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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 = 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.

p0005 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

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Patient history

p0010 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). 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.

p0015 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).

p0020 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.

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Bedside examination

p0025 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).

p0030 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.

p0035 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).

p0040 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

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p0045 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:

- u0005 Video HIT (Bartl et al., 2009; MacDougall et al., 2009). An angular VOR gain below 0.7 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.
- u0010 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 10°/second. This can also be asymmetric.
- u0030 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).

p0065 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).

p0070 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

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from impaired spatial memory and navigation associated with hippocampal atrophy (Schautzer et al., 2003; Brandt et al., 2005).

CLINICAL COURSE OF THE DISEASE

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p0075 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

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p0080 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

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p0085 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

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p0090 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

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p0095 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

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p0100 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

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p0105 The etiology of BVP remained unclear in more than 70% of patients in a case series of 255 patients (Zingler et al., 2007a). 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.

p0110 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

p0115 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

p0120 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

p0125 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

p0130 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.

p0135 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

p0140 Prevention is most important for the group of patients with ototoxic labyrinthine damage, above all, that 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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