The Journal of International Advanced Otology

J Int Adv Otol 2019; 15(3): 442-6 • DOI: 10.5152/iao.2019.7430

Original Article

Menière's Disease and Caloric Stimulation: Some News from an Old Test

Niccolò Cerchiai[1], Elena Navari[1], Mario Miccoli[2], Augusto Pietro Casani[1]

Department of Medicine and Surgery, Pisa University Hospital, Pisa University Hospital, Pisa, Italy (NC, EN, APC)
Department of Clinical and Experimental Medicine, Pisa University Hospital, Pisa University Hospital, Pisa, Italy (MM)

ORCID IDs of the authors: N.C. 0000-0001-8870-1538; E.N. 0000-0001-6047-7546; M.M. 0000-0002-8632-6145; A.P.C. 0000-0001-5261-9129.

Cite this article as: Cerchiai N, Navari E, Miccoli M, Casani AP. Menière's Disease and Caloric Stimulation: Some News from an Old Test. J Int Adv Otol 2019; 15(3): 442-6.

OBJECTIVES: The aim of the present study was to improve the instrumental diagnosis of assessing Menière's disease (MD) if the frequency and slow-phase velocity (SPV) of the thermally induced nystagmus analyzed through the caloric vestibular test (CVT) showed different alterations in relationship with an increasing severity of the cochlear involvement.

MATERIALS and METHODS: The study retrospectively analyzed the CVT results of 72 patients affected by unilateral "definite MD" according to the 2015 Barany Society Diagnostic Criteria and treated only conservatively.

RESULTS: There were 7 (9.72%) patients in stage 1, 27 (37.50%) in stage 2, 35 (48.61%) in stage 3, and 3 (4.16%) in stage 4. The canal paresis (CP) calculated through the frequency of the thermally induced nystagmus on the affected side increased in more severe stages (p=0.033). Conversely, the CP calculated through the SPV was not significantly different among the stages showing abnormal values even in the early phases of the disease (71% in stage 1, 81% in stage 2, 91% in stage 3, and 100% in stage 4), exclusively on the affected side.

CONCLUSION: Abnormalities of the thermally induced nystagmus on the affected side characterize most patients with MD, but only "SPV" alterations are common in the early stages. An increasing severity of the cochlear involvement progressively reflects also on the "frequency" parameter. Detecting a dissociation between these two parameters could represent an instrumental marker of the early forms of MD.

KEYWORDS: Menière's disease, vertigo, caloric test, nystagmus

INTRODUCTION

Menière's disease (MD) is an idiopathic inner ear disorder where the onset of endolymphatic hydrops causes typical symptoms, such as vertigo, aural fullness, tinnitus, and hearing loss. The natural course of MD is characterized by multiple crises, with a progressive inner ear damage [1-3]. Although many types of therapy had been proposed over the years, there is no agreement about the efficacy of conservative therapy in reducing the number of crisis and in preventing both vestibular and cochlear involvement [4-7]. Conversely, ablative therapy with intratympanic gentamicin (ITG) appears to ensure an effective control of the vertigo attacks, even if this procedure could put clinicians at risk of medico-legal problems in case of adverse effects, such as worsening of hearing loss and chronic imbalance [8-10]. Hence, the possibility for the clinicians to employ an ablative treatment (ITG or ablative surgery) should be considered only after achieving a clear diagnosis of *definite MD* and the exclusion of the possibility of a bilateral MD.

The new diagnostic guidelines for MD [11] indubitably characterize better the most important aspects that need to be considered when diagnosing MD. However, the idea of an instrumental diagnosis in MD, potentially able to recognize atypical earlier presentations and bilateral forms, has generated great interest over the years [12-15].

The caloric vestibular test (CVT) is indubitably useful in the follow-up of MD or as "baseline assessment" of the labyrinthine function prior to an ablative treatment; conversely, it is not strictly necessary in case of clear clinical diagnosis. CVT quantifies the function of lateral semicircular canals by measuring the two main parameters of the thermally induced nystagmus: frequency of the jerks

This study was presented at the 30th Barany Society Meeting, June 10-13, 2018, Uppsala, Sweden.

Corresponding Address: Augusto Pietro Casani E-mail: augusto.casani@unipi.it

Submitted: 22.06.2019 • **Revision Received:** 20.08.2019 • **Accepted:** 22.08.2019
Available online at www.advancedotology.org

and slow-phase velocity (SPV). Since only SPV directly reflects the amount of the cupula deflection during the stimulus [16], frequency is rarely employed to calculate the degree of canal paresis (CP).

Although a positive correlation has been demonstrated between CP and time from the onset, CVT does not provide a clear relationship with the severity of symptoms especially in the early phases [12, 17, 18].

The aim of the present study was to assess whether the analysis and the comparison of CVT parameters can reveal any consistent pathological pattern in patients affected by definite MD, according to an increased severity of the cochlear involvement; this would contribute to outline an ideal profile for a future "instrumental diagnosis" of MD.

MATERIALS AND METHODS

The clinical records of patients affected by unilateral definite MD who were referred from November 2014 to October 2017 to our tertiary referral center (ENT Unit, Pisa University Hospital, Pisa, Italy) were retrospectively evaluated. During this 3-year period, all the patients who were referred to our neurotology service underwent the same series of vestibular tests and then were inserted in our regularly updated digital hospital database (Microsoft Access; Microsoft Corporation, Redmond, WA, USA). The review of the clinical records, particularly of the detailed anamnesis and of the pure tone audiometry, allowed us to apply the most recent diagnostic guidelines [11] to precisely select only patients affected by definite MD. The study design considered for the analysis only those clinical records that were collected during intercritical periods of MD. Patients who were seen only during the acute phases of MD were excluded from the study. In case of multiple examinations in the same patient (two or more follow-up visits), only the first in accordance with the Barany Society criteria was included in the study. The protocol considered only patients who underwent conservative therapy over the years. Patients treated with ITG or ablative surgery were excluded. Patients affected by MD but referred to our service only because of other active pathologies of the vestibular system (i.e., refractory benign paroxysmal vertigo), as well as patients with an overlapping vestibular migraine, were also excluded. Once the diagnosis of definite MD was established, the study investigated the relationship of CVT parameters (frequency and SPV) with the severity of cochlear involvement.

The caloric vestibular test was performed according to the modified Fitzgerald–Hallpike technique. The external auditory canal was separately irrigated with 125 ml of warm (44 °C) and cold (30 °C) water in a 30-second period (7 min lasted between each test); the responses were recorded through an infrared eye-tracking system (GN Otometrics, Taastrup, Denmark). The software calculates automatically both the mean frequency and the mean SPV of the thermally induced nystagmus; in accordance with the Jongkees formulae, the software then calculates the degree of CP based on both frequency (freqCP) and SPV (spvCP). In our laboratory, we consider a degree of CP as pathological if it is >25% (pathological CP), but potentially significant if >15% (borderline CP). The cochlear involvement was evaluated based on the Pure Tone Average (PTA), determined by the average dB value of the hearing threshold calculated on 0.5, 1, 2, and 3 kHz frequencies. In turn, PTA determined the stage of MD: stage 1≤25 dB, stage 2 between 26 and 40 dB, stage 3 between 41 and 70 dB, and stage 4>70 dB [19].

All the patients belonging to the study group underwent only routinely performed tests, without invasive or experimental procedures. The study protocol adhered to the principles outlined in the Declaration of Helsinki. Written consent was obtained from all the patients for the collection of their clinical data.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences version 23 (IBM Corp.; Armonk, NY, USA) for statistical analysis. Shapiro–Wilk test was used to verify the normality of the distributions. Kruskal–Wallis test and Dunn test for multiple comparisons were performed to compare quantitative variables. Ordinal logistic regression was conducted to assess the contribution of each instrumental parameter in predicting the severity of the disease (increasing stage). A p value of 0.05 was set as the level of significance.

RESULTS

The review of the clinical records allowed to investigate CVT parameters in 72 patients who met the criteria for definite MD. The study included 7 (9.72%) patients in stage 1, 27 (37.50%) in stage 2, 35 (48.61%) in stage 3, and 3 (4.16%) in stage 4 (Table 1).

The analysis showed greater freqCP values in more severe MD stages (Kruskal–Wallis test, p=0.033), whereas spvCP did not show significant differences among the stages. Descriptive statistics about age of the patient, PTA, freqCP, and spvCP are reported in Table 1.

Based on our laboratory cut-off values, the study showed relevant percentages of CVT alterations. The prevalences of borderline freqCP and spvCP values were 0.00% and 0.00% in stage 1, 18.41% and 14.81% in stage 2, 25.71% and 11.43% in stage 3, and 33.33% and 33.33% in stage 4, respectively; the prevalences of pathological freqCP and spvCP values were 0.00% and 71.43% in stage 1, 29.63% and 66.67% in stage 2, 37.14% and 80.00% in stage 3, and 66.67% and 66.67% in stage 4, respectively (Table 2). The less-functioning side, according to the above-mentioned CVT results, corresponded to the affected ear in 100% of the cases.

Bar graphs show the prevalence of borderline and pathological freqCP and spvCP values at different stages of MD (Figure 1), whereas histograms show all CVT alterations, including both borderline and pathological values (Figure 2).

Considering both borderline and pathological values, in stage 1, spvCP was abnormal in 71% of the cases, whereas freqCP was always normal. The percentage of an abnormal freqCP, always associated with an abnormal spvCP, progressively increased in stages 2, 3, and 4. No cases were characterized by an isolated abnormal freqCP (Figure 2, 3).

The last part of the statistical analysis was made to assess whether any value of CVT parameters could predict the severity of the inner ear involvement (stage of MD). Univariate ordinal regressions were made for freqCP and spvCP (PTA was excluded because it directly determines the MD stage) with the following results: higher values of freqCP were likely to determine higher stages of MD (p=0.003, regression coefficient=0.034, 95% confidence interval=0.010–0.057, goodness of fit=0.659), whereas spvCP was not able to predict any difference in MD stages (p=0.079).

Table 1. Descriptive statistics among MD stages

		Min	Max	Mean	SD	No. of patients (%)
Stage 1	Age (years)	36.00	73.00	57.14	12.75	7 (9.72)
	PTA (dB)	10.00	25.00	21.43	5.56	
	freqCP (%)	0.65	14.75	8.74	5.65	
	spvCP (%)	2.91	81.18	39.46	27.40	
Stage 2	Age (years)	28	82.00	55.33	14.49	27 (37.50)
	PTA (dB)	30.00	40.00	35.37	4.14	
	freqCP (%)	1.22	75.24	17.09	18.99	
	spvCP (%)	0.52	77.78	36.56	22.11	
Stage 3	Age (years)	40.00	89.00	64.20	12.46	35 (48.61)
	PTA (dB)	45.00	70.00	57.28	7.70	
	freqCP (%)	0.43	78.02	25.49	21.44	
	spvCP (%)	2.14	75.11	47.02	20.44	
Stage 4	Age (years)	58.00	78.00	65.33	11.01	3 (4.16)
	PTA (db)	80.00	90.00	83.33	5.77	
	freqCP (%)	16.19	100.00	47.37	45.82	
	spvCP (%)	17.39	100.00	47.79	45.42	

PTA: pure tone average; freqCP: canal paresis by frequency; spvCP: canal paresis by slow-phase velocity

Table 2. The prevalence of abnormal caloric vestibular test parameters

	No. of borderline freqCP (%)	No. of borderline spvCP (%)	No. of pathological freqCP (%)	No. of pathological spvCP (%)
Stage 1	0 (0.00)	0 (0.00)	0 (0.00)	5 (71.43)
Stage 2	4 (18.41)	4 (14.81)	8 (29.63)	18 (66.67)
Stage 3	9 (25.71)	4 (11.43)	13 (37.14)	28 (80.00)
Stage 4	1 (33.33)	1 (33.33)	2 (66.67)	2 (66.67)
All the cases	14 (19.44)	9 (12.50)	23 (31.64)	53 (73.61)

freqCP: canal paresis by frequency; spvCP: canal paresis by slow-phase velocity

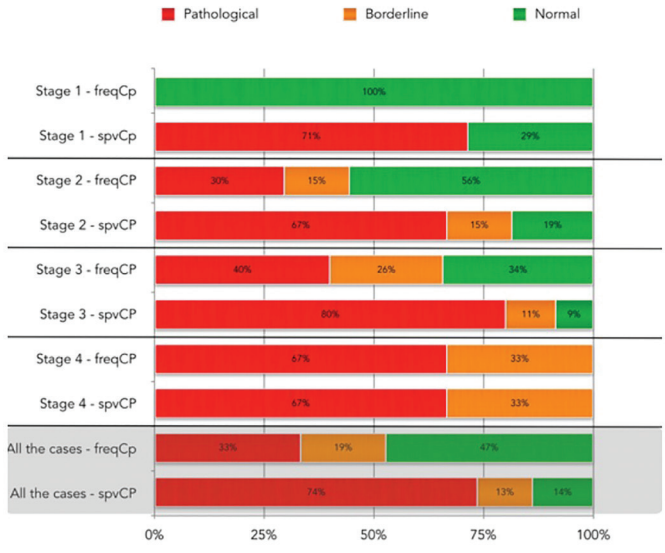

Figure 1. The prevalence of pathological and borderline values according to different stages.
freqCP: canal paresis by frequency; spvCP: canal paresis by slow-phase velocity

DISCUSSION

Despite the improvement of the clinical criteria for the diagnosis of MD [11], the definition of an instrumental profile has generated great interest over the years. The possibility to diagnose an MD in the early stages, when all the clinical features are not fully developed, is of great interest to clinicians who would potentially become able to treat a larger number of patients without encountering medico-legal problems given by the employment of ablative treatment in patients who do not respond to the conventional medical therapy. The definition of an instrumental profile of MD would guarantee an objective method for identifying and characterizing the disease. Recent studies showed interesting results about the dissociation between CVT and video Head Impulse Test results: this instrumental hallmark suggested a frequency-dependent dysfunction of the labyrinth caused by the endolymphatic hydrops [12, 14].

The two main parameters provided by the CVT, represented by frequency and SPV of the thermally induced nystagmus (and consequently freqCP and spvCP), are not routinely both analyzed and compared. Since SPV is considered more sensitive and more representative of the lateral semicircular canal response [16], it is broadly employed alone to estimate the degree of CP. To the best of our knowledge, this is the first study to have compared the investigation of labyrinthine function resulting from the analysis of spvCP with the one obtained from freqCP in MD.

The choice to analyze frequency and SPV of the thermally induced nystagmus according to the PTA level stages was done because, as

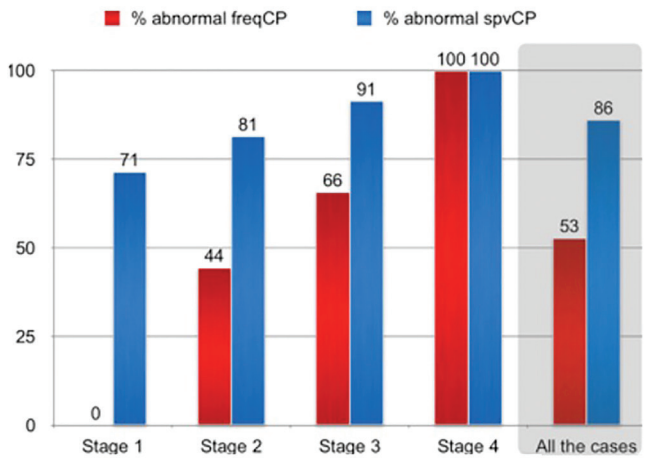

Figure 2. Histograms showing the percentages of abnormal freqCP and spvCP. freqCP: canal paresis by frequency; spvCP: canal paresis by slow-phase velocity

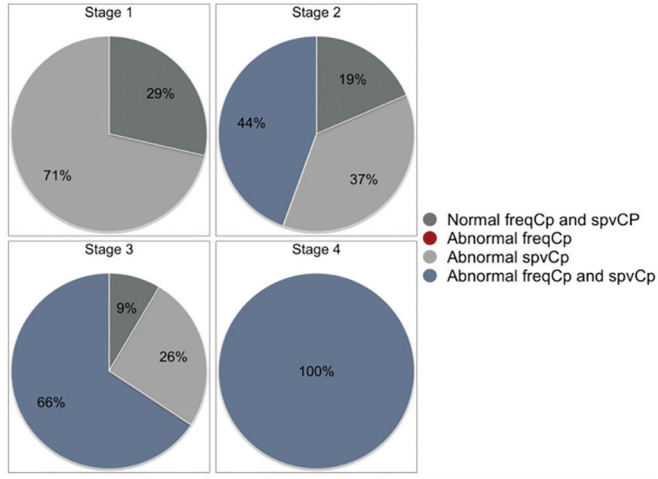

Figure 3. Pie charts showing the prevalence of caloric vestibular test abnormalities. freqCP: canal paresis by frequency; spvCP: canal paresis by slow-phase velocity

reported in literature, hearing is readily measured and closely related to the natural history of MD and useful for its staging [19].

Our data clearly show that the progressive inner ear involvement manifested with a progressively decreased labyrinthine function on the affected side; these results are in accordance with a recent study that put in relationship objective audiometry and vestibular response on CVT [18]. The alteration of SPV parameter on the affected side clearly reflected this aspect and proved to be very sensitive in detecting small degrees of CP already in the early stages of MD (71% of the patients in the very early stage). On the other hand, the frequency parameter did not reveal any impairment if compared with the healthy ear during the early phases of MD, being clearly pathological only after a cochlear dysfunction is established (Figure 2).

Hence, the contemporary evaluation of these two parameters (SPV and frequency) in executing the CVT might offer the possibility to early diagnose the disease also in patients who complain of recurrent vertigo in the absence of a clear cochlear involvement and therefore to differentiate this affection from others characterized by recurrent vertigo. In addition to the known normal response to the video Head Impulse Test [12, 17], this dissociation would may be permit to earlier diagnose MD.

The low number of patients in stage 1 and stage 4 represents the main limitation of our study. However, we think that the trend detected in patients belonging to stage 2 and stage 3 and the 100% concordance with the affected ear in all the stages clearly show the relevance of our findings; certainly, further studies with prospective design and more patients enrolled are needed to validate what we found. It will also be necessary to prospectively compare these results with those obtained from patients affected by other forms of recurrent vertigo (i.e., vestibular migraine).

Another concern that could be elicited by our findings is to have considered for CP a 15% cut-off value as abnormal. However, although a 15% cut-off value can be considered too low, we demonstrated a 100% concordance with the affected side. In this sense, new cut-off values of CP should be determined and validated, allowing to mark as pathological the labyrinthine function of a larger number of patients with MD. Potentially, more patients would present a pathological degree of CP associated with a perfectly normal high-velocity vestibulo-oculomotor reflex gain, highlighting the importance of the dissociation between CVT and video Head Impulse Test findings in MD [12, 17].

Conversely, if some hypotheses could partially explain the reason for a dissociation between CVT and video Head Impulse Test findings [20-22], we still have no theories able to explain the reasons of the early and isolated decrease in SPV parameter on CVT, compared with a preserved response to caloric stimulation in the frequency parameter. However, we retain that this aspect represents an interesting finding, which characterizes most of the affected ears in the early stages of MD.

CONCLUSION

Abnormalities of the thermally induced nystagmus on the affected side characterize most of patients with MD underlining the utility of CVT not only for the follow-up but also when an instrumental support is required for the diagnosis. If on one hand early alterations of SPV characterize most of patients with MD already in the very early stage, on the other hand, abnormal values of the frequency parameter are common only when a cochlear damage is established. Finding a dissociation between these two parameters might be helpful for the diagnosis of a not fully developed MD (so even in case of suspected contralateral involvement). Although further studies are necessary to establish its specificity, the dissociation between freqCP and spvCP could represent a new instrumental marker of the early forms of MD, and we advise clinicians to investigate both parameters employing CVT when MD is suspected.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Informed Consent: Informed consent form was received from all the patients participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - N.C., A.P.C.; Design - N.C., A.P.C., E.N., M.M.; Supervision - A.P.C.; Resource - A.P.C.; Materials - A.P.C., M.M.; Data Collection and/or Processing - N.C., E.N., M.M.; Analysis and/or Interpretation - N.C., M.M., A.P.C.; Literature Search - N.C., A.P.C., E.N.; Writing - N.C., A.P.C., E.N.; Critical Reviews - N.C., A.P.C.

A**cknowledgements:** We thank to Dr. Nicola Vernassa for his technical support.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Albers FW, De Groot JC, Veldman JE, Huizing EH. Ultrastructure of the organ of Corti in experimental hydrops. Acta Otolaryngol 1998; 105: 281-91. [CrossRef]
2. Schuknecht HF. Pathology of the Ear. 2nd Ed. Philadelphia, USA: Lea and Febiger; 1993.
3. Tsuji K, Velazquez-Villasenor L, Rauch SD, Glynn RJ, Wall C, Merchant SN. Menière's disease. Ann Otol Rhinol Laryngol 2000; 109: 26-31. [CrossRef]
4. Adrion C, Fischer CS, Wagner J, Gurkov R, Mansmann U, Strupp M. Betahistine therapy in patients with Menière's disease: primary results of a long-term, multicenter, double-blind, randomized, placebo- controlled, dose-defining trial of efficacy and safety (BEMED trial). BMJ 2016; 352: h6816. [CrossRef]
5. Nauta JJ. Meta-analysis of clinical studies with betahistine in Menière's disease and vestibular vertigo. Eur Arch Otorhinolaryngol 2014; 271: 887-97. [CrossRef]
6. Patel M, Agarwal K, Arshad Q, Hariri M, Rea P, Seemungal BM, et al. Intratympanic methylprednisolone versus gentamicin in patients with unilateral Ménière's disease: A randomised, double-blind, comparative effectiveness trial. Lancet 2016; 388: 2753-62. [CrossRef]
7. A.S. Thirlwall, S. Kundu. Diuretics for Menière's disease or syndrome. Cochrane Database Syst Rev 2006; 19: CD003599.
8. Casani AP, Cerchiai N, Navari E, Dallan I, Piaggi P, Sellari-Franceschini S. Intratympanic gentamicin for Meniere's disease: short- and long-term follow-up of two regimens of treatment. Otolaryngol Head Neck Surg 2014; 150: 847-52. [CrossRef]
9. Casani AP, Piaggi P, Cerchiai N, Seccia V, Franceschini SS, Dallan I. Intratympanic treatment of intractable unilateral Meniere disease: gentamicin or dexamethasone? A randomized controlled trial. Otolaryngol Head Neck Surg 2012; 146: 430-7. [CrossRef]
10. Pullens B, van Benthem PP. Intratympanic gentamicin for Menière's disease or syndrome. Cochrane Database Syst Rev 2011; CD008234. [CrossRef]
11. Lopez-Escamez JA, Carey J, Chung WH, Goebel JA, Magnusson M, Mandalà M, et al. Diagnostic criteria for Menière's disease. J Vestib Res 2015; 25: 1-7. [CrossRef]
12. Cerchiai N, Navari E, Dallan I, Sellari-Franceschini S, Casani AP. Assessment of vestibulo-oculomotor reflex in Menière's disease: defining an instrumental profile. Otol Neurotol 2016; 37: 380-4. [CrossRef]
13. Hornibrook J. Tone Burst Electrocochleography for the Diagnosis of Clinically Certain Meniere's Disease. Front Neurosci 2017; 11: 301. [CrossRef]
14. McCaslin DL, Rivas A, Jacobson GP, Bennett ML. The dissociation of video head impulse test (vHIT) and bithermal caloric test results provide topological localization of vestibular system impairment in patients with "definite" Menière's disease. Am J Audiol 2015; 24: 1-10. [CrossRef]
15. Zhang S, Leng Y, Liu B, Shi H, Lu M, Kong W. Diagnostic Value of Vestibular Evoked Myogenic Potentials in Endolymphatic Hydrops: A Meta-Analysis. Sci Rep 2015; 5: 14951. [CrossRef]
16. Baloh RW, Honrubia V. Clinical neurophysiology of the vestibular system. Contemp Neurol Ser 1979; 18: 1-21.
17. Blödow A, Heinze M, Bloching MB, von Brevern M, Radtke A, Lempert T. Caloric stimulation and video-head impulse testing in Ménière's disease and vestibular migraine. Acta Otolaryngol 2014; 134: 1239-44. [CrossRef]
18. McMullen KP, Lin C, Harris MS, Adunka OF. Correlation of Objective Audiometric and Caloric Function in Ménière's Disease. Otolaryngol Head Neck Surg 2017; 156: 912-6. [CrossRef]
19. Committee on Hearing and Equilibrium. Guidelines for the diagnosis and evaluation of therapy in Menière's disease. Otolaryngol Head Neck Surg 1995; 113: 181-5. [CrossRef]
20. Agrawal Y, Minor LB. Menière's disease and other causes of episodic vertigo. Bronstein MA, editor. Oxford Textbook of Vertigo and Imbalance. Oxford: Oxford University Press; 2013. p. 241-50. [CrossRef]
21. McCall AA, Ishiyama GP, Lopez IA, Bhuta S, Vetter S, Ishiyama A. Histopathological and ultrastructural analysis of vestibular endorgans in Meniere's disease reveals basement membrane pathology. BMC Ear Nose Throat Disord 2009; 9; 4-17. [CrossRef]