ORIGINAL ARTICLE

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

K. Möhwald[a,b], H. Hadzhikolev[a,b], S. Bardins[b], S. Becker-Bense[b], T. Brandt[b,c], E. Grill[b,d], K. Jahn[b,e], M. Dieterich[a,b,f] and A. Zwergal[a,b]

[a]*Department of Neurology, University Hospital, LMU Munich, Munich;* [b]*German Center for Vertigo and Balance Disorders, DSGZ, LMU Munich, Munich;* [c]*Clinical Neurosciences, LMU Munich, Munich;* [d]*Institute for Medical Information Processing, Biometry, and Epidemiology, LMU Munich, Munich;* [e]*Department of Neurology, Schön Klinik Bad Aibling, Bad Aibling; and* [f]*Munich Cluster of Systems Neurology, SyNergy, Munich, Germany*

Keywords:
acute unilateral peripheral vestibulopathy, quality of life, recurrent vestibulopathies, vestibular stroke, video-oculography

Received 20 March 2020
Accepted 5 May 2020

European Journal of Neurology 2020, **27:** 2089–2098

doi:10.1111/ene.14318

Background and purpose: 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: In all, 175 patients with acute vestibular disorders were categorized as 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 (European Quality of Life Score Five Dimensions Five Levels, 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.

Results: Patients with PV had a poorer HRQoL compared to patients with CV and EV (EQ-5D-5L/DHI: PV, 0.53 ± 0.31/56.1 ± 19.7; CV, 0.66 ± 0.28/43.3 ± 24.0; EV, 0.75 ± 0.24/46.7 ± 21.4). 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 was a highly relevant factor for subgroup differences in EQ-5D-5L and DHI, whilst vertical spontaneous nystagmus, subjective visual vertical and sway path were not. EQ-5D-5L decreased significantly with more intense horizontal subjective visual vertical in CV (rho = −0.57) and PV (rho = −0.5) but not EV (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 vestibular-perceptive asymmetry in the roll and pitch plane, suggesting that horizontal visual stability is the most critical for HRQoL.

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

Correspondence: A. Zwergal, Department of Neurology and German Center for Vertigo and Balance Disorders, DSGZ, Ludwig-Maximilian-University München, Marchioninistrasse 15, D-81377 Munich, Germany (tel.: +49 89 4400 72571; fax: +49 89 4400 75584; e-mail: andreas.zwergal@med.uni-muenchen.de).

[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 otolith 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], whilst patients with chronic unilateral 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 are probably modulated by different factors during the acute stage of disease. However, systematic evaluations, which describe the effects of disease aetiology, vestibular impairment and patients' characteristics on symptom intensity, functional impairment and HRQoL in acute vestibular disorders, are missing.

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 were correlated to objective measures of vestibular-ocular motor, vestibular-spinal and vestibular-perceptive signs, as well as patient-specific factors (such as age, gender). It is hypothesized that (i) acute unilateral peripheral vestibulopathies have the highest symptom intensity and lowest HRQoL, (ii) ocular motor signs of vestibular asymmetry are the most important determining factor and (iii) 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 end-points.

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 workup was done during the acute stage of symptoms. (i) 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. (ii) A standardized neurological and neuro-otological clinical examination was performed. (iii) All patients completed scores and scales to quantify generic and disease-specific HRQoL and functioning [European Quality of Life Score Five Dimensions Five Levels (EQ-5D-5L), European Quality of Life Visual Analogue Scale (EQ-VAS), Dizziness Handicap Inventory (DHI)]. The degree of disability was rated by the modified Rankin Scale (mRS). (iv) Vestibular-ocular motor signs were assessed by video-oculography, 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 Bárány Society) [13]. A standardized magnetic resonance imaging (MRI) protocol (whole brain diffusion-weighted imaging, T1-, T2-, T2*-weighted sequences, and time of flight 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 in 24% of patients.

In 175 patients a definite neuro-otological diagnosis according to guideline criteria could be determined. These patients were categorized into three subgroups for further analysis: central vestibular disorders (CV) (vestibular stroke, inflammatory central nervous system lesions, based on MRI and Video – Head impulse test, nystagmus, test of skew) ($n = 40$) [14], peripheral vestibular disorders (PV) (based on Video – Head impulse test 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 the respective diagnostic guidelines] ($n = 67$). A total of 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 transient ischaemic attack, status post BPPV), mixed presentations (e.g. overlap of MD/VM), general medical aetiology (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 23 February 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 EQ-5D-5L including subscores for anxiety, pain, activity, self-care and mobility [overall index score ranged from negative values to 1 (best health status); subscores ranged from 1 to 5 (worst impairment)] [15]. Utility values for the EQ-5D-5L were calculated using a recently published value set [16]. The overall subjective estimation of health status was measured by EQ-VAS [ranging from 0 to 100 (best status)]. Disease-specific HRQoL and symptom intensity were quantified using the DHI [ranging from 0 to 100 points (worst symptoms)] [17]. The degree of disability or dependence was estimated by the mRS (ranging from 0 to 6 points) with major disability defined as mRS $\geq$ 3 [18].

Video-oculographic examination

The following vestibular/ocular motor signs were documented by video-oculography (EyeSeeCam®, Munich, Germany) during the acute stage of symptoms: nystagmus in the 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 [19]. Ten repetitions (five clockwise/five counterclockwise rotations) were performed and a mean of the deviations was calculated. The normal range was defined as 0 $\pm$ 2.5° [19].

Posturographic assessment

A posturographic measurement of body sway was performed using a mobile device (Wii Balance Board®, Nintendo, Kyoto, Japan). Four conditions were tested: bipedal standing with eyes open/closed, upright tandem standing with eyes open/closed. The sway pattern in the medio-lateral (ML) and anterior–posterior (AP) directions 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 [20]) and cardiovascular risk factors [i.e. diabetes mellitus (DM), hypertension and atrial fibrillation (A-Fib)] using Stata 14.2 software (StataCorp LLC, College Station, TX, USA). The subgroup CV was selected as the reference group. A sensitivity analysis with multivariable linear or logistic regression models was conducted for secondary outcome parameters (EQ-VAS, DHI, mRS $\geq$ 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: (i) 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); (ii) SP in the 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 [21]; (iii) SVV, as a measure of vestibular perception derived from otolith and vertical SCC inputs (Fig. 1) [22]. 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 $\pm$ 15.0 years. Patients with CV were older (64.1 $\pm$ 12.2 years) than patients with PV (55.6 $\pm$ 14.6 years) and EV (58.4 $\pm$ 16.1 years) (Table 1). Men were more

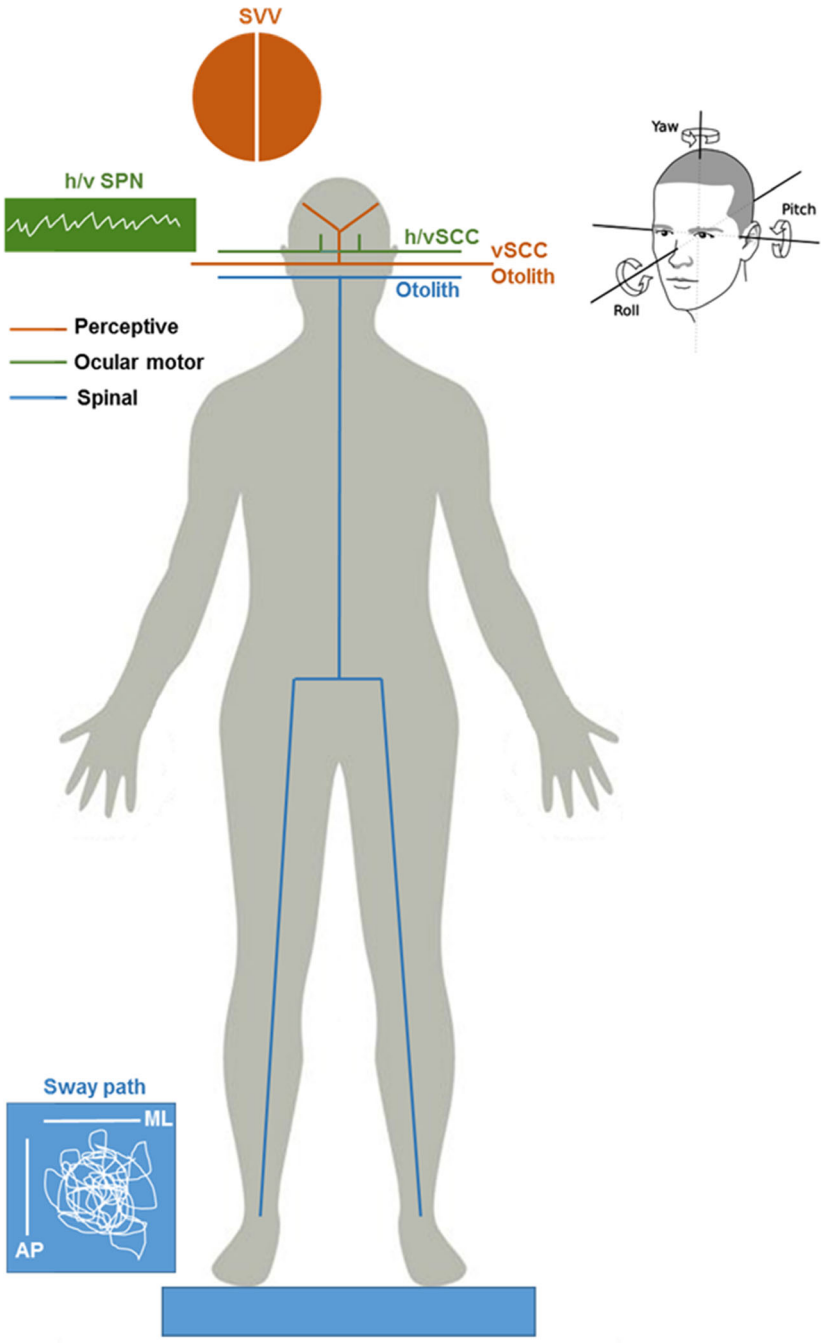

Figure 1 Quantitative parameters of vestibular tone imbalance in acute vestibular disorders. As a marker of vestibular-ocular motor asymmetry, spontaneous nystagmus [SPN, horizontal (h) and vertical (v) component] was registered by video-oculography. SPN represents a tone imbalance derived from the horizontal and vertical semicircular canals (hSCC, vSCC). Vestibular-spinal imbalance was measured by mobile posturography as the sway path in the medio-lateral (ML) and anterior–posterior (AP) axis. Vestibular-spinal posture control is thought mainly 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.

frequently affected in the subgroups with CV (67.5%) and PV (64.7%), whilst 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%) (Table 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 ≥ 3) in 69.1% of all patients (Table 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) (Table 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 ≥ 3 85.3%) than in patients with CV (DHI 43.3 ± 24.0; mRS ≥ 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 ≥ 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 ($F = 12.2$, $P < 0.0001$) (Table 3 (a)) and EQ-VAS ($F = 6.0$, $P = 0.003$) (Table 3(b)). 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 covariable 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 ≥ 3 (adjusted for the above mentioned covariables, respectively) indicated an overall significant difference between subgroups (DHI $F = 4.3$, $P = 0.02$; mRS ≥ 3 $\chi^2 = 14.8$, $P < 0.001$). Again, patients with PV had more severe symptoms than patients with CV ($P = 0.02$) (Table 4(a)) and a higher degree of disability ($P < 0.01$) (Table 4(b)). In the regression model for DHI, age ($P = 0.003$) and female gender ($P = 0.04$) were relevant covariables, and in the model for mRS ≥ 3 female gender ($P = 0.02$). Patients with PV had a clinically relevant

Table 1 Patient characteristics in subgroups

	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[a]	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)

CV, central vestibular disorders; DM, diabetes mellitus; EV, episodic vestibular disorders; PV, peripheral vestibular disorders. Patients with CV were older, more probably of male gender and had more cardiovascular risk factors. [a]Blood pressure > 140/90 mmHg.

Table 2 Quality of life and symptom intensity in patient subgroups

	Total group	CV	PV	EV
N (%)	175 (100)	40 (22.9)	68 (38.9)	67 (38.3)
EQ-5D-5L[a] (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[b] (SD)	53.1 (21.9)	57.2 (18.9)	46.5 (22.7)	57.6 (21.4)
DHI[c] (SD)	49.6 (21.9)	43.3 (24.0)	56.1 (19.7)	46.7 (21.4)
mRS ≥ 3 (%)	121 (69.1)	26 (65.0)	58 (85.3)	37 (55.2)

CV, central vestibular disorders; DHI, Dizziness Handicap Inventory; EQ-5D-5L, European Quality of Life Score Five Dimensions Five Levels; EQ-VAS, European Quality of Life Visual Analogue Scale; EV, episodic vestibular disorders; HRQoL, health-related quality of life; mRS, modified Rankin Scale; PV, peripheral vestibular disorders. Patients with PV had poorer HRQoL and more severe functional impairment than patients with EV and CV. [a]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 [b]EQ-VAS ranging from 0 to 100 with 100 being the best health status [c]DHI ranging from 0 to 100 with 100 being the worst impairment due to dizziness.

higher DHI ($\beta = 11.2$) and proportion of mRS ≥ 3 (odds ratio 4.4) compared to patients with CV after adjusting for the aforementioned variables (Table 4).

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

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

Table 3 Multivariable linear regression analysis for outcome parameters (a) EQ-5D-5L and (b) EQ-VAS

	Coefficient	95% CI	*F*	*P* value
(a) Variable EQ-5D-5L				
Diagnosis			12.2	**<0.0001**
CV	Ref			
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				
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

CI, confidence interval; CV, central vestibular disorders; EQ-5D-5L, European Quality of Life Score Five Dimensions Five Levels; EQ-VAS, European Quality of Life Visual Analogue Scale; EV, episodic vestibular disorders; PV, peripheral vestibular disorders; Ref, reference group. Patients with PV had significantly poorer generic HRQoL compared to CV. Gender was the only significant covariable in this model. Partial *F*-statistic testing the null hypothesis of no difference between patient subgroups, adjusted for covariables. Significant values ($P < 0.05$) in bold.

Table 4 Multivariable linear and logistic regression analysis for outcome parameters (a) DHI and (b) dichotomized mRS ≥ 3

	Coefficient	95% CI	*F*	*P* value
(a) Variable DHI				
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
Variable mRS ≥ 3	**OR**		**χ^2**	
(b)				
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

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. Patients 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 covariables, for mRS gender. For DHI the partial *F*-statistic and for mRS the chi-squared statistic were calculated, testing the null hypothesis of no difference between patient subgroups, respectively, adjusted for covariables. Significant values ($P < 0.05$) in bold.

were not. Significant differences between the subgroups PV and CV disappeared for EQ-5D-5L, DHI and mRS ≥ 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, vestibulo-spinal and vestibulo-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 EQ-5D-5L. DHI increased moderately with a 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) (Table 5). SP-ML or SP-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 SP-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: (i) 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; (ii) vestibular-ocular motor imbalance (indicated by SPN) had the highest effect on HRQoL and symptom intensity in patients with PV and CV; (iii) 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 [23]. 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 (Tables 3 and 4). The difference of 10.8 points in DHI and 0.17 points in EQ-5D-5L between these subgroups and an odds ratio of 4.4 for more severe disability in mRS in patients with PV has to be considered as clinically relevant [17,24,25]. 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 [26,27]. 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 [28].

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 [29,30]. 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 what 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 [31]. 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) [31]. Static signs and symptoms in the roll plane originate from asymmetric vestibular inputs from the vertical SCCs and otoliths [31,32]. Pitch-plane specific signs may be a vertical nystagmus or an AP body sway and mostly arise from bilateral affection of peripheral or central vestibular signal processing [33]. Vestibular tone imbalance in the yaw plane (asymmetric input from the horizontal SCCs) results in a horizontal nystagmus (Fig. 1).

Table 5 Correlation analysis of outcome parameters and neurophysiological measurements

	CV					PV					EV				
	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

CV, central vestibular disorders; DHI, Dizziness Handicap Inventory; EQ-5D-5L, European Quality of Life Score Five Dimensions Five Levels; EQ-VAS, European Quality of Life Visual Analogue Scale; EV, episodic vestibular disorders; PV, peripheral vestibular disorders; SPN h, horizontal spontaneous nystagmus; SPN v, vertical spontaneous nystagmus, SP-ML, sway path in medio-lateral axis; SP-AP, sway path in anterior–posterior axis; SVV, subjective visual vertical. In CV and PV – but not EV – the intensity of SPN h significantly correlated with overall HRQoL (EQ-5D-5L) and symptom intensity (DHI). SPN v and SVV showed no significant and relevant correlations (correlation coefficient > 0.3) in either subgroup (except for SVV correlation in the subgroup of PV). SP-ML and SP-AP moderately correlated with EQ-5D-5L and EQ-VAS in EV. Significant ($P < 0.05$) and relevant correlations (correlation coefficient > 0.3) are indicated in bold.

In the current study, SPN was the most relevant factor for perceived symptom intensity and functional impairment, whilst postural imbalance and SVV tilt did not significantly contribute 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, whilst the vertical component of SPN was not (Table 5). These findings allow three important conclusions.

(i) 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 [34].

(ii) 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 probably be explained by the fact that the yaw plane is the dominant plane for natural eye and head movements in locomotion and spatial orientation [35]. Freezing of gaze to the horizon is a known behavioural strategy to reduce anxiety in patients with fear of heights or visual height intolerance [36]. Therefore, instability of horizontal gaze fixation may cause discomfort and trigger anxiety in patients with acute vertigo/dizziness.

(iii) 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 [22], 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 [21]. 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 [37,38].

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) (Tables 2 and 4). One could speculate that patients with 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, whilst patients with Wallenberg's syndrome recover similarly compared to patients with acute unilateral peripheral vestibulopathy [29,39]. 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].

Episodic vestibular disorders may have a complex impact on HRQoL and functioning. The current study shows (i) a less severe functional impairment in the acute symptomatic stage for these patients compared to patients with non-episodic PV or CV and (ii) 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 [40,41]. Cultural and socio-economic factors may be relevant [42]. 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 [4,7,10,40]. In the current study, the effect of hearing loss on HRQoL was probably underestimated in MD patients because EQ-5D-5L is not sensitive to hearing. The Health Utilities Index Mark 2,3 is more sensitive in this respect [43].

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, whilst 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 probably 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 for the definition of relevant patient-related outcome parameters for future interventional trials in various acute and episodic vestibular disorders.

Acknowledgements

The study was performed as a project of the German Center for Vertigo and Balance Disorders (DSGZ) (grant number 01 EO 0901) with the support of the German Federal Ministry of Education and Research (BMBF) and the Hertie Foundation (to TB). Katie Göttlinger is thanked for copyediting the manuscript.

Disclosure of conflicts of interest

Mr Möhwald has nothing to disclose. Mr Hadzhikolev has nothing to disclose. Mr Bardins has nothing to disclose. Prof. Dr Becker-Bense has nothing to disclose. Prof. Dr Brandt has nothing to disclose. Prof. Dr Grill has nothing to disclose. Prof. Dr Jahn has nothing to disclose. Prof. Dr Dieterich has nothing to disclose. Dr Zwergal has nothing to disclose.

References

1. Ten Voorde M, Van Der Zaag-Loonen HJ, Van Leeuwen RB. Dizziness impairs health-related QoL. *Qual Life Res* 2012; **21:** 961–966.
2. Benecke H, Agus S, Kuessner D, *et al*. The burden and impact of vertigo: findings from the REVERT Patient Registry. *Front Neurol* 2013; **4:** 136.
3. Mueller M, Strobl R, Jahn K, *et al*. Burden of disability attributable to vertigo and dizziness in the aged: results from the KORA-Age study. *Eur J Public Health* 2014; **24:** 802–807.
4. Lahmann C, Henningsen P, Brandt T, *et al*. Psychiatric comorbidity and psychosocial impairment among patients with vertigo and dizziness. *J Neurol Neurosurg Psychiatry* 2015; **86:** 302–308.
5. Schlick C, Schniepp R, Loidl V, *et al*. Falls and fear of falling in vertigo and balance disorders: a controlled cross-sectional study. *J Vest Res* 2016; **25:** 241–251.
6. Grill E, Penger M, Kentala E. Health care utilization, prognosis and outcomes of vestibular disease in primary care settings: systematic review. *J Neurol* 2016; **263:** S36–S44.
7. Brandt T, Dieterich M. 'Excess anxiety' and 'less anxiety': both depend on vestibular function. *Curr Opin Neurol* 2020; **33:** 136–141.
8. Bronstein AM, Dieterich M. Long-term clinical outcome in vestibular neuritis. *Curr Opin Neurol* 2019; **32:** 174–180.
9. Yip CW, Strupp M. The Dizziness Handicap Inventory does not correlate with vestibular function tests: a prospective study. *J Neurol* 2018; **265:** 1210–1218.
10. Best C, Tschan R, Eckhardt-Henn A, *et al*. Who is at risk for ongoing dizziness and psychological strain after a vestibular disorder? *Neuroscience* 2009; **164:** 1579–1587.
11. Decker J, Limburg K, Henningsen P, *et al*. Intact vestibular function is relevant for anxiety related to vertigo. *J Neurol* 2019; **266:** 89–92.
12. Möhwald K, Bardins S, Müller HH, *et al*. Protocol for a prospective interventional trial to develop a diagnostic index test for stroke as a cause of vertigo, dizziness and imbalance in the emergency room (EMVERT study). *BMJ Open* 2017; **7:** e019073.
13. Bisdorff AR, Staab JP, Newman-Toker DE. Overview of the international classification of vestibular disorders. *Neurol Clin*. 2015; **33:** 541–550.

14. Newman-Toker DE, Saber Tehrani AS, Mantokoudis G, *et al*. Quantitative video-oculography to help diagnose stroke in acute vertigo and dizziness: toward an ECG for the eyes. *Stroke* 2013; **44:** 1158–1161.
15. Herdman M, Gudex C, Lloyd A, *et al*. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011; **20:** 1727–1736.
16. Ludwig K, Graf von der Schulenburg JM, Greiner W. German value set for the EQ-5D-5L. *Pharmacoeconomics* 2018; **36:** 663–674.
17. Jacobson GP, Newman CW. The development of the Dizziness Handicap Inventory. *Arch Otolaryngol Head Neck Surg* 1990; **116:** 424–427.
18. Anderson CS, Heeley E, Huang Y, *et al*. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med* 2013; **368:** 2355–2365.
19. Zwergal A, Rettinger N, Frenzel C, *et al*. A bucket of static vestibular function. *Neurology* 2009; **72:** 1689–1692.
20. Kuroda R, Nakada T, Ojima T, *et al*. The TriAGe+ score for vertigo or dizziness: a diagnostic model for stroke in the emergency department. *J Stroke Cerebrovasc Dis* 2017; **26:** 1144–1153.
21. Straka H, Baker R. Vestibular blueprint in early vertebrates. *Front Neural Circuits* 2013; **7:** 182.
22. Glasauer S, Dieterich M, Brandt T. Neuronal network-based mathematical modeling of perceived verticality in acute unilateral vestibular lesions: from nerve to thalamus and cortex. *J Neurol* 2018; **265:** 101–112.
23. Tarnutzer AA, Lee SH, Robinson KA, *et al*. ED misdiagnosis of cerebrovascular events in the era of modern neuroimaging: a meta-analysis. *Neurology* 2017; **88:** 1468–1477.
24. Broderick JP, Adeoye O, Elm J. Evolution of the modified Rankin Scale and its use in future stroke trials. *Stroke* 2017; **48:** 2007–2012.
25. McClure NS, Sayah FA, Ohinmaa A, *et al*. Minimally important difference of the EQ-5D-5L index score in adults with type 2 diabetes. *Value Health* 2018; **21:** 1090–1097.
26. Newman-Toker DE, Hsieh YH, Camargo CA Jr, *et al*. Spectrum of dizziness visits to US emergency departments: cross-sectional analysis from a nationally representative sample. *Mayo Clin Proc* 2008; **83:** 765–775.
27. Zwergal A, Dieterich M. Vertigo and dizziness in the emergency room. *Curr Opin Neurol* 2020; **33:** 117–125.
28. Newman-Toker DE, Edlow JA. TiTrATE: a novel, evidence-based approach to diagnosing acute dizziness and vertigo. *Neurol Clin* 2015; **33:** 577–599.
29. Cnyrim CD, Rettinger N, Mansmann U, *et al*. Central compensation of deviated subjective visual vertical in Wallenberg's syndrome. *J Neurol Neurosurg Psychiatry* 2007; **78:** 527–528.
30. Lacour M, Helmchen C, Vidal PP. Vestibular compensation: the neuro-otologist's best friend. *J Neurol* 2016; **263:** S54–S64.
31. Brandt T, Dieterich M. Vestibular syndromes in the roll plane: topographic diagnosis from brainstem to cortex. *Ann Neurol* 1994; **36:** 337–347.
32. Glasauer S, Dieterich M, Brandt T. Three-dimensional modeling of static vestibulo-ocular brain stem syndromes. *NeuroReport* 1998; **9:** 3841–3845.
33. Brandt T, Dieterich M. The dizzy patient: don't forget disorders of the central vestibular system. *Nat Rev Neurol* 2017; **13:** 352–362.
34. Glasauer S, Schneider E, Jahn K, *et al*. How the eyes move the body. *Neurology* 2005; **65:** 1291–1293.
35. Zwergal A, Schöberl F, Xiong G, *et al*. Anisotropy of human horizontal and vertical navigation in real space: behavioral and PET correlates. *Cereb Cortex* 2016; **26:** 4392–4404.
36. Kugler G, Huppert D, Schneider E, *et al*. Fear of heights freezes gaze to the horizon. *J Vestib Res* 2014; **24:** 433–441.
37. Fritzsch B, Straka H. Evolution of vertebrate mechanosensory hair cells and inner ears: toward identifying stimuli that select mutation driven altered morphologies. *J Comp Physiol A Neuroethol Sens Neural Behav Physiol* 2014; **200:** 5–18.
38. Straka H, Zwergal A, Cullen KE. Vestibular animal models: contributions to understanding physiology and disease. *J Neurol* 2016; **263:** S10–S23.
39. Baier B, Müller N, Rhode F, *et al*. Vestibular compensation in cerebellar stroke patients. *Eur J Neurol* 2015; **22:** 416–418.
40. Eckhardt-Henn A, Best C, Bense S, *et al*. Psychiatric comorbidity in different organic vertigo syndromes. *J Neurol* 2008; **255:** 420–428.
41. Staab JP. Psychiatric considerations in the management of dizzy patients. *Adv Otorhinolaryngol* 2019; **82:** 170–179.
42. Grill E, Akdal G, Becker-Bense S, *et al*. Multicenter data banking in management of dizzy patients: first results from the DizzyNet registry project. *J Neurol* 2018; **265:** 3–8.
43. Furlong WJ, Feeny DH, Torrance GW, Barr RD. The Health Utilities Index (HUI®) system for assessing health-related quality of life in clinical studies. *Ann Med* 2001; **33:** 375–384.

THE IMPORTANCE OF GREY AND WHITE MATTER

In Multiple Sclerosis

Visit GreyAndWhiteMS.com for more information.

Bristol Myers Squibb™