NEUROLOGY OF BODY SYSTEMS

The inner ear and the neurologist

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Inner ear disorders are common and patients with vestibular failure often present to a neurology clinic because of their dizziness, gait unsteadiness and oscillopsia. Vestibular disorders can be divided into peripheral and central vestibular disorders. Most of the peripheral vestibular disorders have a clinical diagnosis, and a thorough history and examination will often provide a clear direction as to the diagnosis. Correct diagnosis allows treatment for many of the peripheral and central vestibular disorders. As inner ear damage is generally irreversible, early diagnosis allowing prompt treatment is important. The aim of this review is to discuss some audiovestibular conditions that may well appear in a neurology clinic, and to discuss some recent advances within the audiovestibular field that may be of interest to neurologists. Some of the most common audiovestibular conditions will be discussed along side more uncommon conditions.

Hearing loss is the most common sensory impairment in humans, affecting >5% of individuals in industrialised nations. It is an important health problem in the elderly, and 40% of the population aged >65 years have a hearing loss great enough to impair communication.[1 2] In addition, a third of the general population report vestibular symptoms.[3] Hearing loss often prompts patients to present to ear, nose and throat, or audiological medicine departments. However, patients with isolated vestibular failure are often seen by a neurologist because of their dizziness, gait unsteadiness and oscillopsia without any hearing symptoms. Accordingly, the focus of this review is on vestibular disorders. The aim is to discuss some audiovestibular conditions that may well appear in a neurology clinic, and to discuss some recent advances within the audiovestibular field that may be of general interest to neurologists. Accordingly, some of the most common audiovestibular conditions will be discussed alongside more uncommon conditions. In addition, commonly used neurological drugs that may cause audiovestibular disorders are enumerated.

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ANATOMY

The inner ear is a minute, complex, fluid-filled structure surrounded by a bony labyrinth and located deep in the temporal bone. The cochlea corresponds to the acoustic end organ, and the vestibular end organs consist of the three semicircular canals with their ampullary tissue, the saccule and the utricle. The endolymphatic sac, also part of the inner ear, is thought to be involved in the fluid regulation of the inner ear. Table 1 gives the recommended websites for those readers wishing to refresh their knowledge of inner ear anatomy.

GENERAL SYMPTOMATOLOGY OF VESTIBULAR DISORDERS

Dizziness may be caused by several recognised medical conditions and psychiatric disorders, but 13% of cases remain idiopathic.[4] Vestibular disorders can be divided into peripheral and central vestibular disorders. Most of the peripheral vestibular disorders have a clinical diagnosis, and the history is therefore extremely important when attempting to diagnose the cause of vertigo. Accordingly, a clear history might provide information that can distinguish between various peripheral and central aetiologies.

Acute peripheral vestibular dysfunction often presents with sudden, unprecipitated, severe vertigo with a subjective sensation of rotation. A typical clinical finding with unilateral loss of vestibular function is horizontal–torsional nystagmus with the fast phase directed away from the affected side. Acute peripheral vestibular dysfunction is often associated with nausea, vomiting, sweating and pallor. If the auditory part of the inner ear is also affected, patients may present with an additional hearing loss and/or tinnitus. Most peripheral vestibular disorders resolve in about 6–12 weeks, due to the effect of a number of different complex mechanisms collectively called vestibular compensation. These involve brain stem, cerebellar, cortical and spinal functions.[5 6] This symptomatic improvement does not parallel recovery of vestibular function, and accordingly the vestibular functional loss is often irreversible. In some patients, especially the elderly and those with central nervous system (CNS) disorders, the vestibular compensation may not be as effective, leading to chronic peripheral vestibular dysfunction or recurring symptoms (ie, decompensation). In chronic peripheral vestibular dysfunction, vertigo is often less severe and of shorter duration than the acute symptoms that accompany a unilateral sudden vestibular loss. These patients may present with recurrent episodes of vertigo and/or a persistent sensation of imbalance. Floating, rocking and disorientation are other frequent illusions. The most common causes of decompensation are psychological disorders, impairment of vision and/or proprioception,

Abbreviations: ABI, auditory brain stem implant; BAHA, bone-anchored hearing aid; BPPV, benign paroxysmal positional vertigo; CNS, central nervous system; NF2, neurofibromatosis type II; NOS, nitric oxide synthase; OME, otitis media with middle ear effusion

Table 1 Useful audiovestibular websites

Subject	Website
Inner ear anatomy/histology	http://www.iurc.montp.inserm.fr/cric/audition/english http://www.siumed.edu/~dking2/ssb/ear.htm
Dizziness, imbalance and hearing disorders; educational information and practical support materials	http://www.dizziness-and-balance.com
Genetic inner ear disorders	http://ghr.nlm.nih.gov/ghr/page/Home
Auditory rehabilitation	http://www.emedicine.com/ent/topic479.htm

comorbid systemic disorders and the use of drugs acting on the CNS.[5]

Psychological factors may aggravate vestibular symptoms and delay or even prevent recovery, resulting in chronic peripheral vestibular dysfunction. No correlation between pathological psychometric parameters and degree of vestibular disorder has been shown. Accordingly, patients with Menière's disease and vestibular migraine, with no vestibular deficits, have been shown to have a higher psychiatric comorbidity than patients with vestibular deficits associated with benign paroxysmal positional vertigo (BPPV) or vestibular neuritis.[7] Panic episodes and other anxiety disorders have been described in association with vertigo, and in some patients, vestibular dysfunction might have an important role in the aetiology of these disorders.[8] Cognitive behavioural therapy has recently been used to treat patients with peripheral vestibular dysfunction.[9 10] However, currently there are no prospective studies that give clear evidence that patients with peripheral vestibular dysfunction and associated anxiety/panic disorders benefit from cognitive behavioural therapy.

Central vestibular dysfunction is often associated with other neurological symptoms and tends to be more insidious and protracted than peripheral vestibular disorders.[11] When vertigo is the only symptom, the differential diagnosis between central and peripheral disorders becomes problematic. A general rule is that a history of subjective motion is characteristic of peripheral disorders. The conditions that often produce central vestibular dysfunction include space-occupying lesions in the posterior fossa, multiple sclerosis, and brain stem or cerebral infarction. Episodic vertigo can be the initial symptom of brain stem or cerebellar stroke, and, accordingly, small infarcts in these areas may present with vertigo and ataxia without other localising symptoms.[12]

AUDIOVESTIBULAR PATHOLOGIES: CLINICAL VARIATIONS

Associated middle ear disorder

Middle ear disorder (eg otitis media with middle ear effusion (OME) and chronic suppurative otitis media) is a common cause of audiovestibular dysfunction. The presence of an auditory abnormality indicates a peripheral rather than central cause for vestibular symptoms. It is therefore extremely important to consider the significance of prevalence or history of middle ear disease and its treatment by ear surgery in patients presenting with vestibular symptoms.

OME (glue ear) is considered to be the most frequent cause of vestibular disturbance in children.[13 14] OME is very common in healthy children between infancy and 5 years, with a prevalence of around 15–40% and a peak incidence during the winter months. In addition to a conductive hearing loss, 33–50% of children have been shown to have abnormal vestibular tests. After drainage of the effusion by myringotomy and insertion of a ventilation tube (grommet), vestibular symptoms have been shown to improve and test results to return to normal. However, a relatively recent study by Casselbrandt *et al*[15] found persistent disturbed balance in a cohort of 4-year-old children who had had documented otitis media in the past but had no middle-ear effusion at the time of testing. The authors suggested that a history of otitis media may result in a longer-term balance dysfunction.

Acquired cholesteatoma is a chronic suppurative, middle ear inflammatory disease, most commonly secondary to chronic otitis media. The chronic inflammation associated with accumulation of keratin causes progressive destruction, and may erode the ossicular chain and subjacent bone with consequent hearing loss, vestibular dysfunction and facial paralysis. Seen as a pearly grey/yellow rounded mass or sometimes obscured from view by an attic crust composed of wax and epithelium, the acquired cholesteatoma is usually situated within a retraction pocket in the posterior–superior part of the middle ear. However, cholesteatoma may also be congenital, developing at a number of sites in the temporal bone where epithelium can be sequestrated during development. These cholesteatomas are often located in the supragenticulate region of the middle ear or at the tympanic ring adjacent to the osteum of the eustachian tube. As these patients have intact tympanic membranes, the presence of cholesteatomas can be discerned only when there is a whitish rounded mass visible deep to the tympanic membrane anteriorly or anterosuperiorly. Other congenital cholesteatomas develop in the petrous apex close to the internal carotid artery, where they grow undetectable by otoscopy, slowly destroying the cochlea, labyrinth and facial nerve.

Conductive hearing loss and intermittent discharge are the most common presenting symptoms with cholesteatoma. The presence of vertigo and facial palsy indicates erosion, and those patients require surgical attention. Untreated cholesteatoma may cause life-threatening intracranial complications such as, meningitis, sinus thrombosis and brain abscess. Surgical management involves radical removal of inflammatory tissue and, if possible, reconstruction of the sound-conducting apparatus. Note that this condition is often overlooked and continues to present late with facial palsy and brain abscess.

Recurrent episodes of vertigo with or without hearing loss

Some of the most common vestibular disorders present with recurrent episodes of vertigo (eg, BPPV, migraine-associated vertigo and Menière's disease).

BPPV is characterised by the sudden onset of brief episodes of severe vertigo, lasting a few seconds to minutes, without associated auditory symptoms. Vertigo is typically triggered by head position—that is, lying down/turning in bed, bending over and neck extension. Posterior canal BPPV is the commonest (85.2%), followed by horizontal canal BPPV (13.6%).[16]

BPPV may be idiopathic, but is also often a sequel to head trauma and other vestibular disorders such as, Menière's disease and vestibular neuritis.[17–19] The diagnosis of BPPV is easily made using the Dix–Hallpike manoeuvre, and the nystagmus seen typically shows latency, fatigability and adapts. The associated provoked nystagmus with posterior canal BPPV

is geotropic, torsional and towards the undermost ear when this is the affected ear. The vertigo with BPPV is commonly violent and patients are often very anxious and not particularly keen to have their symptoms provoked with a Dix–Hallpike manoeuvre.

Although BPPV is usually a self-limiting disorder, treatment with particle-repositioning manoeuvres (eg, the Semont and Epley manoeuvres) should always be considered. Both have been shown to be effective in 80–99% of patients with posterior BPPV.[20 21] The rationale behind the particle-repositioning manoeuvres is based on the assumption that canalolithiasis is the underlying pathophysiological mechanism. This theory proposes that debris from the otolith organ appears as free-floating in the canal, moving together with the endolymph.[22 23] Movement of the free-floating debris has the same effect as a plunger within the narrow canal, causing displacement of the cupula away from the ampulla, initiating a nystagmic response beating in the plane of the affected canal. With these particle-repositioning manoeuvres, the debris is thought to be cleared from the posterior semicircular canal and moved into the utricle. However, BPPV has a high rate of recurrence, and in approximately 50% of patients, symptoms will recur within 40 months after treatment.[20]

Occasionally, positional vertigo and nystagmus occurs with anterior canalolithiasis with downbeating nystagmus induced when either ear is dependent.[24] The rarity of this disorder could be due to spontaneous clearing of debris in the anterior canal in the upright position. Repositioning is not usually effective. This may be explained by the narrowness of the canal or cupulolithisasis (ie, adherence of the debris to the cupula). A similar explanation may account for the failure of some patients with posterior canal BPPV to respond to treatment. More often, downbeating nystagmus is due to central lesions in the cerebellum or brain stem. Typically, central nystagmus shows no fatigue, does not adapt, and there is often surprisingly little vertigo, given the magnitude of the induced nystagmus.[25]

Dizziness is a frequent complication of head injury, reported in 25–90% of cases, and BPPV is the most common complication seen, with an incidence of around 60%.[18] In addition, as many as 70% of patients with dizziness after a head injury have been shown to have semicircular canal dysfunction.[18] In minor head injury, the vestibular dysfunction is thought to be due to labyrinthine concussion. The pathophysiological mechanism of labyrinthine concussion is not fully understood, but intralabyrinthine haemorrhage and disturbed microcirculation of the inner ear have been suggested.[26–28] In more severe head injury, the type of dysfunction depends on the presence and type of any temporal bone fracture; longitudinal fractures commonly involve the middle ear, whereas transverse fractures damage the labyrinth and/or the eighth nerve, and usually cause complete loss of hearing and balance function on the side of the injury. When the incidence of vestibular abnormalities is compared with severity of head injury, the incidence stays constant. Accordingly, the peripheral vestibular system seems to be vulnerable to head trauma, and isolated vestibular loss without simultaneous hearing loss or temporal bone fractures often occurs. One possible explanation for this is the lower compliance of the peripheral vestibular system, owing to the vestibular end organs being firmly attached to the walls of the bony labyrinth and not buffered by a separate fluid compartment as in the cochlea.

Migraine is a common cause of vertigo, both in the adult and the paediatric populations, with migraine-associated vertigo accounting for at least 7% of patients in specialised dizziness clinics.[29] Diagnostic criteria for migraine-associated vertigo have been suggested by Neuhauser *et al*[29] and include: (1) episodic vestibular symptoms of at least moderate severity; (2) migraine according to the International Headache Society criteria (2004); (3) at least two of the following migrainous symptoms during at least two vertiginous episodes: migrainous headache, photophobia, phonophobia, visual or other aurae; and (4) other causes ruled out by appropriate investigations.[29 30] Accordingly, the vertigo episodes can occur during the headache, but most often they appear during a headache-free interval.[31] In addition, patients with migraine often report sensitivity to motion, with car sickness as a child and motion sickness as an adult.

It is not known whether the origin of the vertiginous symptoms associated with migraine is in the central or in the peripheral vestibular system.[31] Clinical findings in 20 patients with acute migrainous vertigo have recently been published.[32] Hearing was not affected in any of these patients. Interestingly, pathological nystagmus was observed in 70% of patients during an acute migrainous vertigo episode. Isolated spontaneous nystagmus in the primary position of gaze with the patient upright, isolated positional nystagmus changing direction or changing slow-phase velocity when the patient was brought from an upright to a horizontal position, and a combination of both were seen. The clinical findings during the acute migrainous vertigo indicated central disorder in 50% of patients, peripheral disorder in 15%, and in 35% the site of involvement could not be determined with certainty. In the three patients with definite peripheral disorder, the head-thrust test showed a deficit of the vestibulo-ocular reflex contralateral to the direction of nystagmus. Accordingly, migraine-associated vertigo seems to be a heterogenous vestibular disorder, and the spectrum of vestibular symptoms indicates that various pathophysiological mechanisms may be involved.

Another common peripheral cause of recurrent vertigo is Menière's disease, with an incidence between 1 and 2 cases per 10 000 per year.[33 34] Here, patients present with longer periods of vertigo, lasting at least 20 min, but more usually for hours. The accompanying auditory symptoms—that is, aural fullness, tinnitus and hearing loss—are pathognomonic. Documented hearing loss, which may fluctuate and mainly affects low frequencies, is a prerequisite for diagnosis. Menière's disease is often initially unilateral, but involvement of the contralateral ear is seen in approximately 30–60% of cases. The diagnosis is clinical and should be based on the strict diagnostic criteria defined by the American Academy of Ophthalmology and Otolaryngology.[35] The underlying pathophysiology is widely accepted to be endolymphatic hydrops.

The treatment of Menière's disease—that is, a strict low-salt diet combined with diuretics (bendrofluazide 2.5–10 mg once daily)—is effective in most patients. When conservative treatment fails in a patient with incapacitating vertigo, intratympanic gentamicin injection or surgical intervention (eg, vestibular neurectomy and labyrinthectomy) may be considered for some bilateral cases. These more invasive treatments are still under discussion, and double-blind randomised studies are needed to establish an evidence base to allow informed decisions. There is at present no general consensus on the optimum concentration and temporal sequence of intratympanic gentamicin instillations. However, in a recent prospective uncontrolled study on 57 patients with Menière's disease, vertigo episodes were completely controlled in 95%.[36] In this study, each instillation consisted of 12 mg of gentamicin, and 53% of patients needed only one instillation to obtain complete vertigo control. To enable better monitoring of delayed ototoxic effects, treatment intervals of 7 days have been suggested. More frequent treatment has been shown to result in hearing loss. Intratympanic injection of dexamethasone has been used in patients with Menière's disease (doses around 2.4–8 mg, varying temporal sequence), with a reported alleviation of vertigo in 54.5–82% of patients.[37 38]

Vestibular neurectomy offers a solution for those patients with incapacitating vestibular symptoms combined with some remaining useful hearing, but is not without risks to hearing or facial nerve function. An interesting study from Kerr and Toner[39] showed that remission can be induced in 50% of patients with Menière's disease by non-specific interventions, such as describing surgical options and placing the patient on a waiting list for vestibular neurectomy. When these patients were reviewed 6–8 weeks later, 13 of the 23 experienced dramatic/full recovery and surgery could be avoided. Similarly, a third to half of patients experienced at least temporary remission after ''threatening with intratympanic gentamicin injection''.[40] Publications like these put the surgical treatment options in a different light and keep the debate alive.

Familial progressive cochleovestibular impairment with Menière's-like symptoms has been shown, with a point mutation in the COCH gene.[41] Cases often present at around 40–60 years of age, with the onset of progressive sensorineural hearing loss and episodes of vertigo, tinnitus and aural fullness. Bilateral vestibular failure has been reported to appear from middle age onwards. The vestibular dysfunction can have complete or reduced penetrance. Interestingly, histopathological examination of cases has shown endolymphatic hydrops, the characteristic of Menière's disease.[42]

Although not a disorder of the inner ear, neurofibromatosis type II (NF2) may present with hearing loss (which can be of sudden onset), tinnitus and recurrent episodes of vertigo. It is characterised by the development of multiple tumours of the brain, spinal cord and peripheral nerves, and, accordingly, additional associated neurological symptoms are common. NF2, with a symptomatic prevalence of 1/210 000, presents both sporadically and as an autosomal dominant inherited familial disorder. The disease has a variable presentation, with a severe subtype having an early and rapid progression and a milder type with later onset and less aggressive course. Bilateral vestibular Schwannomas occur in about 85–90% of NF2 cases and are associated with bilateral deafness. Most of the vestibular Schwannomas derive from the internal auditory canal, and therefore the main symptoms are caused by the tumour compressing the vestibulocochlear nerve. Continued growth of the tumour causes brain stem compression with deficits of adjacent cranial nerves. When vestibular disorder is combined with the motor and sensory deficits caused by additional spinal lesions, the overall handicap is increased considerably. Management guidelines have been published, and all patients with NF2 should be seen in multidisciplinary clinics that are located in major skull base centres and can provide the required expertise.[43] Interference with the internal acoustic artery may lead to impairment of inner ear function and account for occasional patients with acute hearing loss.

Von Hippel–Lindau disease, a genetic disorder of an oxygen-sensing growth factor, is often associated with endolymphatic duct carcinoma. This can result in abnormalities of endolymphatic sac dynamics, causing audiovestibular disturbances. However, these are not well characterised.[44] Many other genetic neurological disorders can be associated with hearing and/or vestibular functional loss—that is, the syndromic audiovestibular diseases. In most, the site of the audiovestibular disturbance is unknown, but in some it is primarily in the end organ. Examples include Fabry's disease, xeroderma pigmentosa, some types of Charcot–Marie–Tooth disease and certain hereditary sensory neuropathies.[45–50] Pathological examination of the end organ is rarely undertaken, and the evidence for a peripheral disorder depends on physiological tests.

Immune-mediated inner ear disorders (including all inner ear disorders with an immune-mediated cause) are the chameleons of inner ear disorders, with a very variable clinical presentation. The audiovestibular dysfunction is typically progressive, over a period of weeks to months, and is often bilateral and asymmetrical.[51] Some of these patients may present with symptoms similar to those of Menière's disease, but differing in that immune-mediated inner ear disorders often affect both ears simultaneously. In addition, sudden deafness and sudden vestibular loss have been reported. The pathogenesis of immune-mediated inner ear disorders remains unknown, although mechanisms involving autoantibodies, autoreactive T cells, immune complex deposition and vasculitis have been suggested.[52 53]

Around one third of patients with immune-mediated inner ear disorders have associated systemic autoimmune disease (eg, systemic lupus erythematosus, Behçet's disease, Sjögren's syndrome, Wegener's granulomatosis, Hashimoto's thyroiditis, Cogan's syndrome and anti-phospholipid/anti-cardiolipin syndrome).[54]

A relatively high prevalence of audiovestibular dysfunction has been reported with some of these systemic immune-mediated disorders, but such abnormality is certainly often overlooked. Accordingly, audiovestibular involvement is a common clinical presentation with Behçet's disease, with a reported incidence of 22–80%. The otological manifestations described with systemic autoimmune disorders include chronic otitis media and sudden/progressive audiovestibular dysfunction which can be of end-organ origin. Note that some of these systemic autoimmune diseases may first present with audiovestibular symptoms.

The diagnosis of immune-mediated inner ear disorders is arbitrary, and is ascertained by the history, clinical findings, an immunological evaluation of the patient's serum and response to immunosuppressive drugs.[55] However, early diagnosis is important, as this is one of few treatable inner ear disorders and, with prompt treatment, may respond well to immunosuppression.

Recurrent episodes of vertigo induced by changes in intracranial or middle ear pressure

Recurrent episodes of vertigo and oscillopsia, induced by stimuli that produce changes in intracranial or middle ear pressure (eg, coughing or loud noises), are associated with a defect in the labyrinthine canal causing a third mobile window in the labyrinth. This appears with superior canal dehiscence syndrome and perilymphatic fistula.[56] Superior canal dehiscence syndrome has been recognised relatively recently, and these patients often have a hypersensitivity to bone-conducted sounds and have a mild low-frequency hearing loss. The enhanced conductive hearing is analogous to the hearing mechanism of submarine mammals (Cetaceae). The Weber-tuning fork test typically shows lateralisation to the affected ear, and patients may also be able to hear a tuning fork placed on the lateral malleolus of the foot. Other unusual symptoms are of hearing their own eye movements or their pulse. Superior canal dehiscence syndrome is caused by a defect of bone overlying the superior (anterior) semicircular canal, enabling changes in intracranial pressure to be pathologically transduced to the superior semicircular canal. Loud sounds applied to the symptomatic ear result in torsional nystagmus appropriate for stimulation of the superior semicircular canal in most cases. Superior canal dehiscence is thought to be congenital because it is often bilateral and is seen in about 1:500 temporal bones in mainly asymptomatic people. The diagnosis is made using high-resolution temporal bone computed tomography scan, which shows the defect of the bone overlying the semicircular canal. Surgical management of superior semicircular canal dehiscence by either plugging the defect with bone wax/paste or resurfacing with a bone graft has been shown to be successful in around 50% of cases.[57 58] The decision to operate is largely

determined by the severity of the patient's symptoms and their effect on quality of life. As with all surgery, there are potential complications that cannot always be avoided. These include loss of hearing and temporal lobe epilepsy. Accordingly, treatment is usually recommended only for those patients significantly incapacitated by their symptoms.

Perilymph fistula is often a manifestation of chronic otitis media, cholesteatoma or temporal bone fractures. However, idiopathic cases have also been reported. The pathophysiological mechanisms are thought to be increased elasticity of the otic capsule or leakage of perilymph, usually at the oval or round window.[59] The fistula test (Hennebert's sign) that involves positive and negative pressure in the external ear canal, causing eye movements and/or vertigo, supports the diagnosis. With positive pressure, a conjugate deviation of the eyes towards the opposite ear is followed by a corrective fast eye movement. Accordingly, the direction of the nystagmus is towards the affected ear and can be horizontal, torsional or vertical, depending on the location of the fistula. There are at present no available tests with high specificity to diagnose perilymphatic fistula. However, cholesteatoma sometimes produces an erosion of lateral semicircular canals visible on computed tomography. If symptoms are disabling, surgical exploration may be considered. Even at the time of surgical exploration, a perilymphatic fistula is often difficult to identify.

Isolated acute episode of vertigo

Patients presenting with the symptoms of acute peripheral vestibular dysfunction will almost certainly be diagnosed as having vestibular neuritis (also known as acute unilateral vestibular neuronitis, labyrinthitis or vestibular paralysis). There is, to our knowledge, only one publication on the prevalence of vestibular neuritis, and this study showed an occurrence rate of around 4 per 100 000.[60] Vestibular neuritis affects both the adult and the paediatric population, but has a peak between 40 and 50 years of age.[60]

Vestibular neuritis may be preceded by an upper airway infection, and there are several lines of evidence that favour a viral aetiology. The virus may infect the vestibular nerve and/or the vestibular membranous labyrinth. There is increasing evidence that several viruses can damage the vestibular labyrinth, including herpes simplex virus type 1, rubella, cytomegalovirus, Epstein–Barr virus, adenovirus, and some strains of influenza types A and B.[61] A study of two cases with acute vestibular neuritis has shown an isolated enhancement of the vestibular nerve on magnetic resonance imaging, supporting the hypothesis of a viral and/or inflammatory cause.[62] However, the picture of acute vestibular failure can be caused by other agents—for example, a vascular origin seems likely in elderly patients with vascular disease, but is rarely proved.

As the pathophysiology of vestibular neuritis remains unclear, there is at present no clear consensus with regard to specific acute treatment. Corticosteroids and antiviral agents (eg, aciclovir) have been suggested, but evidence supporting their efficacy is limited.[63–66] However, in the acute phase, symptomatic treatment of vertigo and nausea is often indicated, with antihistamines, anticholinergic agents and antidopaminergic agents being the most commonly used drugs. Fluid replacement may be required in particularly severe episodes.

Bilateral vestibular failure

Patients with bilateral vestibular failure often have unsteady gait, oscillopsia and episodes of vertigo. Owing to the lack of hearing problems, these patients are often initially seen by a neurologist. Children with early-onset bilateral vestibular failure (genetic or postmeningitic) usually present with delayed motor developmental milestones. Accordingly, they are late in sitting unsupported and in walking. In addition, they often have a history of being clumsy. In all, 30–50% of bilateral vestibular failure is idiopathic, more frequent than the recognised causes such as gentamicin toxicity and sequelae of meningitis.[67] An autoimmune cause has been suggested in some cases of bilateral idiopathic vestibular failure.[68 69] Autoantibodies against the semicircular canals and otolith organs have been shown in one patient who regained function after steroid therapy.[70] In addition, recovery of function correlated with the disappearance of serum autoantibodies to vestibular tissues.

Ototoxic drugs

Over 130 drugs and chemicals have been reported to be potentially ototoxic. The drugs most commonly associated with ototoxicity are aminoglycosides, loop diuretics, cytotoxic drugs, quinine, and aspirin/non-steroidal anti-inflammatory drugs. However, almost all drugs list dizziness as a possible side effect. Table 2 shows the drugs commonly associated with audiovestibular symptoms. Most of these drugs cause dizziness by

Table 2 Drugs causing audiovestibular symptoms

Drug	Cochlear symptoms	Vestibular symptoms
Antidepressants		
Tricyclics, monoamine-oxidase inhibitors, selective serotonin re-uptake inhibitors, venlafaxine	–	++
Tranquillisers		
Phenothiazines, benzodiazepines	–	++
Anticonvulsants		
Phenobarbital, phenytoin, carbamazepine, gabapentin	–	++
Sodium valproate	+	++
Antimigraines		
$5HT_1$ agonists	–	++
Analgesics		
Aspirin, NSAIDs	++	++
Opioid analgesics	–	++
Antihypertensives		
β adrenoceptor-blocking drugs, angiotensin-converting enzyme inhibitors, calcium channel blockers, methyldopa, hydralazine hydrochloride, thiazides	–	++
Loop diuretics	++	++
Anti-angina		
Glyceryl trinitrate, isosorbide dinitrate, nifedipine	–	++
Anti-bacterials		
Aminoglycosides	++	++
Macrolides, antituberculous drugs	++	+
Anti-malarials		
Quinine	++	–
Anti-allergic drugs		
Chlorpheniramine, cyproheptadine, ephedrine, promethazine	–	++
Cytotoxics		
Platinum compounds, alkylating drugs, vinca alkaloids, cytotoxic antibiotics	++	++
Treatment of glaucoma		
Carbonic anhydrase inhibitors	–	++

5HT, 5-hydroxytryptamine; NSAIDs, non-steroidal anti-inflammatory drugs; –, uncommon; +, reported; ++, common.

reducing arterial pressure with subsequent dysfunction of CNS or impairment of visual/proprioceptive information. Both carbamazepine and sodium valproate have been reported to be able to cause temporary hearing abnormalities and tinnitus.[71 72] Reversible hearing loss and tinnitus have also been shown with aspirin overdosage. However, taken in its correct dose, aspirin is very unlikely to have ototoxic effects. Of the antihypertensives, the loop diuretics (eg, furosemide and ethacrynic acid) have a well-documented cochleotoxicity. Sensorineural hearing loss has often been reported with quinine, but is less common with quinine derivatives. The main side effects of cytotoxic drugs are, of course, nausea with dizziness, but, in addition, sensorineural hearing loss is common with cisplatin, carboplatin and oxaliplatin.

Ototoxicity is a major problem with gentamicin, but it is still widely used and the ototoxic effects remain a problem in the developing world, where access to alternative drugs is limited. Gentamicin is mainly vestibulotoxic and this specific vestibulotoxic effect is used to treat patients with Menière's disease by intratympanic infusion. An increased susceptibility to hearing loss due to gentamicin has been shown with two mutations in the mitochondrial 12S rRNA gene, the A1555G deletion and the 961 deletion. The prevalence of these mutations is not clear, but a carrier frequency for the A1555G mutation of 0.09% and for the 961 mutation of 0.6% have been shown in the Texas population.[73] It is recommended that patients with hearing loss and previous aminoglycoside exposure be screened with molecular tests for the presence of the A1555G and 961 mutations.[74 75] It has also been suggested that patients with ''idiopathic'' bilateral sensorineural hearing loss should also be screened. Knowing that an individual carries the A1555G mutation allows for genetic counselling and avoidance of further/future aminoglycoside exposure.[76]

As ototoxicity is generally irreversible, tapering of the drug, if possible, is necessary to prevent further inner ear damage. It is important to establish normal renal function in patients before exposure to ototoxic drugs, as reduced renal clearance may lead to systemic accumulation with abnormal high serum levels. However, the correlation between serum levels of ototoxic drug and ototoxic effect can be poor, owing to interindividual differences and accumulation of the drug in the inner ear fluids. Regular assessments with hearing tests are therefore recommended.

There is evidence that cochlear damage induced by noise or ototoxic drugs can be prevented by several chemical substances.[77] Antioxidants, inhibitors of nitric oxide production, nitric oxide synthase (NOS) inhibitors, calcium blockers, glutamate receptor antagonists and neurotrophins have been found to protect the cochlea from noise-induced and drug-induced ototoxicity.[78] It has been suggested that increased production of reactive oxygen species is involved in noise-induced hearing loss, as well as in cisplatin and gentamicin ototoxicity. NOS is present in the cochlea, and NOS knockout mice have been found to be protected against cisplatin ototoxicity.[79] Glutamate (which is an essential and also highly toxic substance) is the neurotransmitter at the inner hair cell afferent synapse, and excessive release of glutamate is a possible pathophysiological mechanism, particularly in noise-induced hearing loss.[80] Currently, ototoxicity cannot be prevented by treatment with drugs, but many believe that this will be possible in the future.

THERAPY

Rehabilitation

As inner ear damage is generally irreversible, rehabilitation is important in audiovestibular disorders (table 3).

Vestibular rehabilitation therapy is safe and efficient, and is often required to enable recovery and central compensation. It is based on physical exercises, Cawthorne–Cooksey exercises, as well as gait retraining. In several studies, vestibular rehabilitation has been shown to considerably improve both peripheral and central vestibular dysfunction.[81–83] The CNS needs the stimulus of the sensory mismatch for habituation and compensation. Most anti-vertiginous drugs (eg, antihistamines, anticholinergic drugs, phenothiazines, benzodiazepines and butyrophenones) are vestibular sedatives and will suppress such mechanisms. Vestibular sedatives should be used only during the acute phase of disease, and if nausea is a prominent symptom. These drugs are not indicated in patients with chronic dizziness.

Table 3 Summary of some audiovestibular disorders showing presentation of inner ear disorder, type or site of disorder, suggested protein/gene involved and treatment

Disease/disorder	Inner ear disorder	Type/site of disorder	Suggested protein/ gene involved	Treatment
Otitis media with effusion	A+V	Eustachian tube	–	Wait-and-watch, grommet insertion
Cholesteatoma	A+V	Chronic inflammation with middle ear origin	–	Surgical management
Migraine	V	Peripheral/central vestibular system	–	Anti-migranous treatment
Menière's disease	A+V	Endolymphatic hydrops	Type II collagen, Raf-1, β-tubulin, myelin protein orally	Low-salt diet + bendrofluazide
Bilateral idiopathic vestibular failure	V	Autoimmune	188, 49 and 17 kDa inner ear proteins, 45 kDa CNS protein	Immunosuppressive drugs
Trauma	A+V	Peripheral/central audiovestibular system	–	Audiovestibular rehabilitation
Superior canal dehiscence syndrome	V	Defect in superior semicircular canal	–	Surgical management
Genetic audiovestibular disorders	A+V	Sensory/secretory epithelia + supporting cells	GJB2, SLA26A4, A1555G, COCH	Audiovestibular rehabilitation
Immune-mediated inner ear disorders	A+V	Sensory/secretory epithelia	Cochlin, B-tectorin, DEP1/CD148, connexin 26	Immunosuppressive drug

A, auditory; CNS, central nervous system; V, vestibular; DEP1/CD148, cell-density-enhanced protein tyrosine phosphatase-1.

Vestibular symptoms result from an asymmetry of afferent information arising within the vestibular system. Symptoms appear when there is a fluctuation or sudden change in vestibular function. If the vestibular dysfunction is symmetrical and slowly progressive, the patient may be totally asymptomatic. Furthermore, a stable vestibular loss is often fully compensated, and in this situation the patient will also be asymptomatic and the condition will almost certainly remain undiagnosed. One of the most important implications of bilateral vestibular hypofunction is that certain situations may be hazardous for the patient. With vestibular dysfunction, visual and proprioceptive inputs become extremely important to maintain spatial orientation/balance. Lack of these sensory inputs leaves these patients in a potentially dangerous situation—for example, if working with machines at heights or even just swimming.[84] A swimming test has been shown to be a very sensitive method when diagnosing mild vestibular dysfunction in guinea pigs.[85]

Auditory rehabilitation with conventional behind-the-ear hearing aids has improved tremendously with miniaturisation and advances in digital signal processing. Unfortunately, some patients do not benefit fully from these devices. In addition, use of conventional hearing aids is often hindered by lack of acceptance by patients. There is a market for less visible, implanted middle-ear hearing devices. In the US, several devices have now been approved for use in patients with conductive, mixed and sensorineural hearing loss.[86] A middle ear implant is a device that generates vibrational energy to drive directly the ossicular chain of the middle ear.[87] At present, middle ear devices have either a piezoelectric or electromagnetic basis.[88] Examples of various middle ear implants are beautifully illustrated at the website recommended in table 1. Adult patients with moderate to severe sensorineural hearing loss, particularly those with high-frequency loss, are suitable for middle ear implants. Some studies have shown an increased functional gain over conventional hearing aids in a selected group of patients.[89 90] However, the often-claimed additional value of middle ear implants over conventional hearing aids has not yet been proved convincingly, and the most common positive factor in published clinical trials seems to be the subjective preference for the middle ear implants over conventional devices. Second-generation devices are now becoming established, with some totally implantable types.[91]

A bone-anchored hearing aid (BAHA) is a type of bone conduction hearing aid. With BAHA, sound is conducted directly to the cochlea through the skull as vibration, bypassing the external and middle ear. The output of the device is coupled to a titanium screw osseointegrated into the mastoid (illustrated at the website on auditory rehabilitation, table 1). BAHA is an effective rehabilitation in patients with bilateral conductive or mixed hearing loss when middle ear surgery or conventional behind-the-ear hearing aids are not an option (eg recurrent infections, chronic middle ear disorder, and agenesis/atresia of the external or middle ear structures). The latest indications for BAHA are congenital or acquired unilateral sensorineural deafness (eg, after resection of vestibular Schwannoma), where the BAHA helps to restore the binaural aspect of hearing. Here, the BAHA is placed on the side of the deaf ear and acts by rerouting sound to the contralateral ear.

Cochlear implants are indicated for severe to profound hearing loss caused by cochlear disorder in those cases with an intact auditory nerve (eg, some profound congenital or postmeningitic hearing losses). Case reports showing that patients with nerve fibre damage (eg, superficial siderosis and auditory neuropathy) may also benefit have been published.[92 93] The cochlear implant helps those patients who do not get sufficient amplification to hear speech using powerful conventional hearing aids. A cochlear implant is an electronic device consisting of a multichannel electrode inserted into the cochlea through the round window. The electrode is activated by an induction coupler placed under the skin of the post-auricular region. This is connected to an ear-level or body-worn speech processor. The cochlear implant stimulates the spiral ganglion cells directly, and the outcome is often impressive, with improved speech perception. Advances in this field happen continuously. The criteria for implantation are constantly changing, and hybrid devices that use both electrical and auditory stimuli have recently been introduced.

An auditory brain stem implant (ABI) has been developed for those patients whose cochlear implantation has failed or the auditory nerve has been removed, as in NF2. The first patient was supplied with this device in 1991, and to date approximately 500 patients with NF2 have been implanted with ABIs worldwide.[94] The ABI bypasses the VIIIth cranial nerve and stimulates the cochlear nucleus complex directly, mostly the ventral cochlear nucleus, on the dorsolateral surface of the brain stem.[95] The implant is placed in the lateral recess of the fourth ventricle at the time of tumour resection, and is connected to an external processor in the same way as a cochlear implant. Sound is detected through an ear-level microphone and processed by a wearable processor unit. Signals are then transmitted via radio link through the scalp from a small transmitter coil to an implant receiver. The ABI allows the detection of sound, providing the user with a sense of environmental awareness. In addition, ABI provides most subjects with a limited ability to discriminate between some basic temporal and spectral patterns.[96]

The impression of most subjects when ''switching on'' their ABI for the first time is that the sound sensation experienced is extremely unusual.[96] It is clear that the level of performance and the quality of sound available today from the ABI do not reach those obtained with the latest multichannel cochlear implant. This could partly be explained by the preserved tonotopic organisation of the auditory pathways. Tonotopic organisation of the cochlear nuclei is perpendicular to the surface, and therefore it is difficult to get pitch discrimination from a surface paddle. However, further improvement of the device may help to improve speech perception. Accordingly, early trials are in progress with a penetrating electrode that may improve access to the tonotopic organisation.[95]

It is established that ABI provides valuable auditory rehabilitation for patients having NF2 with bilateral vestibular Schwannoma and associated bilateral deafness. The insertion of an ABI at the time of the patient's first vestibular Schwannoma surgery, when there is still preserved contralateral function, has recently been suggested. The rationale for this is that the implant will be there if and when it is required, and could be used for training purposes while hearing is still preserved. In addition, the indications for ABI have recently been expanded, and patients with congenital cochlear aplasia/malformation and acquired cochlear ossification have received implants.[97] It is probably fair to say that the results from ABI to date are not optimum. However, in the context of the alternative, complete deafness without access to any sound, it seems to be an acceptable option.

POSSIBLE FUTURE THERAPEUTIC OPTIONS

Gene therapy

The cochlea is anatomically well suited for in vivo gene therapy, with relatively isolated fluid-filled compartments. The anatomical constitutions of the inner ear and the eye are similar, both providing relatively easy access and allowing local application of vectors with reduced risk of systematic effects. It is therefore very encouraging that recombinant

adeno-associated virus-mediated gene transfer to the retina has been shown to be successful in rodent and large animal models.[98] The round window constitutes an access point that can be used for the perfusion or injection of vectors into the perilymph. Over 90 different genes that affect inner ear function or development have now been identified. The application of stem cells with knock-in genes may prevent or treat inner ear disorders. This is extremely interesting as a potential method for overcoming the lack of proliferation of the sensory cells in the inner ear and in combatting deafness.

Stem cells

Mammalian hair cell loss or damage has always been considered irreversible, and neither the sensory cells nor the primary neural cells of the inner ear have the capacity to spontaneously regenerate. Recently, some hair cell regeneration has been observed in mammalian vestibular sensory epithelia.[99 100] Adult stem cells have been found in several organs including the CNS, and a recent study has shown that the adult mouse utricular sensory epithelium contains pluripotent stem cells capable of regeneration.[101 102] However, spontaneous regeneration does not take place in disorders such as age-related hearing loss. An alternative strategy for replacing damaged spiral ganglion nerve cells or sensory cells would be to apply a substitution therapy based on stem cells to cure deafness and vestibular disorders.

CONCLUSION

Inner ear disorders are common, and patients with audiovestibular disorders, especially vestibular disorder, may well present to a neurology clinic. A thorough history and examination will often provide a clear direction as to the diagnosis. Correct diagnosis allows treatment for many of the peripheral and central vestibular disorders. Audiovestibular rehabilitation should be initiated early in the disease process to prevent chronic symptoms.

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