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Disease-specific sparing of the anterior semicircular canals in bilateral vestibulopathy

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HIGHLIGHTS

- Patterns of semicircular canal loss may indicate different etiologies in bilateral vestibulopathy.
- Anterior canals were relatively preserved for aminoglycoside vestibulotoxicity and Menière's disease.
- Video-head-impulse testing of all six canals may help identify bilateral vestibular loss etiologies.

ABSTRACT

Objective: Bilateral vestibular loss (BVL) is often diagnosed with great delay and an underlying cause is only identified in 50–80%. We measured horizontal and vertical semicircular canal function using the video-head-impulse test (vHIT) and hypothesized that specific vHIT-patterns may be linked to certain etiologies.
Methods: We retrospectively analyzed 109 BVL-patients linked to aminoglycoside vestibulotoxicity ($n = 16$), Menière's disease ($n = 10$), infectious inner-ear disorders ($n = 11$), sensorineural hearing-loss ($n = 11$), cerebellar-ataxia-neuropathy-vestibular-areflexia-syndrome (CANVAS, $n = 5$), other causes ($n = 19$) as well as those with unknown origin ($n = 47$). Vestibulo-ocular reflex gains and cumulative saccade amplitudes were measured with vHIT, and the functional integrity of all semicircular canals was rated.
Results: Overall, anterior canal hypofunction ($n = 86/218$) was identified significantly ($p < 0.001$) less often than horizontal ($n = 186/218$) and posterior ($n = 194/218$) hypofunction. Preserved anterior canal function was associated with aminoglycoside vestibulotoxicity, Menière's disease and BVL of unknown origin, while no such sparing was found for inner-ear infections, CANVAS and sensorineural hearing loss.
Conclusions: Semicircular canal function in BVL shows disease-specific dissociations, potentially related to reduced vulnerability or superior recovery of the anterior canals.
Significance: In patients with suspected BVL we recommend quantifying vHIT gains and saccade amplitudes for all semicircular canals as the pattern of canal hypofunction may help identifying the underlying disorder.

1. Introduction

Bilateral impairment of peripheral-vestibular function is characterized by gait and postural imbalance and oscillopsia (illusionary movement of the visual surroundings during head movements) (Dandy, 1941; Crawford, 1952; Hain et al., 2013). Gait imbalance is present in up to 99% of patients (Zingler et al., 2007), while rates of oscillopsia are more variable (range: 44% (Zingler et al., 2007) – 97% (Black et al., 2004)). The prevalence for severe bilateral vestibular loss (BVL) was estimated at 28/100,000 in US-adults (Ward et al., 2013). In typical dizziness clinics, BVL is pre-

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sent in 2–4% of all outpatients (Zingler et al., 2007; Hain et al., 2013), which makes it a rather infrequent vestibular disorder. Quality of life, however, is considerably affected by BVL (Guinand et al., 2012; Sun et al., 2014), with >80% of patients reporting impairment (Zingler et al., 2008). Likewise, BVL imposes substantial economic burdens on individuals and the society (Sun et al., 2014). The course of disease is chronic in up to 80% (Zingler et al., 2008), albeit recovery from vestibulotoxicity may occur (Black et al., 2001).

These complaints are a consequence of a deficient angular vestibulo-ocular reflex (aVOR) that normally compensates for head perturbations. At the bedside, the head-impulse test (HIT) allows a clinical assessment of the aVOR (Halmagyi and Curthoys, 1988). Investigations for the presence of BVL are often delayed by months to years due to unspecific complaints and lack of recognition by the clinician (Ahmed et al., 2012; van de Berg et al., 2015). A specific cause of BVL is found only in 50–80% of patients (Rinne et al., 1998; Zingler et al., 2007; Kim et al., 2011; Lucieer et al., 2016). Vestibulotoxic drugs such as aminoglycoside antibiotics (10–20%), bilateral Menière's disease (7–15%) and head trauma with bilateral inner-ear damage (<10%) are amongst the most frequently identified disorders linked to BVL (Vibert et al., 1995; Rinne et al., 1998; Zingler et al., 2007; Kim et al., 2011).

Traditionally, semicircular canal (SCC) function was quantified by use of caloric irrigation and rotatory-chair testing (Rinne et al., 1998; Ishiyama et al., 2006; Kim et al., 2011). These approaches, however, have significant limitations, as they only provide information about the functional state of the horizontal SCCs. Only with the recent introduction of video-based quantitative head-impulse testing (vHIT) devices, a detailed assessment of all six horizontal and vertical (anterior, posterior) SCCs became readily available (MacDougall et al., 2009; Weber et al., 2009b; MacDougall et al., 2013a,b).

With different underlying disorders leading to BVL, we hypothesized that the individual pattern of SCC hypofunction may be variable. For example, in temporal-bone specimens of patients with Menière's disease (MD), varying rates of involvement of the individual SCCs and the macular organs have been reported (Okuno and Sando, 1987). Potentially, characteristic patterns of SCC hypofunction will facilitate identifying the underlying cause of BVL and result in earlier and more targeted treatment, eventually improving long-term outcome. We retrospectively analyzed vHIT measurements in all patients with diagnosed BVL since the introduction of the vertical vHIT at our dizziness clinic and explored patterns of vestibular hypofunction with underlying diagnoses.

2. Materials and methods

The protocol was approved by the Cantonal ethics commission Zurich (KEK-ZH-2013-0468) and was in accordance with ethical standards laid down in the 2013 Declaration of Helsinki for research involving human subjects. Since this study was a retrospective database analysis, written informed consent could not be obtained from the participants. This approach was in accordance with the approval from the ethics committee. Prior to analysis patient records/information was anonymized and de-identified.

2.1. vHIT-recording procedure

The standard vHIT procedure at the University Hospital Zurich (UHZ) requires 20 valid head impulses for each canal (MacDougall et al., 2013a), with canals tested in pairs according to the planes of stimulation (horizontal plane, right-anterior-left-posterior (RALP) plane, left-anterior-right-posterior (LARP) plane). For video-oculography, commercially available video-head-impulse testing goggles (GN Otometrics, Taastrup, Denmark) with an infrared camera recording the right eye were used. Horizontal and vertical eye position was measured with a 250 Hz frame rate and head velocity was determined by three orthogonal gyroscopes. For further analysis, eye and head velocity values were calculated.

2.2. Patient identification and statistical analysis

All patients evaluated by vHIT had sought medical attention because of gait ataxia or vertigo/dizziness. The clinical database operated at the UHZ stored all vHITs performed and was searched for patients with hypofunction in at least one SCC on each side (period: October 1st 2012 to December 15th 2014), finding 110 patients out of 2430 recordings from 2123 patients. We re-analyzed aVOR-gains using OtosuiteV 2.0 (GN Otometrics). The gain of the aVOR was calculated as the ratio of cumulative slow-phase eye velocity over cumulative head velocity from the onset of the head impulse to the moment when head velocity crossed zero again (Macdougall et al., 2013b). For the quantification of corrective saccades we used custom-written MATLAB (The MathWorks, Natick, MA, USA) routines, providing cumulative overt saccade amplitudes (Weber et al., 2008, 2009a). Saccades were defined as 'overt', if their onset occurred after head velocity crossed zero after the head impulse. Cumulative saccade amplitude per trial was calculated by adding all overt saccades with peak velocity >20°/s. Vestibular hypofunction was defined as a reduction in aVOR-gain and/or the occurrence of overt compensatory saccades with peak velocities >20°/s. For gains, cut-off values of 0.8 (horizontal canals) and 0.7 (vertical canals) have been proposed by the manufacturer of the video-goggles to distinguish normal from reduced aVOR-function and are in line with age-dependent normative values (McGarvie et al., 2015).

Two experienced neuro-otologists (AAT, KPW) independently reviewed the vHIT-traces and rated individual SCC-function as normal or pathological (Cohen's kappa = 0.86) (Cohen, 1960) based on (1) reduced aVOR-gain, (2) the presence of corrective saccades, or (3) a combination of both. In addition, a second rating was obtained taking the presence/absence of correction saccades into account only. BVL was confirmed in 109 cases, one patient was excluded because of unilateral vestibular hypofunction. Disagreements were settled by discussion amongst the reviewers. The underlying cause of BVL was retrieved from the patients' files. We followed the AAO-HNS 1995 guidelines for diagnosing MD (1995). Details on previous CNS-infections, drug treatment and delay for vestibular symptoms were collected (Supplementary file A). A diagnosis of bilateral sensorineural hearing loss (SNHL) required documented hearing impairment as assessed by pure tone audiogram based on CPT-AMA guidelines (Council on Physical Therapy, 1942) with a CPT value >20% on both sides and exclusion for other causes. Diagnostic criteria for CANVAS (cerebellar ataxia, neuropathy, vestibular areflexia syndrome) were based on the definition provided by Szmulewicz et al. (2011). The individual patterns of vestibular (hypo)function and the reported cause of BVL were correlated and an analysis of the occurrence of specific patterns was made. In those cases with both warm-/cold-water caloric irrigation and vHIT available ($n = 66$), these two approaches were compared. Unilateral hypofunction was defined as a canal paresis factor of >25% with a preserved response on the healthy side (Halmagyi et al., 1997), while for bilateral hypofunction on caloric irrigation a nystagmus with a mean peak slow-phase velocity of less than 5°/s on both sides was required (Zingler et al., 2007).

MATLAB was used for statistical analysis. Fisher's exact test (Bonferroni-corrected) was applied to determine significant differences in the frequency of specific conditions. Median values (±1 median absolute deviation, MAD) were determined for gains and saccade amplitudes and statistics were based on non-parametric analysis of variance (Kruskal–Wallis ANOVA, Tukey–Kramer cor-