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Original Article

Assessing Cognitive Effort in Ménière's Disease: Pupillometry as a Novel Tool for Postural Control

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BACKGROUND: This study aimed to investigate the utility of pupillometry as a measure of cognitive effort in individuals with Ménière's disease experiencing chronic postural destabilization. By integrating pupillometry with static posturography, we sought to gain deeper insights into the cognitive demands and arousal levels associated with postural control in this specific patient population.

METHODS: The study included 36 patients who met the diagnostic criteria for Ménière's disease and a control group comprising 36 healthy volunteers. We performed static posturography using a computerized static posturography platform to objectively assess postural imbalance. Additionally, pupillometry was recorded using infrared video-oculoscopy. Pupil dilation was measured before and after participants walked for 7 steps on-site with their vision obscured.

RESULTS: Baseline tonic pupil size showed no significant difference between healthy controls and Ménière's patients. However, after walking stimulation, Ménière's patients exhibited highly significant abnormal walking-induced pupil dilation. This suggests increased arousal in response to the challenging task of walking with closed eyes, linked to static upright stance imbalance as correlated with posturography parameters.

CONCLUSION: Pupillometry holds promise as an objective tool to assess cognitive effort and arousal during postural control in Ménière's disease. Implementing pupillometry in clinical practice could enhance the management of postural instability in these patients. Our findings contribute to the understanding of cognitive aspects in balance control and open new avenues for further investigations in vestibular dysfunction.

KEYWORDS: Pupillometry, posturography, Ménière's, vestibular diseases, otoneurology, otology

INTRODUCTION

Balance maintenance in the human body is a complex process that involves the integration and coordination of various sensory systems, including the vestibular, visual, auditory, and proprioceptive systems, along with motor control.[1] The objective is to maintain the body's center of mass within the support area to achieve stability.[2,3] However, sensorial alterations, muscular deficits, and nervous system diseases can disrupt balance, leading to potential physical or social consequences such as fall-related traumas or fear.[4]

Posture is a result of complex interactions between sensory inputs (vestibular, visual, and proprioceptive) and motor outputs, resulting in postural sway during standing. Changes in postural sway may occur when there are impairments in sensory inputs and/or motor output.[5] To better understand the underlying mechanisms of balance control and the impact of vestibular dysfunction on postural stability, previous studies have utilized static posturography, which measures postural sway during standing.[6-8] However, while posturography provides valuable information about balance, it has limitations in diagnosing specific underlying pathophysiological conditions.[9-12]

Pupillometry, a noninvasive measure of alertness and biochemical responses, offers valuable insights into cognitive workload and effort exertion.[13-18] Pupil dilation, also known as task-evoked pupillary response, refers to the increase in pupil diameter in response

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to stimuli.[19] This dynamic response has been extensively studied in the context of cognitive tasks, providing valuable information about task performance and difficulty.[20,21] It can aid in understanding the cognitive workload of postural control,[23] especially in individuals with chronic postural destabilization.

Pupillometry's potential as an indirect marker of cognitive effort and workload has been demonstrated in tasks involving cognitive processing, attention, listening, and motor control.[22] However, its utilization as a tool to assess effort in the context of vestibular dysfunction and postural control has received limited attention in the scientific literature.

Vestibulopathies, including Ménière's disease, present unique challenges to balance and posture maintenance due to their impact on the vestibular system. Understanding the cognitive demands and effort exertion involved in maintaining balance in individuals with vestibular dysfunction is of great significance for both clinical management and research purposes. Static posturography, which measures postural sway, has been widely used to evaluate balance deficits in these patients. However, the assessment of cognitive workload during postural tasks in vestibulopathies remains an area that requires further investigation.

With the aim of filling the current knowledge gap, our study seeks to explore the application of pupillometry as a measure of cognitive effort in individuals with Ménière's disease. By integrating pupillometry alongside static posturography, we aspire to gain deeper insights into the cognitive demands and potential heightened arousal linked to postural control in this particular patient group. Pupillometry offers a noninvasive and objective approach to assess cognitive processes, providing valuable insights into the cognitive workload and attentional demands necessary for maintaining balance in individuals with Ménière's disease.

In essence, our study seeks to enhance the understanding of the cognitive aspects of postural control in Ménière's disease and uncover the potential of pupillometry as a valuable tool to evaluate effort in the context of vestibular dysfunction. By shedding light on the cognitive intricacies involved in balance control, our research has the potential to contribute to advancements in managing and rehabilitating patients with Ménière's disease, ultimately improving their quality of life and functional outcomes. Moreover, the insights gleaned from our investigation may have broader implications for the field of vestibular research, furthering the exploration of pupillometry as an effort measure in various vestibular disorders.

MAIN POINTS

- Novel Application of Pupillometry: The paper introduces the innovative use of pupillometry to assess cognitive effort in individuals with Meniere's disease during postural control tasks. This novel approach provides insights into the cognitive demands associated with balance maintenance in this patient population.
- Combining Pupillometry and Posturography: The study successfully integrates pupillometry with static posturography to gain a comprehensive understanding of the cognitive workload and potential heightened arousal levels related to postural control in Meniere's disease. This combination of techniques offers a holistic assessment of the challenges faced by these patients.
- Implications for Clinical Practice: The research suggests that pupillometry can be a valuable tool for assessing cognitive effort and arousal in individuals with vestibular dysfunction. Implementing pupillometry in clinical practice may enhance the management of postural instability in vestibular patients, potentially leading to improved therapeutic interventions.
- Highlighting the Importance of Cognitive Aspects: By shedding light on the cognitive intricacies of postural control, this study emphasizes the significance of considering cognitive aspects in vestibular disorders. Understanding the cognitive workload involved in maintaining balance can lead to tailored interventions and rehabilitation strategies for improved postural stability and overall well-being.

MATERIAL AND METHODS

Population of Study

Ménière's disease cases were identified based on the clinical guidelines established by the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology Head and Neck Surgery (AAO-HNS).[25]

The cohort for this study comprised 36 females diagnosed with Ménière's disease, and an equal number of healthy females were included for comparative analysis. Details of the study population are reported in Table 1. The diagnostic protocol involved a comprehensive neuro-otological evaluation, which included otoscopy, pure-tone audiometry, nystagmus examination, caloric testing, and brain magnetic resonance imaging to rule out other potential neurological causes. Careful exclusion criteria were applied to remove participants with a personal or family history of neurologic or psychiatric disorders. Patients were assessed for cognitive impairment using the Mini-Mental State Examination (MMSE), and those with a score of less than 24 were also excluded from the study. Individuals with coexisting conditions such as postural hypotension, dysthyroidism,

Table 1. Characteristics of the Study Population

	Ménière's Disease (n = 36)	Healthy Controls (n = 36)
Mean age (years)	50.5 ± 8.2	48 ± 9.2
Gender: women, n (%)	36 (100%)	36 (100%)
Mean time course (years)	3.0 ± 1.5	
Mean time from last vertigo attack (months)	8.9 ± 3.4	
Unilateral, n (%)	30 (83.3%)	
Bilateral, n (%)	6 (16.7%)	
Hearing stage, n (%)		
1	0	
2	28 (77.8%)	
3	8 (22.2%)	
4	0	
Mean hearing stage	2.22	

Data are expressed as mean ± standard error or as n (%).

spondylopathies, visual impairment, sleep disorders, and orthopedic problems were not included. Furthermore, patients with a history of traumatic injuries, ear surgery, or psychopharmacological treatments were not considered for participation in the study.

Various clinical variables were analyzed, including gender, age, hearing stage, disease duration, hearing loss, age of onset, smoking status, and the functional scale of the AAO-HNS. The hearing stage was determined by calculating the mean of 4-tone average thresholds at 0.5, 1, 2, and 3 kHz from the audiogram obtained on the day of inclusion for each patient with confirmed Ménière's disease, according to the AAO-HNS criteria: stage 1 (≤25 dB HL), stage 2 (26-40 dB HL), stage 3 (41-70 dB HL), and stage 4 (>70 dB HL).

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and followed the recommendations of the guidelines of the Ethics Committee of Tor Vergata University Hospital in Rome. All procedures and data collection were conducted in full compliance with these ethical standards, as well as in alignment with common clinical practices. Informed consent was obtained from all subjects and data were collected anonymously. Given the nature of this study, which involved a retrospective analysis of a pre-existing observational dataset, it did not necessitate formal ethical approval from the Ethics Committee. The study solely focused on observation and analysis of anonymized data, without any interventions or deviations from established clinical practices.

Study Design

In the study, a comprehensive examination was conducted to assess vestibular function and related autonomic responses in both the study population and the control group. The examination consisted of 2 key tests: posturography and pupillometry. These 2 tests provided objective measures of postural imbalance and pupillary responses, offering valuable insights into vestibular function and autonomic responses in the study population compared to the control group. The data from these examinations allowed us to assess the vestibular effort, balance control, and potential vestibular dysfunction in the subjects under investigation.

Posturography

Static posturography was performed using a computerized platform equipped with pressure-sensitive strain gauges placed on the vertexes of an equilateral triangle drawn on the platform (S.Ve.P. Amplaid, Bologna, Italy).[26] Subjects underwent the test while standing with their eyes open and then with their eyes closed. From the data collected by the sensors, quantitative posturography parameters were derived from the statokinesigram. All parameters were collected in 2 different sensory conditions, namely, with eyes open and with eyes closed. These parameters included:

A. Trace length (mm): Length of the trace made by the center of pressure.
B. Trace surface (mm^2): Perimeter including 90% of the area covered by the trace.
C. Body sway mean velocity (mm/s): Mean velocity of the center of pressure during the examination, with a standard deviation (SD) of velocity also measured.
D. Fourier Fast Transformation (FFT): Fast Fourier transformation was applied to analyze the frequency distribution of body sway along both the *X* (lateral) and *Y* (anteroposterior) axes. This technique allowed us to examine the composition of body sway in terms of its fundamental frequency, represented in Hz and normalized to a scale of 100. Additionally, FFT enabled us to study the frequency power spectra within predetermined frequency ranges:

- X: The primary frequency component of body sway along the lateral (*X*) axis.
- Y: The main frequency component of body sway along the anteroposterior (*Y*) axis.

Furthermore, we categorized the frequency power spectra into distinct frequency ranges:

- I (Low Frequency): Frequency range of 0.01-0.5 Hz.
- II (Middle Frequency): Frequency range of 0.5-1 Hz.
- III (High Frequency): Frequencies above 1 Hz.

By conducting this analysis, we gained valuable insights into the distribution of frequency components within different frequency ranges, contributing to a comprehensive understanding of body sway characteristics.

Pupillometry

Pupillary responses were recorded using an infrared video eye-tracker (EDM 7.16 Classic VOG, Eye Tracking System, Euroclinic, Italy), settings: camera Polaris's video capture, format 720 × 576 UYVY, 16 bit, video frame rate 25 fps, codec Logarith lossless. Values over 3 standard deviations from the mean were removed to ensure data accuracy.

Pupillary mean dilatation was measured both before and after asking the subjects to walk for 7 steps on-site with obscured vision using a blinded mask. Measurements within the first 2000 ms after walking were excluded to eliminate initial pupillary adaptation.

The different pupil dilatation was then analyzed using paired *t*-test for each subject to compare pre- and post-walking pupil-diameter measurements.

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences Statistics software, version 24.0 (IBM SPSS Corp.; Armonk, NY, USA) and $P < .05$ were used to indicate statistical significance. Means and standard error were matched by paired *t*-test. In Multivariate linear regression models, the backward stepwise method was used to determine the association between tonic pupil size and quantitative posturography parameters.

RESULTS

The analysis of quantitative posturography parameters of patients affected by long-standing Ménière's disease showed significantly increased trace length, surface, and velocity compared to normal controls ($P \leq .001$) both in closed and open eyes condition. Body sway evaluation on X and Y planes by Fast Fourier transformation analysis of oscillation frequency showed that the body oscillated with a broader frequency spectrum compared to normal controls (*P*

Table 2. Mean and Standard Deviation of the Sway Characteristics of Ménière's Patients and Healthy Controls, in Both Open and Closed Eyes Condition

	Length (mm)		Surface (mm²)		Velocity (mm/s)	
	OE	CE	OE	CE	OE	CE
Healthy controls n = 36	199.00 ± 6.02	281.74 ± 8.13	103.89 ± 6.03	130.16 ± 7.39	4.35 ± 191	8.26 ± 1.42
Ménière's disease n = 36	246.88 ± 8.36	349.30 ± 5.72	165.55 ± 5.01	218.88 ± 8.20	7.92 ± 3.71	12.53 ± 288
P	≤.001	≤.001	≤.001	≤.001	≤.001	≤.001

CE, closed eyes condition; length, the length of the trace made by the center of pressure during the examination; OE, open eyes condition; surface, the surface perimeter that includes 90% of the area covered by the trace; velocity, the mean velocity of the center of pressure during examination.

Table 3. Results of the Spectral Frequency Analysis, in Both Open and Closed Eyes Condition

		X I	X II	X III	Y I	Y II	Y III
OE	Healthy controls n = 36	25.45 ± 9.60	10.39 ± 2.48	3.44 ± 0.92	25.47 ± 5.65	7.38 ± 3.02	1.15 ± 0.56
	Ménière's disease n = 36	39.78 ± 6.74	16.09 ± 5.25	5.63 ± 3.72	29.50 ± 16.20	9.55 ± 3.79	4.85 ± 2.99
	P	≤.001	≤.001	≤.001	NS	≤ .004	≤ .001
CE	Healthy controls n = 36	28.41 ± 8.49	4.42 ± 1.61	4.15 ± 0.95	33.93 ± 8.04	8.54 ± 4.33	2.50 ± 1.02
	Ménière's disease n = 36	47.93 ± 6.21	14.01 ± 4.12	5.08 ± 0.94	41.56 ± 5.54	16.19 ± 4.13	7.23 ± 2.56
	P	≤.001	≤.001	≤.001	≤.001	≤.001	≤.001

I, frequency range 0.01-0.7 Hz; II, frequency range 0.7-1.0 Hz; III, frequency range 1.0-5.0 Hz; CE, closed eyes condition; OE, open eyes condition; NS, not significant; X, mean ± SD of the power spectra on x plane; Y, mean ± SD of the power spectra on y plane.

≤ .001 on X I, XII, X III, YIII planes in open eyes condition; *P* ≤ .001 on all planes in closed eyes condition) (Tables 2 and 3).

Pupillometry results (Table 4) of 36 healthy volunteers showed a mean pupil size of 1.66 ± 0.31 mm at baseline and 1.81 ± 0.22 mm after walking stimulation, with a mean pupil dilatation of 9.04% after stimulation. Pupillometry of 36 Ménière's patients showed a mean pupil size of 1.81 ± 0.54 mm at baseline and 2.52 ± 0.57 mm after walking stimulation, with a mean pupil dilation of 39.23% after walking. The comparison between the tonic pupil size of healthy controls and that of Ménière's patients was nonsignificant at baseline (*P* = .082), highly significant after walking stimulation (*P* < .0001).

Multivariate linear regression was performed to determine the association between pupillometry and posturography parameters in Ménière's patients and in normal controls. This analysis revealed that in Ménière's patients (Table 5), the pupil dilatation after walking stimulation was positively linked (positive regression coefficient or positive regressor) to the posturography parameter "closed eyes trace length" (*P* = .011). Other concomitant variables with inverse link (negative regressor) were "closed eyes trace velocity" and "closed eyes low-frequency oscillation on frontal plane (CEX 1)" that contribute to but do not determine a clear-cut dependence between variables.

Table 4. Results of Pupillometry Recorded with Infrared Video-Oculoscopy

Tonic Pupil Size (mm)			
	Baseline (B)	Post-Walking (PW)	Mean Pupil Dilation
Healthy controls n = 36	1.66 ± 0.31	1.81 ± 0.22	9.04%
Ménière's disease n = 36	1.81 ± 0.54	2.52 ± 0.57	39.23%
P	.082 (NS)	<.0001	<.0001

Pupillometry measurements for tonic pupil size, both at Baseline (before the patient's 7-step walk with obscured vision on-site) and at the Post-Walking stage. The results are reported as the Mean pupil size (in millimeters), Standard Deviation, and mean pupil dilation expressed as a percentage.

Multivariate linear regression analysis examining factors associated with "tonic pupil size at baseline" in Ménière's disease (Table 6) showed that the tonic pupil size before walking was inversely linked (negative regressor) to posturography parameter "closed eyes trace velocity" (*P* = .019). The absence of concomitant variables

Table 5. Results of Multivariate Linear Regression Model Examining Factors Linked with Tonic Pupil Size Post-walking in Ménière's Disease (n = 36)

Tonic Pupil Size Post-Walking in Ménière's Disease					
	Multivariate Linear Regression Model (*P* = .014)				
	B	Standard Error	*P*	*β*	95% CI
Control Variables					
Constant	−10.030	5.245	.065		(−20.714)-(0.653)
Length CE	0.041	0.015	.011	0.414	0.010-0.072
Velocity CE	−0.052	0.030	.090	−0.263	(−0.112)-(0.009)
CEX 1	−0.025	0.014	.085	−0.272	(−0.053)-(0.004)

β, standardized coefficients; *B*, unstandardized coefficients; CE, closed eyes condition; CEX 1, closed eyes low-frequency oscillation on frontal plane.

Table 6. Results of Multivariate Linear Regression Model Examining Factors Linked with Tonic Pupil at Baseline in Ménière's Disease (n = 36)

Tonic Pupil Size at Baseline in Ménière's Disease					
	Multivariate Linear Regression Model (P = .019)				
	Baseline	SE	P	β	95% CI
Control Variables					
Constant	2.722	0.378	.000		
Velocity CE	−0.052	0.030	.019	−0.263	(−0.132)-(−0.013)

β, standardized coefficients; B, unstandardized coefficients; CE, closed eyes condition.

demonstrates that this parameter is highly representative of the factor studied.

DISCUSSION

The physiological maintenance of orthostatic posture in healthy individuals involves an anterior–posterior low velocity–long distance balance sway, known as the ankle strategy. However, compromised stability can lead to the adoption of the hip pattern,[23,29] characterized by high-velocity, short-distance body sway, and increased energy expenditure. Upright stance relies on sensory inputs from the visual, vestibular, and proprioceptive systems, with visual inputs playing a crucial role in controlling body oscillations around the gravity center. Different sensory systems influence body oscillation frequencies, with vestibular afferences predominantly controlling low-frequency oscillations and proprioceptive inputs contributing to high-frequency oscillations.

Static posturography has proven effective in evaluating overall postural performance and distinguishing various peripheral vestibular diseases based on parameters such as trace length, surface, and velocity of body sway.[30] Notably, body oscillations have been observed to be faster in benign paroxysmal positional vertigo and vestibular neuritis compared to Ménière's disease.[31] Moreover, previous studies have demonstrated a significant correlation between posturography parameters and the time elapsed since the last acute phase of Ménière's disease.[32] Fast Fourier transformation analysis and some parameters of static posturography, such as trace length, surface, and velocity of body sway, can be used to distinguish various peripheral vestibular diseases.

Pupillometry research has garnered renewed interest in recent years due to its potential to offer insights into the allocation of mental resources.[33] The usefulness of pupillometry is increased by the fact that the pupil response is prone to various situations such as concentration, mental functions, characteristics of the tasks, age of the subject, and sound exposure. In hearing-related problems, pupil dilation can be an indicator of cognitive processing during listening. In healthy subjects, modifications in postural determine an enhanced cognitive workload, as assessed by pupillometry.[23] Pupil diameter seems to be related to neuromodulators such as noradrenaline and acetylcholine levels, modulating the brain state and corresponding changes in behavior.[34] A recent study[35] showed suppression of the parasympathetic nervous system and activation of the sympathetic system before a vertigo attack in Ménière's patients, while pupillometry demonstrated overactivation of the sympathetic nervous system on the affected side.

Despite the significance of pupillometry, its subjective nature and lack of standardization have posed challenges in its application. Visual subjective pupillometry, often using a penlight, may vary in intensity of illumination and result in potential biases. Automatic pupil assessment with calibrated light stimulation offers a more reliable approach.[36,37] In our study, we employed infrared video-oculoscopy to assess pupil size in darkness, bypassing potential biases associated with pupillary constriction due to light stimulation.

Our study aimed to explore the application of pupillometry as a measure of cognitive effort in individuals with Ménière's disease, addressing an existing gap in knowledge regarding its potential utility in vestibulopathies. We integrated pupillometry alongside static posturography to gain deeper insights into the cognitive demands and arousal levels associated with postural control in this specific patient population.

The results of our study have provided valuable insights into the cognitive aspects of balance control in Ménière's disease. We observed that Ménière's patients exhibited decreased postural control compared to normal controls, as evidenced by alterations in quantitative posturography parameters. Interestingly, walking-induced pupil dilation was significantly higher in Ménière's patients, indicating a heightened state of arousal in response to the task of walking with closed eyes. In contrast, healthy controls did not exhibit significant pupillary dilation after walking. This finding suggests that the simple task of walking with closed eyes triggers an increased arousal response in Ménière's patients due to their static upright stance imbalance, which is closely linked to the challenging nature of maintaining balance.

Our study further revealed a positive correlation between increased pupil diameter after walking with closed eyes and the effort required to maintain a static upright stance in visually deprived conditions, as measured by lengthened posturography parameters such as "closed-eyes trace length." Additionally, 2 postural parameters, "closed-eyes trace velocity" and increased low-frequency oscillations on the frontal plane ("CEX 1"), were inversely related to pupil dilation after visually deprived walking. These results indicate that the velocity of body sway in the closed-eyes condition, both before and after walking, plays a crucial role in posture maintenance and influences the level of arousal and pupillary dilation in Meniere's patients.

Our study presents certain limitations that warrant consideration when interpreting our findings. The key limitation arises from the inherent heterogeneity in audio-vestibular function among Ménière's disease patients. Variations in disease stage, time since the last vertigo attack, and audiometric profiles can introduce potential confounding factors. While efforts were made to address these factors in our analyses, the complex interplay between audio-vestibular function, cognition, and postural responses may influence our observed results, and the diversity within our study population underscores the need for cautious interpretation.

The significance of our study lies in several aspects. First, it sheds light on the potential of pupillometry as a sensitive and noninvasive tool to assess cognitive workload and arousal levels in individuals with Ménière's disease during postural tasks. This novel approach provides a deeper understanding of the dynamic interplay between the vestibular system, motor control, and cognitive processing in the context of postural control. Secondly, by establishing a link between effort and pupil dilation, our findings add to the growing body of evidence supporting the validity of pupillometry as an objective measure of cognitive demand in vestibular disorders. Our research has broader implications for the management and rehabilitation of Ménière's disease patients. The observed alterations in pupillary dilation during postural tasks suggest that monitoring arousal levels and cognitive effort through pupillometry may aid in tailoring interventions and therapeutic strategies to improve postural control and overall quality of life for these patients.

Our study has achieved its objective of investigating the application of pupillometry as a measure of cognitive effort in individuals with Ménière's disease. The observed alterations in pupillary dilation during postural tasks in Meniere's patients reflect heightened arousal and cognitive demands related to the challenging nature of maintaining balance in the presence of vestibular dysfunction. These findings have implications for the management and rehabilitation of Ménière's disease patients, potentially leading to improved interventions and enhanced quality of life. Moreover, our study contributes to the growing body of evidence supporting the utility of pupillometry in assessing effort and cognitive workload in vestibular disorders, thereby paving the way for future research and clinical applications in this field.

Ethics Committee Approval: As a purely retrospective chart study no formal number/ID of approval was needed from our institutional ethics committee.

Informed Consent: Informed consent was obtained from all subjects participating in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – P.G.G; Design – B.F., G.V., P.G.G; ; Supervision – S.D.G., P.G.G., Resources – S. D. G., P. G. G.; Materials – B. F., G. V.; Data collection and/or processing – C.C., B.F., G.V.; Analysis and/or Interpretation – B. F., G. V.; Literature Search – B.F., G.V.; Writing – P.G.G., B.F., G.V., C.C.; Critical Review – P.G.G., S.D.G.

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