# Rare Disorders of the Vestibular Labyrinth: Of Zebras, Chameleons and Wolves in Sheep's Clothing


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## ABSTRACT

The differential diagnosis of vertigo syndromes is a challenging issue, as many – and in particular – rare disorders of the vestibular labyrinth can hide behind the very common symptoms of "vertigo" and "dizziness". The following paper presents an overview of those rare vestibular disorders that are of special interest for the otorhinolaryngologist. For a better orientation, these disorders are categorized as acute (AVS), episodic (EVS), and chronic vestibular syndromes (CVS) according to their clinical presentation. The main focus is laid on episodic vestibular syndromes sorted by their duration and the presence/absence of triggering factors (seconds, no triggers: vestibular paroxysmia, Tumarkin attacks; seconds, sound- and pressure-induced: "third-window" syndromes; seconds to minutes, positional: rare variants and differential diagnoses of benign paroxysmal positional vertigo; hours to days, spontaneous: intralabyrinthine schwannomas, endolymphatic sac tumors, autoimmune disorders of the inner ear). Furthermore, rare causes of AVS (inferior vestibular neuritis, otolith organ specific dysfunction, vascular labyrinthine disorders, acute bilateral vestibulopathy) and CVS (chronic bilateral vestibulopathy) are covered. In each case, special emphasis is laid on the decisive diagnostic test for the identification of the rare disease and "red flags" for potentially dangerous disorders (e. g. labyrinthine infarction/hemorrhage). Thus, this Chapter may serve as a clinical companion for the otorhinolaryngologist aiding in the efficient diagnosis and treatment of rare disorders of the vestibular labyrinth.

**Contents**

# 1 Introduction

*"When you hear hoofbeats behind you, think of horses, not zebras." (Theodore Woodward, 1914–2004)*

Dr. Theodore Woodward coined this mnemonic in the 1940ies when he taught his medical students at the University of Maryland to consider frequent and obvious causes of a medical condition before assessing rare differential diagnoses. Since then, rare diseases have commonly been referred to as "zebras" [1]. For the individual patient, however, it is irrelevant if he suffers from a common or a rare disease. His primary concern is to receive the correct diagnosis and treatment as soon as possible. Therefore, physicians should also be familiar with rare causes of frequent symptoms, i. e., when hearing hoofbeats, they should think of horses *and* zebras. This goal is particularly challenging when it comes to vertigo and dizziness as cardinal symptoms.

## 1.1 Rare disorders of the vestibular labyrinth

### 1.1.1 Problems

With an estimated one-year-prevalence between 15 and 20 % [2], vertigo is one of the most common cardinal symptoms why people seek medical advice. While the symptom is common, many different and especially rare origins be the underlying cause. The present paper focuses on those "dizzy zebras" that all otorhinolaryngologists should be familiar with – the rare disorders of the vestibular labyrinth.

Alone the definition of the term "rare disease" is challenging in case of vestibular disorders, as numbers about their incidence and prevalence in the medical literature are either lacking (e. g., vestibular paroxysmia) or highly variable (e. g., vestibular neuritis, Menière's disease) [2]. Consulting rare disease databases, such as Orphanet, is only of limited use in this context [4]. According to the definition of rare diseases in the European Union with a maximum of 5 affected individuals per 100,000 inhabitants, these databases list diseases as "rare" that are well-known "horses" for the otorhinolaryngologist, such as acute sensorineural hearing loss (ORPHAcode 90050) or Ramsay-Hunt syndrome (ORPHAcode 3020). On the other hand, important rare differential diagnoses of peripheral vestibular syndromes such as vestibular paroxysmia or intralabyrinthine schwannoma are not mentioned at all.

### 1.1.2 Possible solutions

Fortunately, a number of recent advances in vestibular medicine have facilitated the recognition of "zebras" in daily clinical routine. For instance, the *International Classification of Vestibular Disorders* (ICVD) [5] initiated by the Bárány Society in 2006 aims to provide standardized definitions of vestibular signs, symptoms and disorders. The results are continuously updated and are publicly available on the internet platform of the *Journal of Vestibular Research* [6].

Furthermore, laboratory testing for vestibular disorders has made a huge progress within in the past 20 years. Today, video head impulse test (vHIT) [7] and vestibular evoked myogenic potentials (VEMPs) [8–12] allow fast, innocuous, reproducible and specific assessment of all five vestibular receptor organs of one labyrinth and their afferents [13–15]. While ocular VEMPs (oVEMPs) mainly assess contralateral utricular function, cervical VEMPs (cVEMPs) are predominantly an indicator of ipsilateral saccular integrity [16]. It should be noted that both tests are not 100 % specific for their end organs (partly because 10 % of saccular afferents run in the superior vestibular nerve [17, 18]). Many clinical studies in patients with superior and inferior vestibular neuritis have, however, shown that the specificity of o- and cVEMPs is sufficient for discriminating between utricular and saccular dysfunction in clinical practice [12].

Portable diagnostic devices are now available for bedside tests in the emergency unit and on the patient ward, allowing identification of vestibular disorders in everyday clinical practice that could only be diagnosed in specialized centres with complex technical devices some years ago [19, 20]. Patients are able to record their eye movements during vertigo attacks themselves at home with smartphone cameras or portable devices like the "DizzyCam" [21, 22]. For the individual patient, these recordings may provide the crucial hint for making the correct diagnosis; for vestibular medicine, they help to improve the classification and characterization of vestibular syndromes in general.

The advances in neurophysiological testing are complemented by the huge progress in imaging techniques of the skull base [23, 24], which has a direct impact on the "rarity" of a disease. Twenty years ago, many patients with intralabyrinthine schwannoma were diagnosed with sudden sensorineural hearing loss or Menière's disease because the resolution of cranial MRI was too

poor for diagnosing these small tumors (see Chapter 3.4.1), and too little attention was paid to this rare disease.

Finally, the development of validated diagnostic clinical algorithms allowing to identify the risk of potentially harmful causes for vestibular disorders was another important mildestone. The most famous example are "H.I.N.T.S. to I.N.F.A.R.C.T." (H.I.N.T.S. = **H**ead **I**mpulse, **N**ystagmus, **T**est of **S**kew; I.N.F.A.R.C.T. = **I**mpulse **N**egative, **F**ast **A**lternating (nystagmus), **R**efixation on **C**over **T**est), which help to diagnose brainstem or cerebellar infarction as the cause of a persisting acute vestibular syndrome (AVS) more reliably than an early diffusion-weighted (DWI) MRI (< 48 hours after symptom onset) or cardiovascular risk scores (e. g. ABCD² = age, blood pressure, clinical features, duration, diabetes [25]) [26–31].

### 1.2 "Instruction for use" of this contribution

With this background, the following paper does not intend to provide an exhaustive enumeration of rare vestibular disorders. It is rather meant to be a clinical companion assisting the otorhinolaryngologist in decision-making when vestibular symptoms and signs cannot be explained by frequent vestibular conditions. Therefore, disorders are not classified by etiology here, but by clinical presentation, i. e., acute (AVS), episodic (EVS) and chronic vestibular syndromes (CVS), occurring either spontaneously or with triggers [28, 32]. Special focus is laid on the following questions:

- Which constellation of symptoms or findings should raise my suspicion of a rare disease ("zebra")?
- What are "red flags" for a potentially dangerous cause, i. e., a "wolf in sheep's clothing"?
- What additional investigations do I need to make the diagnosis?

In this sense, I hope to provide the reader with a useful guide through the "zoo" of rare vestibular disorders – with all its zebras, chameleons, and wolves in sheep's clothing.

## 2 Acute Vestibular Syndromes

Acute vestibular syndromes (AVS) are characterized by the following aspects [5, 28, 32]:

- Acute-onset continuous "vertigo", "dizziness", and/or "unsteadiness" according to the ICVD [33]
- Duration of at least 24 hours
- Symptoms and findings of a newly occurring, ongoing vestibular dysfunction (e. g., vomiting, nystagmus, tendency to fall, unsteady gait)

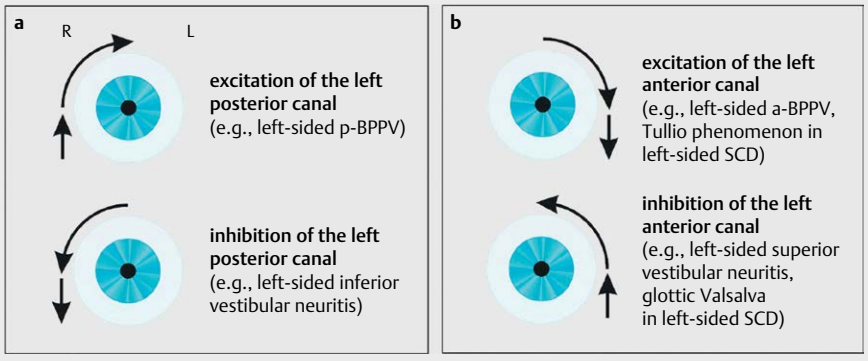
### 2.1 Acute unilateral vestibuloapthy

#### 2.1.1 Inferior vestibular neuritis

While acute unilateral vestibulopathy (AUVP) mostly affects the superior vestibular nerve [34] or its receptor organs (horizontal semicircular canal in 97.7 % of cases, anterior semicircular canal in 90.7 % and utricle in 72.1 %) [35], inferior vestibular neuritis is a real "hummingbird". An *isolated* hypofunction of the inferior branch and its end organs (posterior semicircular canal and/or saccule) is observed in only 1.2 to 5 % of all patients with AUVP [36–43]. The rare occurrence of inferior as compared to superior vestibular neuritis is attributed to the different course of the two nerve branches within the temporal bone. The bony channel of the superior vestibular nerve is narrower and about seven times longer than that of the inferior division. Hence, the superior vestibular nerve is probably more prone to pressure- or swelling-induced lesions caused by inflammatory disease, such as herpes simplex virus reactivation, which is supposed to be the underlying cause of vestibular neuritis [44, 45].

According to Ewald's first law [46], patients with inferior vestibular neuritis typically display a paretic nystagmus beating in the plane of the affected posterior semicircular canal, i. e., a rotatory nystagmus with a downbeat component beating towards the opposite ear. This nystagmus can be suppressed by fixation due to its peripheral vestibular origin (▶ **Fig. 1a**) [47–49]. Nystagmus direction is exactly opposite compared to the excitatory nystagmus (i. e., rotatory upbeat nystagmus directed towards the affected ear) in benign paroxysmal positional vertigo (BPPV) of the same posterior canal (▶ **Fig. 1a**) [50].

A reduced vHIT gain with corrective saccades confirms hypofunction of the posterior canal, while reduced cVEMP amplitudes indicate saccular dysfunction on the affected side. A study by Taylor




▶ **Fig. 1** Nystagmus evoked by excitation and inhibition of the left **a** posterior and **b** anterior semicircular canal according to Ewald's laws [46] and the studies by Cohen [47]. For details, see Chapters 2.1.1 and 3.2.1–3.2.4. Abbreviations: a = anterior, BPPV = benign paroxysmal positional vertigo; p = posterior; SCD = superior canal dehiscence.

et al. [35] showed that the two end organs were not affected by inferior vestibular neuritis simultaneously in one third of cases. Since the superior part of the vestibular nerve remains intact, bithermal caloric irrigation (horizontal canal function), vHIT for the anterior and horizontal canals, and oVEMPs (utricular function) display normal results for the affected side [13, 40, 42, 51].

### 2.1.2 Acute otolith organ specific vestibular dysfunction

An acute vestibular syndrome may also specifically affect the otolith organs without compromising semicircular canal function. The exact incidence of this disorder is unknown so far because independent diagnostic assessment of all five vestibular receptor organs by vHIT, c- and oVEMPs has only become available for routine clinical testing in recent years [52].

Cardinal symptoms of acute unilateral loss of otolith function are: vertigo, dizziness, a sensation of "being pushed from the side or from behind", postural instability, tendency to fall, and severe nausea up to vomiting [52, 53]. It should, however, be noted that patients with otolith organ specific hypofunction may also report rotatory vertigo [54, 55]. Furthermore, a predominantly horizontal paretic nystagmus suppressed by fixation is sometimes observed in patients with acute unilateral utricular loss – despite intact function of the semicircular canals in vHIT and calorics [56, 57].

This somewhat puzzling observation can be explained by the fact that about half of the secondary vestibular neurons in the vestibular nucleus of the brainstem are convergence neurons, i. e., they receive afferent input from the otolith organs *and* the semicircular canals [58–62]. Any difference in neural activity between the right and left vestibular nuclei may result in a spontaneous nystagmus beating towards the side with the higher activity [63] regardless if the difference is caused by reduced input of semicircular canal or otolith afferents. As this nystagmus is of peripheral origin, it can be suppressed by fixation [52, 57].

**Clinical pearl**

**Acute unilateral otolith organ specific hypofunction may present with rotatory vertigo and peripheral spontaneous nystagmus.**

Thus, this rare disorder is an illustrative example of the general rule that vertigo symptom quality does *not* always allow localization of the vestibular damage, such as: rotatory vertigo = semicircular canals, rocking sensation = otolith organs [28]. Therefore, a targeted neurotological examination based on the "H.I.N.T.S. plus" algorithm (see Chapter 1.1.2 and 2.2.1) should be performed in every case of AVS - ideally complemented by vHIT and VEMPs - in order to localize the origin of the vestibular deficit as accurately as possible (peripheral vs. central, semicircular canals vs. otolith organs).

Otolith organ specific vestibular deficits with preserved function of the semicircular canals are often observed after mild traumatic brain injury and blast exposure. This observation is explained by the fact that the sensory epithelium of the otolith organs is more vulnerable to pressure waves than the cristae of the semicircular canals [64]. One study on patients with traumatic brain injury showed that otolith organ specific hypofunction (pathological VEMPs, tilted subjective visual vertical) was diagnosed in 72 % of patients suffering from dizziness, but only in 20 % of those without dizziness [65]. Furthermore, reduced c- and oVEMP responses along with normal semicircular function are often found after blast trauma [66].

### 2.1.3 Therapy

Acute inferior vestibular neuritis and otolith organ specific vestibular hypofunction are treated like other causes of AUVP. Beside glucocorticoids, early individualized vestibular physiotherapy is crucial [67, 68]. Exercises should be tailored to the pattern of peripheral vestibular hypofunction as detected by vHIT and VEMPs.

## 2.2 Acute unilateral audio-vestibular dysfunction

This constellation of symptoms has traditionally been called "labyrinthitis". While this term implies an inflammatory disease of the inner ear, the otorhinolaryngologist should always be aware of the fact that labyrinthine infarction or hemorrhage with potentially dangerous consequences may hide behind these symptoms [31].

### 2.2.1 Labyrinthine infarction

The labyrinthine artery originates from the anterior inferior cerebellar artery (AICA) in 80 % of cases, and less frequently directly from the vertebral / basilar artery (15–20 %) or the posterior inferior cerebellar artery (PICA, 2–3 %) [31, 69]. Since it is a terminal artery with only few collaterals, the inner ear is particularly prone to ischemic damage. Depending on the location of vascular occlusion, ischemia may affect the entire inner ear (i. e., cochlea and vestibular organ) or parts of it [70] (see [71, 72] for an illustration of the single branches of the labyrinthine artery and their supply areas). Inner ear ischemia should particularly be suspected in cases of posterior canal hypofunction combined with sensorineural hearing loss of the cochlear type, because both receptor organs are supplied by the common cochlear artery / the vestibulocochlear artery [72].

Acute labyrinthine infarction carries the risk of progression into brainstem or cerebellar stroke [70, 71]. In several retro- and prospective observational studies, 8–30 % of patients with AICA infarction confirmed by DWI MRI reported symptoms of acute audio-vestibular dysfunction within one month before clinical stroke manifestation [69, 70, 73]. Therefore, the first event of an acute, persisting vestibular syndrome (i. e., duration of >24h) in combination with unilateral sensorineural hearing loss should raise the clinician's suspicion of vascular (labyrinthine infarction) rather than inflammatory (labyrinthitis) disease, especially in patients with cardiovascular risk factors (e. g. ABCD² score ≥ 4) [71, 74, 75].

Diagnosis of labyrinthine ischemia is complicated by several factors. First, isolated ischemia of the inner ear without brainstem or cerebellar involvement is not visible on MRI [70, 71, 75, 76]. Diffusion restriction in the vestibular nerve on high-resolution DWI MRI of the temporal bone (1.4 mm instead of the usual 5 mm slice thickness) has only been described in some single cases so far [78, 87], while diffusion restriction limited to the inner ear labyrinth has not yet been shown [28]. Application of 3D FLAIR sequences (FLAIR = fluid attenuated inversion recovery) increases the sensitivity of MRI for inner ear pathologies in comparison to T1 weighting [79], while it is still not possible to determine exactly whether gadolinium enhancement within the inner ear in the FLAIR sequence

is due to inflammatory or vascular lesions (vascular: [80, 81]; inflammatory [82]).

Second, isolated labyrinthine infarction (without brainstem or cerebellar involvement) does not display the classical "H.I.N.T.S. to I.N.F.A.R.C.T." because it is a peripheral and *not* a central vestibular disorder [31]. Positive "H.I.N.T.S." indicate the location (central *versus* peripheral) and not the cause (inflammatory *versus* vascular) of vestibular dysfunction. The significance of labyrinthine infarction as a possible harbinger for posterior fossa stroke is reflected by the updated "H.I.N.T.S. plus" paradigm, including acute unilateral hearing loss in AVS as an additional "red flag" [27]. In a cross-sectional study of patients with acute vestibular syndrome and increased risk for stroke, "H.I.N.T.S. **plus**" revealed an underlying posterior fossa stroke with a sensitivity of 99.2 % and a specificity of 97.0 %, while sensitivity and specificity for an ABCD² score ≥ 4 were only around 60 %. Within the first 48 hours after symptom onset, sensitivity of "H.I.N.T.S. **plus**" was even superior to that of DWI MRI, because it may take some time – particularly in small strokes – until the structural anatomic changes become visible on MRI [31, 83].

Therefore, Newman-Toker et al. [27] recommended that patients with positive "H.I.N.T.S. plus" not eligible for lysis should be monitored for 48 hours and then receive an MRI. In any case of "H.I.N.T.S. plus", a neurologist should be consulted to plan further neurovascular investigations, treatment and prophylaxis (e. g. acetylsalicylic acid 100 mg p.o. daily) as needed. Details can be found in [32, 84].

**Clinical pearl**

**An acute-onset, ongoing audiovestibular syndrome occurring for the first time is suspicious of labyrinthine infarction unless the contrary is proven. Negative diffusion-weighted cMRI within the first 48 hours after symptom onset does not exclude AICA or PICA infarction.**

Labyrinthine infarction may also be caused by thrombosis of the basilar or vertebral arteries, either due to arterio-arterial embolism or reduced perfusion of the labyrinthine artery [85, 86]. Another exceptional case is labyrinthine infarction secondary to vertebral artery dissection. The latter may occur spontaneously or after trauma (e. g., car crash, manipulation of the cervical spine) and should particularly be considered in younger patients without cardiovascular risk factors [81, 87–89].

### 2.2.2 Labyrinthine hemorrhage

Besides ischemia, labyrinthine hemorrhage may also result in the clinical picture of an acute audiovestibular syndrome. Possible causes include trauma, coagulation disorders, blood dyscrasias (e. g., in leukemia), intake of oral anticoagulants, bleeding into an endolymphatic sac tumor (see Chapter 3.4.2), or superficial siderosis (see Chapter 4.1.3.2.2). Rarely, labyrinthine hemorrhage occurs spontaneously [90–92]. Recently, a case of bilateral labyrinthine hemorrhage has been described in an 18-year-old patient with SARS-CoV-2 infection (*severe acute respiratory syndrome coronavirus 2*) [93].

In contrast to labyrinthine ischemia, hemorrhage is visible in native T1 and FLAIR sequences of temporal bone MRI as a hyperintense lesion without further contrast enhancement [82, 92]. In patients with spontaneous labyrinthine hemorrhage, coagulation disorders should be excluded as a possible cause. Beside treatment of the underlying disease, systemic or intratympanic application of glucocorticoids should also be taken into consideration. In single case reports, partial recovery of inner ear function has been described [90].

### 2.2.3 Labyrinthitis

The term "(neuro)labyrinthitis" should actually only be applied if clinical signs for an inflammatory disease of the middle / inner ear (e. g., otitis media) or the vestibulocochlear nerve (e. g., meningitis) are present that may satisfactorily explain acute-onset, ongoing vestibular hypofunction [31]. Beside acute otitis media with inner ear involvement, this may be an infection with neurotropic viruses (e. g., herpes zoster, measles, mumps, CMV, EBV, HIV) or bacteria (e. g., borrelia) [82, 94]. Therefore, the otorhinolaryngologist should pay attention to typical efflorescences on head, neck and the rest of the body.

No systematic analyses on the impact of SARS-CoV-2 on the vestibular labyrinth are available so far (see also Chapter 2.2.2) apart from single case reports without detailed neurootological investigations (e. g. [93, 96]). The neurotropic character of the virus [97] and the occurrence of acute sensorineural hearing loss in patients with COVID-19 disease (*coronavirus disease 2019*), however, allow the assumption of vestibular involvement which should be considered especially with regard to long-term sequelae of the disease [98–102].

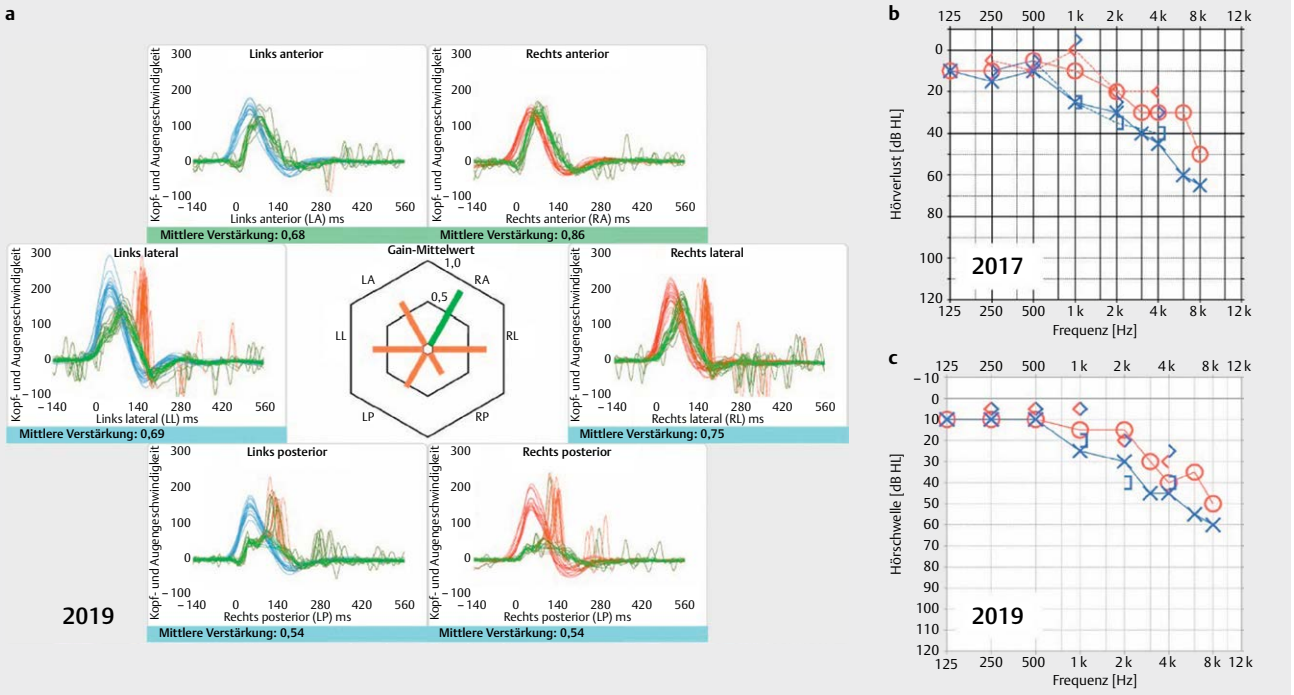
Basal meningitis is an important differential diagnosis of (neuro-)labyrinthitis if additional cranial nerve palsies develop simultaneously or sequentially with vestibulocochlear nerve dysfunction. The underlying cause may be tuberculosis or syphilis – even in the 21st century [103]. In addition, carcinomatous meningitis or CNS lymphoma may cause cranial nerve palsies. In these cases, patients should be referred to a neurologist – ideally with an expertise in neuroimmunology / neuroinfectiology – for further investigations (e. g., lumbar puncture, CNS imaging) and treatment.

## 2.3 Acute bilateral vestibulopathy

Acute simultaneous hypofunction of both vestibular organs or their afferents occurs very rarely and is mostly due to toxic (e. g., aminoglycosides), traumatic (e. g., bilateral temporal bone fracture), or infectious causes (e. g. basal meningitis) (see case examples in ▶ **Figs. 2** and ▶ **3**). Furthermore, simultaneous ischemia of both labyrinthine arteries (e. g., due to a megadolichobasilaris) may result in acute bilateral loss of vestibular function [104]. Bilateral vestibular neuritis is a true vestibular "hummingbird" that has only been reported twice so far [105, 106].

Etiology, symptoms, clinical findings and additional investigations in bilateral vestibulopathy (BVP) are presented in detail in Chapter 4 because it usually occurs as a chronic vestibular syndrome. Unfortunately, the acute type of the disease is often missed in clinical practice as the symptoms are very unusual for an acute vestibular syndrome. Therefore, acute BVP is mentioned in this Chapter for systematic reasons.

In contrast to unilateral AVS, patients with acute simultaneous BVP do *not* present with typical symptoms and signs of afferent




▶ **Fig. 2** Gentamicin-induced bilateral vestibulopathy (BVP). This 59-year-old male patient was treated with systemic gentamicin (May to June 2019) because of endocarditis following aortic valve replacement. Three weeks later, he noticed oscillopsia and unsteady gait, but no spontaneous vertigo and no hearing loss. No spontaneous nystagmus was observed either. **a** The video head impulse test (vHIT) revealed the typical pattern of aminoglycoside-associated BVP with a reduced gain and corrective saccades for the horizontal (=lateral) and posterior semicircular canals on both sides ("rechts"=right, "links"=left), while bilateral anterior canal function was preserved (normal gain, no corrective saccades). For details, see Chapter 4.1.3. **b** and **c** No additional hearing loss was detected in pure tone audiometry after gentamicin treatment (**c**) compared to a previous recording from 2017.

discharge asymmetry, such as spinning or non-spinning vertigo and spontaneous nystagmus. Instead, oscillopsia during head movements and unsteadiness / imbalance when standing or walking are the cardinal symptoms (for details, see Chapter 4.1.1). Diagnosis can be made with three simple bedside tests: the clinical head impulse test for the horizontal semicircular canals reveals bilateral refixation saccades, extreme postural instability is observed during the Romberg test on foam with eyes closed, and reduced dynamic visual acuity is detected in bedside testing with a visual acuity chart [107]. Additional investigations with vHIT, c- and oVEMPs allow quantifying and monitoring the extent of hypofunction in the individual vestibular end organs (▶ **Figs. 2** and ▶ **3**; for details, see Chapter 4.1.2).

**Clinical pearl**

**Patients with acute bilateral vestibulopathy show a bilaterally positive head impulse test, but usually no spontaneous nystagmus.**

# 3 Episodic Vestibular Syndromes

Episodic vestibular syndromes (EVS) are characterized by [5, 28, 32]:

- transient vertigo, dizziness or unsteadiness
- duration of seconds to hours, rarely days
- features suggestive of temporary, short-lived vestibular dysfunction (e. g., nausea, nystagmus, falls)

Since the duration of symptoms plays an important role in the differential diagnosis of episodic vestibular syndromes, the following "zebras" are listed by increasing attack duration. Some of these disorders, in particular third-window syndromes (see Chapter 3.2), are real vestibular "chameleons" mimicking several other episodic vestibular syndromes. This aspect will addressed in the relevant sub-Chapters.

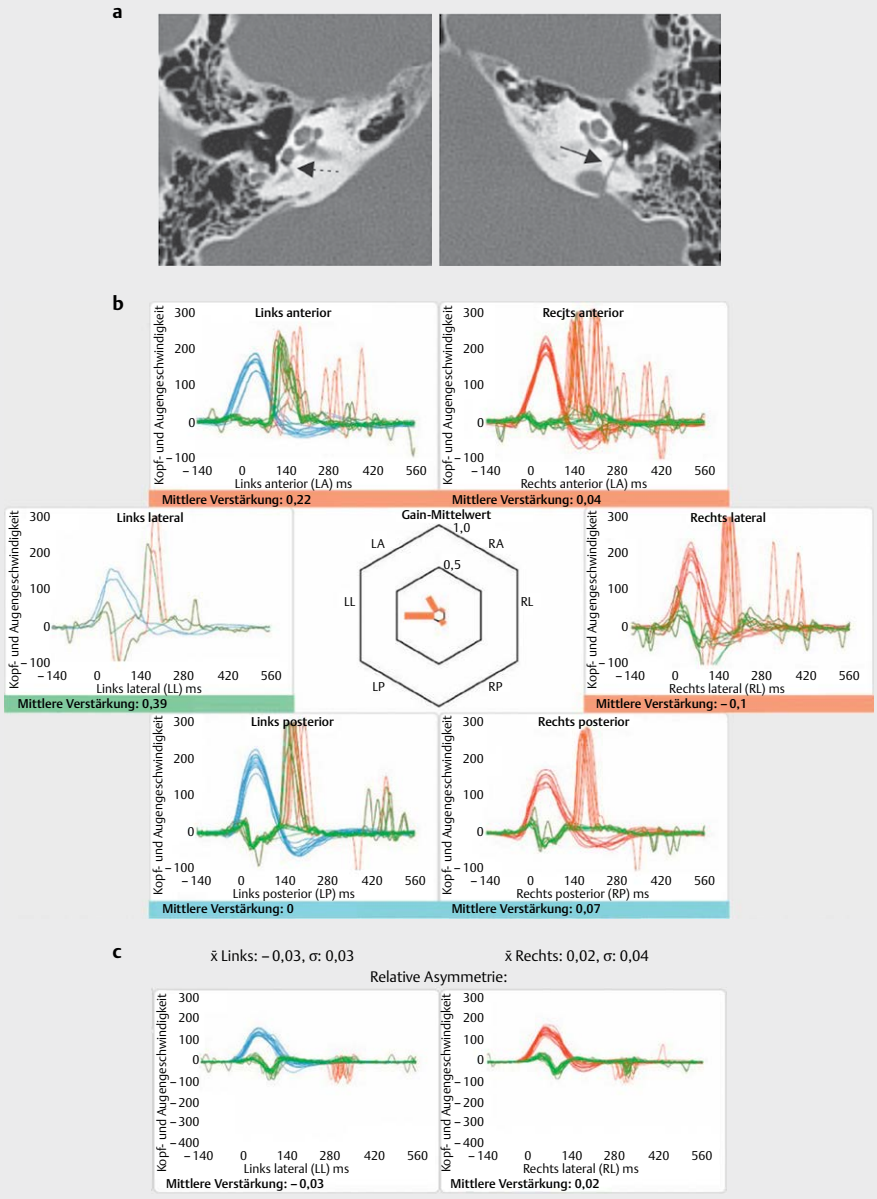
## 3.1 Spontaneous episodic vertigo for seconds

### 3.1.1 Vestibular paroxysmia

#### 3.1.1.1 Pathogenesis

Up to now, no data have been published regarding the incidence and prevalence of this rare vestibular disorder that is defined as a neurovascular cross-compression syndrome of the eighth cranial nerve [3]. Chronic contact between the vestibulocochlear nerve and a pulsating vascular loop is supposed to cause focal demyelination and subsequent hyperexcitability of the axons. Ephaptic transmission of neuronal impulses between the "bare" axons finally results in short attacks of vertigo, auditory symptoms or tinnitus – depending on which part of the nerve is affected by neurovascular cross-compression [108–111].

Distance between the compressing vessel and the brainstem varies between 0 to 10.8 mm on MRI [112]. This range corresponds




▶ **Fig. 3** Bilateral transverse temporal bone fracture with acute bilateral cochleo-vestibular loss after falling down the stairs. The 63-year-old male patient did not complain of vertigo, had no spontaneous nystagmus, but displayed a very unsteady gait. **a** Axial HRCT of the left temporal bone with an obvious fracture line through the vestibulum (solid arrow) and a hairline fracture of the right labyrinth (dashed arrow). Note the air in the vestibulum on both sides as a tell-tale sign for a labyrinthine fracture. **b** Bilateral vestibulopathy with involvement of all six semicircular canals: the patient's cooperation during video head impulse testing (vHIT) was limited due to bilateral deafness (artifacts in the measurement of the left lateral semicircular canal). For all six semicircular canals, a clearly reduced gain <0.25 with significant corrective saccades ("overt" saccades) was determined ("rechts" = right, "links" = left) **c** Measurement of horizontal (= lateral) canal SHIMPs (**s**uppression of **h**ead **imp**ulses) showed no saccades, which indicates a complete bilateral loss of the horizontal vestibulo-ocular reflex (for details, see [418]). Ocular and cervical vestibular evoked myogenic potentials (VEMPs) were absent on both sides (not displayed).

to the so-called central myelin portion of the vestibulocochlear nerve which is produced by oligodendrocytes and is particularly susceptible to focal demyelination as compared to the peripheral myelin sheath produced by Schwann cells [111, 113]. The compressing vessel is the AICA in 75 % of cases, the vertebral artery or a vein in 10 % each, while the PICA is only involved in 5 % of cases [112].

### 3.1.1.2 Symptoms and diagnostic criteria

Patients suffering from vestibular paroxysmia (VP) report sudden-onset, stereotyped bouts of spinning or non-spinning vertigo lasting only some seconds and occurring up to 100 times per day in extreme cases [3, 110]. Mostly, these attacks appear spontaneously, but they may be triggered by certain head movements as well. Depending on the involvement of the auditory nerve, hearing

sensations are elicited together with or independently from the vertigo attacks. Typically, patients describe a staccato-like tinnitus reminiscent of a mechanical typewriter sound ("Typewriter tinnitus") [114].

The diagnostic criteria of the Bárány Society distinguish between "vestibular paroxysmia" and "probable VP" [3]. Apart from the higher number (10 vs. 5) and the shorter duration required for the attacks (< 1 vs. < 5 min), diagnosis of "vestibular paroxysmia" requires improvement of the symptoms to treatment with a sodium channel blocker (see below).

**Clinical pearl**

**The diagnosis of "vestibular paroxysmia" according to the Bárány Society criteria requires a response of symptoms to sodium channel blockers. Evidence for a neurovascular cross-compression of the eighth cranial nerve on MRI is not necessary.**

#### 3.1.1.3 Audio-vestibular signs

If the examiner is lucky enough to observe one of the very short attacks, a horizontal-rotatory irritative nystagmus directed towards the affected ear is seen. Hyperventilation for three minutes is able to trigger a nystagmus beating in the same direction in around 70 % of patients [110]. Hyperventilation does most probably not trigger an attack in VP, but rather causes an alkalosis in the extracellular fluids reducing the concentration of free $Ca^{2+}$, which finally results in a further decrease in the excitation threshold of the demyelinated eighth nerve axons [115].

In 30–40 % of the patients, a mild (audio-)vestibular dysfunction was observed on the affected side in free intervals between attacks. Furthermore, signs of vestibular hyperexcitability (e. g., irritative nystagmus to the affected side) and hypofunction (e. g., paralytic nystagmus to the contralateral side; caloric paresis, reduced vHIT gain, reduced VEMP amplitudes on the affected side) may co-exist in one patient [110, 112].

#### 3.1.1.4 Imaging

A neurovascular contact is defined by the absence of the hyperintense signal of the cerebrospinal fluid (CSF) between the nerve and the adjacent vessel in a strongly T2-weighted sequence (CISS = constructive interference in steady state or FIESTA = fast imaging employing steady state acquisition) on a thin-sliced (≤ 0.7 mm) MRI of the cerebellopontine angle [111, 116]. While the presence of a neurovascular contact on MRI is very sensitive for the diagnosis of VP (95 %), a specificity of only 65 % was observed in one study, which means that the MRI displayed a neurovascular contact in 35% of those study participants who did not show any symptoms of VP [110, 112].

#### 3.1.1.5 Differential diagnoses

An MRI of the brain and the temporal bone is primarily performed to identify possible "zebras" mimicking the symptoms of VP, e. g., arachnoid cysts or tumors of the cerebellopontine angle [117–119]. Due to its tortuous course, an abnormally dilated vertebrobasilar artery (vertebrobasilar dolichoectasia) may cause cross-compression syndromes of several cranial nerves including the vestibulo-cochlear nerve [120]. Dilation of the basilar or vertebral arteries is frequently associated with arterial hypertension and bears the risk of brainstem infarction [121]. In these cases, a consequent therapy of the elevated blood pressure and additional neurovascular investigations (e. g., cerebrovascular ultrasound) are necessary in addition to symptomatic therapy of the neurovascular conflict (see below). Finally, radiotherapy of the cerebellopontine angle can also provoke symptoms of VP by damaging the oligodendrocytes producing the central myelin portion of the VIIIth cranial nerve. The symptoms of radiation-induced VP have been reported to respond well to sodium channel blockers [115].

#### 3.1.1.6 Therapy

Treatment with sodium channel blockers (carbamazepine 200–800 mg p.o. or oxcarbazepine 300–900 mg p.o. per day) reduces the ephaptic transmission and thus results in a significant reduction of both attack frequency and severity within a few days or weeks [110], as shown in a double-blind randomized controlled clinical trial for oxcarbazepine *versus* placebo [122]. It should, however, be noted that there was a high drop-out rate due to adverse effects in this study. An alternative sodium channel blocker that seems to be tolerated better is lacosamide [123]. Phenytoin or valproate may be used as well. Microvascular decompression of the eight cranial nerve should be reserved for those rare cases where a treatment with sodium channel blockers is not possible or not successful [3].

### 3.1.2 Tumarkin attacks

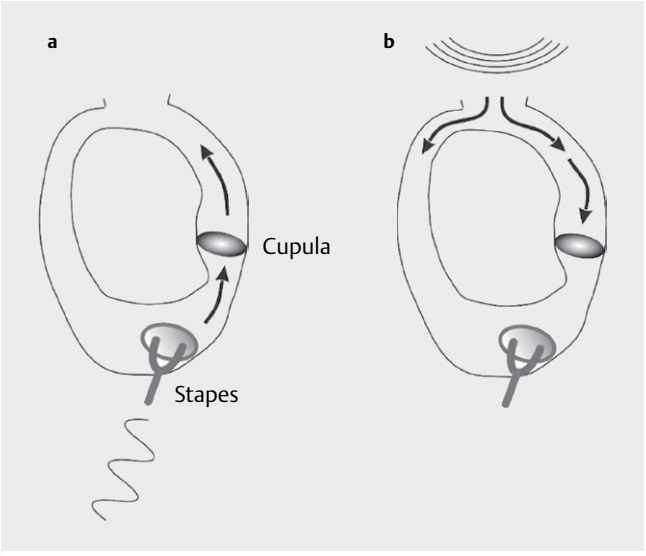
These spontaneously occurring drop attacks without loss of consciousness are reported by about 10 % of patients with Menière's disease. Patients typically experience a sudden sensation of "being pushed from behind" or as "if someone knocked them off their feet" without a sensation of vertigo or autonomic symptoms. Drop attacks only last a few seconds, and after getting up, patients are able to resume their previous activities. Due to the sudden occurrence without prodromal symptoms, however, the risk of injuries is high [124, 125].

First described by Tumarkin in 1936 as "otolithic catastrophes", these attacks are assumed to be caused by a sudden stimulation of the otolith organs due to unstable endolymphatic pressure. The resulting abrupt activation of the vestibulo-spinal pathways is supposed to result in a sudden loss of muscle tone in the legs ("like a ragged doll whose strings have been cut") with a subsequent fall [126, 127]. This hypothesis is supported by recent results of inner ear imaging (increased vestibular endolymphatic hydrops in Menière's disease patients with Tumarkin attacks) and VEMPs (residual utricular function) [53, 124, 125]. The debilitating attacks respond well to intratympanic application of gentamicin (Class A control of 80 %) [125], which is explained by the rather selective vestibulotoxic effect of aminoglycosides on type I vestibular hair cells (see Chapter 4.1.3.1.1).

## 3.2 Sound- and pressure-induced episodic vertigo for seconds – third-window syndromes

These disorders are caused by an abnormal "third" window between the bony otic capsule of the inner ear and the middle ear / the intracranial space in addition to the two natural windows (i. e., oval and round window). The third window acts as a "*locus minoris resistentiae*", changing inner ear fluid dynamics with subsequent characteristic audio-vestibular symptoms.

A third window of the otic capsule may be due to an enlargement of an existing neurovascular foramen (e. g., internal auditory canal, vestibular aqueduct), a new bony defect (e. g., semicircular canal dehiscence) or a thinning of the bone ("near dehiscence"). While most of the additional openings in the labyrinth are anatomically discrete, bone dyscrasias of the temporal bone (e. g., Paget's disease, osteospongiosis, osteogenesis imperfecta, fibrous dysplasia) can cause so-called "diffuse" third windows (see also the article by Dr. Weiss [128]). Here, the resistance of the bony otic capsule is generally reduced, sometimes in combination with several microfractures that altogether may have the effect of a third window [129–131]. Finally, it should be noted that inflammatory (e. g., cholesteatoma), infectious (e. g. syphilis), neoplastic (e. g., multiple myeloma, Langerhans cell histiocytosis, sarcomas), and vascular (e. g., paragangliomas) destructive processes of the lateral skull base may induce bony dehiscences of the otic capsule beside their many other clinical manifestations [129, 130, 132]. For further details see the contribution by Dr. Weiss [128].




▶ **Fig. 4** Endolymph flow in superior canal dehiscence (SCD). **a** Increased middle ear pressure (e. g., air-conducted sound, nasal Valsalva, Hennebert's sign): the ampullofugal = excitatory endolymph flow results in an excitatory nystagmus in the plane of the superior semicircular canal. **b** Increased intracranial pressure: endolymph flow (ampullopetal = inhibitory) and nystagmus direction are opposite to **a**, according to Ewald's third law. See also ▶ **Fig. 1** and ▶ **Table 1**.

### 3.2.1 Pathophysiology and cardinal symptoms

The effects of an additional third window in the otic capsule on the auditory and the vestibular system have been comprehensively investigated in animal and mathematical models [133–138]. The clinical symptoms and electrophysiological findings can be classified into four major categories:

**Pressure-induced vertigo** Variations in intracranial pressure (e. g., sneezing, coughing, straining) or middle ear pressure (e. g., rapid changes in altitude) are directly transmitted to the fluid-filled spaces of the inner ear via the newly created third window (▶ **Fig. 4**). The subsequent endolymph flow in the vestibular labyrinth in case of a bony canal dehiscence causes a short vertigo sensation combined with a nystagmus beating mainly in the plane of the affected semicircular canal, according to Ewald's first law (▶ **Fig. 1**, ▶ **Table 1**). Thus, the dehiscent canal may be identified based on nystagmus characteristics (for details, see Chapters 3.2.2 to 3.2.5).

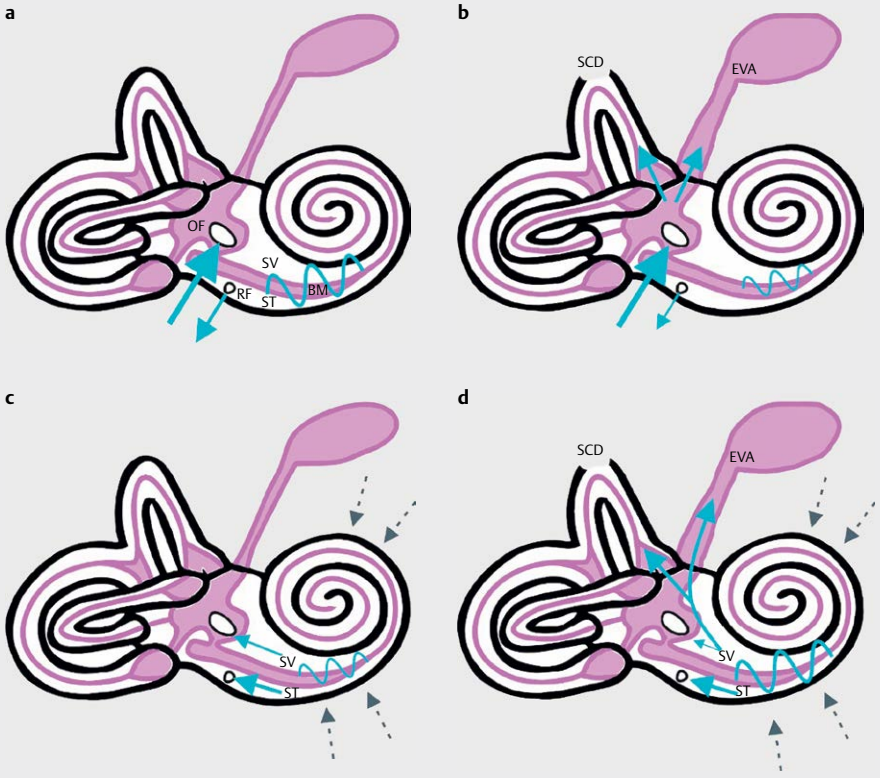
**Sound-induced vertigo (Tullio phenomenon) [139, 140]** When air-conducted sound (ACS) is transferred from the middle to the inner ear in case of a third-window syndrome, part of the sound energy follows the path of least resistance to the newly created opening of the bony capsule. The resulting abnormal endolymph displacement causes deflection of stereocilia with a subsequent change of hair cell potential and afferent discharge in the affected canal, resulting in vertigo and nystagmus according to Ewald's laws (▶ **Fig. 4a**, ▶ **Table 1**).

**Inner-ear conductive hearing loss** Part of the air-conducted sound energy is shunted away from the cochlea to the third window, resulting in a decreased pressure gradient between the oval and the round window, and thus decreased basilar membrane motion. Hence, stereocilia of cochlear hair cells are less deflected,

▶ **Table 1** Clinical tests for third-window syndromes and characteristic nystagmus findings as observed in left superior canal dehiscence (SCD), according to [142]

| Test | Results | Nystagmus |
|---|---|---|
| **Hennebert's sign** [157]: tragus pressure | increased middle ear pressure (▶ **Fig. 4a**)<br>→ pressure wave through the SC directed towards the dehiscence<br>→ ampullo-fugal (= excitatory) endolymph flow | left, rotatory downbeat nystagmus (▶ **Fig. 1b**) |
| **nasal Valsalva**: "blow air into the ears against pinched nostrils" | increased middle ear and intracranial pressure. If increase of middle ear pressure prevails (▶ **Fig. 4a**):<br>→ ampullo-fugal endolymph flow through the SC (see Hennebert's sign) | left, rotatory downbeat nystagmus (▶ **Fig. 1b**) |
| **glottic Valsalva**: "strain as if you want to lift something heavy" | increased intracranial pressure (▶ **Fig. 4b**)<br>→ pressure wave from the dehiscence through the SC directed towards the utricle<br>→ ampullopetal (= inhibitory) endolymph flow | right, rotatory upbeat nystagmus (▶ **Fig. 1b**) |
| **Tullio sign** [139]: presentation of pure tones from 125 to 4000 Hz via headphones | sound wave → ossicular chain → oval window → SC → dehiscence (▶ **Fig. 4a**)<br>→ ampullofugal (= excitatory) endolymph flow | left, rotatory downbeat nystagmus (▶ **Fig. 1b**) |

Abbreviations: SC = superior canal




▶ **Fig. 5** Inner-ear conductive hearing loss and bone-conduction hyperacusis in third-window syndromes. **a** Endolymph flow in the intact inner ear caused by air-conducted sound. **b** In case of a third window (SCD or EVA), part of the sound energy dissipates through the third window, resulting in a decreased travelling wave along the basilar membrane (BM) and thus elevated air-conduction hearing thresholds. **c** Endolymph flow in the intact inner ear due to bone-conducted vibration. **d** In case of a third window, the pressure gradient between the oval and the round window increases, resulting in an increased travelling wave along the basilar membrane and thus improved bone-conduction thresholds. For details, see Chapter 3.2.1 and [131]. Abbreviations: BM = basilar membrane; EVA = enlarged vestibular aqueduct; SCD = superior canal dehiscence; OF = oval window ("ovales Fenster"); RF = round window ("rundes Fenster"); SV = scala vestibuli; ST = scala tympani.

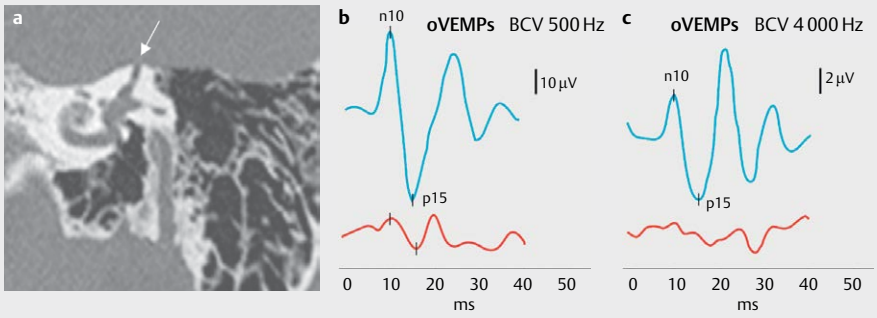
▶ **Table 2** Differential diagnosis of middle-ear and inner-ear conductive hearing loss (CHL) [131] (see Chapter 3.2.1)

| Audio-vestibular test | Middle-Ear Conductive Hearing Loss | Inner-Ear Conductive Hearing Loss |
|---|---|---|
| tympanogram | type A, B or C | type A |
| stapedial reflex | often absent | present |
| otoacoustic emissions | absent | present |
| bone-conduction thresholds | rarely < 0 dB nHL | frequently < 0 dB nHL for frequencies < 2 kHz |
| ACS VEMPs | reduced or absent amplitudes (for CHL ≥ 10 dB) | increased amplitudes, reduced thresholds despite CHL |

Abbreviations: ACS VEMPs = vestibular evoked myogenic potentials (VEMPs) evoked by air-conducted sound (ACS); nHL = normal hearing level.

which finally results in inner-ear conductive hearing loss (▶ **Fig. 5a**). Due to the hydrodynamic properties of inner ear fluids, frequencies of < 2 kHz are particularly affected [131]. ▶ **Table 2** summarizes features that help to distinguish between middle- and inner-ear conductive hearing loss.

**Bony hyperacusis / autophony** If the third window is located within the vestibular organ or in the cochlear *scala vestibuli*, supranormal bone-conduction thresholds up to < 0 dB nHL (normal hearing level) are observed ("bony hyperacusis"). In case of an intact bony inner ear capsule, bone-conducted sound energy is transmitted to the cochlear fluid spaces (▶ **Fig. 5c**). Due to the adjacent stapes footplate, acoustic impedance is higher at the oval than at the round window, so that the sound wave within the cochlea travels from the oval to the round window, creating a basilar membrane motion and thus a hearing percept. If in case of a third window, however, part of the sound energy is shunted away from the




▶ **Fig. 6** Superior canal dehiscence (SCD) in the left labyrinth. After a viral cold with severe coughing, this 55-year-old female patient noticed a "blocked" left ear, autophony (hearing her own heartbeat and steps in the left ear) and diplacusis. Sneezing, coughing, straining and hearing loud sounds (e. g., when singing in the church choir) triggered short attacks of non-spinning vertigo. The Weber tuning fork test was lateralized to the left ear, even when the tuning fork was placed on the left ankle. **a** Bony dehiscence between the left superior canal and the middle cranial fossa (arrow) in the coronary plane of temporal bone HRCT. **b** oVEMPs evoked with 500 Hz bone-conducted vibration (BCV) at Fz (midline of the forehead at the hairline): significantly increased absolute n10p15 amplitude of 67 µV for the left utricle (blue) in contrast to the normal amplitude for the right utricle (red, 15 µV), asymmetry ratio (AR) = 60.5 %. **c** BCV oVEMPs to 4 kHz at Fz: a n10p15 amplitude of 9 µV is evoked for the left utricle (blue) indicating SCD, but not for the right side (normal finding). Please note the different scaling of the y-axis in **c** *versus* **b**. For details, see Chapter 3.2.2.

cochlea before reaching the oval window, the pressure gradient between the oval and round window increases even more, resulting in larger basilar membrane motion and thus improved bone-conduction thresholds (▶ **Fig. 5c**) [131].

Patients typically report autophony (perception of internal bodily sounds, e. g., eye movements, heartbeat, chewing, intestinal sounds), distorted perception of their own voice (diplacusis) or a pulse-synchronous tinnitus (improved bone-conducted transmission of turbulent blood flow from vessels to the cochlea) in the affected ear [141, 142].

The clinical manifestation of these four cardinal symptoms is extremely variable between disorders and affected individuals. As a general rule, a third-window syndrome should always be considered when at least one of these symptoms is present.

**Clinical pearl**

**Ask your audiologist to follow bone conduction thresholds down to supranormal values ( < 0 dB nHL) if you suspect a third-window syndrome [131,142].**

## 3.2.2 Superior canal dehiscence

### 3.2.2.1 Epidemiology and causes

Superior canal dehiscence (SCD) (▶ **Fig. 6a**) was first described by Lloyd Minor and colleagues in 1998 [143]. Incidence and prevalence in the general population can only be estimated, which is due to several reasons. First, volume averaging artifacts in temporal bone CT bear the risk of SCD overdiagnosis – both with regard to its existence and size (see Chapter 3.2.2.3) [144, 145]. Second, many cases of radiologically diagnosed SCDs remain asymptomatic [146]. A series of temporal bone CT scans (0.625 slice thickness) in an emergency unit revealed a bony dehiscence of the superior canal in 5.8 % of temporal bones [147]. Only 11.8 % of these individuals, however, showed characteristic symptoms or findings of SCD, which amounts to 0.5 % of the entire study population. This estimated prevalence corresponds to the finding of a dehiscent bony covering of the superior semicircular canal in 0.5 % of temporal bone specimens in a *post mortem* study [148].

SCD may occur spontaneously; in about one quarter of cases, however, patients report a preceding event, e. g., traumatic brain injury, straining during childbirth [149], or severe coughing (see case examples in ▶ **Fig. 6** and [132]). Additional dehiscences may be found in the tegmen tympani or the posterior canal (see Chapter 3.2.4) [150–152], referred to as "honeycomb mastoid" [153, 154]. In rare cases, SCD can also be caused by adjacent anatomical structures eroding the bony covering of the superior semicircular canal, such as meningioma or the superior petrous sinus (▶ **Table 3**) [155].

### 3.2.2.2 Symptoms and signs

SCD is a veritable otological "chameleon". Often, patients report pressure- or sound-induced vertigo (37.4 and 42.7 %, respectively), autophony (42.5 %), and pulse-synchronous tinnitus (13.7 %) [156]. Around half of the patients presenting for surgical closure of the dehiscence (see Chapter 3.2.2.4) show a positive Hennebert's sign (vertigo and nystagmus triggerd by tragus compression) [157] (▶ **Table 1**). Most patients display nystagmus during Valsalva maneuvers and / or presentation of loud pure tones (125–4000 Hz, 110 dB nHL) to the affected ear via headphones (Tullio phenomenon) [142]. ▶ **Table 1** summarizes the resulting nystagmus directions according to Ewald's laws. In rare cases, even normal intracranial pressure oscillations transmitted to the dehiscent superior canal may suffice to trigger a pulse-synchronous, predominantly vertical nystagmus [158].

Finally, SCD may mimic BPPV of the anterior semicircular canal (a-BPPV) (see Chapter 3.3.2, ▶ **Table 4**) [159]. In a sitting position the bony dehiscence in the roof of the superior canal is covered by the brain, whereas lying down may cause an "unplugging" of the canal resulting in ampullofugal ( = excitatory) endolymph flow, resulting in excitatory nystagmus of the anterior semicircular canal – just like in a-BPPV (▶ **Fig. 1b**). In contrast to a-BPPV, no "unwin-

▶ **Table 3** Semicircular canal dehiscence syndromes and associated disorders.

| |
|---|
| **Superior Semicircular Canal** |
| ▪ meningioma [371]<br>▪ bony erosion caused by the superior petrous sinus [372–376]<br>▪ Ehlers-Danlos syndrome [377] |
| **Posterior Semicircular Canal** |
| ▪ anomalies of the jugular vein bulb (high-riding bulb, diverticulum), also in association with a dehiscent vestibular aqueduct [183–188]<br>▪ fibrous dysplasia [183]<br>▪ iatrogenic, e. g., after mastoidectomy or vestibular schwannoma surgery [183]<br>▪ apex cholesteatoma [378]<br>▪ congenital cholesteatoma of the mastoid [379]<br>▪ eosinophilic granuloma [189]<br>▪ multiple inner ear dehiscences [151, 152, 183, 380–381]<br>▪ inner ear malformations, e. g. enlarged vestibular aqueduct, Mondini malformation [185]<br>▪ complex malformation syndromes, e. g. Apert syndrome [185], Hallermann-Streiff syndrome (oculo-mandibulo-facial syndrome) [382] |
| **Lateral Semicircular Canal [**[142,182]**]** |
| ▪ cholesteatoma<br>▪ iatrogenic |

▶ **Table 4** Important rare differential diagnoses of benign paroxysmal positional vertigo (BPPV, see Chapter 3.3.2).

| Disease | Clinical Findings | Pathophysiology | *„red flags“* |
|---|---|---|---|
| vestibular schwannoma | direction-changing positional nystagmus | compression / traction of the tumor mass on vestibular nerve fibers, depending on body position [383] | unilateral cochleo-vestibular hypofunction |
| intralabyrinthine schwannoma (Chapter 3.4.1) | | different impact of tumor mass on inner ear fluid dynamics depending on body position [384] | |
| superior canal dehiscence (Chapter 3.2.2) | nystagmus in the plane of the anterior semicircular canal when lying down | *“unplugging”* of the anterior semicircular canal when lying down [159] | no reversal of nystagmus direction when sitting up |
| enlarged vestibular aqueduct (Chapter 3.2.6) | nystagmus during rapid head movements and position changes | undamped transmission of intracranial pressure changes onto inner ear fluid spaces [207] | no latency, no reversal of nystagmus direction when changing the position, additional hearing loss |
| labyrinthine ischemia (Chapter 2.2.1) | p-BPPV | ischemia of the posterior semicircular canal and cochlea due to infarction of the common cochlear artery [72] | simultaneous acute ispilateral sensorineural hearing loss |
| cerebellar lesions | central positional nystagmus | near-midline lesions of the cerebellum (e. g., vermis, nodulus, superior cerebellar peduncle) [50] | see overview in Chapter 3.3.2 (apart from hearing loss) |

ding nystagmus” is observed in SCD when sitting up from the lying position.

According to Ewald’s first law, nystagmus direction in SCD generally corresponds to the plane of the affected superior canal [160]. In case of a clear discrepancy between nystagmus direction and plane of the superior semicircular canal, additional dehiscences in other canals should be considered (see Chapters 3.2.4 and 3.2.5) [161].

Vibration-induced nystagmus (VIN) is a very sensitive test for detecting SCD (sensitivity of 84–100 %), which is unfortunately often neglected in clinical practice. At a vibration frequency of 100 Hz, the nystagmus beats mostly horizontally directed towards affected ear indicating an enhanced global sensitivity of the dehiscent labyrinth for vibrational stimuli. At 500 Hz, mastoid vibration causes an excitatory rotatory-vertical nystagmus in the plane of the affected superior canal (see [162–164] for details and the neurophysiological basis of the different nystagmus directions at different frequencies).

Bony hyperacusis of the dehiscent labyrinth is revealed by the Weber tuning fork test (512 Hz): the sound is heard in the affected ear, even if the tuning fork is placed at the medial malleolus [165]. Sometimes, it is already sufficient to ask the patient to hum in order to provoke nystagmus [141, 166]. The pure tone audiogram shows the above-mentioned typical features of a third window, i. e. a low-frequency inner-ear conductive hearing loss with supranormal bone conduction thresholds < 0 dB nHL.

In the early days of SCD diagnostics, lower thresholds for 500 Hz ACS cVEMPs were used as a tell-tale sign for a bony dehiscence

of the superior canal. Nowadays, the n10p15 amplitude of oVEMPs to 500 Hz ACS or bone-conducted vibration (BCV) is preferred as a diagnostic marker due to the higher diagnostic accuracy of this test [167]. In particular, an increased oVEMP n10p15 amplitude at 500 Hz ACS or BCV measured below the contralateral eye (crossed reflex pathway of oVEMPs!) is a reliable indicator for SCD with a sensitivity and specificity of > 90 % (▶ **Fig. 6b**). The exact diagnostic accuracy depends on the chosen stimulus parameters, control groups, and the normal values defined in a particular study (for details, see also [167–170]). The diagnostic accuracy can be further increased by measuring oVEMPs at 4 kHz [171, 172]. While usually no VEMPs can be elicited at this frequency in an intact inner ear, a positive response indicates an SCD with a diagnostic accuracy > 90 % (▶ **Fig. 6c**; see [138, 173] for neurophysiological basics).

Although increased VEMP amplitudes are considered as pathognomonic for a third-window syndrome, they may also be found - albeit more rarely - in other disorders affecting inner ear fluid dynamics, such as early-stage Menière's disease [12] and intracochlear schwannomas (see Chapter 3.4.1) [174].

Finally, electrocochleography (ECochG) in patients with SCD reveals an increased SP/AP ratio (SP = summating potential; AP = action potential) as known from patients with endolymphatic hydrops / Menière's disease. This observation is explained by a reduction in perilymph pressure due to the dehiscent superior canal resulting in a compensatory increase in endolymph pressure ("*hydrops e vacuo*"). ECochG may also be applied for intraoperative monitoring during SCD surgery. After successful closure of the dehiscence, the pathognomonic electrophysiological findings - such as SP/AP ratio, VEMP amplitudes and thresholds – normalize, thus indicating successful closure of the dehiscence and recovery of inner ear fluid dynamics [12, 175, 176].

#### 3.2.2.3 Imaging

High-resolution computed tomography (HRCT) of the temporal bone with slices ≤ 0.625 mm and reconstruction in the plane of the superior canal ("Pöschl view") and orthogonal to it ("Stenvers view") is the gold standard in diagnosis of SCD [130]. Meanwhile, digital volume tomography (DVT) and cone beam tomography (CBT) are considered at least equal to HRCT in diagnosing SCD. For both techniques, radiation exposure is reduced, resolution is better, and costs are lower as compared to HRCT [177, 178].

Heavily T2-weighted MRI sequences (e. g., CISS or FIESTA) are as sensitive as HRCT in detecting SCDs; in 40 % of cases, however, a false-positive diagnosis of SCD is made as compared to the CT scan. Therefore, HRCT, DVT or CBT should be performed to confirm the diagnosis if SCD is suspected in temporal bone MRI and the patient shows compatible signs and symptoms [179].

Because of the general overestimation of SCD in imaging, the diagnostic criteria suggested by Ward et al. [161] also include the presence of at least one characteristic symptom (i. e., sound- or pressure-induced vertigo, autophony, pulse-synchronous tinnitus) and at least one pathognomonic electrophysiological finding that may be explained by the third window (i. e., supranormal bone-conduction thresholds for frequencies < 2 kHz, characteristic VEMP or ECochG findings) beside the radiological evidence of a dehiscence on HRCT .

#### 3.2.2.4 Therapy

Establishing the correct diagnosis is already a major part of treatment in SCD. Patients are often relieved to learn that there is a logical explanation for their strange - sometimes even bizarre - symptoms, such as hearing their own eye and bowel movements. In many cases, triggers such as loud sounds or changes in ambient / middle ear pressure can be avoided [142]. If symptoms are mainly triggered by pressure changes in the middle ear (e. g., rapid change of altitude), tympanostomy tube insertion may be helpful [177].

Surgical closure of the bony dehiscence is the only causal therapy to date and is chosen by about 30 to 50 % of SCD patients. The different surgical approaches (transtemporal vs. transmastoidal) and closure techniques ("plugging", "resurfacing", or a combination of both) along with their indications, risks and success rates are discussed in detail in [142, 161, 177]. In case of a "honeycomb mastoid" with multiple dehiscences in the tegmen tympani, it is possible to tailor custom-made glass ceramic implants by means of computer-aided design (CAD) in order to resurface the tegmen [154].

### 3.2.3 "Near dehiscence" syndrome of the superior canal

The characteristic symptoms and signs of SCD may also be caused by a "near dehiscence", i. e. an extremely thin (< 0.1 mm) and flexible bone covering the superior canal [180], which was found in 1.4 % of temporal bones in a *post mortem* study. Compared to a frank dehiscence of the superior canal, symptoms and signs are often milder in "near dehiscence" syndrome. [180, 181]. Surgical treatment either consists of reinforcing the thin overlying bone (e. g., with fascia or bone cement) without opening the labyrinth or a combination of "plugging" and subsequent "resurfacing" like in frank SCD. In some cases, a radiologically diagnosed SCD turns out to be a "near dehiscence" intraoperatively, which is another illustrative example for the risk of overdiagnosing SCD radiologically [146, 180].

**Clinical pearl**

**No matter if "near" or "frank" dehiscence of the superior semicircular canal: the decision for surgery should always be based on the patient's symptoms, clinical signs and audiovestibular findings – and never on imaging alone**

### 3.2.4 Posterior canal dehiscence

With a prevalence of 0.2 % in a *post mortem* temporal bone study, posterior canal dehiscence is rarer than SCD [95]. It is frequently found in association with jugular bulb (JB) abnormalities, such as a high-riding jugular bulb or a JB diverticulum (30 %), fibrous dysplasia of the temporal bone or it may be iatrogenic (15 %) (▶ **Table 3**) [182, 183]. Beside eroding the bony covering of the posterior canal, JB abnormalities may also result in a dehiscence of the vestibular aqueduct that may serve as an additional third window as well [184–188].

The symptoms and clinical signs of posterior canal dehiscence (PCD) correspond to those of SCD. It should, however, be noted that the nystagmus now beats in the plane of the affected *posterior* canal according to Ewald's first law, i. e., a rotatory upbeat nystagmus towards the affected side in case of excitation (▶ **Fig. 1a**)

[48, 189, 190]. Furthermore, patients with PCD often display inner-ear conductive hearing loss with negative bone conduction thresholds for frequencies of < 2 kHz [191]. Due to the rarity of this disease, no systematic investigations of cVEMP and oVEMP responses have been performed so far. Some case reports indicating ipsilaterally reduced thresholds and increased amplitudes for cVEMPs are available [183, 185].

Imaging (HRCT, DVT or CBT) is performed in analogy to SCD including reconstruction in Pöschl and Stenvers view. Surgical closure is performed via a transmastoid approach with plugging of the posterior semicircular canal. In cases of JB abnormalities, the natural wall between the bulb and the posterior canal is reinforced with cartilage or fascia in addition to plugging of the canal [192–194].

### 3.2.5 Horizontal canal dehiscence

Compared to SCD and PCD, a third window in the horizontal semicircular canal is a real "hummingbird". The rarity of a dehiscence in this location might be due to the fact that the horizontal semicircular canal does not directly adjoin the intracranial space – in contrast to the superior and posterior canals. Thus, its bony wall is not exposed to intracranial pressure oscillations that are a possible factor in the development of SCD and PCD [182]. Dehiscence of the horizontal semicircular canal is mostly found in association with cholesteatomas of the middle ear or as a sequela of surgical interventions (▶ **Table 3**) [142].

In compliance with Ewald's first law, pressure- and sound-induced nystagmus beat in the horizontal direction [195]. Audiovestibular findings have to be interpreted with great care if the dehiscence was caused by middle ear disease, as the typical signs of a third window may be masked by those of middle ear pathology (▶ **Table 2**).

The disorders presented up to now are all caused by a new, non-natural opening of the bony vestibular labyrinth. In addition, there are a number of vestibular syndromes, where an abnormal enlargement of a natural neurovascular foramen may serve as a third window, including the enlarged vestibular aqueduct (see Chapter 3.2.6) and X-linked familial deafness with stapes gusher (see Chapter 3.2.7). These will be presented in the next two sub-Chapters.

### 3.2.6 Enlarged vestibular aqueduct / endolymphatic sac

The most common representative of this group is the enlarged vestibular aqueduct (EVA, also called large vestibular aqueduct, LVA) that is mostly associated with an enlarged endolymphatic sac and occurs bilaterally in 60–80 % of cases (▶ **Fig. 7**). Patients with EVA often show additional inner ear malformations [196]. In particular, it is the most frequently observed inner ear malformation in children with congenital hearing loss (0.6–13 %) [197].

#### 3.2.6.1 Imaging

According to the Cincinatti criteria, an EVA is defined by a width of the vestibular aqueduct > 0.9 mm at the midpoint between the vestibulum at the operculum or by a width > 1.9 mm at the operculum on axial HRCT of the temporal bone (see case example in ▶ **Fig. 7**). As a rule of thumb, the diameter of the aqueduct should not exceed that of the neighbouring posterior semicircular canal [198]. HRCT and temporal bone MRI are equally suitable for diagnosis of enlarged vestibular aqueduct and endolymphatic sac. Visibility of the endolymphatic sac in the T2- or CISS-sequence of the MRI is considered a reliable indicator for an enlarged vestibular aqueduct because the endolymphatic sac is usually not seen on MRI [197, 199].

#### 3.2.6.2 Pathophysiology

The enlarged vestibular aqueduct is a real "chameleon", mimicking the clinical picture of many other inner ear diseases. A short glance at the underlying pathophysiology aids in understanding and correctly interpreting the plethora of clinical signs and symptoms. Mostly, EVA is caused by a homozygous mutation of the *SLC26A4* gene encoding the anion exchanger protein "pendrin" (see Chapter 3.2.6.6 and ▶ **Table 5**) [200, 201]. Pendrin is expressed in surface epithelia of the endolymphatic sac, where it transports $HCO_3^-$ ionsions into the lumen of the sac in exchange for chloride ions, a crucial step in maintaining a neutral pH value in the endolymph. Lack of pendrin function results in acidification of the endolymph, as has been shown in a mouse model with an *Slc26a4* mutation [202, 203]. The effects of an increased $H^+$ concentration on water and ion homeostasis in the inner ear along with the subsequent clinical manifestations are summarized in ▶ **Table 6**.

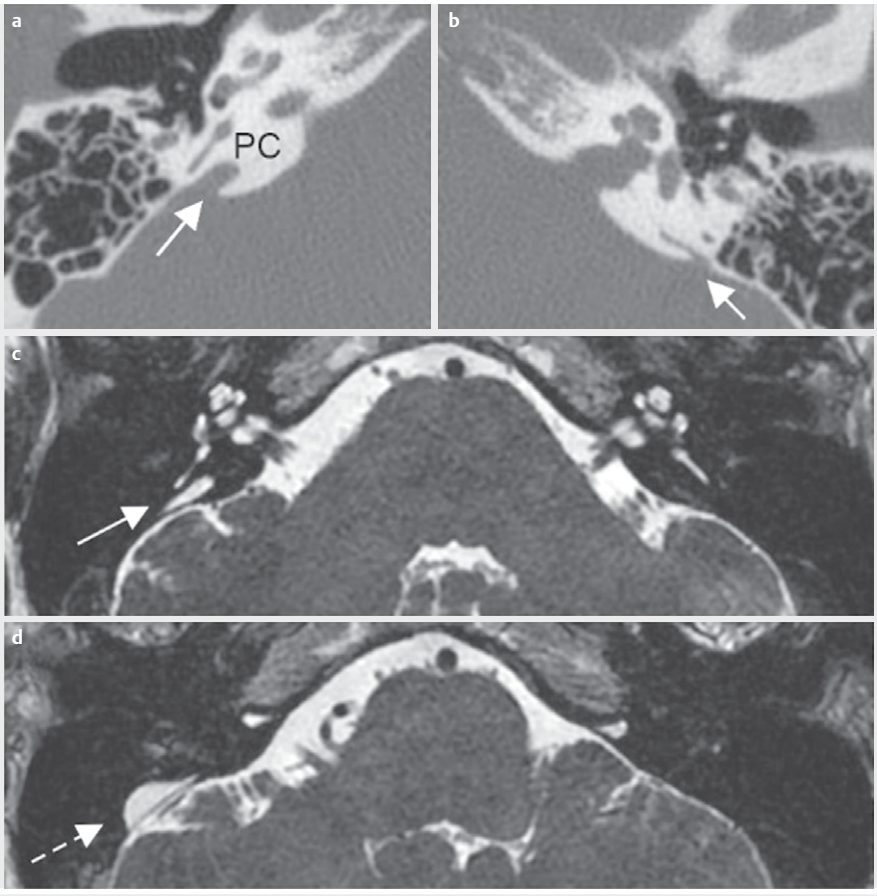
#### 3.2.6.3 Audiological symptoms and findings

Pure tone audiometry (PTA) in EVA patients covers the whole spectrum from low-frequency inner-ear conductive hearing loss (indicative of a third window) up to high-grade sensorineural hearing loss for all frequencies (representing the chronic degeneration of the cochlear sensory epithelium) [204–207]. Beside slowly-progressive sensorineural hearing loss, there are also cases where a rapid deterioration of hearing thresholds is observed immediately after a mild head trauma or pressure changes in the intracranial space / the middle ear (e. g., Valsalva maneuver, rapid changes in ambient pressure). Sometimes, such events are the first manifestation of an up to then silent EVA (see case example in ▶ **Fig. 7**). Based on these experiences, patients are often recommended to avoid contact sports or activities with frequent pressure changes (e. g., scuba diving, parachuting, weight-lifting). It remains, however, elusive if there actually is a causal correlation or rather a "reporting bias" [208]. Long-term progression of sensorineural hearing loss in EVA seems to occur independently from head trauma [209].

#### 3.2.6.4 Vestibular signs and symptoms

Compared to audiological outcomes, reports about vestibular manifestations of EVA are relatively scarce. They cover the full spectrum form third-window symptoms (e. g., sound- and pressure-induced vertigo) to chronic vestibular hypofunction (e. g., persistent imbalance) [205, 206] (▶ **Table 6**). Furthermore, an association with mild head trauma / pressure changes has also been reported for vestibular symptoms in EVA [205, 210, 211].

**Third window** A positive Tullio phenomenon and a vibration-induced nystagmus beating towards the affected ear are characteristic signs of a third window commonly observed in EVA [205, 207]. Furthermore, reduced o- and cVEMP thresholds and increased oVEMP amplitudes have been reported for the affected ear [204, 205, 212–214]. In contrast to SCD, enhanced oVEMP amplitudes have only been obtained for stimulus frequencies < 2 kHz (and not




▶ **Fig. 7** Enlarged vestibular aqueduct (EVA) on the right side. The 27-year-old female patient noticed short-term swaying sensations when sneezing, coughing, and straining, that occurred initially after Eustachian tube dysfunction during a parachute jump. **a** Axial HRCT of the temporal bone shows an EVA on the right (solid arrow, diameter = 3.1 mm at the opercular aperture). Note that the diameter of the aqueduct is clearly wider compared to the neighbouring posterior canal (PC). **b** Normal findings on the left side. **c** and **d** T2-weighted MRI confirmed the diagnosis of right-sided EVA (arrow in **c**). In addition, an enlarged endolymphatic sac was found on the right side (dashed arrow in **d**). Normal findings on the left side, i. e., the endolymphatic duct and sac are not visible on MRI.

up to 4 kHz like in SCD), probably because semicircular canal neurons additionally contribute to the oVEMP response in SCD, but not in EVA (see Chapter 3.2.2.2 and [138]).

Rapid head movements and changes in body position may trigger nystagmus and vertigo, which may be due to an undamped transmission of intracranial pressure oscillations to the inner ear endolymph space through the enlarged vestibular aqueduct. In contrast to BPPV, this type of nystagmus appears without latency, cannot be attributed to a certain semicircular canal and does not respond to repositioning maneuvers [207] (▶ **Table 4**).

**Benign paroxysmal positional vertigo** On the other hand, around 20 % of patients with EVA experience "true" BPPV that might be caused by a disturbed calcium homeostasis in the inner ear (▶ **Table 6**). Typically, BPPV is recurrent and associated with EVA-type hearing loss (see above) in these patients [211, 215, 216].

**Menière-like symptoms** Menière-like (audio-)vestibular symptoms (i.e, recurrent attacks with vertigo and hearing loss for several hours) have been described in a number of studies on EVA since the first report by Valvassori in 1969 [217–219]. In line with these clinical observations, temporal bone MRI detected a cochleo-vestibular endolymphatic hydrops in six patients with bilateral EVA [220]. Furthermore, a discrepancy between caloric paresis and a normal vHIT gain for the horizontal semicircular canal, which is regarded to be an indicator for ELH, was observed in 75 % of EVA patients [221, 222].

**Chronic vestibular hypofunction** The following findings indicate chronic uni- or bilateral vestibular hypofunction in EVA: caloric paresis of the affected horizontal semicircular canal, a reduced vHIT gain and refixation saccades for the semicircular canals of the affected labyrinth [211, 219, 222], vibration-induced nystagmus beating towards the ear with better vestibular function [205], or reduced VEMP amplitudes on the affected side [213].

**Association with vestibular migraine** Finally, an association of EVA with (vestibular) migraine has been described [205, 219] – similar to SCD [142, 177]. Vestibular hypersensitivity due to the additional third window may be a trigger for migraine symptoms under these circumstances.

### 3.2.6.5 Therapy

Therapeutic options in EVA are extremely limited. If acute hearing loss or vertigo are clearly associated with noise and/or pressure changes, these triggers should be avoided whenever possible. Intratym-

▶ **Table 5** Genetic disorders of the vestibular labyrinth (modified according to [224, 354]).

| Gene (Gene Product) | Location | Associated Diseases (Mode of Inheritance) | Phenotype |
|---|---|---|---|
| ***VHL*** (von Hippel-Lindau tumor suppressor) | 3p25.3 | von Hippel-Lindau syndrome (AD) | multiple tumors, ELST in 3.6 % of cases [280] (Chapter 3.4.2.2) |
| ? | 6q | familial bilateral vestibulopathy (AD) | BVP [385] (Chapter 4.1.3.4) |
| ***POU4F3*** | 5q32 | DFNA15 (AD) | progressive sensorineural hearing loss with variable vestibular dysfunction [354] |
| ***GRHL2*** (grainyhead-like 2) | 8q22.3 | DFNA28 (AD) | |
| ***CLIC5*** (chloride intracellular channel 5) | 6p12.3 | DFNB102/103 (AR) | |
| ***COCH*** (cochlin) | 14q12 | DFNA9 (AD) | |
| | | DFNB110 (AR) | |
| ***MYO7A*** (myosin 7A) | 11q13.5 | DFNA11 (AD) | |
| | | DFNB2 (AR) | |
| | | Usher syndrome 1B (USH1B) (AR) | hearing loss/deafness + variable vestibular dysfunction + retinitis pigmentosa [358, 359] (Chapter 4.1.3.4) |
| ***SLC26A4*** or ***PDS*** (pendrin) | 7q22.3 | DFNB4 with EVA (AR) | enlarged vestibular aqueduct + hearing loss/deafness + variable vestibular dysfunction (Chapter 3.2.6) |
| | | Pendred syndrome (AR) | additionally: euthyroid (rarely hypothyroid) goiter [200–202, 225, 226] (Chapter 3.2.6.6) |
| ***POU3F4*** | Xq21.1 | X-linked deafness with stapes gusher DFNX2 (XR) | "*incomplete partition type III*" [77] congenital hearing loss/deafness, "corkscrew" cochlea, third window between cochlea and internal auditory canal (see Chapter 3.2.7) |

Abbreviations: AD = autosomal dominant; AR = autosomal recessive; BVP = bilateral vestibulopathy; DFNA = autosomal dominant non-syndromic deafness; DFNB = autosomal recessive non-syndromic deafness; DFNX2 = X-linked deafness with stapes gusher; ELST = endolymphatic sac tumor; EVA = enlarged vestibular aqueduct; USH1B = Usher syndrome type 1B; VHL = von Hippel-Lindau syndrome.

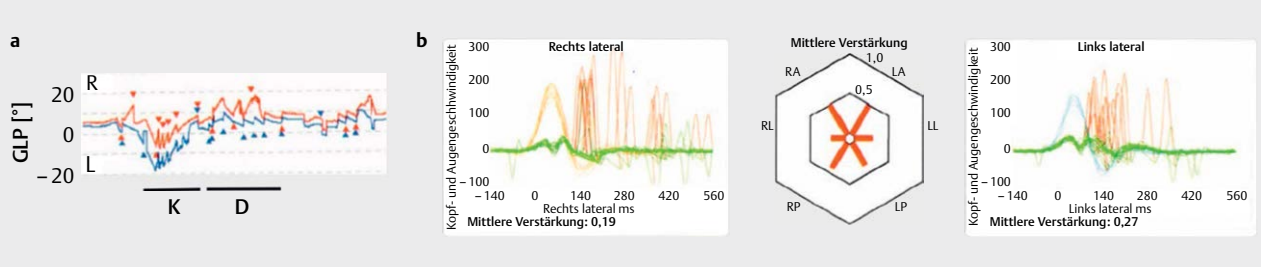
▶ **Table 6** Pathophysiology of enlarged vestibular aqueduct syndrome (Chapter 3.2.6).

| Pathophysiological Basis | Consequence | Clinical Manifestation |
|---|---|---|
| expression / function of epithelial sodium channels (ENaCs) in the endolymphatic sac ↓ [203, 386] → fluid retention in the endolymphatic space ↑ | ▪ dilation of the endolymphatic duct and sac | ▪ third-window syndrome |
| | ▪ endolymphatic hydrops [386–387] | ▪ Menière-like symptoms |
| function of epithelial cation channels (TRPV 5/6) in the endolymphatic sac ↓ [388] | endolymphatic [$Ca^{2+}$] ↑<br>▪ „giant otoliths" ($CaCO_3$) in the utricle, calcium oxalate stones in the saccule<br>▪ degeneration of the otolith membrane [389] | benign paroxysmal positional vertigo |
| enlarged endolymphatic space | undamped transmission of intracranial pressure fluctuations onto the cochleovestibular sensory epithelium [206] | ▪ progressive cochleovestibular hypofunction<br>▪ possible association between minor head trauma and acute deterioration of cochleovestibular function |

panic or systemic glucocorticoids are applied for acute cochleovestibular symptoms although prospective trials regarding their benefit are still lacking [206]. Patients with profound sensorineural hearing loss can be treated with cochlear implants. There is an increased risk of intraoperative perilymph leakage when opening the inner ear ("oozer") in these patients [223]. Surgical procedures on the endolymphatic sac are contraindicated because they have no positive effect on symptoms and carry the risk of deafness [154].

### 3.2.6.6 Associated disorders

An enlarged vestibular aqueduct is also found in different types of hereditary hearing loss (overview in ▶ **Table 5**). Patients with au-




▶ **Fig. 8** Vestibular atelectasis. A 51-year-old male patient complained of short-term spinning vertigo triggered by blowing his nose. On inquiry he described long-standing balance difficulties in darkness. **a** Videooculography of both eyes (right eye: red; left eye: blue) during compression (K) and decompression (D) of a Politzer balloon in the left external ear canal. Y-axis: slow phase velocity (GLP) of the nystagmus. During compression of the ear canal (i. e., excitation of left horizontal canal vestibular hair cells), a purely horizontal left-beating nystagmus is detected, while decompression (i. e., inhibition) induces a horizontal right-beating nystagmus. **b** Video head impulse test (vHIT): the hexaplot (middle) reveals a reduced gain for all six semicircular canals, corresponding to bilateral vestibulopathy (BVP) with unsteady gait in darkness. Exemplarily, the results for both horizontal (= lateral) canals with reduced gains (right: 0.19; left: 0.27) and corrective saccades are displayed ("rechts" = right, "links" = left). Both horizontal canals were unresponsive to bithermal caloric irrigation (not included in the figure). For details, see Chapter 3.2.8.1.

tosomal-recessive non-syndromic deafness with EVA (DFNB4, OMIM #6000791) carry a homozygous mutation of the *SLC26A4* gene in 50–70 % of cases [201, 224].

Like DFNB4, Pendred syndrome (OMIM #274600) is an autosomal-recessive form of hereditary hearing loss. Around 90 % of patients display a homozygous *SLC26A4* gene mutation [200, 225, 226]. With a prevalence of 7.5 to 10 / 10,000 people, it is considered the most frequent type of syndromic hereditary hearing loss [202]. The cardinal features are an enlarged vestibular aqueduct (often in association with further inner ear malformations), progressive sensorineural hearing loss and a mostly euthyroid goiter in 50–80 % of cases. Vestibular symptoms and findings correspond to those of EVA.

Pendrin is involved in the transport of iodide into the lumen of the thyroid follicles in the thyroid gland. Depending on the nutritional intake of iodine, patients may be eu- or hypothyroid. Regular ultrasound is recommended to monitor nodular alterations in the thyroid gland and to detect a rarely observed progression into follicular thyroid carcinoma. Finally, a human geneticist should always be involved for genetic counselling and testing [202].

**Clinical pearl**

**A basic screening of thyroid function (ultrasound, thyroid hormones, TSH) should be performed in all patients with enlarged vestibular aqueduct for early diagnosis of an underlying Pendred syndrome.**

Beside DFNB4 and Pendred syndrome, EVA is associated with many other inner ear malformations, such as incomplete partition type II (formerly called Mondini malformation) [227] or complex malformation syndromes with inner ear involvement like CHARGE syndrome (see also the contribution by Prof. Dr. Warnecke), branchio-oto-renal syndrome, oto-facio-cervical syndrome, Waardenburg syndrome, and Noonan syndrome [206].

### 3.2.7 X-linked deafness with stapes gusher (DFNX2)

This X-linked recessively inherited disease almost exclusively affects males and is often associated with a *POU3F4* gene mutation (▶ **Table 5**). Similar to EVA, it is caused by an abnormal enlargement of a natural neurovascular foramen, i. e., the internal auditory canal. In addition, an incomplete bony separation between the cochlea and the internal auditory canal is found. Thus, intracranial pressure variations may be transmitted directly onto the inner ear fluid spaces via the enlarged internal auditory canal resulting in progressive damage of the sensory epithelium. The dysplastic cochlea often looks like a corkscrew (incomplete partition type III). This malformation frequently results in deafness, and perilymph gusher must be expected during cochlear implantation [77, 129, 130, 223].

### 3.2.8 Differential diagnoses of third-window syndromes

#### 3.2.8.1 Vestibular atelectasis

Vestibular atelectasis has been suggested as a possible underlying pathology in patients with a combination of bilateral vestibulopathy (see Chapter 4.1) and pressure- / sound-induced nystagmus or vertigo (see case example in ▶ **Fig. 8**) [141, 228–230]. Bilateral vestibular hypofunction (caloric paresis, reduced vHIT gain for the affected canals) is explained by reduced endolymph flow due to a collapse of the membranous labyrinth. In some patients, however, high-frequency canal function as measured by vHIT is relatively well preserved despite caloric paresis of the horizontal canals. This discrepancy is explained by the fact that in cases of a collapsed membranous labyrinth, low-frequency caloric stimulation cannot create sufficient endolymphatic flow for excitation of the vestibular hair cells while the higher-frequency acceleration during head impulse testing is strong enough to induce stereocilia deflection and thus an excitation / inhibition of vestibular hair cells [228].

Triggering of vertigo by loud sounds or pressure changes in the middle ear despite bilateral vestibular hypofunction is explained by a direct contact between the collapsed membranous labyrinth and the stapes footplate allowing for a direct transmission of middle ear pressure changes onto inner ear fluid spaces. This finding indicates that bilateral vestibulopathy in vestibular atelectasis is not caused by functional loss of vestibular hair cells but rather by a mechanical cause preceding signal transduction in the hair cells, such as a collapse of the membranous labyrinth [228].

Until recently, it was unclear if the clinical combination of pressure- and sound-induced vertigo with bilateral vestibulopathy ac-

tually corresponds to the histopathological findings of vestibular atelectasis [231] first reported by Merchant and Schuknecht in 1988 [232]. Recent advances in high-resolution inner ear MRI allowed visualization of the collapsed endolymphatic space and identification of uni- and bilateral vestibular atelectases in 3D FLAIR sequences recorded four hours after intravenous gadolinium application [233–235].

Therapeutic options for vestibular atelectasis are very limited. Similar to third-window syndromes, it is already very reassuring for patients to know the underlying cause of their symptoms. Triggering factors should be avoided. Depending on the extent of bilateral vestibulopathy, an intratympanic gentamicin application may be discussed as *ultima ratio* in case of debilitating vertigo attacks [228]. Physiotherapy of bilateral vestibulopathy is performed as described in Chapter 4.1.5.

#### 3.2.8.2 Other differential diagnoses

Generally, pressure- or sound-induced vertigo and nystagmus can be triggered in all disorders of the middle and inner ear where the membranous labyrinth comes into direct contact with the stapes footplate [140], e. g., inflammatory causes as mentioned in the first description of Hennebert's signs for patients with syphilis [157], malformations of the middle ear, or post-operative / -traumatic scar formation between the stapes footplate and the vestibule [236, 237].

Sometimes, patients with Menière's disease report short pressure- or noise-induced vertigo sensations as well. This may be explained by the fact that the membranous labyrinth of the vestibule is dilated by endolymphatic hydrops to such an extent that it gets into temporary contact with the stapes footplate. If middle ear pressure increases (e. g., during a Valsalva maneuver) or the stapes footplate is deflected by loud sounds, the pressure wave is transmitted directly to the vestibular endolymph resulting in short bouts of vertigo due to transitory excitation of vestibular hair cells [238–240].

## 3.3 Positional vertigo for seconds to minutes

### 3.3.1 Rare variants of benign paroxysmal positional vertigo (BPPV)

With a lifetime prevalence of 2.4 %, benign paroxysmal positional vertigo (BPPV) is one of the most common peripheral vestibular disorders [2, 241]. In more than 90 % of cases, the otoliths dislodge into the long arms of the posterior or horizontal semicircular canals. Besides, there are rare manifestations like canalolithiasis of the anterior ( = superior) semicircular canal (a-BPPV), which is observed in about 3 % of BPPV patients [242, 243]. In addition, clinical presentations have been described that may be explained by dislocation of otoliths into the short arms of the posterior or horizontal semicircular canals or into the common crus of the posterior and the anterior semicircular canal. A comprehensive overview about symptoms, nystagmus patterns, and specific therapeutic maneuvers is presented in [50].

Ewald's three laws apply for all types of BPPV [46]: the nystagmus beats in the plane of the affected semicircular canal (Ewald's first law), and the direction of the nystagmus indicates excitation or inhibition of that canal (Ewald's second and third laws) (▶ **Fig. 1**). Video-oculographic recording of the nystagmus in different gaze directions is recommended particularly for rare types of BPPV in order to identify the individual nystagmus components (torsional, horizontal, vertical) and thus the affected semicircular canal [49, 244].

In case of so-called type 2 BPPV, the Dix-Hallpike maneuver does usually not evoke vertigo or nystagmus, while sitting up from the maneuver on the affected side results in short spells of vertigo and retropulsion of the trunk. Symptoms typically attenuate during repeated sit-ups from the Dix-Hallpike maneuver. Dislocation of otoliths into the short arm of the posterior canal is assumed to be the underlying pathology here [245, 246].

### 3.3.2 Rare differential diagnoses of BPPV

The "hoofbeats" of BPPV may also belong to "zebras" with similar clinical presentations. Generally, the diagnosis of BPPV should be critically reviewed in the following situations [50, 247]:

- The direction of the positional nystagmus does not correlate with the plane of the semicircular canal that is stimulated or inhibited by a certain positional maneuver.
- The nystagmus is purely torsional or vertical.
- The features of the nystagmus are not characteristic for BPPV, e. g., no latency after the positional maneuver, no crescendo-decrescendo pattern, no reversal of nystagmus direction for the vertical semicircular canals when sitting up ("unwinding" nystagmus) or when turning from one side to the other for the horizontal semicircular canals.
- The symptoms do not improve despite repeated correct performance of repositioning maneuvers for the supposedly affected semicircular canal.
- Nystagmus and vertigo intensity during positioning maneuvers do not correspond.
- Additional hearing loss is present in the supposedly affected ear (see also Chapters 2.2.1 and 3.2.6).

In these cases, further (audio-)vestibular investigations and imaging of the brain and temporal bone should be initiated (CT scan or MRI, depending on the symptoms). ▶ **Table 4** summarizes the most important diseases that may mimic BPPV.

## 3.4 Spontaneous episodic vertigo for hours to days

The following disorders are "zebras" particularly mimicking Menière's disease, i. e., they present with spontaneously occurring recurrent (audio-)vestibular symptoms lasting for hours (up to days). While the early stage of disease is typically characterized by episodic or fluctuating vestibular symptoms, progressive deterioration resulting in a chronic vestibular syndrome (Chapter 4) is often observed in the long term. Apart from the disorders mentioned in this Chapter (intralabyrinthine schwannomas, tumors of the endolymphatic sac, autoimmune inner ear disease), it should be kept in mind that an EVA (see Chapter 3.2.6) can imitate the "hoofbeats" of Menière's disease as well.

### 3.4.1 Intralabyrinthine schwannoma

#### 3.4.1.1 Epidemiology and classification

This peculiar schwannoma of the eighth cranial nerve – also called primary inner ear schwannoma [248] – originates from Schwann cells of the vestibular or cochlear nerve within the labyrinth [249, 250]. Although first described back in 1917 [251], these be-

nign inner ear tumors were considered a rarity for many years. Improved quality of inner ear MRI and a growing awareness of their existence have resulted in an increased number of diagnosed intralabyrinthine schwannomas (ILS) in recent years [252]. Currently, their annual incidence is estimated to be >1/100,000 [253] and they are considered to represent 10 % of all schwannomas of the eighth cranial nerve [254]. Up to now, about 500 cases have been described in the literature [255]. Classification of intralabyrinthine schwannomas, e. g. according to Kennedy [256], Salzman [257] and Van Abel [248] is based on location and extension of the tumor. Intracochlear schwannomas are the most frequent subtype making up for 50 % of all ILS. Bilateral tumors have been described in patients with neurofibromatosis type II [258] and sporadically [259].

#### 3.4.1.2 Clinical presentation and imaging

The most common symptom is unilateral hearing loss, which is found in 99 % of patients with ILS. Depending on the location of the tumor, vertigo and balance disorders may also occur. The time course of cochleo-vestibular symptoms is extremely variable; they may be episodic, fluctuating, or progressive. In one observational study, 39 % of ILS patients were initially diagnosed with Menière's disease [248] because both disorders present with similar symptoms. The fluctuating nature of ILS symptoms is suggestive of secondary endolymphatic hydrops. Beside similar audiovestibular findings in both disorders [260], the recently described radiological evidence of endolymphatic hydrops in ILS supports this notion [261, 262].

**Clinical pearl**

**All patients with unilateral audiovestibular dysfunction (stable, fluctuating or progressive) should undergo MRI of the temporal bone with the explicit question of intralabyrinthine schwannoma [116].**

It is essential to specifically ask the radiologist for the presence of an ILS as these tumors are easily overlooked due to their small size and uncommon location, even if they are visible on the MRI scan [254, 263]. This also explains the long latency (7 years on average) from symptom onset to diagnosis [248]. Beside Menière's disease, ILS may also mimic the clinical manifestation of BPPV (see Chapter 3.3.2 and ▶ **Table 4**). Rare differential diagnoses of ILS include intralabyrinthine hemorrhage (see Chapter 2.2.2), fibrosis and lipoma [264, 265].

#### 3.4.1.3 Therapy

Patients with ILS have mostly been treated with a 'wait-and-test-and-scan' strategy for many years, especially when hearing on the affected side was still functional. With the progress in microsurgical techniques and cochlear implant surgery, new therapeutic approaches are currently arising, e. g., early tumor resection via a partial, subtotal or near-total cochleoectomy (depending on the size of the tumor) with simultaneous cochlear implant surgery for intracochlear schwannomas [252, 254, 266]. Very good hearing outcomes are achieved for perimodiolar CI electrodes that are approximated to the spiral ganglion cells in the modiolus using a cartilage-in-perichondrium-bed technique for cochlear reconstruction [267, 268]. In addition, it is possible to preserve semicircular canal function during cochleoectomy [263]. Reports on stereotactic radiotherapy of intralabyrinthine schwannomas are rare [269, 270]. Here, it should be particularly noted that cochlear spiral ganglion neurons are located within the radiation field, which might result in their degeneration and subsequent neural deafness over the years [262].

### 3.4.2 Endolymphatic sac tumor

#### 3.4.2.1 Clinical manifestation and imaging

Endolymphatic sac tumors (ELSTs) are low-grade malignant papillary neoplasms (low-grade adenocarcinomas) that originate from the epithelium of the endolymphatic duct or sac in the area of the bony vestibular aqueduct (▶ **Fig. 9**) [271–273]. They are characterized by a locally destructive and infiltrating growth pattern, whereas metastases are very rare (only three cases with spinal or cerebellar metastases reported so far) [274, 275]. Currently, less than 200 cases of ELSTs have been described in the medical literature [276]. The clinical manifestation with fluctuating, progressive or chronic unilateral (audio-)vestibular hypofunction resembles that of Menière's disease [273, 275, 277]. Accordingly, a – most likely secondary – endolymphatic hydrops has been visualized on inner ear MRI of ELST patients [278]. An upregulation of type 2 vasopressin receptors in the endolymphatic sac is discussed as a possible underlying pathophysiology of secondary endolymphatic hydrops in ELST in addition to a mechanical blockage of the endolymphatic drainage [279].

The radiological presentation of ELSTs is very heterogeneous. Contrast enhancement on T1-weighted MRI sequences is observed for the solid portions of these vascularized lobular tumors, while intra-tumor hemorrhages are hyperintense on native T1 series, and cystic components appear hyperintense in T2-weighted images (▶ **Fig. 9**). Tumor extension into the cerebellopontine angle and the cerebellum is possible. In addition to MRI, HRCT of the temporal bone should be performed to assess bone destruction. Typically, lytic bony lesions with a moth-eaten appearance are observed [275].

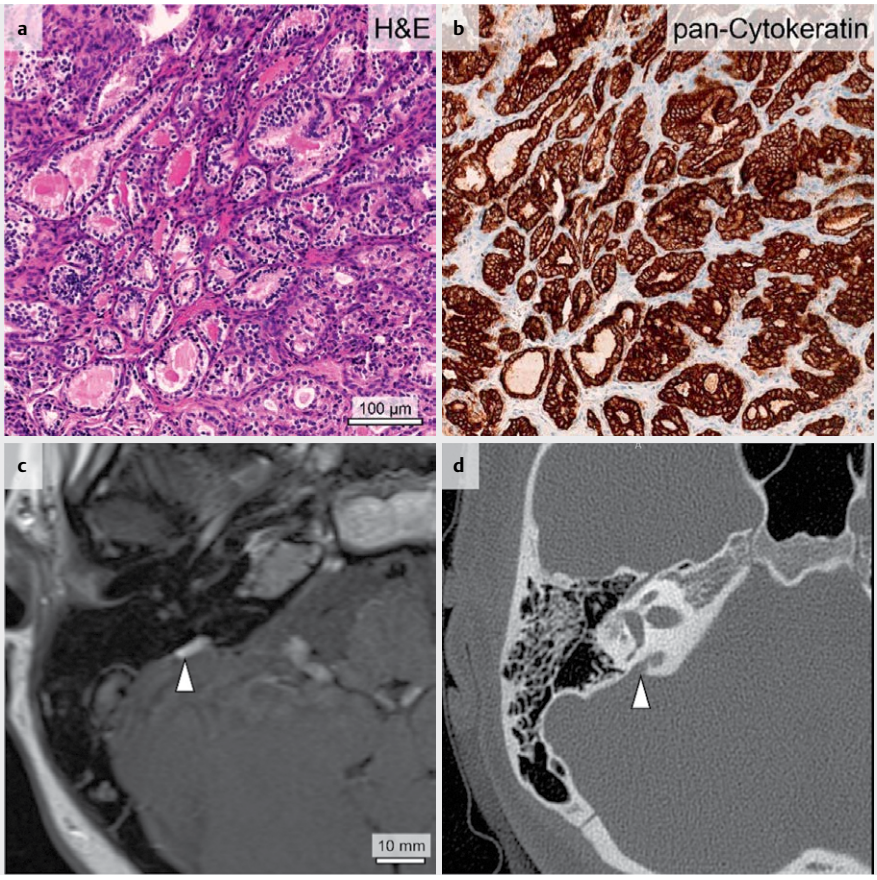
#### 3.4.2.2 Association with von Hippel-Lindau syndrome

In about 30 % of cases, an endolymphatic sac tumor represents the first manifestation of von Hippel-Lindau syndrome (vHL, OMIM: #193300) [280]. This rare autosomal dominant disorder (estimated prevalence of 1/39,000) is due to a mutation in the *VHL* gene (chromosome 3p25.3) (▶ **Table 5**) [224]. Patients with vHL are often affected by multiple tumors beside ELST, such as hemangioblastomas of the CNS and the retina, pheochromocytomas of the adrenals, clear-cell renal cell carcinomas, and endocrine tumors of the pancreas [281].

**Clinical pearl**

**Every patient with an endolymphatic sac tumor should be investigated for von Hippel-Lindau syndrome.**

The diagnostic work-up includes an MRI of the brain, the temporal bone, the spinal cord and the abdomen, an ophthalmologic examination and genetic counselling [275]. In a large, multi-center European registry study from 2016, ELSTs were present in 3.6 % of patients with vHL syndrome (bilateral in 20 % of cases) [280].




▶ **Fig. 9** Endolymphatic sac tumor (ELST). **a** and **b** Typical papillary pattern in hematoxylin-eosin (H&E) and pan-cytokeratin staining of the histological specimen. Pre-operative imaging displayef a cystic tumor of the right endolymphatic sac on T2-weighted cMRI (arrowhead in **c**) with enlargement and erosion of the vestibular aqueduct on HRCT of the temporal bone (arrowhead in **d**). Images provided by courtesy of David Bächinger, MD, Zurich, Switzerland.

#### 3.4.2.3 Therapy

The mainstay of therapy is a complete resection of the tumor via a translabyrinthine, retrosigmoid, or subtemporal approach, depending on tumor extension [282]. In cases of early resection, hearing preservation is often possible. If complete resection is not possible, adjuvant radiotherapy is recommended. With this concept, a long-term tumor-free survival is usually achieved. Radiotherapy alone is not able to control tumor growth [275, 276]. Finally, single case reports have been published about tumor reduction with tyrosine kinase inhibitors as salvage therapy for non-resectable tumors [283].

### 3.4.3 Autoimmune inner ear disease

With an estimated annual incidence of < 5/100,000, autoimmune inner ear disease (AIED) is very rare. The actual figure is probably higher as many cases might be missed due to the clinical heterogeneity of the disorder and the absence of reliable diagnostic markers. Overall, around 1 % of cochleo-vestibular disorders are supposed to be of autoimmune origin [284]. Following the metaphor of "horses" and zebras", AIED comprises a whole "zoo" of different disorders. Their systematic description would go far beyond the scope of this manuscript. The following Chapter is meant to sharpen the otorhinolaryngologist's awareness for AIED and enable him to perform basic investigations. In 15 to 30 % of cases, AIED occurs as a manifestation of systemic autoimmune disease (secondary AIED) [285]. The most important causes are summarized in ▶ **Table 7**, Susac's syndrome is presented in detail by Prof. Warnecke [286].

#### 3.4.3.1 Definition

The common observation that much more is known about cochlear than vestibular manifestations of inner ear disease (see also Chapter 3.2.6.4) holds true for AIED as well, starting with the diagnostic criteria. The central feature of AIED is defined as bilateral, fluctuating and progressive sensorineural hearing loss developing over weeks to months. The time course of progression is too slow for sudden sensorineural hearing loss (i. e., longer than 72 hours) and too rapid for presbyacusis. As a rule of thumb, a bilateral sensorineural hearing loss of at least 30 dB nHL at any frequency should be present that shows a progression in at least one ear on two pure tone audiograms performed three months apart. Progression is defined by a threshold shift of at least 15 dB at one frequency or 10 dB at two neighbouring frequencies [284, 287]. Furthermore, the hearing loss must not be better explained by other origins (e. g., noise-induced hearing loss, ototoxic substances) [285, 288]. In about 50 % of cases, hearing loss starts in one ear before developing into symmetric or asymmetric bilateral sensorineural hearing

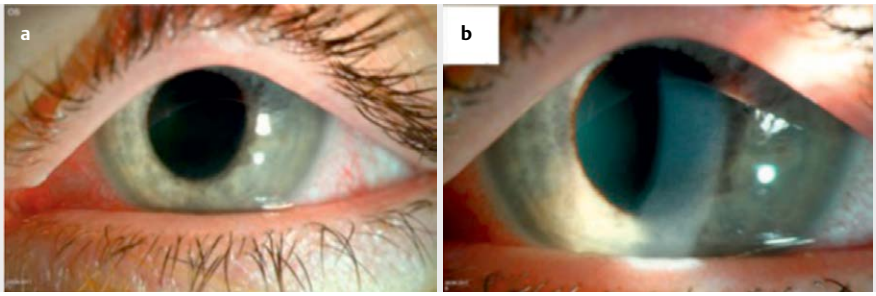
▶ **Table 7** Differential diagnoses of immune-mediated diseases affecting the inner ear, the eye, and the brain ("brain-eye-ear" syndromes, according to [287, 289, 290]).

| | Diagnosis | Pecularities /«*red flags*» | Characteristic findings |
|---|---|---|---|
| vasculitis [294] | Cogan's syndrome [390–392] | triad of vertigo, hearing loss, and "red eye" | ▪ ophthalmological examination: interstitial keratitis, uveitis, conjunctivitis<br>▪ slit lamp examination: cells in the anterior chamber of the eye (▶ **Fig. 10**) |
| | Susac's syndrome | triad of encephalopathy, branch retinal artery occlusions (BRAOs), and sensorineural hearing loss | ▪ brain MRI: "snowball"-like lesions (T2) near the corpus callosum, "punched-out" holes in the corpus callosum (T1)<br>▪ fundus fluorescin angiography of the retina: BRAOs |
| | ANCA-associated vasculitis | granulomatosis with polyangiitis (GPA; formerly: Wegener's granulomatosis): chronic otitis media | elevated cANCA |
| | | eosinophilic granulomatosis with polyangiitis (EGPA) : chronic sinusitis, nasal polyps | elevated pANCA |
| | Behçet's disease | ▪ aphthous oral and genital lesions<br>▪ cerebral venous sinus thrombosis (CVST) | ▪ positive pathergy test<br>▪ often positive for HLA-B51 |
| others | sarcoidosis [297] | ▪ Heerfordt syndrome: triad of uveitis, swelling of the parotid gland and facial nerve palsy<br>▪ erythema nodosum | ▪ elevated ACE<br>▪ thorax imaging: bilateral hilar lymphadenopathy |
| | Sjögren's syndrome | ▪ «dry eyes, dry mouth»<br>▪ increased risk for lymphoma of the parotid gland | ▪ elevated anti-Ro, anti-La<br>▪ Ultrasound of the parotid gland: "leopard skin" pattern |
| | systemic lupus erythematodes (SLE) [393] | "butterfly rash" | elevated ANA, anti-ds-DNA, anti-SmD antibodies |
| | antiphospholipid syndrome (APS) | recurrent thrombosis<br>▪ CNS: apoplex, TIA, CVST<br>▪ eye: "amaurosis fugax", visual field impairment<br>▪ uterus: recurrent abortion | elevated levels of anti-phospholipid antibodies (anti-cardiolipin, anti-beta-2 glycoprotein, anti-lupus coagulant) |
| | Vogt-Koyangi-Harada syndrome | alopecia, vitiligo, poliosis (predominantly affects melanocytic tissue) | ▪ fundus fluorescence angiography: "starry sky"<br>▪ optic coherence tomography: subretinal fluid accumulation |
| | relapsing polychondritis [394–395] | involvement of ear, nose, and laryngeal/tracheal cartilage (perichondritis, otitis externa, Eustachian tube dysfunction, saddle nose, laryngotracheomalacia, subglottic stenosis) | cartilage biopsy: inflammatory infiltrates |
| | rheumatoid arthritis | ossicular chain involvement in 15–20 % | elevated RF, anti-CCP (ACPA), ANA |
| | Hashimoto's thyroiditis | Steroid sensitive encephalopathy | elevated anti-TPO |

Abbreviations: ACE = angiotensin-converting enzyme; ANA = antinuclear antibody; ANCA = anti-neutrophilic cytoplasmatic antibody (c = cytoplasmatic, p = perinuclear staining); anti-CCP ( = ACPA) = anti-cyclic citrullinated peptide antibody; anti-ds-DNA = anti-double stranded DNA antibody; anti-TPO = anti-thyreoperoxidase antibody; anti-SmD = anti-Smith antibody (subgroup D); APS = antiphospholipid antibody syndrome; BRAO = branch retinal artery occlusion; CVST = cerebral venous sinus thrombosis; EGPA = eosinophilic granulomatosis with polyangiitis; GPA = granulomatosis with polyangiitis; RF = rheumatoid factor; TIA = transient ischemic attack.

loss [285]. While accompanying vestibular dysfunction is described in around half of the AIED cases, clear diagnostic criteria for vestibular AIED are currently not available [285].

Fluctuating (audio-)vestibular symptoms reminiscent of Menière's disease are particularly common in the early stage of the disease. It should be noted that cochlear and vestibular symptoms may occur independently [289]. AIED should always be considered as a possible differential diagnosis in cases of bilateral Menière's disease [285, 287].




▶ **Fig. 10** Ophthalmological findings in Cogan's syndrome. **a** Conjunctivitis. **b** Slit lamp examination reveals cells in the anterior chamber of the eye indicating uveitis. Images provided by courtesy of Elias Flockerzi, MD, Homburg/Saar, Germany.

### 3.4.3.2 Diagnostic approach

**History taking and clinical examination** In addition to the temporal course of (audio-)vestibular symptoms, special attention should be paid to possible other otorhinolaryngological manifestations of autoimmune disease (see ▶ **Table 7** and Dr. Weiss' contribution [128]). History taking should comprise a complete review of systems, in particular ophthalmological and neurological symptoms (▶ **Fig. 10**). Autoimmune disorders affecting the brain, eyes and ears are summarized as "brain-eye-ear syndromes" (BEE) (▶ **Table 7**) [290]. Medical history is completed by questions about symptoms of the gastrointestinal tract (e. g., Crohn's disease, ulcerative colitis, celiac disease) [291–293], the locomotor system (e. g., rheumatoid arthritis), the kidneys (e. g., ANCA-positive vasculitis), and the thyroid gland (e. g., autoimmune thyroiditis) [285].

**Audio-vestibular investigations** Pure tone audiometry typically displays uni- or bilateral sensorineural hearing loss. An additional conductive hearing loss is possible, e. g., in chronic otitis media due to ANCA-associated vasculitis, ossicular chain ankylosis in rheumatoid arthritis, or Eustachian tube dysfunction in relapsing polychondritis (▶ **Table 7**) [285, 294]. PTA hearing threshold can be used for monitoring disease activity and response to treatment (see Chapter 3.4.3.3). Nowadays, mobile tablet-based audiometers allow the patient to monitor his hearing threshold at home [289, 295].

Every patient with AIED should be examined with vHIT, c- and oVEMPs in order to identify the involvement of the individual vestibular end organs. Due to their high test-retest reliability, these tests are suitable for monitoring vestibular function in the course of the disease – like a kind of "pure tone audiometry" of the balance organ [289]. Collecting these data from large patient populations is not only an important prerequisite for an independent definition of autoimmune *vestibular* disease (see above) but also allows to quantify treatment response of the vestibular organs [296]. Both factors are crucial for performing randomized clinical therapeutic trials in AIED (see Chapter 3.4.3.3).

**Imaging** An MRI of the brain and the temporal bone should be performed in every suspected case of AIED in order to exclude other pathologies with similar symptoms (e. g., vestibular and intralabyrinthine schwannomas, endolymphatic sac tumors, multiple sclerosis) and to obtain further information regarding a possible BEE syndrome (see ▶ **Table 7**). Contrast enhancement in the vestibulocochlear nerve and the basal meninges is commonly seen on brain MRI in patients with autoimmune disorders involving the CNS [285, 288, 290, 297, 298].

**Laboratory investigations** Unfortunately, there are no established guidelines for laboratory investigations in suspected AIED. The parameters listed in ▶ **Table 8** based on [284, 287–290] have been shown to provide useful basic information in clinical practice. This list may be modified depending on the clinical picture and known medical conditions of the patient. In this context, close cooperation with an immunologist is recommended, in particular regarding further laboratory tests and initiation of an immunosuppressive therapy [285].

Infections with neurotropic bacteria or viruses may follow a similar clinical course as AIED. Since they belong to the few treatable causes of inner ear diseases, the according serological testing should be performed despite their rarity (see Chapter 2.2.3 and [103]).

**Ophthalmological and neurological assessment** As known from neurotological examination, the eyes are the proxy for the inner ear, which holds also true for AIED [289]. While inflammatory lesions of autoimmune disease are not visible in the living inner ear, the ophthalmologist can see them in the patient's eye (▶ **Fig. 10**) and may thus provide crucial hints for the presence of AIED in the sense of BEE syndromes (▶ **Table 7**).

Depending on the clinical picture, a neurologist/neuroimmunologist should be consulted to decide about additional investigations such as lumbar puncture (detection of oligoclonal bands, intrathecal antibody production, antibodies against neurotropic bacteria and viruses, tumor cells in case of carcinomatous meningitis) and about treatment of central manifestations in BEE syndromes [289, 290].

### 3.4.3.3 Therapy

An early treatment of AIED is crucial because audiovestibular dysfunction is potentially reversible. Due to the rarity and clinical heterogeneity of AIED, only few, mostly non-randomized and uncontrolled clinical trials have been performed with small patient groups. In addition, different outcome parameters make it difficult to compare individual studies. Thus, treatment of AIED remains a tightrope act between preserving audiovestibular function and avoiding potential side effects of the treatment. A current overview about AIED pharmacotherapy is found in [299].

▶ **Table 8** Laboratory investigations for suspected autoimmune inner ear disease (AIED) (according to [284, 287–290]).

| | Investigation | Characteristic findings / associated disorders |
|---|---|---|
| screening for inflammatory diseases | ▪ complete blood count[1]<br>▪ serum: liver and kidney function tests, electrolytes, serum protein levels, fT4, TSH, immunoglobulines (IgG subclasses, IgA, IgM)<br>▪ urine analysis including protein, calcium, albumin | e. g. anemia of chronic inflammation, elevated immunoglobulin levels / signs of systemic manifestation in autoimmune disease |
| | CRP, ESR[2] | generally elevated in autoimmune disease |
| complement system | C3c, C4 | generally reduced in autoimmune disease (increased consumption) |
| enzymes | ACE | elevated in sarcoidosis |
| anti-nuclear antibodies (ANAs) | ANA | generally elevated in autoimmune diseases |
| | anti-ds-DNA, anti-SmD | elevated in systemic lupus erythematodes |
| | anti-SSA (Ro) / anti-SSB (La) | elevated in Sjögren's syndrome |
| anti-cytoplasmatic antibodies (ANCAs) / ANCA-associated vasculitis | cANCA (anti-proteinase 3 (PR3) antibodies) | elevated in GPA |
| | pANCA (anti-myeloperoxidase (MPO) antibodies) | elevated in microscopic polyangiitis and EGPA |
| other antibodies | RF Anti-CCP (ACPA) | elevated in in rheumatoid arthritis |
| | anti-cardiolipin, anti-beta-2-glycoprotein, anti-lupus coagulant | elevated in antiphospholipid syndrome (APS) |
| | anti-TPO | elevated in Hashimoto's thyroiditis |
| infectious diseases | serology for treponema pallidum, HIV, Lyme disease | differential diagnosis of infectious diseases |

[1] including immunophenotyping of peripheral blood lymphocytes if required (reduced levels of CD4+ and CD8+ lymphocytes) [288]. [2] if needed also neopterin (inflammatory marker), soluble IL2 receptor (sIL2-R) and IL6 (monitoring of disease activity). Abbreviations: CRP = C-reactive protein, ESR = erythrocyte sedimentation rate. For further abbreviations, see ▶ **Table 7**.

#### 3.4.3.3.1 Glucocorticoids

Treatment with systemic glucocorticoids is the mainstay of therapy (e. g., prednisone 1 mg/kg body weight p.o. for four weeks). If hearing thresholds improve within the first four weeks, therapy is continued until monthly pure tone audiometry shows stable hearing thresholds. At that point, oral prednisone is tapered over a period of 8 weeks until a maintenance dose of 10 mg per day is reached. If hearing thresholds are stable after a six-month course of corticosteroids, the treatment is ended. In case of relapsing symptoms during oral glucocorticoid therapy, an immunologist should be consulted to decide whether the corticoid dosage should be increased or whether corticosteroid-sparing agents (immunosuppressants or biologicals) should be added (see below). In case symptoms do not improve within the first four weeks of therapy, oral prednisone is tapered within 12 days.

While around 70 % of patients respond positively to the first application of systemic glucocorticoids, steroid resistance may develop in the long term. Here, immunosuppressants and biologicals are applied as an alternative to glucocorticoids. In general, audiometry should be performed once per month until hearing thresholds are stable, and from that point on every six months [285, 288]. The following regimen should be followed to avoid steroid-associated adverse effects: daily intake of vitamin D and calcium (osteoporosis prophylaxis), daily intake of pantoprazole (gastric ulcer prophylaxes) and sulfamethoxazole / trimethoprim twice a week (prophylaxis of *Pneumocystis carinii* pneumonia)

In case of contraindications for systemic glucocorticoid therapy, intratympanic application, e. g., once per week in the affected ear over two months, seems to be an alternative. In a trial with 11 patients, 54 % reported improved hearing and balance function after intratympanic application of 6-methylprednisolone [300] (in this context, see also [301] for correct nomenclature of glucocorticoids in local inner ear application).

#### 3.4.3.3.2 Further therapeutic options

Depending on the course of the disease and further medical conditions of the patient, immunosuppressants like cyclophosphamide, methotrexate, azathioprine, cyclosporine, or mycophenolate mofetil may be applied under the lead of an immunologist. Patients have to be monitored regularly for possible side effects [285, 288].

In some studies, biologicals like anti-TNFα antibodies (golimumab, infliximab, etanercept), IL1β blockers (anakinra) and anti-CD20 antibodies (rituximab) were applied when AIED symptoms relapsed during treatment with oral steroids. Infliximab may also be injected intratympanically [302]. Despite positive response in single cases, there is still too little data available to recommend biologicals as a primary alternative to systemic steroid therapy. Likewise, the significance of plasmapheresis in AIED is currently unknown [284, 285, 288, 299].

If AIED finally results in deafness, cochlear implant surgery should be pursued as soon as possible in order to avoid inflammation-induced fibrosis or ossification of the cochlea [284] observed as early as eight weeks after onset of deafness in Cogan's syndrome [303]. The therapy of bilateral vestibulopathy is performed according to Chapter 4.1.5.

**Clinical pearl**

**The care of patients with autoimmune inner ear disease and brain-eye-ear syndromes requires a close cooperation within a multidisciplinary team of otorhinolaryngologists, neurologists, ophthalmologists and immunologists.**

# 4 Chronic Vestibular Syndromes

Chronic vestibular syndromes (CVS) are characterized by [5]:

- persistent vertigo, dizziness or unsteadiness
- duration of weeks to years
- symptoms and signs of an ongoing vestibular disorder (e. g. oscillopsia, nystagmus, unsteady gait)

It is the common final pathway of acute and episodic vestibular syndromes when peripheral vestibular function does not recover. While chronic unilateral vestibular disorders are usually identified in clinical practice within short time, bilateral vestibulopathy often challenges the treating physician's diagnostic skills [304].

## 4.1 Bilateral vestibulopathy

Bilateral vestibulopathy (BVP) is a rare disease not only with respect to the general population (estimated prevalence of 28/100 000, based on the United States National Health Interview Survey of 2008) [305], but also in specialized vertigo clinics, where only 0.7 to 7 % of patients receive this diagnosis [68, 298]. The rare occurrence of the disease and the absence of typical vestibular symptoms and signs (e. g., sensation of vertigo, nystagmus) are two major reasons for the long odyssey of BVP patients who consult on average seven physicians until the diagnosis is made, which may take up to 15 years after the first onset of symptoms [306, 307].

### 4.1.1 Symptoms

As mentioned before in Chapter 2.3, symptoms and signs of BVP are very different from those of unilateral vestibular hypofunction. Patients with BVP do usually *not* present with vertigo and spontaneous nystagmus. Both features indicate asymmetric baseline firing rates of vestibular afferents, and are thus absent in bilateral symmetrical vestibular hypofunction [63, 304, 306].

Instead, chronic imbalance when standing or walking is the cardinal symptom of BVP in more than 90 % of patients. Imbalance increases with eyes closed and on uneven surfaces [307–309]. Already a short, unconscious closure of the eyes may cause loss of balance with falls, as illustrated in the self-observation by Crawford, a physician who experienced BVP after treatment with aminoglycosides in the 1950s [310].

Sitting and lying with the head still generally does not cause vestibular symptoms in BVP. On the contrary, even minor head movements (e. g., when reading, chewing, or driving in a car over bumpy roads) may provoke irritative oscillopsia [311], which is due to a bilateral failure of the vestibulo-ocular reflex (VOR, ▶ **Fig. 2** and ▶ **3**). It is often very difficult for patients to describe these unusual symptoms. This is also reflected by the fact that the number of patients complaining of oscillopsia / blurred vision varies significantly (20–98 %) between individual observational studies [307, 308, 311, 312]. Many patients with BVP and oscillopsia consult an ophthalmologist in the first place, who will most likely not be able to make the correct diagnosis in a sitting patient holding his head still, because the VOR is not "in action" in this situation.

If BVP is suspected, patients should be asked the following questions:

- When going for a walk, do you have to stand still to read street signs etc.?
- Have you ever experienced that you do not recognize people's faces when walking through the street, even if they are familiar to you?

If the patient answers positively to one of these two questions, BVP should be taken into consideration.

Many patients also report cognitive problems. While it is well-known that partial and total bilateral vestibular loss may result in reduction of hippocampal volume, impairment of spatial orientation and spatial memory [313, 314], more recent investigations have revealed cognitive disorders in other domains, e. g., attention, short-term memory, and executive functions [315, 316]. The complex multi-faceted symptoms of BVP cause severe impairment of the patients' quality of life, especially with regard to autonomy, social contacts, and professional life [307, 317, 318].

### 4.1.2 Classification and vestibular testing

For the diagnosis of "probable bilateral vestibulopathy" according to the criteria of the Bárány Society, a bilateral pathological horizontal head impulse test has to be present beside the above-mentioned typical symptoms with chronic imbalance and/or oscillopsia. The diagnosis of "bilateral vestibulopathy" additionally requires the evidence of a bilaterally pathological horizontal VOR documented by vHIT *or* bithermal caloric irrigation *or* rotary chair testing [311].

Function of vertical semicircular canals and otolith organs is currently not part of the Bárány Society definition of BVP. Recent investigations have revealed a broad spectrum of bilateral hypofunction in all vestibular end organs, e. g., an isolated hypofunction of both posterior semicircular canals [319] or both saccules [320, 321]. Further studies are necessary to assess the clinical significance of these findings, particularly in the long term [322].

Bilateral pathological VEMPs have been reported in 60 to 80 % of BVP patients (defined as bilateral horizontal canal hypofunction) [319, 323, 324]. Currently, VEMPs are regarded as a complementary test in BVP that can help to define the extent of damage to both labyrinths. Due to the good test-retest reliability, they are suitable for monitoring peripheral vestibular function in the course of the disease, in combination with the vHIT [322].

Beside using head impulse testing, disorders of the vestibulo-ocular reflex can also be determined by measuring dynamic visual acuity (DVA) with a visual acuity chart [311, 325]. In addition, computer-based measurement methods are available for exact quantification of DVA loss [325]. A pathological Romberg's test with eyes

▶ **Table 9** Possible etiologies of bilateral vestibulopathy (modified according to [298, 304, 309]).

| | |
|---|---|
| toxic (Chapter 4.1.3.1, ▶ **Fig. 2**) | aminoglycosides (especially gentamicin and tobramycin), cisplatin, loop diuretics, salicylate in high doses (5g/d) [396], penicillin + non-steroidal anti-inflammatory drugs [397], amiodarone [398], hydroxychloroquine [399], styrene poisoning [400], chronic exposure to jet fuel [401], cobalt toxicosis (e.g., hip replacement) [402] |
| metabolic | kidney failure, vitamin-B1, -B6, -B12 or folic acid deficiency [403], hypothyroidism, diabetes mellitus [404], alcohol abuse |
| neurodegenerative disease (Chapter 4.1.3.2) | CANVAS and its differential diagnoses (spinocerebellar ataxia, Friedreich's ataxia, multiple system atrophy, Wernicke's encephalopathy) [344, 405], superficial siderosis, peripheral polyneuropathy (degenerative, inflammatory, hereditary) [406–408] |
| iatrogenic (Chapter 4.1.3.3) | bilateral surgery of the lateral skull base, e.g. cochlear implants, skull base tumors |
| genetic (Chapter 4.1.3.4) | see ▶ **Table 5** |
| traumatic | labyrinthine concussion, bilateral temporal bone fracture (▶ **Fig. 3**) |
| congenital / syndromic | inner ear malformations, e.g., CHARGE syndrome, semicircular canal aplasia [409–411], enlarged vestibular aqueduct (Chapter 3.2.6, ▶ **Fig. 7**); pre-/perinatal infections (CMV, rubella) |
| infectious | meningitis, neurosyphilis [103], neuroborreliosis [94], neurotropic viruses (HSV, VZV, CMV, EBV, HIV) |
| autoimmune (Chapter 3.4.3) | see ▶ **Table 7** [296] |
| Usually unilateral diseases occurring bilaterally | vestibular neuritis [105, 106, 412] (Chapter 2.3), Menière's disease [2] |
| neoplastic | neurofibromatosis type II [413], skull base meningiomas, carcinomatous meningitis, metastases / lymphoma in the cerebellopontine angle [414] |
| others | aseptic meningitis [415], vestibular atelectasis (Chapter 3.2.8, ▶ **Fig. 8**), presbyvestibulopathy [416], auditory neuropathy spectrum disorders, otosclerosis [417] |

closed or on foam is highly sensitive for BVP. The specificity, however, is rather low because increased sway may also be caused by cerebellar or sensorimotor ataxia [107, 304].

### 4.1.3 Etiology

The possible causes of BVP are manifold (see ▶ **Table 9**). Their relative frequencies vary between reports by different research groups; in 20–50 % of cases, etiology remains elusive despite intensive investigations ("idiopathic BVP") [209, 308, 309, 321]. In summary, all disorders with fluctuating or progressive bilateral loss of peripheral vestibular function may result in BVP (see previous Chapters). Thus, it is of paramount importance for the patient's prognosis to early recognize potentially reversible causes in order to delay progress of the disease or - at best - achieve a (partial) recovery of peripheral vestibular function.

Time course of the disease and pattern of end organ involvement in vHIT and VEMP testing already allow some conclusions about BVP etiology. Recurrent vertigo attacks with secondary development of bilateral vestibular hypofunction are mainly found in bilateral Menière's disease and in autoimmune disorders of the inner ear (see Chapter 3.4.3). A slowly progressive course is frequently observed in idiopathic BVP, while toxic and autoimmune origins rather present with a rapid progression. The presence of additional neurological symptoms in BVP patients requires the otorhinolaryngologist's special attention (see Chapter 4.1.3.2) [309].

Infectious causes of BVP (see ▶ **Table 9**) and CANVAS (cerebellar atrophy, neuro(no)pathy, vestibular areflexia syndrome, see Chapter 4.1.3.2.1) typically display reduced vHIT gain values for all six semicircular canals, while function of the anterior canals is often preserved in cases of bilateral Menière's disease and aminoglycoside toxicity (see Chapter 4.1.3.1.1 and ▶ **Fig. 2**). The reasons for this peculiar pattern are still unknown. Pathological oVEMPs are observed more frequently in aminoglycoside toxicity than in bilateral Menière's disease. Finally, the number of affected end organs represents a possible differential diagnostic hint (infections: 8.7 > aminoglycoside: 8.0 > Menière's disease: 5.5) [319, 324, 326].

In the following paragraphs, some origins of bilateral vestibulopathy that are of particular significance in clinical routine or that contribute to a better understanding of the underlying pathophysiology will be covered in greater detail.

#### 4.1.3.1 Toxic and metabolic causes

##### 4.1.3.1.1 Aminoglycosides

The most commonly identified origin of BVP is treatment with vestibulotoxic aminoglycosides, especially gentamicin [298, 308, 309] (▶ **Fig. 2**). In general, every administration of gentamicin, regardless of dosage, frequency, or route of application, may result in BVP [306, 312, 327]. None of the mitochondrial 12S rRNA gene mutations that predispose for a severe *cochleotoxic* effect of aminoglycosides (e. g. A1555G) have been detected in patients with aminoglycoside-associated or idiopathic BVP so far [328, 329]. Nevertheless, patients should be asked about a positive family history for aminoglycoside ototoxicity before they receive the first dosage themselves.

The deleterious effect of gentamicin on the vestibular labyrinth results from its pharmacological and pharmacokinetic properties. It particularly damages type I vestibular hair cells, while cochleotoxicity is comparatively low [330, 331]. Hence, subjective hearing loss as a "red flag" for a potential ototoxic effect is usually missing

[298, 332] (▶ **Fig. 2**). Type I vestibular hair cells are highly specialized sensors for rapid changes in acceleration, e. g., quick head or body movements [333]. Since patients are mostly severely sick and bedridden while they receive aminoglycosides, the vestibulotoxic effect usually becomes apparent with a certain delay – at earliest when the patient is mobilized in bed, but mostly after discharge from the hospital. Many patients – and their physicians – do not make a connection between the occurrence of BVP and the previous application of gentamicin at this time, or they do not even know that they received aminoglycosides at all. Therefore, patients should not only be asked about treatment with aminoglycosides when taking their history for diagnosing BVP, but also about longer inpatient stays due to complicated surgery, sepsis, etc. Sometimes, only the specific request for hospital drug treatment charts brings clarification [306].

Another risk of gentamicin consists in its cumulative vestibulotoxic effect. The substance accumulates in the inner ear over months; in guinea pigs, the elimination half-life is as long as six months. Thus, the drug is able develop its destructive effect even at normal serum levels and after administration has been stopped [334]. Furthermore, it must be taken into consideration that the additional nephrotoxic effect of gentamicin may delay its renal clearance, which further increases its vestibulotoxicity. Finally, combination with vancomycin (glycopeptide) may also drastically increase the vestibulotoxic effect of gentamicin [298, 312].

Beside gentamicin, tobramycin has also been associated with vestibulotoxic side effects. Inhalation of tobramycin is often used for therapy of pulmonary pseudomonas infections in patients with cystic fibrosis or bronchectasia. Vestibulotoxicity has been reported for inhalative tobramycin in single cases – even in patients with normal renal function [335–337].

**Clinical pearl**

**Vestibulotoxic aminoglycosides may cause bilateral vestibulopathy, regardless of dosage, frequency or route of application – even if hearing function and serum levels are normal.**

#### 4.1.3.1.2 Monitoring of vestibular function

If aminoglycoside toxicity is detected early, further deterioration of vestibular function may be prevented, e. g., by switching to another antibiotic if possible. At best, peripheral vestibular function will recover to a certain degree, as vestibular hair cells have a certain regenerative potential even in adult mammals – in contrast to cochlear hair cells [338–341].

In order to minimize aminoglycoside-related vestibulotoxicity, regular monitoring of vestibular function is necessary during antibiotic therapy and in the months afterwards (cumulative toxicity!) [312]. In contrast to established recommendations for monitoring auditory function during treatment with cochleotoxic drugs (high-frequency PTA and otoacoustic emissions), systematic monitoring of vestibulotoxic effects has been neglected for a long time [342]. With vHIT and VEMPs, effective tools are available today for detection and quantification of vestibulotoxic damage in all vestibular end organs. Both tests are particularly suited for this purpose, as they predominantly assess the function of type I vestibular hair cells, which are the main targets of vestibulotoxic aminoglycosides [333].

### 4.1.3.2 Neurodegenerative diseases

The percentage of additional neurological disorders in patients with BVP varies depending on the focus of a vertigo clinic between 4.5 % (otorhinolaryngological focus) and 30 % (neurological focus) [309, 343]. For the otolaryngologist, it is important to be aware of this overlap and to recognize additional neurodegenerative disorders in patients with BVP. Thus, a neurologist can be consulted and involved in the patient's treatment early on.

#### 4.1.3.2.1 CANVAS

Patients presenting with bilateral vestibulopathy, cerebellar syndrome, and sensory neuro(no)pathy present a particular diagnostic challenge. This peculiar combination of neuro(oto)logical disorders may either be incidental (e. g., cerebellar atrophy + gentamicin-associated BVP) or due to CANVAS (cerebellar atrophy, neuronopathy, vestibular areflexia syndrome). The latter disorder most likely follows an autosomal recessive inheritance pattern with late manifestation, the underlying genetic mutation has not been found yet. Diagnostic criteria have been published by Szmulewicz et al. [344].

Each of the three disease components may present as ataxia. Therefore, it is crucial to pay attention to pathognomonic signs of each disorder during neurotological examination, especially with regard to cerebellar oculomotor disorders (saccadic pursuit, hypermetric saccades, gaze-evoked nystagmus, rebound nystagmus, downbeat nystagmus, impaired fixation suppression of the VOR) [345, 346]. Video examples are shown in [347]. BVP is diagnosed by a bilateral impairment of the vestibulo-ocular reflex in (video) head impulse testing. A saccadic visually enhanced vestibulo-ocular reflex (vVOR) (see video in [344]) is a tell-tale sign of bilateral BVP plus impaired cerebellar function.

**Clinical pearl**

**The visually enhanced vestibulo-ocular reflex (vVOR) is a helpful bedside test to identify combinations of bilateral vestibulopathy and cerebellar syndrome.**

Therapy of BVP as part of a neurodegenerative disease is based on treatment of the underlying disorder. In cases of disturbing downbeat nystagmus that - in contrast to BVP - may cause oscillopsia even without head movements, aminopyridines (cave: prolonged QTc interval in ECG!), chlorzoxazone, or baclofen may be applied [348].

#### 4.1.3.2.2 Superficial siderosis

This extremely rare disease is characterized by hemosiderin deposits particularly in glial cells of the CNS due to recurrent subarachnoid hemorrhage. Overall, only 30 case reports describing vestibular involvement in superficial siderosis are available in the medical literature so far [349]. Beside progressive bilateral audiovestibular dysfunction, patients often display cerebellar symptoms and other neurological deficits [350, 351]. Hemosiderin deposits are visualized particularly well as hypointense "etching" along the pial and arachnoid surfaces in gradient echo T2 sequences (T2 * ) of the cra-

nial MRI [352]. History taking should include the question of intradural surgeries or severe head injury. In this context, it should be noted that the onset of symptoms in superficial siderosis may be delayed for years after the initial event. Identification and removal of the bleeding source in cooperation with neurologists and neurosurgeons is the only causative therapy [352, 353]. Often, however, no definite source can be found despite intensive research. The significance of iron chelators for treatment is still unknown [350].

#### 4.1.3.3 Iatrogenic causes

Prior to surgical interventions on the lateral skull base, the vestibular endorgans of both ears should be assessed with vHIT and VEMPs. Sometimes, peripheral vestibular hypofunction is incidentally detected on the contralateral side (e.g., right-sided vestibular schwannoma with preserved vestibular function on the right and incidental vestibular hypofunction on the *left*). In these cases, the therapeutic concept should be individually modified by the interdisciplinary skull base team of otorhinolaryngologists, neurosurgeons and radiation oncologists in order to minimize the risk of post-interventional bilateral vestibulopathy.

Particularly thorough pre-operative assessment of vestibular function is essential before surgery of the "second" side, e. g., in cases of skull base meningiomas, bilateral vestibular schwannomas, or in cochlear implant surgery [237]. When unilateral peripheral vestibular hypofunction after surgery of the first side was compensated well, it is often believed that this will also be the case after second-side surgery. This will, however, *not* happen because the functional labyrinth required for central-vestibular compensation is missing in case of second-side surgery with a pre-existing damage of the contralateral labyrinth.

Surgical or destructive therapy of Menière's disease is another important topic in this context. Within ten years after initial diagnosis, up to 35 % of patients with initially unilateral Menière's disease develop bilateral involvement of the inner ear [2]. If destructive therapy has been performed in the primarily affected ear (e. g., intratympanic gentamicin application, labyrinthectomy, neurectomy of the vestibular nerve), BVP may result when the second ear gets affected. Therefore, the otorhinolaryngologist has to inform the patient about this possible development when planning the next therapeutic steps in order to find a compromise between reduction of the attacks and the risk of BVP ("shared decision making"). Identification of potential predictors for bilateral Menière's disease (e. g., certain gene expression patterns [354, 355], endolymphatic hydrops on the (still) healthy contralateral side, or a certain morphology of the vestibular aqueduct / endolymphatic sac [356, 357]) is therefore a highly relevant topic for future clinical studies.

Radiotherapy of the skull base may be vestibulotoxic as well. Currently, only limited data are available about the long-term outcome of vestibular function after irradiation of the temporal bone. It is generally recommended to include vestibular testing in the diagnostic work-up before radiosurgical interventions on the lateral skull base.

**Clinical pearl**

**Bilateral assessment of all vestibular endorgans with vHIT and VEMPs should be performed before every intervention on the lateral skull base. The results are essential for the interdisciplinary team of neurosurgeons, otorhinolaryngologists and radiation oncologists to plan the optimal therapy for the patient.**

#### 4.1.3.4 Genetic causes

In contrast to hereditary hearing loss (see also Prof. Warnecke's article [286]), only little is known about genetic factors in BVP (▶ **Table 5**). Usher syndrome, the most frequent hereditary cause of deaf-blindness, is characterized by a triad of profound bilateral sensorineural hearing loss, BVP and retinitis pigmentosa (retinal rod and cone dystrophy with night blindness and peripheral visual field restriction). Depending on the clinical course, three (sometimes four) subgroups are distinguished based on mutations in nine different genes. In more than 50 % of families with Usher syndrome type I, an autosomal-recessive mutation in the myosin 7A gene (*MYO7A*) is found [224, 358, 359]. As explained for AIED above, a comprehensive review of systems and cooperation with an ophthalmologist is essential (see Chapter 3.4.3.2), and patients should be referred for genetic counselling.

### 4.1.4 Additional investigations

Physicians caring for patients with BVP are regularly faced with the dilemma that they do not want to miss any treatable cause of the disorder, while on the other hand even cost- and time-intensive additional investigations fail to determine the underlying etiology in around 20–50 % of cases.

The following diagnostic work-up according to [309] has proven effective in clinical practice:

- Every BVP patient should undergo pure tone audiometry and MRI of the skull / temporal bone (including T2 * sequence for diagnosis of superficial siderosis) [116]. Bilateral contrast enhancement in the cerebellopontine angle is not only observed in neoplastic, but also in infectious and autoimmune lesions. HRCT of the temporal bone should be performed to identify skull base fractures (▶ **Fig. 3**) or inner ear malformations (see Chapter 3.2.6) [309].
- Laboratory tests should be focused on detection of treatable causes, such as vitamin B or folic acid deficiency, diabetes mellitus, hypothyroidism or alcohol abuse (▶ **Table 10**). Infectious origins of BPV are rare. Nevertheless, serological testing for neurotropic bacteria and viruses is justified, as these are potentially treatable causes. In case of positive results, an expert in infectious diseases of the nervous system should be consulted [298].
- In a retrospective observational study of 154 BVP patients, the additional analysis of auto-antibodies (e. g., ANAs, ANCAs, rheumatoid factor) changed therapy in only one case (treatment with corticosteroids). Thus, it is useful to plan autoimmune investigations together with an immunologist / rheumatologist in accordance with the patient's medical history and clinical disease presentation [309].
- If neurological symptoms are detected additional to bilateral peripheral vestibular hypofunction (see Chapter 4.1.3.2),

▶ **Table 10** Basic laboratory tests in bilateral vestibulopathy (modified according to the recommendations of the German Society for Neurology for peripheral polyneuropathy [360]).

| **Complete Blood Count** |
|---|
| serum: CRP, ESR, protein immunoelectrophoresis + immunofixation (diagnosis of monoclonal gammopathy), electrolytes, liver and kidney function tests, glucose / HbA1c (diabetes mellitus), vitamin-B1, -B6, -B12, folic acic, CDT (increased in alcoholism), TSH, fT4 |
| urine: urine analysis including protein (Bence-Jones proteins with monoclonal gammopathy) |
| serology: Lyme disease, treponema pallidum, neurotropic viruses (HSV, VZV, CMV, EBV, HIV) |

Abbreviations: CDT = carbohydrate deficient transferrin. For further abbreviations see ▶ **Tables 7** and **8**.

patients should be referred to a neurologist in order to plan further investigations (e. g. lumbar puncture, determination of antineuronal antibodies, electrophysiological examinations) and therapy [360].

### 4.1.5 Therapy

Currently, no therapy is available in clinical practice that is able to reconstitute peripheral vestibular function in BVP. Therefore, it is essential to avoid possible risk factors, to identify early symptoms, and – if possible – to treat underlying origins. In order to avoid further deterioration of vestibular function, patients and their general practitioners should be informed about potentially vestibulotoxic drugs so that these may be avoided or replaced (▶ **Table 9**). Patients with BVP benefit from specific vestibular rehabilitation therapy, which promotes central vestibular compensation (in case of residual vestibular function) and somatosensory substitution (compensation for lost vestibular function by the visual and somatosensory systems) [67, 361, 362].

Somatosensory assistance systems (e. g., vibrotactile feedback) or transmastoid stimulation with galvanic noise to improve postural and gait stability in BVP patients are currently evaluated in clinical trials. Noisy galvanic vestibular stimulation, which requires some degree of residual peripheral vestibular function, lowers the threshold for the detection of vestibular stimuli by the principle of stochastic resonance [62, 363, 364].

According to the current state of research, reconstitution of lost peripheral vestibular function is only possible by means of a vestibular implant. In analogy to the sound processor of a cochlear implant, a head-fixed gyroscope detects rotational acceleration of the head. The implant transforms the incoming information into an electrical signal, which is then transmitted to the individual ampullary nerves via implanted stimulation electrodes. Different types of implants are currently under investigation in clinical studies with first positive results [365–370].

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