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ORIGINAL ARTICLE

Chronic vestibular syndromes in the elderly: Presbyvestibulopathy—an isolated clinical entity?

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Abstract

Background and purpose: Recently, the Classification Committee of the Bárány Society defined the new syndrome of "presbyvestibulopathy" for elderly patients with chronic vestibular symptoms due to a mild bilateral peripheral vestibular hypofunction. However, control of stance and gait requires multiple functioning systems, for example, the somatosensory, visual, auditory, musculoskeletal, and cardio- and cerebrovascular systems. The aim of this cross-sectional database-driven study was to evaluate the frequency and characteristics of presbyvestibulopathy and additional gait-relevant comorbidities.

Methods: In total, 707 patients aged ≥60 years with chronic vertigo/dizziness were admitted to our tertiary hospital and received detailed neurological, neuro-orthoptic, and laboratory audiovestibular examination. Medical history, comorbidities, functional impairment, and quality of life (Dizziness Handicap Inventory [DHI], European Quality of Life Scale, Vestibular Activities and Participation) were compared between presbyvestibulopathy and bilateral vestibulopathy in a matched-paired study.

Results: In 95.5% of patients, complaints were better accounted for by another vestibular, neurological, cardiac, or psychiatric disease, and 32 patients (4.5%) met the diagnostic criteria for presbyvestibulopathy. Of these 32 patients, the majority showed further relevant comorbidities in other sensorimotor systems. Only one patient of 707 had “isolated” presbyvestibulopathy (0.14%). The mean total DHI scores indicated lower moderate impairment in presbyvestibulopathy than in bilateral vestibulopathy (40.6 vs. 49.0), which was confirmed by significant differences in the matched-paired analysis ($p < 0.001$).

Conclusions: Isolated presbyvestibulopathy is a very rare entity. It is regularly accompanied by other multisensory dysfunctions. These results indicate a potential role of mild vestibular hypofunction as a cofactor in multifactorial impairment. Thus, patients should be treated in an interdisciplinary setting with an awareness of diverse comorbidities.

KEYWORDS
bilateral vestibulopathy, comorbidity, elderly, presbyvestibulopathy, sensorimotor function

Katharina Johanna Müller and Sandra Becker-Bense contributed equally.

INTRODUCTION

Chronic dizziness, unsteadiness, and disorders of balance and gait are common complaints in the elderly and contribute significantly to a reduced quality of life [1]. It is foreseeable that their public health impact will further increase due to the ongoing demographic shift toward increasing age of the population [2]. A cross-sectional analysis using the 2008 US National Health Interview Survey reported a 1-year prevalence of developing dizziness of 8.1% among all adults [3]. Furthermore, it is well known that the prevalence of chronic dizziness significantly increases with age; whereas it still ranges between 50% and 60% among individuals aged ≥65 years, it increases to approximately 85% in individuals aged ≥80 years [3,4].

Age-related deterioration of vestibular function and response is in line with common findings in other sensory systems, for example, in the visual, somatosensory, and auditory systems [5–7]. Its causes are obvious and multifactorial. First, there is a loss of sensory function with increasing age due to various peripheral structural mechanisms, for example, decrease in the number of hair cells and cells in Scarpa's ganglion as well as numbers and volumes of otoconia in the otoliths in the vestibular end organs [7,8]. Second, various age-related anatomical but also functional alterations have been reported for the central vestibular system; anatomical changes concerning the volume and neuronal density of the vestibular nuclear complex as well as of the cerebellar vermis have been detected [9-11]. Recently, functional imaging studies of the human brain additionally depicted changes in blood oxygen level-dependent magnetic resonance imaging responses, and functional connectivity was not exclusively attributed to structural brain changes, but to additional central processes, for example, modulation of reciprocal corticocortical inhibition or central sensitization to compensate for peripheral vestibular decline [10,11].

In 2019 the Classification Committee of the international Bárány Society defined diagnostic criteria for a chronic vestibular syndrome in the elderly aged ≥60 years, called presbyvestibulopathy (PVP) [12]. PVP was defined as unsteadiness, gait disturbance, and/or recurrent falls in the presence of mild bilateral peripheral vestibular hypofunction of the vestibulo-ocular reflex (VOR) documented by laboratory findings between normal values and the thresholds established for bilateral vestibulopathy (BVP; Table 1) [13].

However, control of stance and gait involves not only vestibular, but also other multisensory, for example, visual, somatosensory, and auditory, as well as musculoskeletal and cardio- and cerebrovascular systems [14,15]. Interestingly, recent neuro-otological investigations reported a clinically relevant relation between vestibular and auditory decline in the elderly, showing a beneficial effect of hearing amplification in patients with PVP [16,17].

However, data about the frequency of gait-relevant comorbidities in PVP patients are still lacking. A previous study on PVP, conducted by Soto-Varela and colleagues, concentrated on various epidemiologic and lifestyle parameters in a geriatric patient sample; it lacks specific neuro-otological examination [18,19].

The aim of our study was to evaluate the frequency of PVP as the single source of chronic dizziness, and to determine the presence of additional gait-relevant comorbidities in other sensory systems. We therefore conducted a cross-sectional database-driven study in a large patient cohort of a tertiary dizziness center.

METHODS

Study population

A total of 707 patients fulfilling the inclusion criteria below were identified in the standardized database Dizziness Register ("DizzyReg") of the interdisciplinary German Center for Vertigo and Balance Disorders at the University Hospital of Munich (between 2015 and 2019). The DizzyReg is a prospective clinical patient registry that centralizes all information stored in electronic health records or medical discharge letters [20]. It systematically collects a variety of patient data including sociodemographic factors, patient history, comorbidities, medication (e.g., antiepileptic drugs, benzodiazepines, antidepressants), clinical and technical assessments, diagnosis, therapy, and outcome. Comorbidities were recorded in clusters (e.g., visual, auditory, or somatosensory deficits, musculoskeletal prediagnosis, and cerebro-/cardiovascular events). All patients underwent structured history-taking, a detailed clinical neurological and neuro-otological examination including video-oculography during bithermal water calorics and head impulse test (HIT), posturography, hearing tests, and a neuro-orthoptic examination including vision testing, fundus photography, and assessment of perceptual vestibular deficits by measurements of the subjective visual vertical in a standardized manner. Depending on the individual cases, additional cervical vestibular evoked myogenic potentials (cVEMP) and ocular vestibular evoked myogenic potentials (oVEMP), gait analyses, and electroneurography were applied.

Inclusion criteria were the following: presence of vestibular symptoms lasting for at least 3 months and age ≥60 years. Inclusion criteria filtering for PVP was applied using the diagnostic criteria of the Bárány Society (Table 1). Due to Criterion D, all patients with symptoms that were better accounted for by another disease were excluded from the PVP subgroup.

For BVP, the current diagnostic criteria (bilaterally pathological horizontal angular VOR gain < 0.6 in the video-HIT and/or reduced caloric responses with a sum of bithermal maximal peak slow phase velocity (SPV) on each side < 6°/s) were applied (Table 1) [13].

To compare the particular degree of functional impairment and quality of life in PVP versus BVP, a matched-paired analysis was conducted, thereby minimizing systematic bias due to age-, gender-, or comorbidity-related effects. Two equivalent groups of 15 patients with either PVP or manifest BVP were identified with the highest degree of equivalence for sex, age (±5 years), and distribution comorbidities (±1 multifactorial deficit).

TABLE 1 Diagnostic criteria of PVP and BVP by the Classification Committee of the Bárány Society

PVP	BVP
A Chronic vestibular syndrome (at least 3 months duration) with at least two of the following symptoms: 1. Postural imbalance or unsteadiness 2. Gait disturbance 3. Chronic dizziness 4. Recurrent falls	A Chronic vestibular syndrome with the following symptoms:1. Unsteadiness when walking or standing plus at least one of 2 or 3 2. Movement-induced blurred vision or oscillopsia during walking or quick head/body movements and/or 3. Worsening of unsteadiness in darkness and/or on uneven ground
B Mild to bilateral peripheral vestibular hypofunction documented by at least one of the following: 1. VOR gain measured by video-HIT between 0.6 and 0.8 bilaterally 2. VOR gain between 0.1 and 0.3 upon sinusoidal stimulation on a rotatory chair (0.1 Hz, V_{max} = 50–60°/s) 3. Reduced caloric response (sum of bithermal maximum peak SPV on each side between 6 and 25°/s)	B Bilaterally reduced or absent angular VOR function documented by: 1. Bilaterally pathological horizontal angular VOR gain < 0.6, measured by video-HIT or scleral-coil technique and/or 2. Reduced caloric response (sum of bithermal maximum peak SPV on each side < 6°/s) and/or 3. Reduced horizontal angular VOR gain < 0.1 upon sinusoidal stimulation on a rotatory chair (0.1 Hz, V_{max} = 50°/s) and a phase lead > 68° (time constant < 5 s)
C Age ≥ 60 years	C No symptoms while sitting or lying down under static conditions
D Not better accounted for by another disease or disorder	D Not better accounted for by another disease or disorder

Note: After Agrawal et al. [4] and Strupp et al. [13].

Abbreviations: BVP, bilateral vestibulopathy; HIT, head impulse test; PVP, presbyvestibulopathy; SPV, slow phase velocity; VOR, vestibulo-ocular reflex.

Clinical examination and instrument-based audiovestibular testing

Clinical evaluation

Clinical evaluation was performed by a trained neurologist and included the patient´s medical history and a neurological examination. In accordance with the current diagnostic algorithms, sensory function was assessed by the combination of history-taking, clinical findings (such as hypesthesia, dysesthesia, allodynia, pain, paresis, muscle atrophy, loss of reflexes, trophic disorders, anhidrosis), vibration tests using a 64-Hz tuning fork (scored 0–8/8, classified pathological at a score below 6/8), and/or corresponding electroneurographic and laboratory test results [21,22].

All patients underwent a detailed neuro-orthoptic examination including ocular motor and visual acuity testing using the Snellen chart (pathological threshold: visual acuity < 0.5 uni- or bilaterally). To determine the signs of vestibular graviceptive dysfunction and vestibular tone imbalance in the roll plane, that is, the components of an ocular tilt reaction such as head tilt, skew deviation, ocular torsion, and perceptual tilts, additional examinations with Frenzel glasses, cover test, fundus photography by a laser ophthalmoscope, and standardized static and dynamic testing for tilt of the perceived subjective visual vertical (SVV) were performed [23,24]. SVV, a sensitive test for acute dysfunction of graviceptive pathways, was measured in a motor-operated hemispheric dome as the deviation from the objective vertical axis in degrees. A mean deviation of more than ±2.5° from the true vertical was considered a pathological SVV deviation. These detailed examinations were useful to exclude central vestibular disorders (e.g., central nystagmus syndromes) as well as acute vestibular tone imbalance (Figure S1).

Caloric testing

Caloric testing, for the function of the horizontal semicircular canals in the low-frequency range of the vestibulo-ocular reflex, was done using 30°C cool and 44°C warm water irrigation measuring peak SPV of caloric nystagmus by video oculography (EyeSeeCam, Interacoustics).

Standardized video-HIT measurements of the semicircular function in the high-frequency range were obtained in a bright room with a red target affixed at eye level at a distance of 1.8 m using the EyeSeeCamHIT system (Interacoustics) [25], with the procedure as described in Heuberger et al. [26].

Posturographic measurements

Posturographic measurements were performed using a stabilometer platform (Kistler 9261A; Kistler Group) in an upright standing position. Displacement of center of gravity was assessed by the total sway path for the x, y, and z directions (m/min for x- and y-axes and kN/min for z-axis) for 10 different standing conditions of increasing difficulty. In addition to the regular analysis, sway patterns were analyzed over all conditions by an artificial neuronal network and categorized as normal, functionally phobic, cerebellar, orthostatic, or vestibular patterns [27].

Pure tone audiometry

Pure tone audiometry was performed in a standardized manner and was conducted at 0.5, 1, 2, 4, 8, and 10 kHz. Hearing loss (HL)

was classified in mild (21–40 dB), moderate (41–60 dB), severe (61–80 dB), and profound (>81 dB), and a pure tone average of the better hearing ear > 20 dB HL was considered pathological according to the current diagnostic criteria [28].

The frequency of neuro-ophthalmological findings and laboratory test results are depicted in Figure S1.

Self-report measures and standardized questionnaires

Patients completed several standardized questionnaires regarding vertigo and dizziness phenomenology, associated symptoms, and clinical impairment: the Dizziness Handicap Inventory (DHI), Vestibular Activities and Participation (VAP) questionnaire, and European Quality of Life Scale (EuroQoL) questionnaire (EQ-5D-3L) [29,30].

The DHI is a well-established 25-item measurement of self-perceived limitations caused by vertigo and dizziness evaluating different aspects of disability [29]. The DHI score ranges from 0 to 100, with a score of 0 being the best possible and with higher scores indicating more impairment. It is divided into three subcategories: emotional (36 points), functional (36 points), and physical handicap (28 points). A mild handicap is defined as results between 16 and 34 points, a moderate handicap as 36 to 52 points, and a severe handicap as ≥54 points. Health-related quality of life was assessed with the generic EuroQoL questionnaire (EQ-5D-3L), subdivided into five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) [30]. These health states parameters were converted into EQ-5D scores using the German time trade-off scoring algorithm. The resulting total score ranges from 0 to 1, with higher scores indicating better quality of life. The VAP questionnaire rates vestibular activities and participation via six items in two subcategories measured by an ordinal Likert scale (0–4), with higher scoring indicating higher impairment [31].

Because cognitive impairment was not systematically assessed in all patients by a standardized screening test, this aspect was not evaluated further in our study.

Statistical analyses

Statistical analyses were performed on the total collective and the 15 equivalent matched pairs. The Statistical Package for the Social Sciences 27.0 (IBM) was used to test for statistical significance. In addition to the collective characterization described above, the group differences were calculated using mean or percentage bilateral analysis using Kruskal–Wallis one-way analysis of variance. Post hoc correction Bonferroni analyses were then performed. Significant thresholds were $p < 0.05$, $p < 0.01$, or $p < 0.001$ for all analyses. Friedman two-way analysis of variance for associated samples was performed to test for differences in the two matched-paired groups.

Protocol approval and patient consent

The data protection clearance and institutional review board of the Ludwig Maximilian University of Munich, Germany approved the study (414-15), and all patients gave informed consent. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

RESULTS

Of our total cohort of 707 patients over 60 years (Table 1, criteria A/C), in the majority ($n = 675$, 95.5%) the complaints were accounted for by a manifest vestibular, neurological, cardiac, or psychiatric disorder. The most frequent diagnoses explaining the chronic vertigo/dizziness symptoms were benign paroxysmal positional vertigo (BPPV; 13.3%), Ménière disease (11.2%), polyneuropathy (10.3%), unilateral vestibulopathy (10.0%), functional vertigo/dizziness (9.2%), BVP (6.1%), and cardiogenic dizziness (5.8%; Table 2).

From the total patient cohort, we found 84 of 707 (11.9%) cases with a mild peripheral vestibular hypofunction fulfilling Criterion B for PVP (Table 1), independently from diagnosis. However, in 52 patients with mild peripheral vestibular hypofunction, there was another leading disease as the source of their chronic dizziness syndrome: Ménière disease (11/84, 13.1%), neurodegenerative disorder (9/84, 10.7%), polyneuropathy (9/84, 10.7%), cardiogenic dizziness (7/84, 8.3%), BPPV (6/84, 7.1%), idiopathic sensorineural hearing loss (3/84, 3.5%), functional dizziness (3/84, 3.5%), brain infarction (2/84, 2.4%), central oculomotor disturbances (1/84, 1.2%), and traumatic brain injury (1/84, 1.2%).

In the remaining 32 of 707 patients (4.5%), the diagnosis of PVP was established by the combination of the following findings: (i) they fulfilled the criteria of clinical and instrument-based neurological and neuro-otological examination (Table 1, PVP: Criterion B) and (ii) they showed no other explaining disease as the source of their chronic dizziness syndrome (Table 1, PVP: Criterion D).

In the PVP subgroup, gender was equally distributed, mean age was 75.1 ± 7.1 years, and age distribution showed a peak frequency in the age group of 70–80 years (Table 3). All PVP patients self-classified their dizziness symptoms as chronic dizziness, 28% of them additionally as gait disturbance, and 21.9% as postural imbalance. Fifty percent of PVP patients reported recurrent falls in the past 12 months. The majority of the 32 patients (59.4%) categorized their symptoms as having lasted for >2 years before presentation in our outpatient clinic, and 40.6% categorized them as having lasted for between 3 months and 2 years (Table 3). Other lifestyle factors, current medication, self-ratings concerning alcohol and nicotine consumption, and activity levels are given in Table 3 and Table S1. For details and laboratory test results of the matched pairs of PVP and BVP patients, please see Table S2. There was no significant difference regarding clinical findings or lifestyle factors; in both groups, 40% suffered from anxiety and depression.

TABLE 2 Patient characteristics and main diagnoses in the total cohort (age ≥ 60 years, $n = 707$)

Characteristic	Value
Age, mean, years	70.7 ± 6.9
Sex	
Female	363 (51.3%)
Male	344 (48.7%)
Main diagnoses	
Benign paroxysmal positional vertigo	94 (13.3%)
Ménière disease	79 (11.2%)
Polyneuropathy	73 (10.3%)
Unilateral vestibulopathy	71 (10.0%)
Functional vertigo/dizziness	65 (9.2%)
Vestibular migraine	50 (7.1%)
Bilateral vestibulopathy	43 (6.1%)
Cardiogenic dizziness	41 (5.8%)
Orthostatic dysregulation	27 (3.9%)
Cardiac arrhythmia	5 (0.7%)
Valvular heart disease	3 (0.4%)
Hypertensive heart disease	3 (0.4%)
Subclavian steal syndrome	3 (0.4%)
Presbyvestibulopathy	32 (4.5%)
Neurodegenerative diseases	30 (4.2%)
Parkinson syndrome	11 (1.6%)
Alzheimer disease	7 (1.0%)
Vascular dementia	5 (0.7%)
Multiple system atrophy	4 (0.6%)
CANVAS	3 (0.4%)
Central oculomotor disturbances	29 (4.1%)
Cerebellar syndrome	13 (1.8%)
Downbeat nystagmus syndrome	10 (1.4%)
Brain stem syndrome	6 (0.8%)
Vestibular paroxysmia	26 (3.7%)
Cerebral infarction	21 (3.0%)
Tumor	12 (1.7%)
Acoustic neuroma	10 (1.5%)
Ependymoma	1 (0.1%)
Cholesteatoma	1 (0.1%)
Depressive episode	9 (1.3%)
Spinal canal stenosis	5 (0.7%)
Hearing loss	3 (0.4%)
Epilepsy	2 (0.3%)
Traumatic brain injury	2 (0.3%)
Adverse drug reaction	2 (0.3%)
Blindness	1 (0.1%)
Others	17 (2.4%)

Note: Mean Age, distribution of gender, and distribution of main diagnoses are provided in absolute numbers and percentage values. CANVAS is cerebellar ataxia, neuropathy and vestibular areflexia syndrome.

In the PVP subgroup, 18 of 32 (56.3%) patients had additional somatosensory, 16 of 32 (50%) visual, and 10 of 32 (31.3%) auditory deficits. Mild hearing loss was present in seven of 32 (21.9%), moderate hearing loss in one of 32 (3.1%), severe hearing loss in two of 32 (6.3%), and high-frequency hearing loss in six of 32 (18.8%) PVP patients (Table 3).

Twelve of 32 patients (37.5%) presented with gait-relevant musculoskeletal and eight of 32 (25.0%) with symptomatic cardio- or cerebrovascular comorbidities (Figure 1). In total, 18 of 32 (56.3%) patients showed ≥2 gait-relevant comorbidities. A dual impairment of the visual and auditory system (pathological visual and audiometric testing) was detected in 25.0% of PVP patients.

Only one of the 32 PVP patients (3.1%) and total of 707 patients with chronic dizziness (0.14%) presented with an "isolated" PVP (Figure 1).

Self-perceived impairment

The mean DHI score in the total cohort of patients was 43.1 ± 21.4 ($n = 625$), indicating an overall moderate impairment. The physical DHI subscore was 12.8 ± 7.4 ($n = 607$), the functional 17.4 ± 9.6 ($n = 611$), and the emotional 13.2 ± 8.0 ($n = 511$). The mean value of the five-dimensional questionnaire EQ-VAS was 60.0 ± 19.6 ($n = 637$), and the index value EQ-5D-3L was 0.89 ± 0.21 ($n = 638$), which is comparable to age-matched index scores (e.g., 0.871 in the age group 40–49 years) [32]. Mean values of the VAP scales for functioning and participating were 9.97 ± 3.99 ($n = 559$) and 8.32 ± 4.41 ($n = 595$), indicating a substantial impairment and differing significantly between the subgroups ($p < 0.01$) [31].

Comparing the distribution of total DHI scores in the different subgroups of main diagnosis, the highest mean DHI values were found in functional vertigo/dizziness with 52.2 ± 19.5 ($n = 65$; Figure 2), followed by unilateral vestibulopathy with 48.1 ± 21.0 ($n = 57$). The lowest mean DHI values were calculated for cardiogenic dizziness with 30.1 ± 19.7 ($n = 37$) and polyneuropathy with 41.2 ± 20.3 ($n = 59$). The lowest mean index scores of health-related quality of life measured by the EQ-5D-3L were found in neurodegenerative syndromes (0.73 ± 0.27, $n = 27$) and BVP (0.76 ± 0.27, $n = 39$). The highest VAP score values were measured in unilateral vestibulopathy (10.34 ± 3.7, $n = 60$) and the lowest in cardiogenic dizziness (6.19 ± 3.5, $n = 34$). The distribution of mean DHI and VAP score values in the different subgroups of main diagnosis were significantly different by Kruskal–Wallis one-way analysis of variance (DHI, $p = 0.04$; VAP Scale 2, $p = 0.01$); post hoc Bonferroni analysis between the subgroups showed statistically significant differences of mean DHI values and VAP score values, as presented in Figure 2.

For the PVP cohort ($n = 32$) a mean total DHI of 40.6 (±26.8, $n = 28$) was calculated, also reflecting a moderate impairment level similar to the values in the total cohort. For PVP, the physical DHI was 13.7 (±8.5, $n = 29$), the functional DHI 15.7 (±11.1, $n = 30$), and the emotional DHI subscore 11.9 (±9.4, $n = 31$). In contrast, the BVP cohort ($n = 45$) showed a higher mean total DHI of 49.0 ± 22.4

TABLE 3 Clinical characteristics and laboratory test results of presbyvestibulopathy patients ($n = 32$)

Characteristic	Value	
Sex		
Male	16 (50%)	
Female	16 (50%)	
Age		
Mean years	75.1 ± 7.1	
60–70	8 (25%)	
70–80	15 (47%)	
>80	9 (28%)	
Symptoms		
Chronic dizziness	32 (100%)	
Falls in past 12 months	16 (50.0%)	
Postural imbalance	9 (28%)	
Gait disturbance	9 (28%)	
Symptoms duration		
3 months	4 (12.5%)	
3 months to 2 years	9 (28.1%)	
2–5 years	7 (21.9%)	
5–10 years	7 (21.9%)	
>10 years	5 (15.6%)	
Current medication		
ASA or/and clopidogrel	5 (15.6%)	
Beta-blockers	5 (15.6%)	
Oral anticoagulation	5 (15.6%)	
Tricyclic antidepressants	1 (3.1%)	
Benzodiazepines	1 (3.1%)	
SSRI	1 (3.1%)	
Comorbidities		
Arterial hypertension	13 (40.6%)	
Cardiac arrhythmia	10 (31.3%)	
Bronchial asthma	7 (21.9%)	
Heart failure	5 (15.6%)	
Chronic kidney disease	2 (6.3%)	
COPD	1 (3.1%)	
Diabetes mellitus type 2	1 (3.1%)	
Laboratory test results		
VOR gain, L/R	0.73 ± 0.1	0.67 ± 0.2
Caloric response, L/R [°/s]	15.41 ± 8.1	11.05 ± 5.1
Visual acuity, L/R	0.69 ± 0.22	0.64 ± 0.22
Pure tone average, L/R, dB	20.36 ± 11.9	21.45 ± 10.4
Mild HL	7 (21.9%)	
Moderate HL	1 (3.1%)	
Severe HL	2 (6.3%)	
High-frequency HL	6 (18.8%)	

Note: Laboratory test threshold values: VOR gain measured by video head impulse test (between 0.6 and 0.8), caloric irrigation with response values (sum of bithermal maximum peak slow phase velocity between 6 and 25°/s), visual acuity tested by Snellen chart (<0.5 uni- or bilaterally), pure tone audiometry with pure tone average (better hearing ear >20 dB HL, mild [21–40 dB], moderate [41–60 dB], severe [61–80 dB], profound [>81 dB]).

Abbreviations: COPD, chronic obstructive pulmonary disease; HL, hearing loss; L, left; R, right; SSRI, selective serotonin reuptake inhibitor; VOR, vestibulo-ocular reflex; ASA, acetylsalicylic acid; EQ-VAS, Euro-Qol-visual analogue scales.

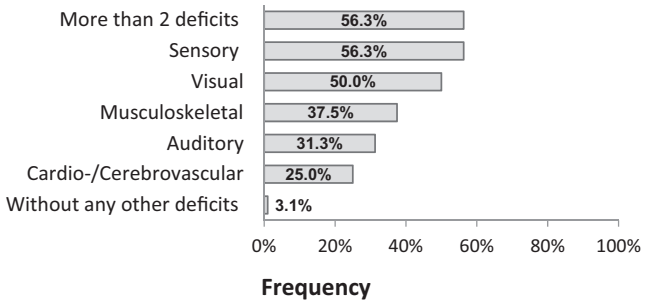

FIGURE 1 Frequency distribution of multifactorial deficits in presbyvestibulopathy (PVP). Of all 32 PVP patients, 56.3% showed two or more gait-relevant comorbidities. Only one patient showed isolated PVP (1/32, 3.1%)

($n = 35$), as well as higher mean values in all three subscores (physical DHI, 15.2 ± 7.4, $n = 37$; functional DHI, 20.3 ± 8.8, $n = 37$; emotional DHI, 14.4 ± 8.1, $n = 36$). Matched-pair Friedman two-way analysis of ranks revealed a significant difference ($p < 0.001$, Cohen $r = 0.94$) between the PVP and BVP subgroups ($n = 15$), with significantly higher DHI values in BVP (Figure 3).

DISCUSSION

The key findings of our monocentric, database-driven, cross-sectional study in 707 chronic dizziness patients with an age of 60 years and older concerning the frequency, characteristics, and clinical impact of PVP were the following: (i) the great majority (>95%) of patients with chronic dizziness suffered from another leading vestibular, neurological, cardiac, or psychiatric disease (Table 2); (ii) of the 4.5% patients fulfilling the diagnostic criteria for PVP (32/707), PVP occurred in 96.9% together with other gait-relevant deficits in sensorimotor function (Figure 1), and approximately 56.3% of PVP patients had deficits in two or more systems; (iii) PVP was an isolated disorder in only one patient; (iv) approximately 50% of all PVP patients reported recurrent falls and showed a moderate impairment (DHI) in daily activities (Table 3, Figure 2); and (v) comparing PVP and BVP patients directly in the matched paired analysis, significantly higher physical DHI values were found in BVP patients (Figure 3), indicating a higher impairment due to stronger reduction of function.

Typically, the process of aging involves physiologic declines in multiple systems. Age-related hypofunction in the peripheral vestibular system is a well-known finding similar to impairments in other sensory systems such as polyneuropathy and impaired visual and auditory acuity [33]. However, the clinical impact of mild vestibular hypofunction in humans is still not well understood [7]. Since the entity of PVP was defined recently in analogy to presbyopia and presbyacusis, there is still a lack of epidemiological studies describing the frequency, characteristics, and clinical impact of PVP [12]. The study by Soto-Varela and colleagues focused on patients´ self-perception of disability and the identification of variables influencing DHI in a geriatric cohort. [18,19]. The data are not comparable to our unselected cohort including all patients

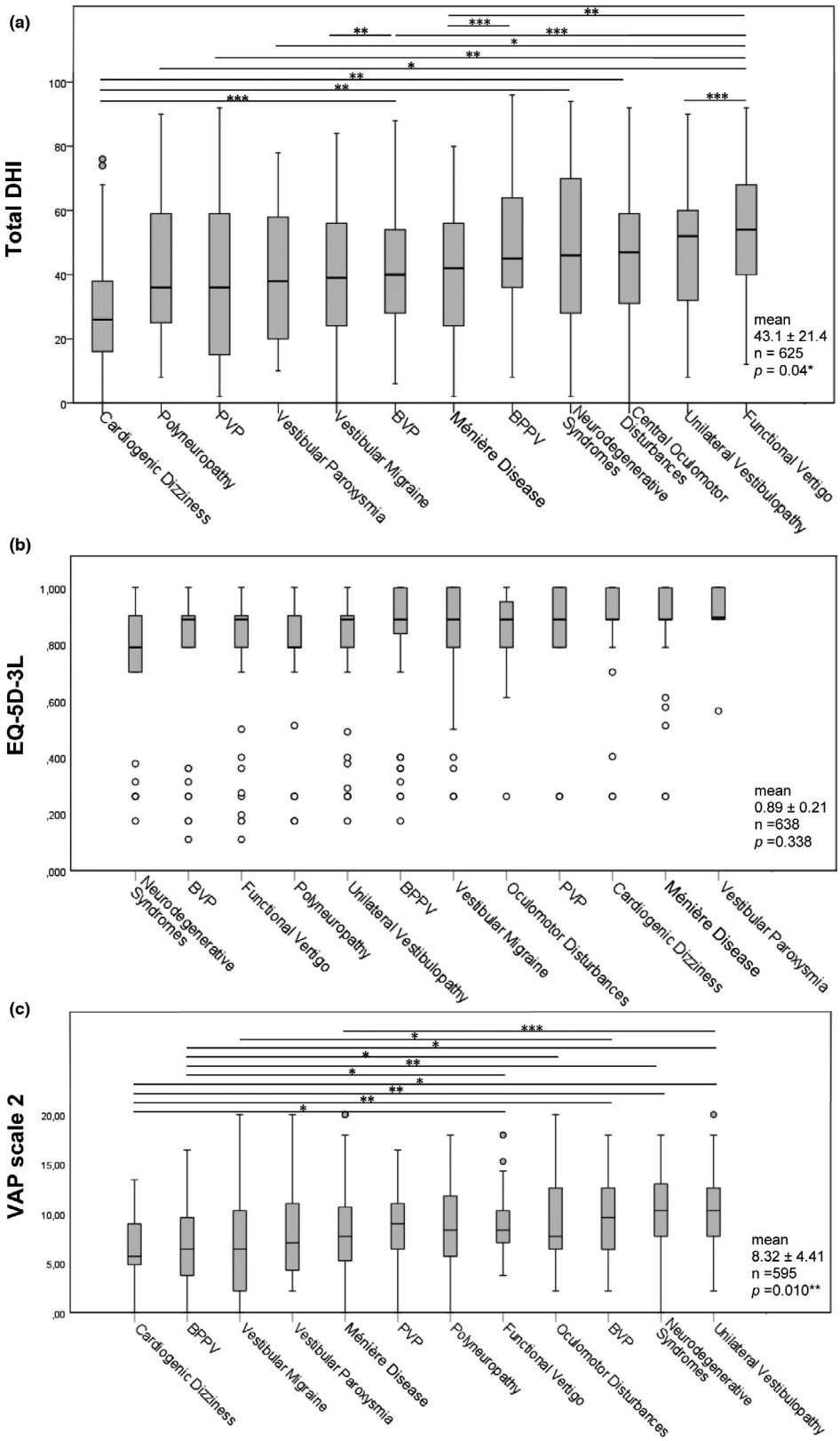

FIGURE 2 Dizziness Handicap Inventory (DHI), European Quality of Life Scale (EQ-5D-3L), and Vestibular Activities and Participation (VAP) score frequency distribution in the total patient cohort. Functional impairment measured by the DHI (a) and VAP (c) and health-related quality of life reflected by the EQ-5D-3L (b). Mean DHI and VAP score values differed significantly between the different main diagnostic groups: Kruskal-Wallis one-way analysis of variance for DHI scores $p < 0.04$, $n = 625$ and for VAP scores $p = 0.010$, $n = 595$. For post hoc Bonferroni analysis between the groups, statistically significant differences are marked with asterisks (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$). BPPV, benign paroxysmal positional vertigo; BVP, bilateral vestibulopathy; PVP, presbyvestibulopathy

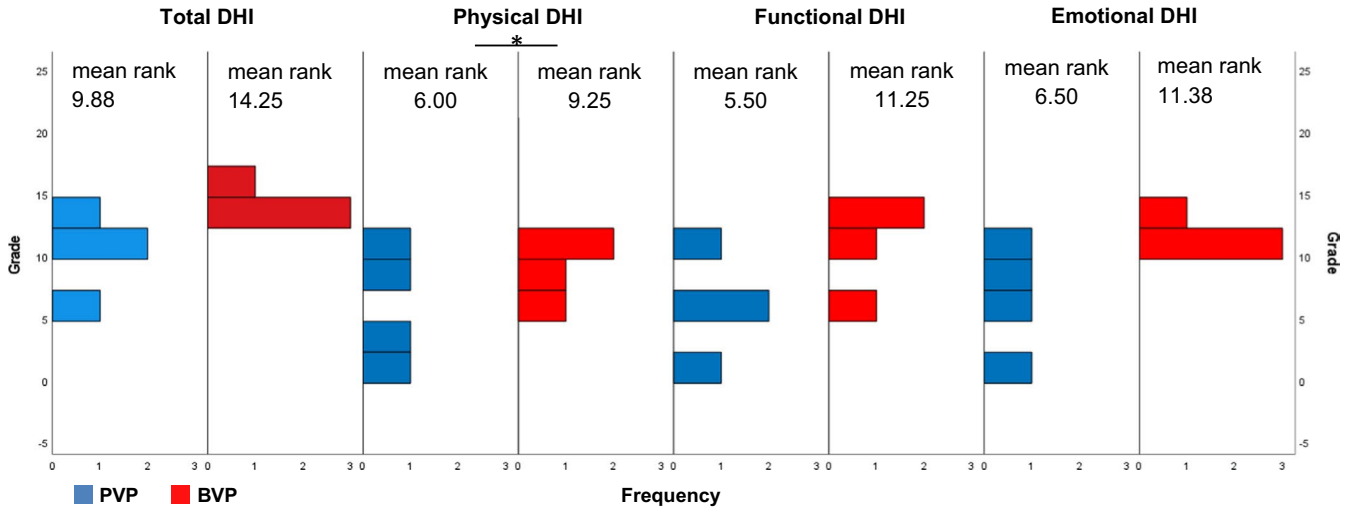

FIGURE 3 Pairwise comparative analysis of Dizziness Handicap Inventory (DHI) in the matched paired analysis, presbyvestibulopathy (PVP) versus bilateral vestibulopathy (BVP; $n = 30$). Physical DHI score values showed significantly higher values (mean ranks) in BVP compared to PVP in pairwise Friedman two-way analysis of variance by ranks ($^*p < 0.001$, effect size of Cohen $r = 0.94$). Total, functional, and emotional DHI score values did not differ between the matched pairs

aged ≥60 years with chronic dizziness, because of their different approach, selecting highly impaired elderly patients and not applying specific neuro-otological assessment or breakdown of comorbidities in functionally relevant systems [18].

In our study, the great majority of patients with chronic vestibular symptoms suffered from another leading neurological or vestibular disease (>95%) and did not fulfill the PVP criteria (Tables 1 and 2). The most frequent diagnoses in our patient cohort were BPPV, Ménière disease, polyneuropathy, unilateral vestibulopathy, functional vertigo/dizziness, and BVP (Table 2), all of which are among the 10 most frequently made main diagnoses in tertiary European dizziness centers except for polyneuropathy [34,35]. A certain decline in sensory function of the peripheral nerves is a common finding in the elderly older than 65 years, with a prevalence of approximately 7%, and increasing with age, even in asymptomatic individuals [36]. According to current diagnostic algorithms, accurate assessment of sensory leg function was based on the combination of clinical history-taking, neurological findings (e.g., vibration test), and electroneurography to avoid an overestimation of a physiological decline of sensory function [22,37].

In more than half of all cases, PVP was accompanied by at least two gait-relevant deficits in other sensorimotor systems (Figure 1). Most often additional somatosensory (56.3%), visual (50.0%), auditory (31.3%), musculoskeletal (37.5%), and cardio- or cerebrovascular (25%) comorbidities were evident. Only one patient of the 707 (0.14%) showed "isolated" PVP.

Our data thereby highlight the rarity of isolated PVP in the elderly as the single cause of chronic vertigo/dizziness. Furthermore, the data suggest that mild bilateral vestibular hypofunction might become clinically relevant as a concomitant factor in cases with multisensory deficits also contributing to and hindering central compensation. This interpretation is supported by analogous data in the elderly for presbyopia and presbyacusis, in which coexistence of sensory deficits led to higher clinical impairment [38,39]. There is a link between spatial hearing and balance. Although the auditory system has not been given the same credit for contributing to balance and postural stability as the visual and somatosensory systems, it is integrating fast and accurate balance-related signals [40,41].

When operating in a multisensory environment, auditory cues are primarily used to guide our attention to important objectives and assist us in orienting in space when events occur outside of our range of view [42]. Concomitant mild and high-frequency hearing loss in PVP patients seems to be clinically relevant (Table 3), and fits with the results of a recent systematic review that reported a correlation between hearing amplification and improvement of spatial orientation [16].

The current laboratory diagnostic criteria for PVP presupposing only mild pathological values close to normal might bear the risk of false positive results. This appears to be particularly true in cases where only the video-HIT shows mild bilateral hypofunction and caloric and/or rotatory chair testing reveal normal values, as there are some pitfalls for the operators of video-HIT [43] leading to inter-examiner differences [44,45]. A recent study even reported a slight but significant physiological decrease in VOR function with age in asymptomatic subjects without previous history of vestibular disorders [46]. In conclusion, repeated measurements over time might be useful, also to uncover early a progress in peripheral vestibular dysfunction toward manifest BVP [47].

Overall DHI values varied significantly between the different vertigo syndromes with the highest mean DHI values in functional vertigo/dizziness, whereas DHI in BVP and PVP was lower (Figure 3). These results are in line with former epidemiological studies on psychiatric comorbidity in dizzy patients based on

Structured Clinical Interviews and anxiety questionnaires reporting the worst vertigo-related handicaps in patients with combined nonorganic vestibular vertigo/dizziness and psychiatric comorbidity [48,49], but not in BVP. Furthermore, another cross-cultural study reported significantly higher Vertigo Handicap Questionnaire anxiety scores in functional dizziness as compared to BVP [50].

Compared to the study by Soto-Varela and colleagues, the mean DHI values in our PVP cohort were lower, thus reflecting only moderate impairment (40.6 vs. 53.65) [18]. As expected by the lesser peripheral vestibular dysfunction, patients with PVP showed significantly lower clinical impairment measured by physical DHI than patients with BVP in the matched-paired analyses (Figure 3).

The main limitations of the present study that need to be considered are its retrospective analytic approach (although the DizzyReg itself is prospective) and a potential selection bias because of the patients' admission to an interdisciplinary tertiary university hospital center. Thus, the results cannot easily be transferred to the general population and do not reflect the prevalence of PVP in the German population or patient collectives in geriatric or general practices. The main difference of the patient cohort from those of the latter is the presence of leading vestibular symptoms (dizziness, imbalance of stance and gait) as the reason for admission. Being aware of the relatively small number of patients with PVP, the distribution of clinical characteristics must be interpreted with caution.

CONCLUSIONS

An isolated diagnosis of PVP without gait-relevant multifactorial deficits in other systems was a rare condition in our patient cohort study. Instead, dizziness in the elderly was usually explained by another leading vestibular, neurological, cardiac, or psychiatric disease, and PVP was typically accompanied by common age-related decline in other sensorimotor functions. Thus, elderly patients with chronic dizziness should be treated in an interdisciplinary setting in which physicians are aware of frequent comorbidities. Further prospective longitudinal investigations are warranted to clarify the prevalence of PVP, its potential disease progression toward BVP, and the clinical impact and interplay of concomitant multifactorial impairment in the elderly population.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Katharina Johanna Müller: Data curation (equal), formal analysis (lead), investigation (equal), methodology (equal), visualization (equal), writing–original draft (lead), writing–review & editing (equal). **Sandra Becker-Bense:** Conceptualization (equal), investigation (equal), methodology (equal), supervision (equal), writing–original draft (equal), writing–review & editing (equal). **Ralf Strobl:** Data curation (equal), software (equal). **Eva Grill:** Data curation (lead), software (lead). **Marianne Dieterich:** Conceptualization (lead), funding acquisition (equal), project administration (lead), supervision (lead), writing–review & editing (lead).

DATA AVAILABILITY STATEMENT

Data are available on request from the corresponding author.

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SUPPORTING INFORMATION

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