

Persistence of Non-Vertigo Symptoms in Meniere Disease During Remission – A Preliminary Report

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ABSTRACT:

Background: Though the absence of vertigo in Meniere disease is often interpreted as remission, patient-centered subjective assessment of quality of life remains the best indicator of such remission.

Study Objective: To assess the presence and severity of aural pressure/tinnitus, hearing loss, unsteadiness, nausea and vomiting in MD patients during remission.

Setting: Urban tertiary care referral hospital in a developing country.

Methodology: Consecutive patients with diagnosis of Definite Meniere were selected from the Balance and Dizziness Clinic of National Hospital Abuja for the study. Quality of life assessment was carried out using 3 validated tools – Modified MD-POSI, Vertigo Symptom Scale and Tinnitus Handicap Inventory (THI). Patients were included only when they have been vertigo free for at least 4 weeks. Pure tone audiometry was carried out in those with subjective hearing loss at recruitment and 4 weeks later.

Results: A total of 26 patients completed the study. All had cinnarizine for acute vertigo control and Betahistine for maintenance of vertigo control. There was female preponderance (17:9). The age range was 32–56 years. The duration of MD ranges from 4 months to 12 years. The total and subscale MD-POSI scores for “between attacks” significantly correlated with hearing, unsteadiness and tinnitus/pressure when compared to during attack. 69.2 per cent of participants experienced symptoms of unsteadiness during remission. 13/26 of participants reported persistent, though less annoying tinnitus that poorly correlated with THI score during remission.

Conclusion: Our study showed that significant non-vertigo symptoms affect the quality of life during remission. Perhaps there is need to properly define, in future studies, what constitutes remission in patients with MD.

KEYWORDS:

Meniere disease, Non-Vertigo Symptoms, remission

ABBREVIATIONS

EQ-5D – EuroQol 5D

ICD-10 – The International Classification of Diseases

MD – Meniere disease

MD POSI – Meniere’s Disease Patient-Oriented Symptom-Severity Index

NAS – numeric analog scale

QoL – quality of life

SVV – subjective visual vertical

THI – Tinnitus Handicap Inventory

TTO – time trade-off

VSS-A – VSS-vertigo anxiety subscale

VSS-V – VSS-vertigo balance subscale

INTRODUCTION

Meniere disease (MD), initially described by Prosper Meniere, consists of a triad of episodic vertigo, fluctuating sensorineural hearing loss and tinnitus, often with an added symptom of aural fullness,

and occasionally with systemic symptoms of nausea and vomiting. Of the symptoms of MD, vertigo is often the most distressing to the sufferer, and it is not unusual for clinicians to assume that the patient is on remission when vertigo subsides.

The International Classification of Diseases (ICD-10) coded MD into 386.00 with subsets coded as 386.01 (Active MD Cochleovestibular), 386.02 (Active MD Cochlear), 386.03 (Active MD Vestibular) and 386.04 (MD in remission or inactive MD) [1]. Implicated in this classification is the confusion of what constitutes “remission” especially with respect to cochleovestibular MD. It is not clear from published literature whether MD in remission should be defined as the absence of vertigo (as is commonly done) or the absence of the major symptoms (vertigo, tinnitus and hearing loss).

Published research work on Meniere disease has shown that the majority of patients receive benefit from either lifestyle modifications (low salt intake), or from medical (diuretics, use of labyrinthine sedatives – Cinnarizine, Betahistine) or surgical intervention (intratympanic steroid or aminoglycosides, endolymphatic sac surgery, vestibular neurectomy, labyrinthectomy). While some

Tab. I. Correlation of non-vertigo symptoms with MD POSI, THI and VSS.

NON-VERTIGO SYMPTOMS	PEARSON CORRELATION COEFFICIENT (R) WITH QOL TOOLS			
	*MD POSI – A	**MD POSI – B	***VSS-V	****VSS-A
Unsteadiness (n = 18)	0.37	0.26	0.62	0.56
	THI-Functional	THI-Emotional	THI-Catastrophic	
Tinnitus/Ear pressure (n = 13)	-0.43	-0.27	-0.44	
	MD-POSI – “Hearing During”	MD-POSI – “Hearing Between”	MD-POSI – “Tinnitus/Ear Pressure”	
Hearing Loss (n = 9)	0.55	0.75	0.35	

*MD POSI “balance during” (at recruitment)

** MD POSI “balance between” (administered 4 weeks after)

*** vertigo symptom scale – balance subscore

**** Vertigo symptom scale – anxiety subscore

Tab. II. Correlation of comorbid factors with MD POSI, THI and VSS.

CO-MORBID CONDITIONS	PEARSON CORRELATION COEFFICIENT (R) WITH QOL TOOLS				
	*MD POSI “A”	**MD POSI “B”	***VSS-V	****VSS-A	THI
Hypertension (n = 8)	0.18	0.22	0.29	0.14	0.48
Diabetes mellitus (n = 3)	0.34	0.28	0.31	0.22	0.24
^ Past History of Migraine (n = 1)	0.20	0.18	0.24	0.32	0.16

*MD POSI “A” “balance during” (at recruitment)

** MD POSI “B” “balance between” (administered 4 weeks after)

*** vertigo symptom scale – balance subscore

**** Vertigo symptom scale – anxiety subscore

THI = Tinnitus Handicap Inventory Score (Total)

^ One episode of hemicranial headache 5 years previously. Not on anti-migraine medication

of these treatment options are controversial, they are effective in suppressing vertigo though most have potential secondary effects including unsteadiness and sensorineural hearing loss [2].

In resource-constraint settings like in Africa, vertigo management relies on astute clinical observation and special attention to symptoms, and individualizing management. We had earlier reported our experiences with running a low-key vertigo clinic in Africa [3] and documented our experiences with intra-tympanic gentamicin in the management of Meniere disease [4].

Publication on vestibular status of patients with MD in remission is sparse. Nakagawa et al. observed that the subjective visual vertical (SVV) in patients with MD in remission is lower than those with active MD but higher than those observed with normal subjects [5]. Masuyama et al. observed that cholinergic receptor maximal binding (Bmax) value in Meniere patients during the remission state was higher than that in normal controls, implying cholinergic hyperactivity in MD in remission [6]. Kitahara et al. (2007) observed that patients with MD in remission with low canal paresis (cp%) did not always develop vestibular compensation compared to those with higher cp% [7].

Kakigi and Takeda (2009) observed that for patients with MD in remission, the plasma anti diuretic hormone (p-ADH) and plasma osmolality (p-Osm) levels were higher than the normal limits. In the acute phase, the p-ADH level was higher than that in remission but the p-Osm was unchanged [8].

The common extrapolation from these studies is that the vestibular status of patients with MD in remission could be dynamically

placed between those with acute MD and the normal subjects. We believe that clinical evaluation of this status is best achieved with patient-oriented quality of life tools.

METHODOLOGY

This study was carried out according to the Declaration of Helsinki regarding scientific research in humans. Consent was sought and approval given by each of the study participants prior to recruitment. It is a prospective non-randomized longitudinal study of consecutive patients with MD in remission attending the Balance & Dizziness Clinic of National Hospital Abuja, between January 2016 and December 2017. The selection criteria includes a) diagnosis of definite Meniere disease, based on 2015 diagnostic criteria [20], b) symptom-free of vertigo for at least 4 weeks, and c) willingness to participate. Patients that presented with active MD were followed up for 4, 8, 12, and 16 weeks until they have been symptom-free of vertigo for at least 4 weeks, before inclusion into the study. The inability to achieve clinical remission from vertigo at 16 weeks was an exclusion criterion. Also excluded were patients with Meniere disease reporting headache in the preceding three years, whether on anti-migraine medications or not and those with autoimmune inner ear diseases. MD associated with BPPV was also excluded.

Selected participants were then specifically asked to rate the following symptoms on a numeric analog scale (NAS) of 1 to 5 (least to most worrisome): hearing loss, unsteadiness, tinnitus/aural fullness, nausea and vomiting. They then had three validated QoL tools administered to them. These were 1) Meniere’s Disease Pa-

tient-Oriented Symptom-Severity Index (MD POSI), 2) Vertigo Symptom Scale (VSS) and 3) Tinnitus Handicap Inventory (THI).

MENIERE'S DISEASE PATIENT-ORIENTED SYMPTOM-SEVERITY INDEX (MD POSI)

This age and gender neutral tool was developed and validated by Murphy & Gate in 1999 as psychometric testing of a new self-report instrument for quantifying the impact of Meniere disease (MD) on patients' lives [9]. MD POSI is a valid and reliable instrument to evaluate the impact of MD on patients' disease-related quality of life, and it is responsive to change in the status of the disorder. MD POSI is suitable for use in clinical practice and clinical research in people with MD [10]. In this study, MD POSI was administered to participants at two successive visits, 4 weeks apart, and the "during attack," "between attack" and quality of life (QoL) subscores were compared. Its modification that excluded the Employment subscore was utilized in the current study.

VERTIGO SYMPTOM SCALE

Vertigo Symptom Scale (VSS) – short form, is a common tool used to assess both the balance issue and the associated psychological factors. It has two subscales: vestibular-balance and autonomic-anxiety. The short form of VSS, previously validated by Kondo et al. [11] was utilized in the current study. VSS is applied to the participant during the second clinic visit 4 weeks after vertigo-free status has been documented.

TINNITUS HANDICAP INVENTORY (THI)

This tool was developed by Newman, Jacobson and Spitzer in 1996 and grouped tinnitus-related quality of life items into functional, emotional and catastrophic subscales and has been shown to significantly correlate with symptom rating scales [12]. THI was applied to participants during the second clinic visit, 4 weeks after vertigo-free status has been documented. Where Meniere disease affected both ears, participants were asked to score the worse ear affected.

RESULT

Of the 37 patients recruited for the, only 26 completed the study, giving an attrition rate of 29.7%. The reasons for attrition include failure to follow-up and acute exacerbation of symptoms during the study. All participants had Cinnarizine for acute vertigo control and Betahistine for maintenance of vertigo control. There was female preponderance (17:9). The age range was 32–57 years (Mean = 38 years, Std. Dev. = 7.25). The duration of diagnosis of Meniere disease ranges between 4 months to 12 years.

Meniere disease affected the left ear in 34% (n = 8), right ear in 35% (n = 9) and was bilateral in 35% (n = 9). There was no significant difference in the numerical analog score of vertigo, tinnitus and unsteadiness symptoms between the unilateral and bilateral MD groups during remission.

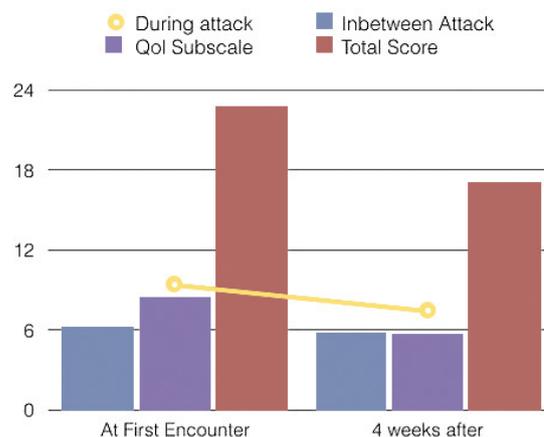


Fig. 1. Mean Sub scores of the Meniere's Disease Patient Oriented Symptom Index (MD POSI) obtained 4 weeks apart, among 26 patients with Meniere's Disease in Remission. Note the 'in-between attack' score dip more than other subscores.

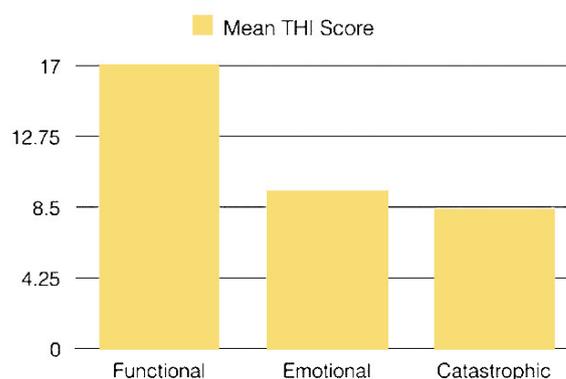


Fig. 2. Subscore of THI in 13 cases of MD in remission 4 weeks after last vertigo attack.

17/26 of participants had vertigo-free remission longer than 8 weeks (Mean 13 weeks, Std. Dev. 4.85) while 9/26 participants were recruited after achieving vertigo-free remission for at least 4 weeks (Mean 6 weeks, Std. Dev. 2.12). The total score of Pearson's correlation coefficient of MD POSI compared significantly to the intensity of unsteadiness symptom from the NAS score for these 2 groups ($r = 0.632$, and $r = 0.755$ respectively, $p < 0.05$). However, there is no significant correlation between the duration of the last attack of vertigo and the total score of MD POSI ($r = 0.112$, $p < 0.05$).

The MD POSI mean subscores for balance "during attack" were 9.43 and 7.5, respectively (Std. Dev 1.35) and the subscores "between attack" were 6.19 and 5.83 (Std. Dev 0.25). The mean quality of life (QoL) subscores on MD POSI were 8.42 and 5.67 (Std. Dev 1.94). The total MD POSI scores were 22.73 and 17.00, respectively (Std. Dev 4.05).

18/26 participants reported unsteadiness. The mean NAS score for unsteadiness was 2.67 (Std. Dev = 0.80). This unsteadiness score showed a weak correlation with the total score of MD POSI at 4 weeks ($r = 0.37$) and the "between attacks" score ($r = 0.26$), but negatively with the QoL score ($r = -0.04$). However, the two

balance-related items (“balance during” and “balance between”) show a good correlation with disequilibrium score (0.56, and 0.8 respectively, $P < 0.05$).

The mean vertigo symptoms scale score for Meniere disease on remission studied was 9.22 (range 0–22) for the VSS-vertigo balance subscale (VSS-V) and 4.78 (range 1–14) for the VSS-vertigo anxiety subscale (VSS-A). There was a significant positive correlation between the unsteadiness score and both the VSS-V ($r = 0.62$, $P < 0.05$) and VSS-A ($r = 0.56$, $P < 0.05$).

13/26 (50%) participants who had MD in remission reported tinnitus during remission. 8/13 of these (61.5%) had ongoing hypertension and were on medications. The mean THI score was 16 for the functional (range 6–32), 9.5 for emotional (range 0–20) and 8.4 for catastrophic (range 2–16) subscale. There was a negative correlation between the tinnitus scoring and the scoring on all subscales of THI for those without hypertension co-morbidity, but a significant positive correlation among those with hypertension co-morbidity ($r = 0.52$, $p < 0.05$).

The three hearing-related items of MD POSI showed a good correlation with the NAS hearing score in 9/26 participants that complained of residual hearing loss during remission. These include “hearing during” ($r = 0.55$, $p < 0.05$), “hearing between” ($r = 0.75$, $p < 0.05$), and “tinnitus/pressure” ($r = 0.35$, $p < 0.05$). The commonest observed audiogram feature is the slow-rising (low frequency) sensorineural type with normal thresholds at mid and high frequencies. The mean pure tone average thresholds at 125, 250 and 500 KHz “during attack” and “between attack” were 37.5 dB and 36 dB, respectively.

No participants with MD in remission scored nausea and vomiting in the present study.

The main comorbid conditions identified in the participants were hypertension (8/27), diabetes mellitus (3/27) and a past history of migraine (1/27). Of these, only hypertension showed a significant positive correlation with the total THI score (Tab. II.).

DISCUSSION

The current study examines the quality of life of individuals with Meniere disease in remission using 3 validated tools and a NAS scoring of unsteadiness, tinnitus/ear pressure, hearing loss, nausea and vomiting. We studied unsteadiness in place of disequilibrium or imbalance, since disequilibrium or imbalance has earlier been noted to be ambiguous [12]. We observed that neither the disease duration, nor the duration of the last attack showed a significant correlation with the NAS score for non-vertigo symptoms during remission. This is in contrast to the observation of Levo et al., who, using the EuroQol 5D (EQ-5D) tool, observed a significant relationship between the visual analog score and time trade-off (TTO) in patients with MD, and attributed the TTO-VAS difference to attitudes towards the illness [13]. Our NAS scale employed 5 non-vertigo symptoms and this might explain the observed difference.

Unsteadiness was reported and scored in 69 percent ($n = 18$) of our participants with MD in remission. An earlier study by Boleas-Aguirre et al. (2007) noted that 15.5% of MD patients still complained of unsteadiness 5 years after treatment with intra-tympanic gentamicin [14], and unsteadiness and disequilibrium are reported to be common in patients with chronic Meniere syndrome [15]. Both the subscores of vertigo symptom scale – VSS-V assessing balance, and VSS-A assessing anxiety – showed positive correlations with the numerical analog score for unsteadiness ($r = 0.62$ and $r = 0.56$ respectively, $P < 0.05$). In addition, 2 balance-related items of the MD POSI – “balance between” and “balance during” showed a good correlations with the unsteadiness NAS score ($r = 0.56$ and $r = 0.8$ respectively, $p < 0.05$). The implication is that for the majority of participants with Meniere disease in remission, unsteadiness significantly impacts the quality of life.

Fifty percent ($n = 13$) of our study participants reported significant tinnitus during remission. We found a negative correlation between the THI total and THI subscores when compared to the NAS score for tinnitus. However, we found a positive correlation between co-morbid hypertension and THI total scores (Tab. II.). In a study of tinnitus in long-standing Meniere disease, Stephens et al. (2012) used EQ-5D and similarly observed that tinnitus, a significant component of disease-specific quality of life (QoL), did not relate significantly to the generic measures used [16]. We find it difficult to explain why despite the participants’ mean functional subscore being higher than either mean emotional and mean catastrophic subscores, the observed correlation of the NAS score for tinnitus with both the total THI score as well as THI subscores were negative, except for those with co-morbid hypertension. It is possible that some medications used for control of hypertension might modulate the tinnitus noted in this group. We believe that the issue regarding tinnitus QoL in patients with either active MD or MD in remission deserves further research.

One third of participants in the current study ($n = 9$, 34.6%) had residual hearing loss at low frequency. The observed correlation of analog score for hearing with the hearing-related items of MD POSI is in keeping with the observation of Quatre et al. (2018) who reported that MRI hydrops imaging in patients with definite MD was correlated with hearing loss [17].

We did not observe full recovery of hearing loss in any of the participants recruited for this study during remission. This may be due to the short duration of the study. Bailey, Graham & Lawrence (1992) reported that 3 out of 5 cases with partial or complete recovery after prolonged sensorineural hearing loss had Meniere disease attributed to temporary obstruction of capillaries in the stria vascularis [18]. We also did not observe a significant drop in hearing during the 2 encounters. Sakurai, Yamane & Nakai had earlier reported that patients whose hearing (during remission) dropped by more than 10dB from the initial hearing level within 3 years of the first audiovestibular examination tended to show a further declining hearing level afterwards [19].

The majority of patients ($n=25$, 96.1%) with MD in remission seen in our series had classical MD without migraine and without auto-

immune disorder, similar to Group 1 phenotype of MD as recently reported by Frejo et al. [21, 22]. It is not clear if this phenotype is responsible for the observation noted in our study.

We did not observe significant difference in the numerical analog score (NAS) of symptoms during remission between unilateral and bilateral MD groups. This is in contrast with the observation reported earlier by Lopez-Escamez, Viciano, and Garrido-Fernandez (2009) [23]. The difference might be due to our exclusion criteria that eliminate all MD cases with headache and also those with active MD.

SUMMARY

1. Unsteadiness, tinnitus and hearing loss are common non-vertigo symptoms observed in MD in remission in our environment. These symptoms significantly impact the patient's quality of life;
2. Both subscales of the vertigo symptoms scale show a good correlation with the numeric analog score for unsteadiness;

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CONCLUSION

While the status of MD patients is well-known and documented, what constitutes the status of the MD patient during remission is not so clear. This preliminary study showed that significant non-vertigo symptoms affect the quality of life in MD during remission. It is possible that medications for hypertension modulate the tinnitus component of these symptoms. Perhaps there is scope for further in-depth studies to characterize what constitutes remission in patients with MD.

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