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Health-related quality of life and functional impairment in acute vestibular disorders

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ABSTRACT

Background: Acute vestibular symptoms have a profound impact on patients' well-being. In this study, health-related quality of life (HRQoL) and functional impairment were investigated prospectively in patients with different peripheral and central vestibular disorders during the acute symptomatic stage to decipher the most relevant underlying factors.

Methods: 175 patients with acute vestibular disorders were categorized in central vestibular (CV, n=40), peripheral vestibular (PV, n=68) and episodic vestibular disorders (EV, n=67). All patients completed scores to quantify generic HRQoL (EQ-5D-5L) and disease-specific HRQoL (Dizziness Handicap Inventory, DHI). Vestibular-ocular motor signs were assessed by video-oculography, vestibular-spinal control by posturography and verticality perception by measurement of subjective visual vertical (SVV).

Results: Patients with PV had a poorer HRQoL compared to patients with CV and EV (EQ-5D-5L/DHI: PV: $0.53\pm0.31/56.1\pm19.7$; CV: $0.66\pm0.28/43.3\pm24.0$; EV: $0.75\pm0.24/46.7\pm21.4$). After adjusting for age, gender, cardiovascular risk factors and non-vestibular brainstem/cerebellar dysfunction patients with PV persisted to have poorer generic and disease-specific HRQoL (EQ-5D-5L: -0.17, DHI: +11.2) than patients with CV. Horizontal spontaneous nystagmus (SPN) was a highly relevant factor for subgroup differences in EQ-5D-5L and DHI, while vertical SPN, SVV and sway path were not. EQ-5D-5L decreased significantly with more intense horizontal SPN in CV ($\text{Rho}=-0.57$) and PV ($\text{Rho}=-0.5$), but not EV ($\text{Rho}=-0.13$).

Conclusions: Patients with PV have the highest functional impairment of all patients with acute vestibular disorders. Vestibular-ocular motor disturbance in the yaw plane has more impact than vestibular-spinal or – perceptive asymmetry in the roll and pitch plane, suggesting that horizontal visual stability is most critical for HRQoL.

ABBREVIATIONS

AP	Anterior-Posterior
A-Fib	Atrial Fibrillation
BPPV	Benign Peripheral Positional Vertigo
CV	Central Vestibular Disorders
DHI	Dizziness Handicap Inventory
DM	Diabetes Mellitus
DWI	Diffusion-Weighted Image
EQ-5D-5L	European QoL Scale - 5 Dimensions - 5 Levels
EQ-VAS	European QoL Scale - Visual Analogue Scale
EV	Episodic Vestibular Disorders
HRQoL	Health-related Quality of Life
MD	Menière's Disease
ML	Medio-Lateral
MRI	Magnetic Resonance Imaging
OR	Odds Ratio
PV	Peripheral Vestibular Disorders
SCC	Semicircular Canal
SPN	Spontaneous Nystagmus
SP	Sway Path
SPV	Slow Phase Velocity
SVV	Subjective Visual Vertical
TOF	Time-Of-Flight

VAS	Visual Analogue Scale
v-HINTS	Video-Head Impulse Test, Nystagmus, Test of Skew
v-HIT	Video-Head Impulse Test
VM	Vestibular Migraine
VOG	Video-Oculography
VOR	Vestibulo-Ocular Reflex

INTRODUCTION

Vertigo and dizziness have profound implications for health-related quality of life (HRQoL) and functioning [1-3]. The most important reasons are restrictions in mobility, falls and secondary psychological consequences like anxiety, panic disorders or depression [4,5]. In chronic vestibular disorders, several factors were identified, which contribute to symptom severity, HRQoL, and psychological comorbidity [6-8]. Symptom intensity in chronic central and functional vestibular disorders

is higher than in peripheral vestibular disorders. Subjective symptoms do not correlate with objective tests of semicircular canal (SCC) or otholith function in the chronic stages of disease [9]. Episodic vestibular syndromes like vestibular migraine or Menière's disease are most frequently associated with anxiety and depression [4,10], while patients with chronic uni- or bilateral vestibulopathies do not have more psychiatric comorbidities than healthy controls [11].

Acute vestibular disorders differ from chronic vestibulopathies, in that central compensation and behavioural strategies of coping - like physical activity or cognitive resilience - have less impact on perceived symptom intensity and impairment. Symptom severity and HRQoL likely are modulated by different factors during the acute stage of disease. However, we are missing systematic evaluations, which describe the effects of disease etiology, vestibular impairment and patients' characteristics on symptom intensity, functional impairment and HRQoL in acute vestibular disorders.

Therefore, in the current study, symptom severity, HRQoL and functioning were investigated prospectively in a large cohort of patients with peripheral and central vestibular disorders during the acute stage of symptoms and correlated to objective measures of vestibular-ocular motor, vestibular-spinal, and vestibular-perceptive signs, as well as patient-specific factors (like age, gender). We hypothesized that 1) acute unilateral peripheral vestibulopathies have the highest symptom intensity and lowest HRQoL, 2) ocular motor signs of vestibular asymmetry are the most important determining factor, and 3) deficits in the yaw plane have the greatest impact on symptom severity. The results are important for clinicians to correctly interpret the patients complaints during the acute stage of vestibular disorders and for future design of clinical studies in acute vestibulopathies to define the most relevant functional endpoints.

METHODS

Patient characteristics and study protocol

In total, 342 consecutive adult patients with acute and isolated presentations of vertigo/dizziness were prospectively included in the study at the Emergency Department of the Ludwig-Maximilian University, Munich [12]. The following work-up was done during the acute stage of symptoms: 1) A structured medical history was taken including questions for previous attacks of vertigo/dizziness, accompanying ear symptoms, headaches, or central symptoms, and cardiovascular risk factors. 2) A standardized neurological and neuro-otological clinical examination was performed. 3) All patients completed scores and scales to quantify generic and disease-specific HRQoL and functioning (EQ-5D-5L, EQ-VAS, DHI). Degree of disability was rated by modified rankin scale (mRS). 4) Vestibular-ocular motor signs were assessed by video-oculography (VOG), vestibular-spinal control by mobile posturography and verticality perception by measurement of subjective visual vertical (SVV) using the bucket test method. The final diagnosis was made following standard diagnostic guidelines for vestibular disorders (by the Barany Society). A standardized magnetic resonance imaging (MRI) protocol (whole brain DWI, T1-, T2-, T2*-weighted

sequences, and TOF-angiography) was done in 96% of patients to confirm or rule out acute central lesions or vestibular schwannoma. Orthoptic testing was done in 67%, caloric testing in 52%, audiometry in 35%, and vestibular evoked myogenic potentials (VEMP) in 24% of patients.

In 175 patients a definite neuro-otologic diagnosis according to guideline criteria could be determined. These patients were categorized in three subgroups for further analysis: central vestibular disorders (CV) (vestibular stroke, inflammatory CNS lesions - based on MRI and v-HINTS) (n=40) [13], peripheral vestibular disorders (PV) (based on v-HIT and caloric testing) (n=68), and episodic vestibular disorders (EV) (vestibular migraine (VM) (n=26), Menière's disease (MD) (n=20), benign paroxysmal positional vertigo (BPPV) (n=21) – based on respective diagnostic guidelines) (n=67). 167 patients did not fulfil the criteria for a definite neuro-otological diagnosis. The most common reasons were the following: first attack of vertigo/dizziness (e.g., suspicious of a beginning MD, VM), transient symptoms (e.g., suspicious of vestibular TIA, status post BPPV), mixed presentations (e.g., overlap of MD/VM), general medical etiology (e.g., orthostatic dizziness, metabolic, toxic, infectious disorders). These patients were excluded from further analysis.

Protocol approval and patient consent

The study was approved by the Ethics Committee of the University of Munich on 02/23/2015 (57-15). The study was conducted according to the Guideline for Good Clinical Practice, the Federal Data Protecting Act and the Helsinki Declaration of the World Medical Association. All subjects gave their informed, written consent to participate in the study. The study was listed in the German Clinical Trial Registry under the ID DRKS00008992 and the Universal Trial Number ID U1111-1172-8719.

Data Availability

Data reported in this article will be shared with any appropriately qualified investigator on request.

Scores for HRQoL and symptom intensity

Generic HRQoL and functioning was assessed by the European Quality of Life Score - 5 Dimensions - 5 Levels (EQ-5D-5L) including subscores for anxiety, pain, activity, self-care and mobility (overall index score ranging from negative values to 1 (best health status); subscores ranging from 1-5 (worst impairment)) [14]. Utility values for the EQ-5D-5L were calculated using a recently published value set [15]. The overall subjective estimation of health status was measured by EQ Visual Analogue Scale (EQ-VAS) (ranging from 0-100 (best status)). Disease-specific HRQoL and symptom intensity was quantified using the Dizziness Handicap Inventory (DHI) (ranging from 0-100 points (worst symptoms)) [16]. The degree of disability or dependence was estimated by the modified rankin scale (mRS) (ranging from 0-6 points) with major disability defined as mRS \geq 3 [17].

Video-oculographic examination

The following vestibular/ocular motor signs were documented by VOG (EyeSeeCam®) during the acute stage of symptoms: nystagmus in straight ahead position (with/without fixation), horizontal vestibulo-ocular reflex (VOR) (gain threshold: 0.7, compensatory saccades), gaze holding (lateral/vertical gaze positions), saccades (horizontal/vertical direction), smooth pursuit (horizontal/vertical direction), horizontal VOR-suppression, skew deviation (cover test in six gaze positions) [12].

Testing of SVV

The SVV was measured by the bucket test method as described previously [18]. Ten repetitions (5 clockwise/5 counter clockwise rotations) were performed and a mean of the deviations calculated. The normal range was defined as $0\pm2.5^\circ$ [18].

Posturographic assessment

A posturographic measurement of body sway was performed using a mobile device (Wii Balance Board®). Four conditions were tested: bipedal standing with eyes open/closed, upright tandem standing with eyes open/closed. The sway pattern in medio-lateral (ML) and anterior-posterior (AP) direction was analysed per condition as normalized sway path (SP) length.

Statistics

For descriptive analysis mean values and standard deviations were calculated for all parameters (e.g., EQ-5D-5L, EQ-VAS, DHI). For statistical comparison of the subgroups CV, PV, and EV a multivariable linear regression model with the main outcome EQ-5D-5L was calculated adjusting for the covariates age, gender, symptom characteristics (e.g., brainstem/cerebellar dysfunction) (according to [19]) and cardiovascular risk factors (i.e., diabetes mellitus (DM), hypertension and atrial fibrillation (A-Fib)) using Stata 14.2 software. The subgroup CV was selected as reference group. A sensitivity analysis with multivariable linear or logistic regression models was conducted for secondary outcome parameters (EQ-VAS, DHI, mRS ≥ 3) adjusting for the same covariates as in the primary analysis. In an extended model further quantitative cofactors were included to analyse their impact for subgroup differences: 1) Spontaneous nystagmus (SPN) without fixation (in horizontal/vertical direction, expressed as slow phase velocity (SPV)). These parameters were taken as ocular motor equivalents for horizontal and vertical SCC tone asymmetry. 2) SP in ML/AP direction during stance on firm ground with eyes open, which is considered as a marker of imbalanced vestibular spinal tone originating from asymmetric otolith input [20]. 3) SVV, as a measure of vestibular perception derived from otolith and vertical SCC inputs (Fig.1) [21]. Spearman's rank correlation coefficient was calculated for outcome parameters (EQ-5D-5L, EQ-VAS, DHI) and the quantitative vestibular tests (SPN horizontal/vertical, SP-ML/AP, SVV).

RESULTS

Patient characteristics

Mean age of all 175 patients was 58.6 ± 15.0 years. Patients with CV were older (64.1 ± 12.2 years) than patients with PV (55.6 ± 14.6 years) and EV (58.4 ± 16.1 years) (Tab.1). Men were more frequently affected in the subgroups with CV (67.5%) and PV (64.7%), while gender was balanced in the subgroup with EV (men: 50.7%). Patients with CV had more cardiovascular risk factors, namely DM (10%), hypertension (72.5%) and A-Fib (15%), compared to the patients with PV (DM: 2.9%, hypertension 64.7%, A-Fib: 4.4%) and EV (DM: 3.5%, hypertension: 65.7%, A-Fib: 9.0%) (Tab.1).

Generic and disease-specific HRQoL and functional impairment in acute vestibular disorders

In the entire study cohort, patients' generic HRQoL was significantly affected (overall EQ-5D-5L: 0.64 ± 0.29). EQ-5D-5L subscores indicated the highest impairments for the domains activity (3.0 ± 1.6) and mobility (2.6 ± 1.3). Judgement of overall health status by EQ-VAS also showed relevant affection (53.1 ± 21.9). Disease-specific HRQoL was severely impaired in most patients (DHI: 49.6 ± 21.9). Rating of the degree of disability indicated a moderate to severe impairment ($mRS \geq 3$) in 69.1% of all patients (Tab.2). Subgroup analysis showed that patients with PV consistently had a poorer HRQoL (EQ-5D-5L: 0.53 ± 0.31 ; subscore activity: 3.6 ± 1.4 , mobility: 3.2 ± 1.3) and subjective health status (EQ-VAS: 46.5 ± 22.7) compared to patients with CV (EQ-5D-5L: 0.66 ± 0.28 ; subscore activity: 2.9 ± 1.7 , mobility: 2.3 ± 1.2 ; EQ-VAS: 57.2 ± 18.9) and EV (EQ-5D-5L: 0.75 ± 0.24 ; subscore activity: 2.4 ± 1.5 , mobility: 2.2 ± 1.1 ; EQ-VAS: 57.6 ± 21.4) (Tab.2). In EV, patients with VM had worse HRQoL compared to MD and BPPV (EQ-5D-5L: VM: 0.71 ± 0.23 ; MD: 0.84 ± 0.19 ; BPPV: 0.70 ± 0.28). Disease-specific HRQoL was worse in patients with PV (DHI: 56.1 ± 19.7 ; $mRS \geq 3$: 85.3%) than in patients with CV (DHI: 43.3 ± 24.0 ; $mRS \geq 3$: 65.0%) and EV (DHI: 46.7 ± 21.4 (VM: 51.9 ± 22.1 ; MD: 41.6 ± 21.1 ; BPPV: 45.1 ± 20.4); $mRS \geq 3$: 55.2% (VM: 66.4%; MD: 50.0%; BPPV: 47.6%)).

Multivariable linear and logistic regression models in subgroups of acute vestibular disorders

A comparison of the subgroups CV, PV and EV in multivariable regression models (adjusted for age, sex, DM, hypertension, A-Fib and non-vestibular signs of brainstem/cerebellar dysfunction), showed a statistically relevant difference between all subgroups for the variables EQ-5D-5L ($F=12.2$, $p<0.0001$) (Tab.3A) and EQ-VAS ($F=6.0$, $p=0.003$) (Tab.3B). This effect resulted from a significant difference between the subgroups CV and PV for EQ-5D-5L ($p<0.01$) and EQ-VAS ($p=0.02$). Only female gender had a significant effect as a covariate in the model for EQ-5D-5L ($p=0.01$) and EQ-VAS ($p=0.02$). Patients with PV had clinically relevant lower scores for EQ-5D-5L ($\beta=-0.17$) and for EQ-VAS ($\beta=-10.8$) compared to patients with CV.

Multivariable linear and logistic regression models for DHI and mRS \geq 3 (adjusted for the above mentioned covariates, respectively) indicated an overall significant difference between subgroups (DHI: F=4.3, p=0.02; mRS \geq 3: Chi 2 =14.8, p<0.001). Again, patients with PV had more severe symptoms than patients with CV (p=0.02) (Tab.4A) and a higher degree of disability (p<0.01) (Tab.4B). In the regression model for DHI, age (p=0.003) and female gender (p=0.04) were relevant covariates, in the model for mRS \geq 3 female gender (p=0.02). Patients with PV had a clinically relevant higher DHI (β =11.2) and proportion of mRS \geq 3 (OR: 4.4) compared to patient with CV after adjusting for the aforementioned variables (Tab.4).

Effect of vestibulo-ocular motor, -spinal and –perceptive asymmetry on functional outcome parameters

Patients with PV had a more intense horizontal SPN (SPV: 2.3 \pm 3.0°/sec) compared to patients with CV (SPV: 0.4 \pm 0.5°/sec, p<0.001) and EV (SPV: 0.3 \pm 0.3°/sec, p<0.001) (ANOVA: p< 0.0001). Vertical SPN was only different for the subgroups PV (SPV: 0.6 \pm 0.9°/sec) versus EV (SPV: 0.3 \pm 0.3°/sec, p=0.05), but not CV (SPV: 0.4 \pm 0.5°/sec, p=0.5) (ANOVA: p=0.05). Mean SVV deviation was not significantly different in patients with PV (6.3 \pm 5.4°) and patients with CV (5.0 \pm 4.8°, p=0.37), but higher than in patients with EV (1.5 \pm 1.6°, p<0.001) (ANOVA: p<0.0001). SP was comparable in PV (ML: 0.47 \pm 0.31m, AP: 0.86 \pm 0.48m), CV (ML: 0.48 \pm 0.29m, AP: 0.76 \pm 0.37m) and EV (ML: 0.46 \pm 0.31m, AP: 0.73 \pm 0.52m) (ANOVA SP-ML: p=0.92; ANOVA SP-AP: p=0.37). When horizontal SPN, SVV and SP was included in the multivariable regression models for EQ-5D-5L, EQ-VAS, DHI, and mRS \geq 3 the following effects were found: SPN was a highly relevant cofactor for subgroup differences, while SVV and SP were not. Significant differences between the subgroups PV and CV disappeared for EQ-5D-5L, DHI and mRS \geq 3, when SPN was included in the model.

Correlation analysis of functional outcome parameters with measures of vestibular asymmetry

Correlation analysis of outcome parameters with vestibulo-ocular motor, -spinal and -perceptive signs of vestibular asymmetry indicated that EQ-5D-5L decreased strongly and significantly with higher SPV of horizontal SPN (Rho=-0.57, p<0.01), but not vertical SPN (Rho=-0.18) in patients with CV and PV (horizontal SPN: Rho=-0.5, p<0.001; vertical SPN: Rho=-0.18). In patients with EV neither horizontal (Rho=-0.13) nor vertical SPN (Rho=-0.07) correlated with to EQ-5D-5L. DHI increased moderately with higher intensity of horizontal SPN in the CV (Rho=0.34, p=0.04) and the PV subgroups (Rho=0.41, p<0.01), but not in the EV subgroup (Rho=-0.07) (Tab.5). SP-ML or -AP was not significantly correlated with EQ-5D-5L, EQ-VAS or DHI for the subgroups CV and PV. In patients with EV SP-ML and -AP correlated moderately and significantly with EQ-5D-5L (Rho:-0.3/-0.32) and EQ-VAS (Rho:-0.36/-0.31). SVV had a moderate inverse correlation with EQ-5D-5L (Rho=-0.37, p<0.01) in patients with PV only.

DISCUSSION

In this prospective study, HRQoL and functional impairment were systematically investigated in patients with different types of acute vestibular disorders and analysed against ocular motor, spinal and perceptive signs of vestibular asymmetry and differential affection of functional vestibular inputs (from the SCCs and otoliths). The major findings were the following: 1) Patients with PV had a poorer generic and disease-specific HRQoL, higher symptom intensity and more severe functional impairment than patients with CV and EV. 2) Vestibular-ocular motor imbalance (indicated by SPN) had the highest effect on HRQoL and symptom intensity in patients with PV and CV. 3) Affection of the horizontal SCC input had more impact on HRQoL than disturbed vertical SCC or otolith inputs in PV and CV.

Differential impairment in subtypes of acute vestibular disorders - clinical relevance

Previous studies showed that physicians tend to classify vestibular disorders with a subtle symptom intensity and a relatively moderate disability as benign [22]. Our data contradict this view, because patients with CV (like acute stroke) indeed had on average a lower symptom intensity of vertigo/dizziness, better HRQoL and were less severely impaired than patients with PV (Tab.3,4). The difference of 10.8 points in DHI and 0.17 points in EQ-5D-5L between these subgroups, and an OR of 4.4 for more severe disability in mRS in patients with PV has to be considered as clinically relevant [16,23,24]. Emergency physicians should be aware that acute CV may be misdiagnosed, if the clinical judgement relies overly on symptom characteristics like intensity of vertigo/dizziness or subjectively perceived impairment [25,26]. Modern concepts of symptom-based differentiation of vestibular disorders are guided more by the presence of triggers preceding vestibular symptoms, the time course of symptom onset and evolution, and the previous history of vestibular attacks [27].

Pathophysiological basis of perceived functional impairment in acute vestibular disorders

The acute stage of vestibular disorders differs from the subsequent course in that mechanisms of vestibular compensation or behavioural adaptation have not yet fully evolved to ameliorate signs and symptoms of vestibular asymmetry [28,29]. Consequently, reduced vestibular input from the sensory organs in the inner ear (SCCs, otoliths) or altered central projection of vestibular signals to the eyes, spinal cord or cortex may translate more directly into perception of symptoms or functional impairment in acute vestibular disorders. However, it is unknown, to which extent the disturbance of distinct vestibular domains and networks (vestibular-ocular motor: gaze stability, vestibular-spinal: postural control, vestibular-perceptive: verticality perception) contributes to functional impairment, and, whether the direction of the affected plane alters perceived symptom intensity and disability in patients with acute vestibular disorders. Following the anatomy of the labyrinth, the vestibular system is organized along the three planes roll, pitch and yaw [30]. Clinical signs of a vestibular tone imbalance in the roll plane are a rotatory nystagmus (ocular motor), a lateral falling tendency (posture) and SVV tilt (perception) [30]. Static signs and symptoms in the roll plane originate from asymmetric vestibular inputs from the vertical SCCs and otoliths [30,31]. Pitch-plane

specific signs may be a vertical nystagmus or a AP-body sway and mostly arise from bilateral affection of peripheral or central vestibular signal processing [32]. Vestibular tone imbalance in the yaw plane (asymmetric input from the horizontal SCCs) results in a horizontal nystagmus (Fig.1).

In the current study, SPN was the most relevant factor for perceived symptom intensity and functional impairment, while postural imbalance and SVV tilt were not significantly contributing to subgroup differences in the multivariable regression models of PV and CV. The horizontal component of SPN was associated strongly and significantly with lower EQ-5D-5L and higher DHI scores in PV and CV, while the vertical component of SPN did not (Tab.5). These findings allow three important conclusions: 1) Impaired gaze stability and oscillopsia are perceived as the most disabling symptoms in patients with acute PV and CV. Postural control seems to be less prominently rated. It is reasonable that gaze stability is weighted as the strongest factor for HRQoL by patients, as it is the prerequisite for stable visual exploration of the environment and visual guidance of balance control [33]. 2) Deficits in the yaw plane contribute more to functional impairment than in the roll and pitch plane. Only the horizontal component of SPN was a significant factor for disability in the regression models. Signs of vestibular asymmetry in the roll plane (SVV, SP-ML) and pitch plane (vertical SPN, SP-AP) were not as significantly associated with symptom severity and functional impairment. The plane-specific effect can likely be explained by the fact that the yaw plane is the dominant plane for natural eye and head movements in locomotion and spatial orientation [34]. Freezing of gaze to the horizon is a known behavioural strategy to reduce anxiety in patients with fear of heights or visual height intolerance [35]. Therefore, instability of horizontal gaze fixation may cause discomfort and trigger anxiety in patients with acute vertigo/dizziness. 3) Deficient vestibular input from the horizontal SCCs is more disabling than from the vertical SCCs and the otoliths. This can be derived from a minor effect of SVV deviation in PV only, which relies on vertical SCC and otolith signs [21], and a missing effect of the vertical component of SPN for all subgroups, which reflects affection of the vertical SCCs. Furthermore, SP, which is influenced by otolith signals to the spinal cord, was not associated significantly with functional impairment in PV and CV [20]. The prevalent role of the horizontal SCC could be explained ontologically, because it is the oldest and most important for gaze stabilization in different species [36,37].

Differences in HRQoL and functioning in acute, episodic and chronic vestibular disorders

Disease duration seems to play a critical role for the subjective judgement of functional impairment in different vestibular disorders. Patients with chronic CV (e.g., after vestibular stroke) have a higher DHI compared to patients with persisting peripheral vestibular deficits (e.g., long-standing unilateral vestibulopathy, bilateral vestibulopathy) [9]. Our study shows the opposite during the acute stage of vestibular symptoms (DHI in PV>CV) (Tab.2,4). One could speculate that CV compensate less effectively, if vestibular-cerebellar structures with critical impact for central plasticity mechanisms are damaged. It has

been shown that patients with midline and cortical cerebellar lesions tend to compensate inadequately, while patients with Wallenberg's syndrome recover similarly compared to patients with acute unilateral peripheral vestibulopathy [28,38]. Another factor may be that vestibular-ocular motor dysfunction contributes less to perceived symptoms in the chronic stage of PV and CV, compared to postural instability and falls, which are more frequent in patients with CV [5]. In a previous study, VOR parameters did not correlate with DHI in chronic PV and CV [9].

EV may have a complex impact on HRQoL and functioning. The current study shows 1) a less severe functional impairment in the acute symptomatic stage for these patients compared to patients with non-episodic PV or CV, and 2) a poorer HRQoL in patients with VM, compared to MD and BPPV. It could be hypothesized that some degree of habituation to acute vestibular symptoms may appear in patients with EV, which is independent of the degree of objectively measured vestibular dysfunction. Influencing factors could be rather the emotional resilience to deal with symptoms, the coping strategies and the degree of psychiatric comorbidity [39,40]. Cultural and socio-economic factors may be relevant [41]. The potential to adapt to recurrent vestibular symptoms may furthermore depend on the underlying vestibular disorder. Patients with VM develop secondary psychiatric comorbidities like anxiety or depression more often than patients with MD or recurrent BPPV [4,7,10,39]. In the current study, the effect of hearing loss on HRQoL was likely underestimated in MD patients, because EQ-5D-5L is not sensitive to hearing. The Health Utilities Index (HUI) Mark 2,3 is more sensitive in this respect [42].

Conclusions

This prospective study establishes a more comprehensive view of the factors relevant for generic and disease-specific HRQoL and functioning in acute vestibular disorders: In acute PV and CV, gaze stability in the yaw plane plays a key role for perceived symptom severity and impairment, while postural stability and verticality perception in the roll and pitch plane are less important. This finding underlines the importance of a stable horizontal gaze fixation for suppression of imbalance-related discomfort and anxiety, as well as for postural stability. In EV, perceived symptom intensity and HRQoL likely depend less on the impairment of vestibular signal input, but rather on behavioural cofactors (like coping, resilience or comorbid anxiety). This knowledge is of importance for the treatment of patients with different vestibular disorders and the definition of relevant patient-related outcome parameters for future interventional trials in various acute and episodic vestibular disorders.

Table 1

	Total group	CV	PV	EV
N (%)	175 (100)	40 (22.9)	68 (38.9)	67 (38.3)
Age in years (SD)	58.6 (15.0)	64.1 (12.2)	55.6 (14.6)	58.4 (16.1)

Female; N (%)	70 (40.0)	13 (32.5)	24 (35.3)	33 (49.3)
Risk factors (%)				
DM	9 (5.1)	4 (10.0)	2 (2.9)	3 (4.5)
Hypertension [#]	117 (66.9)	29 (72.5)	44 (64.7)	44 (65.7)
Atrial fibrillation	15 (8.6)	6 (15.0)	3 (4.4)	6 (9.0)

Table 1: Patient characteristics in subgroups. Patients with CV were older, more likely of male gender and had more cardiovascular risk factors. [#] blood pressure > 140/90 mmHg. CV: central vestibular disorders, EV: episodic vestibular disorders, PV: peripheral vestibular disorders, SD: standard deviation.

Table 2

	Total group	CV	PV	EV
N (%)	175 (100)	40 (22.9)	68 (38.9)	67 (38.3)
EQ-5D-5L [#] (SD)				
Overall index score	0.64 (0.29)	0.66 (0.28)	0.53 (0.31)	0.75 (0.24)
Subscore Anxiety	2.0 (1.1)	2.1 (1.2)	1.9 (1.1)	1.9 (1.1)
Subscore Pain	2.2 (1.2)	2.3 (1.2)	2.4 (1.3)	2.0 (1.0)
Subscore Activity	3.0 (1.6)	2.9 (1.7)	3.6 (1.4)	2.4 (1.5)

Subscore Self-care	1.8 (1.1)	1.6 (1.1)	2.3 (1.2)	1.5 (0.9)
Subscore Mobility	2.6 (1.3)	2.3 (1.2)	3.2 (1.3)	2.2 (1.1)
EQ-VAS [†] (SD)	53.1 (21.9)	57.2 (18.9)	46.5 (22.7)	57.6 (21.4)
DHI [§] (SD)	49.6 (21.9)	43.3 (24.0)	56.1 (19.7)	46.7 (21.4)
mRS \geq 3 (%)	121 (69.1)	26 (65.0)	58 (85.3)	37 (55.2)

Table 2: QoL and symptom intensity in patient subgroups. Patients with PV had poorer HRQoL and more severe functional impairment than patients with episodic and CV. [#] overall index score ranging from negative values to a maximum of 1 with 1 indicating the best health status. Subscores ranging from 1 to 5 with 5 indicating worst impairment. [†]EQ-VAS ranging from 0 to 100 with 100 being the best health status. [§]DHI ranging from 0 to 100 with 100 being the worst impairment due to dizziness. CV: central vestibular disorders, DHI: Dizziness Handicap Inventory, EQ-5D-5L: EuroQoL 5 Dimensions 5 Levels QoL questionnaire, EQ-VAS: European QoL Visual Analogue Scale, EV: episodic vestibular disorders, mRS: modified Rankin Scale, PV: peripheral vestibular disorders, SD: standard deviation.

Table 3

A) Variable EQ-5D-5L	Coefficient	95% CI	F	p-value
Diagnosis				
CV	Ref		12.2	<0.0001
PV	-0.17	[-0.29, -0.05]		<0.01
EV	-0.06	[-0.06, 0.19]		0.33
Age	-0.0001	[-0.003, 0.003]		0.95
Sex				
Male	Ref			
Female	-0.11	[-0.20, -0.02]		0.01

Diabetes	-0.06	[-0.25, 0.13]		0.54
Hypertension	-0.01	[-0.11, 0.08]		0.79
Atrial Fibrillation	-0.09	[-0.25, 0.06]		0.24
Brainstem/cerebellar dysfunction	-0.07	[-0.19, 0.05]		0.25

B) Variable EQ-VAS	Coefficient	95% CI	F	p-value
Diagnosis			6.0	0.003
CV	Ref			
PV	-10.8	[-20.2, -1.5]		0.02
EV	1.1	[-8.5, 10.7]		0.82
Age	0.1	[-0.1, 0.3]		0.40
Sex				
Male	Ref			
Female	-8.1	[-14.7, -1.5]		0.02
Diabetes	-12.0	[-26.3, -2.4]		0.10
Hypertension	-6.6	[-13.7, 0.6]		0.07
Atrial Fibrillation	4.9	[-6.9, 16.7]		0.42
Brainstem/cerebellar dysfunction	-0.7	[-10.0, 8.5]		0.87

Table 3: Multivariable linear regression analysis for outcome parameters EQ-5D-5L (A) and EQ-VAS (B). Patients with PV had significantly poorer generic HRQoL compared to CV. Gender was the only significant covariate in this model. CI: confidence interval, CV: central vestibular disorders, EQ-5D-5L: EuroQoL 5 Dimensions 5 Levels QoL questionnaire, EQ-VAS: European QoL Visual Analogue Scale, EV: episodic vestibular disorders, PV: peripheral vestibular disorders, Ref: reference group; Partial F-statistic testing the null hypothesis of no difference between patient subgroups, adjusted for covariates. Significant values ($p<0.05$) in bold.

Table 4

A) Variable DHI	Coefficient	95% CI	F	p-value
Diagnosis			4.3	0.02
CV	Ref			
PV	11.2	[2.0, 20.4]		0.02
EV	2.4	[-7.0, 11.9]		0.61
Age	-0.4	[-0.6, -0.1]		0.003

Sex				
Male	Ref			
Female	7.0	[0.5, 13.5]		0.04
Diabetes	1.3	[-12.9, 15.5]		0.85
Hypertension	1.1	[-5.9, 8.2]		0.75
Atrial Fibrillation	-8.8	[-20.5, 2.9]		0.14
Brainstem/cerebellar dysfunction	5.2	[-3.9, 14.3]		0.26

B) Variable mRS\geq3	OR	95% CI	Chi²	p-value
Diagnosis			14.8	<0.001
CV	Ref			
PV	4.4	[1.4, 13.2]		<0.01
EV	0.8	[0.3, 2.3]		0.71
Age	0.98	[0.96, 1.0]		0.22
Sex				
Male	Ref			
Female	2.5	[1.15, 5.4]		0.02
Diabetes	2.1	[0.38, 11.8]		0.39
Hypertension	1.5	[0.7, 3.4]		0.29
Atrial Fibrillation	0.5	[0.2, 1.9]		0.34
Brainstem/cerebellar dysfunction	2.7	[0.9, 8.4]		0.08

Table 4: Multivariable linear and logistic regression analysis for outcome parameters DHI (A) and dichotomized mRS \geq 3 (B). Patient with PV had a significantly higher symptom intensity, lower disease-specific HRQoL and more severe functional impairment compared to CV. For DHI, age and gender were significant covariates, for mRS gender. CI: confidence interval, CV: central vestibular disorders, DHI: Dizziness Handicap Inventory, EV: episodic vestibular disorders, mRS: modified Rankin Scale; OR: odds ratio, PV: peripheral vestibular disorders, Ref: reference group. For DHI partial F-statistic and for mRS Chi² statistic was performed, testing the null hypothesis of no difference between patient subgroups, respectively adjusted for covariates. Significant values ($p<0.05$) in bold.

Table 5

	CV	PV	EV
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	SPN h	SPN v	SP- ML	SP- AP	SVV	SPN h	SPN v	SP- ML	SP- AP	SVV	SPN h	SPN v	SP- ML	SP- AP	SVV
EQ-5D-5L	-0.57	-0.18	0.0	-0.05	-0.24	-0.50	-0.18	-0.14	-0.15	-0.37	-0.13	-0.07	-0.30	-0.32	-0.18
EQ-VAS	-0.06	-0.14	0.08	0.08	-0.11	-0.14	-0.09	0.12	0.05	0.03	-0.05	0.01	-0.36	-0.31	-0.09
DHI	0.34	0.21	-0.08	-0.04	0.23	0.41	0.26	0.16	-0.06	0.21	-0.07	-0.14	0.06	-0.13	-0.16

Table 5: Correlation analysis of outcome parameters and neurophysiological measurements. In CV and PV – but not EV - the intensity of horizontal spontaneous nystagmus (SPN h) significantly correlated with overall HRQoL (EQ-5D-5L) and symptom intensity (DHI). The vertical component of spontaneous nystagmus (SPN v) and subjective visual vertical (SVV) showed no significant and relevant correlations (correlation coefficient >0.3) in neither subgroup (except for SVV correlation in the subgroup of PV). Sway path (SP) in medio-lateral (ML) and anterior-posterior (AP) moderately correlated with EQ-5D-5L and EQ-VAS in EV. CV: central vestibular disorders, DHI: Dizziness Handicap Inventory, EQ-5D-5L: EuroQoL 5 Dimensions 5 Levels QoL questionnaire, EQ-VAS: European QoL Visual Analogue Scale, EV: episodic vestibular disorders, PV: peripheral vestibular disorders. Significant ($p<0.05$) and relevant correlations (correlation coefficient >0.3) are indicated in bold.

Figure

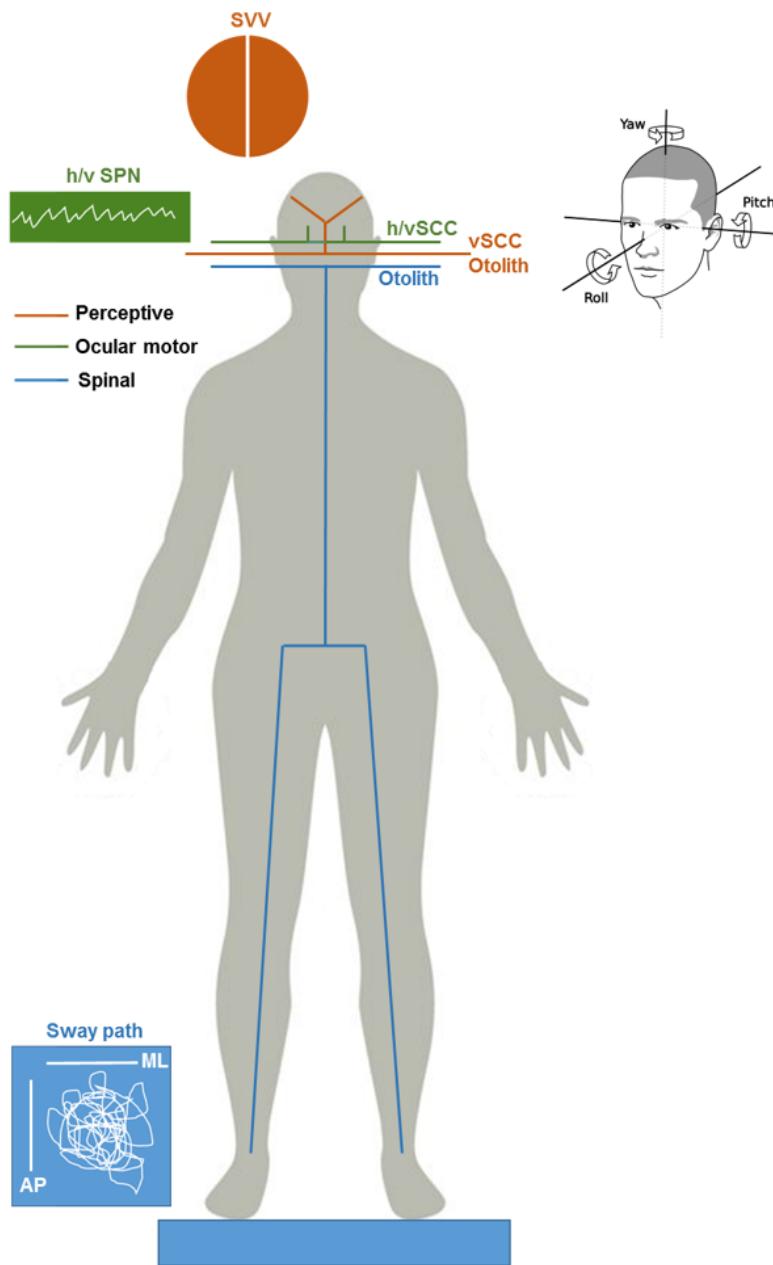


Figure 1: Quantitative parameters of vestibular tone imbalance in acute vestibular disorders. As a marker of vestibular-ocular motor asymmetry, spontaneous nystagmus (SPN, horizontal (h) and vertical (v) component) was registered by video-oculography. SPN represents a tone imbalance derived from horizontal and vertical semicircular canals (hSCC, vSCC). Vestibular-spinal imbalance was measured by mobile posturography as sway path in the medio-lateral (ML) and antero-posterior (AP) axis. Vestibular-spinal posture control mainly is thought to rely on otolith inputs. Vestibular perception was quantified by assessment of subjective visual vertical (SVV), which is integrated from otolith and vertical SCC signs.

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