhaps around 6–7 years of age, although sometimes susceptibility may onset before this (Reason and Brand, 1975), and peaks around 9 years (Turner and Griffin, 1999a; Henriques et al., 2014). The reasons for this are uncertain. Puberty begins later (around 10–12 years) than the age for onset of motion sickness susceptibility. This implies that sex hormonal changes *per se* are not a direct explanation for the onset of motion sickness susceptibility. Another possibility is that the perceptuomotor map is still highly plastic and not fully formed until around 7 years of age. Most theories of motion sickness propose that this perceptuomotor map provides the "expected" invariant patterns for detecting possible sensory mismatches in the relationships between vestibular, visual, and kinesthetic inputs, i.e., the "internal model (see section above on mechanisms). Following the peak susceptibility, there is a subsequent decline of susceptibility during the teenage years toward adulthood around 20 years. This doubtless reflects habituation. Although it is often stated that this decline in susceptibility continues in a more gradual fashion throughout life toward old age, the evidence is somewhat limited, given that older people may avoid motion environments if they know that they are susceptible. Indeed, longitudinal evidence from individuals who have been studied objectively in the laboratory suggests that, toward older age, susceptibility may increase in a minority of individuals.

A multiplicity of other possible predictors of susceptibility have been examined over the years, with relatively few being found to be of significance. Cross-sectional surveys show that individuals with high levels of aerobic fitness appear to be more susceptible to motion sickness, and longitudinal experiments show aerobic fitness training increases motion sickness susceptibility (e.g., Cheung et al., 1990). The reasons are unclear, with one suggestion being that a more reactive autonomic nervous system (including hypothalamic–pituitary–adrenal axis) in aerobically fit individuals may sensitize them. Psychologic variables such as mood may modify susceptibility in contradictory directions: state variables, such as extreme fear or anxiety conditioned to motion, may contribute indirectly to motion sickness susceptibility, although, by contrast, extreme arousal "fight or flight," such as observed in warfare, may suppress motion sickness (Reason and Brand, 1975). Personality trait variables such as extraversion or neuroticism do not strongly predict motion sickness susceptibility, with only minor correlations being observed between extraversion or similar personality traits with reduced susceptibility (Reason and Brand, 1975; Gordon et al., 1994) and higher levels of trait anxiety associated with increased susceptibility (Paillard et al., 2013).

Reliable physiologic markers for predicting individual motion sickness susceptibility have proved elusive. Otolith asymmetry between left and right labyrinths, as measured during parabolic flight, has been proposed as an indicator of susceptibility for space sickness (Diamond and Markham, 1991). However in a more general sense, individual variation in sensory thresholds to angular or translational accelerations does not seem to relate to susceptibility in any obvious fashion. Although motion sickness produces profound autonomic changes, baseline autonomic characteristics are unlikely to provide useful predictors for motion sickness susceptibility (Farmer et al., 2014). Similarly, although motion sickness can cause postural instability, the evidence that individual differences in postural stability or perceptual style (e.g., Riccio and Stoffregen, 1991) are major predictors of motion sickness susceptibility seems limited (Golding and Gresty, 2005; Diels and Howarth, 2013; Lackner, 2014). Shorter time constants of the central vestibular velocity store have been suggested to correlate with reduced motion sickness susceptibility (Dai et al., 2011; Lackner, 2014), but others have found no evidence of such a relationship (Golding and Gresty, 2005; Furman et al., 2011). In an attempt to resolve this apparent contradiction, it has been proposed that it may not be the absolute duration of the time constant *per se*, but the ability to modify readily the time constant that may be a candidate marker for success in motion sickness habituation (Golding and Gresty, 2005). In a similar vein, reduced thresholds for cervical vestibular-evoked myogenic potentials (cVEMPs) predict future habituation to sea sickness, the suggestion being that cVEMP at lower thresholds indicates that the individual has broader dynamic range in which the reflex can respond and adapt to a wider array of stimulus amplitudes (Tal et al., 2013). Individual differences in brain white-matter structure revealed by fMRI may relate to nausea susceptibility (Napadow et al., 2013b).

Special groups: blindness, vestibular disorders, and migraine

Blind or blind-folded normally sighted individuals can be made motion-sick using real physical motion, although obviously optokinetic stimuli (Table 27.2) will be ineffective. Blind individuals, ranging from congenital to late-acquired blindness, are as susceptible to motion sickness as sighted individuals with eyes closed, and their range of susceptibility tends to be comparable to normal-sighted people when exposed to provocative cross-coupled motion (Graybiel, 1970).

Certain groups with medical conditions may be at elevated or reduced risk. Individuals who have complete bilateral loss of labyrinthine (vestibular apparatus) function appear to be immune to motion sickness. However, this may not be absolutely true under all circumstances, since some bilateral labyrinthine-defective individuals are still susceptible to motion sickness provoked by visual stimuli designed to induce self-vection during pseudo-Coriolis stimulation, i.e., pitching head movements in a rotating visual field (Johnson et al., 1999). When well-characterized patients with complete bilateral vestibular failure were exposed to highly provocative off-vertical-axis rotation (OVAR), a few showed minor symptoms of motion sickness (Murdin et al., 2015). This may have been due to residual vestibular function or, more probably, due to aversive sensations of whole-body motion and visual disturbances, since the OVAR was performed in the light.

The reason for the elevated motion sickness susceptibility in migraineurs (without overt vestibular disease) is not known (Murdin et al., 2015). It has been proposed that there may be a genetic link caused by defective calcium ion channels shared by the brain and inner ear, leading to reversible hair cell depolarization, producing vestibular symptoms, and that the headache might just be a secondary phenomenon (Baloh, 1998). An alternative hypothesis is that it may be due to altered serotonergic system functioning (Brey, 2005; Drummond, 2005). Support for this possibility was provided by the observation that the serotonin 1B/1D agonist rizatriptan provided significant antimotion sickness effects in migraineurs (Furman et al., 2011). However, rizatriptan did not provide significant protection against exposure to more provocative vestibular stimulation, suggesting that the role of rizatriptan in this context is more likely to be as a modulator of susceptibility rather than a direct blocker of motion sickness.

It is possible that there are several underlying and overlapping mechanisms for this link, including pain pathways and autonomic reactivity (Cuomo-Granston and Drummond, 2010). The complexity of any association between migraine and motion sickness is illustrated by Bosser et al. (2006), who surveyed the general population (i.e., unselected for severe migraine, by contrast with migraineurs requiring medical help or attending migraine clinics). This survey demonstrated the expected significant bivariate association between elevated motion sickness susceptibility and migraine. However, when these data were reanalyzed using multivariate techniques, the existence of any independent association of motion sickness with migraine disappeared and was replaced by other more important predictors, such as syncope and autonomic reactivity (Bosser et al., 2006). Patients with vestibular migraine are especially susceptible to motion sickness (Boldingh et al., 2011; Paillard et al., 2013; Murdin et al., 2015). Patients with Menière's disease seem to have elevated motion sickness susceptibility compared to controls, but not as elevated as patients with vestibular migraine, as suggested by a telephone survey (Sharon and Hullar, 2014). The data from a much larger-scale survey of Menière's disease patients versus healthy controls would appear to confirm this overall elevated susceptibility for Menière's patients (unpublished data of the author).

An overview of the motion sickness susceptibility of some special patient groups is given in Figure 27.1 from studies using both validated self-report motion sickness susceptibility questionnaires and nauseogenic OVAR (Paillard et al., 2013; Murdin et al., 2015). In Figure 27.1, compared with controls, patients with bilateral vestibular loss were either completely resistant to motion sickness or had very low symptom scores. Unilateral vestibular loss (UVL) also decreased susceptibility, but to a lesser extent than bilateral vestibular loss; however, it should be noted that these were "compensated" UVL patients, i.e., patients who had adapted to sensory conflict caused by the loss of vestibular function on one side, since in the acute phase the usual observation is that UVL patients may be more sensitive to motion. Patients with vestibular neuritis or benign paroxysmal positional vertigo showed no overall difference in susceptibility compared to controls. But, within this broad picture, many individuals had up- or downregulated their sensitivity to motion in response to their disease. Vestibular migraine led to greatly elevated susceptibility. Patients attending migraine clinics, but without vestibular migraine, had equivalent elevations of susceptibility.

MAL DE DÉBARQUEMENT

Mal de débarquement is the sensation of unsteadiness and tilting of the ground when a sailor returns to land. Whittle (1689) provided an early description of *mal de débarquement*, after the landing and during the advance of the troops of William of Orange in Torbay in 1688:

> *As we marched here upon good Ground, the Souldiers would stumble and sometimes fall because of a dissiness in their Heads after they had been so long toss'd at Sea, the very Ground seem'd to rowl up and down for some days, according to the manner of the Waves.*

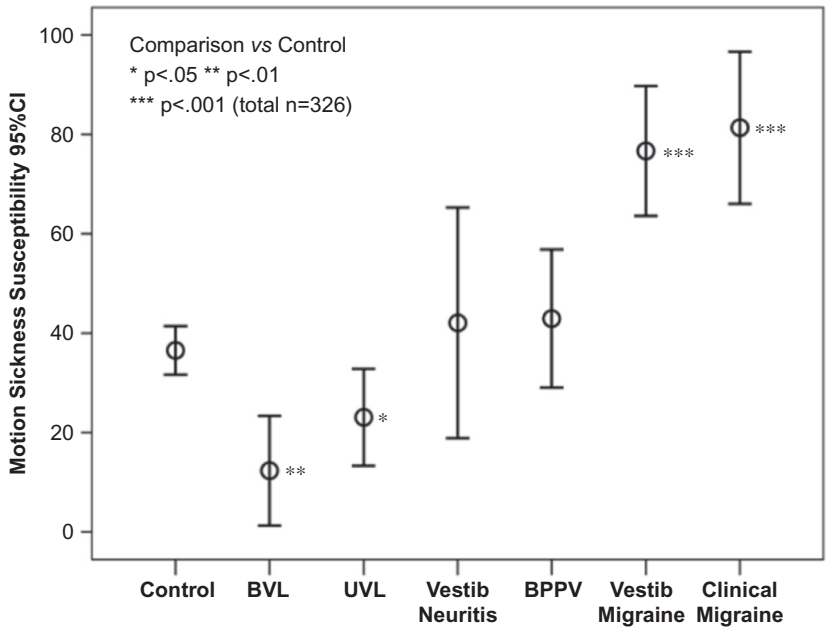

Fig. 27.1. Motion sickness susceptibility scores are shown for patient groups together with significances of comparison with age-equivalent healthy controls. The 95% confidence interval (CI) is smaller for controls as a consequence of larger numbers. Motion sickness susceptibility for Menière's disease is probably similar to migraine groups. BVL, bilateral vestibular loss; UVL, unilateral vestibular loss; BPPV, benign paroxysmal positional vertigo. See text for details. (Data source: combined from Paillard et al., 2013, Murdin et al., 2015, and data on file.)

A similar effect is observed in astronauts returning to 1 **g** on earth after extended time in weightlessness in space. *Mal de débarquement* can lead to motion sickness, but symptoms usually resolve within a few hours as individuals readapt to the normal land environment. Individuals susceptible to *mal de débarquement* may have reduced reliance on vestibular and visual inputs and increased dependence on the somatosensory system for the maintenance of balance (Nachum et al., 2004). It has long been known that view of a stable horizon reference can increase resistance to motion sickness (see next section), but provision of an artificial horizon failed to have any effect on *mal de débarquement* (Tal et al., 2014).

In a small minority of individuals, symptoms persist for months and years and can be troublesome. Patients with persistent *mal de débarquement* syndrome exhibit impaired postural stability but do not exhibit differences in intracortical excitability compared to controls (Clark et al., 2013). Customized vestibular exercises have been proposed as a treatment (Murdin et al., 2011). Some temporary relief can be obtained by re-exposure to motion, but this is not a viable treatment. Standard antimotion sickness drugs appear ineffective, but benzodiazepines appear to offer some relief (Cha, 2009). It has been suggested that repetitive transcranial magnetic stimulation can reduce symptoms for persistent *mal de débarquement* syndrome (Cha et al., 2013).

BEHAVIORAL COUNTERMEASURES

Behavioral countermeasures to motion sickness may be broadly classified into habituation versus more immediate short-term behavioral modifications, such as changes in body posture and visual attention. Habituation offers the surest countermeasure to motion sickness but, by definition, is a long-term approach. Habituation is superior to antimotion sickness drugs, and it is free of side-effects (Cowings and Toscano, 2000). The most extensive habituation programs, often denoted "motion sickness desensitization," are run by the military, where antimotion sickness medication is contraindicated for pilots because of side-effects, including drowsiness and blurred vision. These programs have success rates exceeding 85% (Benson, 1999; Lucertini et al., 2013), but can be extremely time consuming, lasting many weeks. Critical features include: (1) the massing of stimuli (exposure at intervals greater than a week almost prevents habituation); (2) use of graded stimuli to enable faster recoveries and more sessions to be scheduled, which may help avoid the opposite process of sensitization; and (3) maintenance of a positive psychologic attitude to therapy (Yen Pik Sang et al., 2005). Whether or not antimotion sickness drugs are of any practical use in this context is debatable. For example, although some studies appear to show that antimotion sickness drugs can improve the rate of adaptation (Lackner and Graybiel, 1994;

Cohen et al., 2008), other studies in both the laboratory (Wood et al., 1986) and at sea (Van Marion et al., 1985) have shown that, although antimotion sickness medications may speed habituation compared to placebo in the short term, in the longer term they are disadvantageous. This is because, when the antimotion sickness medication is discontinued, the medicated group relapses and is worse off than those who were habituated under placebo.

Habituation, itself, is often stimulus-specific, producing the problem of lack of generalization and transfer of habituation from one type of motion to another. For example, tolerance acquired to car travel may confer no protection to sea sickness (Murdin et al., 2011). Thus, to foster transfer, it is useful to use as wide a variety of provocative motions as possible. The studies by Kaufman (2005) underline the specificity of habituation to different types of motion, with different anatomic patterns of neuronal functional changes (presumably reflecting learning) in the vestibulo-olivo-cerebellar network to different classes of provocative stimuli. Neural structures such as the amygdala as well as areas such as the nucleus tractus solitarius are thought to be important in processes of induction of and habituation to motion sickness (Nakagawa et al., 2003; Pompeiano et al., 2004).

The scope of applications of habituation training is diverse, e.g., to reduce motion sickness produced by short arm rotors intended to provide artificial gravity in future space flight (Young et al., 2003). Research continues to optimize habituation approaches (Cheung and Hofer, 2005; Stroud et al., 2005). On a positive note, although stimulus specificity of motion habituation may be a problem for some people, some generalization of habituation acquired from one type of stimulus to another can be demonstrated. Exposing subjects to visual-vestibular interaction in the laboratory reduces their sensitivity to motion sickness during travel in buses, for example (Dai et al., 2011). Similarly, a controlled trial demonstrated that optokinetic training gave improvements in reducing sea sickness in 71% of those treated versus 12% of controls (Ressiot et al., 2013).

Immediate short-term behavioral counter measures include reducing head movements, aligning the head and body with GIF (Golding et al., 2003; Wada et al., 2012), or lying supine (Golding et al., 1995). Consistent with the general observation that reducing head movements can reduce motion sickness, movement restraint of head, shoulders, hips, and knees reduced motion sickness induced by playing a video game while standing (Chang et al., 2013). However, such protective postures and restriction of movement may be incompatible with task performance under many circumstances. It is usually better to be in active control, i.e., to be the driver or pilot, rather than a passenger (Rolnick and Lubow, 1991), a finding replicated in the laboratory (Golding et al., 2003). Similarly, enhanced perceptions of control and predictability appear to reduce motion-induced nausea (Levine et al., 2014). In a different context, exertion of control reduced motion sickness induced by playing video games on a tablet computer (Stoffregen et al., 2014).

Avoidance of tasks such as reading in a moving vehicle that enhance visuovestibular conflict is often recommended. The importance of this may be gauged by the observation that up to a quarter of co-drivers became motion-sick in rally cars if they were reading a book or sitting in the back seat (Perrin et al., 2013). Stroboscopic illumination protected against motion sickness for backseat military helicopter personnel, perhaps because it reduces retinal slip and visual-vestibular conflicts (Webb et al., 2013). Although galvanic vestibular stimulation (GVS) can cause vertigo and nausea, the opposite effect has been proposed, i.e., that it may provide a novel, modulatory countermeasure for motion sickness. GVS synchronous with the visual field may normalize electrogastrographic and autonomic responses and reduce motion sickness during flight simulation (Cevette et al., 2012). The mechanism perhaps involves reducing visual-vestibular conflicts. Obtaining a stable external horizon reference is helpful (Turner and Griffin, 1999b; Bos et al., 2005). However, although a direct view out of a car window reduced sickness, a real-time video display of the view ahead failed to reduce sickness in rear-seat car passengers (Griffin and Newman, 2004). Standing with a wider stance width and view of the horizon may reduce postural instability and motion sickness at sea (Stoffregen et al., 2013).

Controlled regular breathing has been shown to increase motion tolerance to provocative motion, being approximately half as effective as standard antimotion sickness drugs, yet rapid to implement and free of side-effects. The mechanism by which controlled breathing has its effect is uncertain but may involve activation of the known inhibitory reflex between respiration and vomiting (Yen-Pik-Sang et al., 2003a,b). Supplemental oxygen may be effective for reducing motion sickness in patients during ambulance transport. By contrast, it does not alleviate or prevent motion sickness in individuals who are otherwise healthy. This apparent paradox is explained by the suggestion that supplemental oxygen may work by ameliorating a variety of internal states in ill patients that sensitize for motion sickness, rather than blocking motion sickness directly (Ziavra et al., 2003). Some report acupuncture and acupressure to be effective against motion sickness (Bertalanffy et al., 2004). However, well-controlled trials find no evidence for their value (Bruce et al., 1990; Miller and Muth, 2004). Anecdotally, modification of diet has been said to alter susceptibility to motion sickness. Unfortunately,

the evidence is contradictory; for example, one study suggested that protein-rich meals inhibit motion sickness (Levine et al., 2004), whereas another study drew the opposite conclusion, that any meal of high-protein or dairy foods 3–6 hours prior to flight should be avoided to reduce air sickness susceptibility (Lindseth and Lindseth, 1995).It has been suggested that ginger (main active agent gingerol) acts to calm gastrointestinal feedback (Lien et al., 2003), but conflicting reports of its effect on motion sickness indicate that any such effects are weak (Palatty et al., 2013). For habitual smokers the temporary abstinence and consequent withdrawal from nicotine provide significant protection against motion sickness (Golding et al., 2011). Indeed, this finding may explain why habitual smokers are at reduced risk for PONV, whereas nonsmokers have elevated risk. The other main PONV risk factors are female sex, greater motion sickness susceptibility, and previous episodes of PONV. The unavoidable temporary nicotine withdrawal perioperatively and the consequent increased tolerance to sickness may explain why smokers have reduced risk for PONV (Golding et al., 2011).

Placebo effects can be strong but very variable (Lackner, 2014). Combining positive verbal instructions and placebo can promote reductions in motion sickness (Horing et al., 2013). Providing pleasant (or unpleasant) scents had no effect on motion sickness sensitivity, although the reverse effect occurred, since motion sickness enhanced sensitivity to odors (Paillard et al., 2014). By contrast, another study claimed pleasant odors alleviated motion sickness (Keshavarz et al., 2014). In an unpublished study several years ago the present author used pleasant odors to prevent motion sickness of participants in parabolic flight; at the initial stages of motion sickness some alleviation occurred, but at higher levels of motion sickness the pleasant odor became aversive and exacerbated symptoms. The contradictory nature of such findings suggests that the effect of pleasant odors is likely to be weak and of little practical use as a countermeasure for motion sickness. Listening to pleasant music can reduce motion sickness elicited by cross-coupled motion (Yen-Pik-Sang et al., 2003a), a finding replicated with visually induced motion sickness (Keshavarz and Hecht, 2014).

PHARMACOLOGIC COUNTERMEASURES

The majority of drugs currently used against motion sickness were identified and proven over 40 years ago (Wood and Graybiel, 1969). They may be divided into the categories: antimuscarinics (e.g., scopolamine), H_1 antihistamines (e.g., dimenhydrinate), and sympathomimetics (e.g., amphetamine). Combinations, e.g. scopolamine + dexamphetamine, are highly effective, since both drugs combine their different antimotion sickness properties and their respective side-effects of sedation and stimulation cancel each other out. Commonly used antimotion sickness drugs are shown in Table 27.4. However, these drugs, alone or in combination, are only partially effective. The more recently developed potent antiemetics are not effective against motion sickness, including D_2 dopamine receptor antagonists and 5-HT_3 antagonists used for side-effects of chemotherapy (Levine et al., 2000) or neurokinin NK_1 receptor antagonists (Golding, 2006b). This is probably because their sites of action may be at vagal afferent receptors or the brainstem chemoreceptor trigger zone, whereas antimotion sickness drugs act elsewhere.

All antimotion sickness drugs can produce unwanted side-effects, drowsiness being the most common; promethazine is an example (Cowings and Toscano, 2000). Scopolamine may cause blurred vision in a minority of individuals, especially with repeated dosing. The combination amphetamine + scopolamine (so-called "scopdex") is probably the most effective, with the fewest side-effects, at least for short-term use. This is because both scopolamine and amphetamine have antimotion sickness activity and act through different pathways so they have additive efficacy, while their side-effects of sedation and stimulation cancel each other out. For legal reasons (drug abuse potential) the scopdex combination is no longer available apart from specialized military use. Unfortunately, new atypical stimulants such as modafinil have been shown to be of no use as a replacement for amphetamine in the treatment of motion sickness (Hoyt et al., 2009). Some drugs, such as transdermal scopolamine or the calcium channel antagonist cinnarizine, are significantly less sedating than others (Gordon et al., 2001).

Oral administration must anticipate motion since motion sickness induces gastric stasis, consequently preventing drug absorption by this route (Stewart et al., 2000). Injection overcomes the various problems of slow absorption kinetics and gastric stasis or vomiting. Transdermal delivery offers the advantage of providing protection for up to 72 hours with low constant concentration levels in blood, thus reducing side-effects. The slow onset time (6–8 hours) of transdermal scopolamine can be offset by simultaneous administration of oral scopolamine, enabling protection from 30 minutes or so onwards (Nachum et al., 2001). Unfortunately, there may be variability in absorption via the transdermal route, which alters effectiveness between individuals (Gil et al., 2005). Chewing gum formulations offer the prospect of motion sickness prophylaxis with reduced side-effects compared to tablets, due to a more sustained release (Seibel et al., 2002). Buccal absorption is effective with scopolamine but an even faster route is via nasal

Table 27.4

Common antimotion sickness drugs

Drug	Route	Adult dose	Time of onset	Duration of action (hours)
Scopolamine	Oral	0.3–0.6 mg	30 minutes	4
Scopolamine	Injection	0.1–0.2 mg	15 minutes	4
Scopolamine	Transdermal patch	One	6–8 hours	72
Promethazine	Oral	25–50 mg	2 hours	15
Promethazine	Injection	25 mg	15 minutes	15
Promethazine	Suppository	25 mg	1 hour	15
Dimenhydrinate	Oral	50–100 mg	2 hours	8
Dimenhydrinate	Injection	50 mg	15 minutes	8
Cyclizine	Oral	50 mg	2 hours	6
Cyclizine	Injection	50 mg	15 minutes	6
Meclizine	Oral	25–50 mg	2 hours	8
Buclizine	Oral	50 mg	1 hour	6
Cinnarizine	Oral	15–30 mg	4 hours	8

Adapted from Benson (2002).

scopolamine spray. Although not yet available for routine use, with higher (alkaline) pH-buffered formulations to promote absorption, peak blood levels may be achieved in 9 minutes (Ahmed et al., 2000), and this route has been shown to be effective against motion sickness (Simmons et al., 2010).

Research into new antimotion sickness drugs includes re-examination of old drugs such as phenytoin, as well as the development of new agents. The range is wide, including phenytoin, betahistine, chlorpheniramine, cetirizine, fexofenadine, benzodiazepines, and barbiturates, the antipsychotic droperidol, corticosteroids such as dexamethasone, tamoxifen, opioids such as the μ-opiate receptor agonist loperamide, neurokinin NK_1 receptor antagonists, vasopressin V_{1a} receptor antagonists, *N*-methyl-D-aspartate antagonists, 3-hydroxypyridine derivatives, 5-HT_{1a} receptor agonists such as the antimigraine triptan rizatriptan, selective muscarinic M_3/m5 receptor antagonists such as zamifenacin and darifenacin (for review, see Golding, 2006b). So far, none of these drugs has proven to be of any major advantage over those currently available for motion sickness (Golding, 2006b). The reasons are various and include relative lack of efficacy, complex and variable pharmacokinetics, or in those that are effective, unacceptable side-effects. A possible candidate for an effective antimotion sickness drug with fewer side-effects might be a selective antagonist for the m5 muscarinic receptor (Golding and Stott, 1997b).

Future development of drugs with highly selective affinities to receptor subtypes relevant to smotion sickness should aim to produce an antimotion sickness drug of high efficacy and with few side-effects. The elucidation of neurophysiologic mechanisms and pharmacologic mapping of brain regions and pathways associated with motion sickness may provide the grounds for the rational development of more effective medication in the future.

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Chapter 28

Mal de débarquement syndrome

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Abstract

Mal de débarquement syndrome (MdDS) is typified by a prolonged rocking sensation – for a month or longer – that begins immediately following a lengthy exposure to motion. The provoking motion is usually a sea voyage. About 80% of MdDS sufferers are women, and most of them are middle-aged. MdDS patients are troubled by more migraine headaches than controls. Unlike dizziness caused by vestibular disorders or motion sickness, the symptoms of MdDS usually improve with re-exposure to motion. The long duration of symptoms – a month or more – distinguishes MdDS from land-sickness. Treatment of MdDS with common vestibular suppressants is nearly always ineffective. Benzodiazepines can be helpful, but their usefulness is limited by the potential for addiction. Studies are ongoing regarding treatment with visual habituation and transcranial magnetic stimulation.

Mal de débarquement syndrome (MdDS), literally, "bad disembarkment," refers to prolonged and inappropriate sensations of movement after exposure to motion. The syndrome typically follows a lengthy sea voyage (Brown and Baloh, 1987), but it has also been observed following extended airplane travel, train travel, and space flight (Stott, 1990). Symptoms include rocking, swaying, and imbalance. MdDS is distinguished from ordinary motion sickness, seasickness (*mal de mer*), and sometimes from "land-sickness" by persistence of symptoms for a month or longer. Also, unlike disorders of the inner ear and seasickness, most individuals with MdDS report that their symptoms improve with re-exposure to motion, such as driving a motor vehicle (Hain et al., 1999; Cha et al., 2008).

A typical case history is as follows: a 50-year-old woman went on an ocean cruise. She developed motion sickness on the cruise, which responded to transdermal scopolamine. Immediately after returning from the cruise and getting on to solid ground, she developed imbalance and a rocking sensation, accompanied by fatigue and difficulty concentrating. Her description was: "Imagine feeling like you are on rough seas 24 hours a day, 7 days a week." This sensation persisted for several months.

A meta-analysis of MdDS was recently published by Van Ombergen and associates (2015). MdDS is a disorder that mainly affects middle-aged women. The proportion of males affected by MdDS varies between 0 and 25% (Van Ombergen et al., 2015). Symptoms last at least 1 month (in most studies) and usually abate before 6 months have elapsed. However, symptoms can persist for years, as well as recur after periods of remission. MdDS patients are often very distressed by their symptoms (Arroll et al., 2014) and also are troubled by more migraine headaches than controls (Cha and Cui, 2013).

Between 41% and 73% of persons disembarking from seagoing voyages experience unsteadiness (Gordon et al., 1995, 2000; Cohen, 1996). This is commonly called land-sickness. Land-sickness typically persists for 2 days or less. Some authors use an alternative term for land-sickness – "transient *mal de débarquement*," defining the transient syndrome as symptoms lasting less than 48 hours (Van Ombergen et al., 2015). We prefer the more common term.

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Table 28.1

Features distinguishing *mal de débarquement* syndrome from land-sickness

	Mal de débarquement syndrome	Land-sickness
Duration	1 or more months, can last for years	2 days maximum
Gender	About 80% female	Equal distribution
Motion-sick on boat	No	Yes
Relieved by driving	Yes	No

Table 28.1 lists the features that distinguish MdDS from land-sickness. Persons with land-sickness are also likely to have seasickness (Gordon et al., 1995), while persons with MdDS generally are untroubled by seasickness. Males and females do not appear to differ significantly in the incidence, intensity, or duration of land-sickness symptoms (Cohen, 1996). Land-sickness, confusingly, is also termed "*mal de débarquement*," without the transient qualifier, by some authors.

MdDS also has similarities to motion sickness or seasickness (*mal de mer*). However, MdDS is easily distinguished from motion sickness, as motion sickness starts during motion rather than after motion as does MdDS, by the shorter duration of motion sickness, and because motion sickness often provokes nausea and vomiting, while MdDS generally does not. Most persons with MdDS have relief of rocking symptoms when in motion, such as driving a car, but experience recurrence of rocking once motion has stopped (Hain et al., 1999; Cha et al., 2008). In motion sickness, many persons find driving, entailing more motion, very difficult. This is also often true for persons with vestibular disorders.

MdDS also overlaps with a little-studied group of patients with rocking sensations, who develop similar symptoms to MdDS, without a preceding motion exposure (Cha and Cui, 2013). Often these patients develop head or trunk rocking. In our clinical experience, the age, gender, and pattern of medication responsiveness of this group are similar to those of MdDS.

CAUSE OF MdDS: PERSISTENT ADAPTATION TO SWAYING ENVIRONMENTS?

MdDS syndrome does not have the features of a "pathologic" disease, in the sense that it does not follow an injury and is not associated with structural damage to the inner ear or a blood chemistry abnormality. Rather, it is provoked by exposure to motion that does not trouble most individuals. While on the boat, the brain must adjust leg and body motion so that they counter the rhythmic pattern of shipboard motion. Adaptation to such movement is sometimes called "gaining sea legs." A common explanation for MdDS is that persons with MdDS are good at adapting to unusual motion situations, such as ocean travel, but slow to give up their adaptation when they return to stable ground (Mair, 1996). This is a reasonable general suggestion, but it lacks specifics.

Let us consider the visual, somatosensory, and vestibular consequences of boat motion in the anterior–posterior plane, and how the brain might develop adaptive "rules" to handle them. Traveling on a boat exposes a person to angular and linear movement, some of which is predictable and some of which is not. For small rotations of the boat under the person, there is no vestibular consequence, as bodily inertia tends to keep the person upright in space. Vision is accurate on the deck but inaccurate inside. Although there is rotation around the ankle joint, and thus somatosensory input, there should be no "righting" response from the person because the body is upright in space. As vision is unreliable, a "rule" about using visual cues cannot be made. The rule then for pitch rotation of the boat is that one should ignore somatosensory information signaling rotation. Thus, for pitch of the boat, a selective "down-weighting" of somatosensory information, or both somatosensory and visual information, according to context, would be reasonable.

For linear acceleration of the boat under the person, or "surge," as it is called in nautical contexts, inertia tends to keep the person still in space, but because of shear force at the feet, the person rotates at the ankles and becomes destabilized. Then vision, vestibular and somatic senses are activated by the bodily rotation with respect to the boat, and an active response is needed to prevent a fall. Thus, for surge of the boat, no relative sensory down-weighting would be appropriate, but increased responses to all types of input might be helpful.

As different weightings would be useful for different types of boat motion, no single weighting rule would be optimal. A potential solution that also explains persistent symptoms is that in MdDS there is prediction of boat motion through an internal model of boat motion – an internal oscillator. By using prediction, one can determine the best rule to follow – one should ignore (down-weight) ankle and visual inputs that are entrained with boat rocking, but attend to or perhaps up-weight sensory input that is uncorrelated with boat rocking.

With respect to the hypothesis that MdDS is caused by persistent reweighting of visual, vestibular, or somatosensory input, the data so far are contradictory. Furthermore, the data are largely based on studies of the more

abundant subject groups having land-sickness (largely sailors), but that have almost no overlap with the usual demographic characteristics of the MdDS population (i.e., middle-aged women).

Nachum and associates (2004) used posturography to study young males aged 18–22 with motion sickness and land-sickness (they considered land-sickness to be equivalent to *mal de débarquement*). They reported that these young men developed increased reliance on somatosensory input after motion exposure, and reduced weighting of vision and vestibular input. While the accuracy of visual input depends on whether one is inside the boat or on the deck, semicircular canal input is accurate on boats, and somatosensory input is intermittently accurate. Accordingly, it is difficult to understand a rationale for this adaptation. Another study, that of Stoffregen and associates (2013), also miscategorized land-sickness as MdDS and also studied a population with almost no overlap with the MdDS patients reported in the medical literature.

A more reasonable possibility than increased reliance on somatosensory input is that individuals with MdDS may develop an increased reliance on visual and vestibular information. This occurs in normal subjects who are exposed to situations where somatosensory feedback is distorted (Peterka, 2002), and would also be a reasonable adaptation to boat pitch. Either adaptation might result in inaccurate land sensorimotor integration. Nevertheless, neither of these adaptations explains the rocking sensation of MdDS or the characteristic improvement when driving a car.

In an attempt to explain the prolonged duration of MdDS and the characteristic improvement with driving, in 2007 we first proposed that MdDS might be explained by internal model theory. In particular, an internal model of periodic boat motion – an internal oscillator that is entrained by boat motion – might allow one to select out salient sensory input (boat surge) and ignore the non-salient input (boat pitch) (Hain, 2007). Cha (2015) recently offered a similar theory involving "intrinsic brain networks driven by oscillatory motion exposure." In support of this idea, some animals exhibit persistent oscillations in central neurons after periodic movement ends (Barmack and Shojaku, 1992). Also, postmovement illusions of rocking can be induced by sinusoidal rotation in some individuals (Lewis, 2004). Such an internal oscillator might be activated and produce a persistent rocking sensation because of noise related to activities of daily life, even when there is no ongoing periodic motion.

Moeller and Lempert (2007) proposed that MdDS might be due to "pseudo-hallucinations from vestibular memory," similar to the Charles Bonnet syndrome that afflicts some persons with severe visual loss. They also suggested that MdDS might be a secondary complication involving anxiety and focused attention on symptoms. While possible in some cases, these ideas do not provide an explanation for the age and female gender distribution of MdDS.

The most recent mechanistic proposition for MdDS is that of Dai and associates (2014). They proposed that MdDS was caused by maladaptation of the vestibulo-ocular reflex (VOR) to roll of the head during rotation, and reported that a 5-day-long protocol attempting to readapt the VOR resulted in "substantial recovery on average for approximately 1 year" of 17 of 24 subjects (Dai et al., 2014). While these results are encouraging, this theory does not explain why patients with MdDS are better while driving. Furthermore, it is difficult to see why ordinary movement through the environment should not recalibrate the VOR over a few days – the usual upper limit for the duration of land-sickness. At the time of writing (2015), the roll adaptation theory and treatment protocol need more study.

TREATMENT OF MdDS

The usual clinical treatment strategy for MdDS is to attempt to make the patient comfortable, while waiting for the MdDS to end by itself (typically within 6 months). Conventional vestibular suppressants that affect anticholinergic pathways, such as meclizine and transdermal scopolamine, are not helpful in MdDS (Hain et al., 1999). Benzodiazepines, such as clonazepam, are of the most benefit (Hain et al., 1999; Cha, 2012), but risk of addiction limits their use. Selective serotonin reuptake inhibitor-type antidepressants are also suggested as being potentially helpful (Cha, 2012). There are also reports of good responses to gabapentin, amitriptyline, and venlafaxine – all medications that are also helpful in migraine.

After 6 months have gone by, if the MdDS patient is no better, there is more pressure to find another intervention. While vestibular physical therapy would seem reasonable, Cha (2012) commented that "only rare patients seem to be cured by vestibular therapy." In fact, the only peer-reviewed literature describing physical therapy treatment for MdDS are two case reports (Zimbelman and Watson, 1992; Liphart, 2015). Of course, it is not known how these cases would have done without intervention. In general, while many individuals with MdDS undergo vestibular rehabilitation, again because of a lack of controls, it is not possible to determine whether they did any better than persons who were not treated (Hain et al., 1999). Thus the efficacy of vestibular rehabilitation for MdDS is unknown.

Motion sickness has been treated successfully with habituation (Dai et al., 2011) and one might reasonably

argue that, if MdDS is a motion sickness variant, it might also respond to a similar approach. Habituation entails a down-weighting of motion input, and can reduce the long-duration vestibular responses commonly associated with motion sickness susceptibility (Dai et al., 2007). Dai and associates (2014) reported that rolling the head from side to side while watching a rotating full-field visual stimulus was a successful treatment in 17 of 24 MdDS subjects.

Although there are well-developed self-directed motion habituation protocols such as the Puma exercises (Puma, 2010), there are presently no reports of their efficacy in MdDS. In as much as patients with MdDS initially became ill after repetitive motion exposure, it is also reasonable to conjecture that more motion exposure, as is required for habituation, might worsen MdDS.

Repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex was reported by Cha et al. (2013) to be associated with short-term symptom improvement in a pilot study, as well as helpful in more recent studies (Guofa et al., 2014; Pearce et al., 2015). More study is needed of this treatment modality for MdDS. In particular, a treatment protocol that accomplishes long-term improvement in this disorder that lasts months to years is crucial.

If MdDS is caused by an internal oscillator developed to predict boat motion or psychologic mechanisms rather than cross-axis VOR adaptation, as suggested by Dai and associates (2014), or inappropriate sensory weighting, as suggested by many others, one's treatment strategy should reasonably be aimed at manipulation of psychologic variables. Patients need to ignore their aberrant internal signal, in the same way that most persons with tinnitus eventually develop an ability to ignore abnormal internally generated sounds. Treatments that decrease vigilance, obsessiveness, and anxiety, as well as "tincture of time," would be the optimum strategy. If this conjecture is correct, as is the case with tinnitus, therapy that focuses attention on the rocking sensation could even be counterproductive.

To summarize, MdDS is an uncommon disorder in which individuals, mainly middle-aged women, develop a prolonged, inappropriate illusion of rocking motion, paradoxically relieved by actual motion such as driving. The rare entity of MdDS differs from the common entity of land-sickness, primarily in that MdDS must last at least a month to be diagnosed. Treatments of MdDS that reduce anxiety (such as benzodiazepine medication) and medications effective for migraine are currently the best established treatments of MdDS. There are recent reports of successful treatment of MdDS using transcranial magnetic stimulation and habituation. The visual stimulus-based habituation treatment as developed by Dai and associates (2014) is especially promising.

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