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The role of endogenous Antisecretory Factor (AF) in the treatment of Ménière's Disease: A two-year follow-up study. Preliminary results

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ABSTRACT

Purpose: To evaluate the effects of increased endogenous Antisecretory Factor (AF) synthesis using specially processed cereals (SPC) in a sample of patients with defined unilateral Meniere's disease (MD), compared to the results of a treatment protocol of intravenous glycerol and dexamethasone.
Materials and methods: Twenty-six patients with unilateral MD were divided in 2 groups and treated with SPC and with intravenous glycerol and dexamethasone for 24 months. Audio-vestibular evaluation was performed before (T0) and every six months. The number of vertigo spells were evaluated before and after therapy and the Efficacy Index (EI) was calculated. Questionnaires for hearing loss, tinnitus and quality of life were administered.
Results: EI decreased in the SPC group after 18 (T18) (p = .0017) and 24 (T24) months of therapy (p = .0111). There was a significant reduction for tinnitus score in the SPC group at T24 (p = .0131). No significant differences were found between the two groups at T0 (p = .4723), while a significant difference was found at T24 (p = .0027). Quality of life showed a significant improvement in daily activities in the SPC group (p = .0033) compared to the infusion therapy group. No statistically significant changes in PTA thresholds were found in both groups between T0 and T24.
Conclusion: The preliminary results of our study show a significant reduction of vertigo spells and a positive effect on tinnitus severity and on quality of life in patients with unilateral MD treated with SPC and when compared to patients treated with intravenous glycerol and dexamethasone. No effects on hearing thresholds were noted in both groups.

1. Introduction

Meniere's disease (MD) is a clinical condition characterized by spontaneous vertigo episodes associated with fluctuating hearing loss, tinnitus and aural fullness in the affected ear [1]. The average age of onset is 40 to 50 years, and the incidence is about 17 to 500 per 100.000. Current evidence suggests that the pathophysiological mechanism underlying typical symptoms of MD is the distension of the membranous labyrinth caused by the presence of endolymphatic hydrops (EH) in the inner ear [2,3].

Histopathological findings suggest an overproduction and/or a decrease in the absorption of endolymph as possible causes of EH. However, EH alone cannot explain the pathophysiology of cochlear and vestibular symptoms; accumulating evidence suggests that the causes of MD symptoms are multifactorial and involve different pathogenic mechanisms [4–7].

Hereupon, among treatments proposed for MD, none has shown a reasonable and shared evidence of efficacy [8–12]. The first-line

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treatment commonly includes dietary modification such as restriction of salt, caffeine and alcohol intake; however, there is no evidence from randomized controlled trials that supports the effectiveness of dietary restriction in MD [13]. Several drugs have been proposed for MD, both for acute attacks (dimenhydrinate, benzodiazepines), and as a prophylactic therapy (betahistine, β-blockers, diuretics), although evidence of their efficacy is lacking [14,15].

Intratympanic gentamicin has been proposed for intractable cases, although controversy about dosage and method still exists [16].

Recently, numerous studies focused on the possibility that fluid and ion homeostasis in the inner ear may play a role in the pathogenesis of MD [17] with a possible role of genetic factors [18]. Based on this, some experiences have been developed on the possible action of the Antisecretory Factor (AF) in the treatment of MD [19–24]. AF is a 41 kd protein, produced mainly in pituitary gland in response to infection. It was originally isolated because of its ability to inhibit diarrhoea. Endogenous AF activity increases after exposure to bacterial toxins [25] and in combination with the immune system plays a role in the innate defence against the inflammatory and secretory components of diarrheal diseases [26].

It has been hypothesized that AF can act as a modulator of water and ions by regulating the homeostasis of chloride through the membranes interacting with the aquaporins [27]. Some immunohistochemical studies confirmed the presence of AF and flotillin-1 binding protein in the inner ear of rats and humans [19,28].

AF activity can also be increased by the intake of specially processed cereals (SPC) optimized to increase endogenous AF plasma levels [21]. Clinical studies have shown that intake of SPC can improve the clinical outcome not only in patients suffering from diarrhoeal diseases, but also in patients suffering from inflammatory bowel diseases [29], endocrine diarrhoea [30], and mastitis [26].

A 14–28 day period of SPC intake is necessary to obtain a significant AF plasma concentration, although an increased AF response is achieved after two to three days, when it comes to a second period of intake of SPC. Thus, there exists some sort of 'biological memory' for the human capability of AF synthesis, and the first period of intake of SPC seems to be responsible for the 'priming' of the secondary enhanced AF response [30].

In the last decade, the use of SPC-flakes has been proposed to increase endogenous AF synthesis to improve symptoms of MD with controversial results [20,22–24]. In a recent study, Scarpa et al. noted that, in a 12-month period, patients with unilateral MD treated with SPC showed a decrease in the number of vertigo attacks, a reduction in the discomfort produced by tinnitus and a better quality of life, compared to the patients treated with a pharmacological protocol including intravenous glycerol and dexamethasone [31].

The aim of this study is to evaluate the effects on hearing, tinnitus, dizziness and quality of life of increased endogenous AF synthesis using SPC administration over a 24-month period in a sample of patients with defined unilateral MD not responding to dietary restrictions and drug treatment, and compare the results to a treatment protocol of intravenous glycerol and dexamethasone.

2. Materials and methods

2.1. Patients

Twenty-six (8 males and 18 females) patients with a diagnosis of definite MD according to the Barany Society criteria [1], evaluated between January 2017 and January 2019, were enrolled in this multicentre prospective cohort study.

Inclusion criteria were age between 18 and 65 years, a clinical diagnosis of unilateral MD, no response to dietary restrictions (salt, caffeine and alcohol intake) and pharmacological treatment (betahistine, 48 mg/day).

Exclusion criteria were a clinical diagnosis of bilateral MD, ipsilateral or contralateral middle ear pathology, previous treatment with intratympanic steroids, contralateral SNHL, retro-cochlear pathology, previous ear surgery, previous intake of SPC-flakes.

2.2. Experimental treatment

The patients were divided into two groups. The first group (*SPC group*) included 13 patients (10 females and 3 males, mean age 51.8 ± 15.4) that were treated with SPC-flakes, Piam Farmaceutici S.p.A, Italy. Patients took cereals twice a day, at a dose 1 g/kg of body weight/day, in accordance with previous studies [20,23,24] and with the recommendation by the SPC manufacturer for 30 consecutive days each other month for twelve cycles. The second group (*IT - infusion therapy group*) included 13 patients (9 females and 4 males, mean age 53.76 ± 12.6) treated with infusion therapy consisting of 10% glycerol, 250 ml/day in 200 ml/h infusion rate and dexamethasone 8 mg/2 ml per day in single bolus and pantoprazole 40 mg per day, diluted in 100 ml of 0.9% sodium chloride. Patients in the IT group were treated each month for 3 consecutive days.

Total duration of treatment for both groups was 24 months.

2.3. Audio-vestibular evaluation

All patients underwent an anamnestic interview, full otolaryngology examination, an audio-vestibular test battery with pure tone audiometry (PTA), acoustic immittance test and vestibular bedside examination.

All patients were asked to self-compile a clinical report with the number of vertigo spells for the entire duration of the study.

Audio-vestibular examination was performed 6 months before starting therapy (T0), at 6 months (T6) at 12 months (T12), at 18 months (T18) and at 24 months of therapy (T24).

PTA was measured at frequencies of 125, 250, 500, 1000, 2000, 3000, 4000, and 8000 Hz using Piano Clinical Audiometer (Inventis, Padua, Italy); data from the frequencies 500, 1000, 2000 and 4000 Hz were used in the study.

Acoustic immittance measures were performed to evaluate the functional integrity of the eardrum and middle ear using tympanometry and acoustic stapedial reflex tests (AT 235 Tympanometer Interacoustics, Denmark).

The bedside vestibular examination was performed by video-goggles (GN Otometrics, Taastrup, Denmark).

Vertigo spells were elaborated based on the self-compiled clinical report calculating the Efficacy Index (EI) 18 and 24 months after beginning of therapy.

The EI after 18 months of therapy was calculated using the formula $[Y/X \times 100]$ where (Y) is the mean of the number of vertigo spells/month after 18 months of therapy and (X) is the mean of the number of vertigo spells/month for a 6 month-period before starting treatment (pre-treatment period).

The EI after 24 months of therapy was calculated using the formula $[Z/X \times 100]$ where (Z) is the mean of the number of vertigo spells/month during the last 6 months of therapy (after 24 months of therapy) and (X) is the mean of the number of vertigo spells/month for the pre-treatment period (6 months before therapy).

Based on the result obtained, the patients were divided into six classes according to the AAO-HNS criteria [35] (Table 1).

2.4. Self-assessment questionnaires

Self-assessment questionnaires regarding hearing loss (Hearing Handicap Inventory for Adults, HHIA [32]), tinnitus (Tinnitus Handicap Inventory, THI [33,34]), and quality of life (QoL) (Functionality Level Scale, FLS, AAO-HNS [35]) were administered at T0 and T24.

Table 1
Efficacy index. The numerical value is the ratio of the average number of vertigo spells during the pre-treatment period (6 months) divided by the average number of vertigo spells for the same number of months at the end of the reporting period.

Numerical value	Class
0	A
1–40	B
41–80	C
81–120	D
> 120	E
Secondary treatment initiated because disability from vertigo	F

2.5. Statistical analysis

MedCalc Statistical Software version 19.1.7 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org) was used to perform statistical analysis. The *t*-test was used to compare the numerical values within the two groups before and at different treatment timepoints.

3. Results

3.1. Hearing assessment

PTA thresholds in both groups are shown in Fig. 1.

In the SPC group, average PTA was 46.7 dB at T0 and 46.5 dB at T24 (p = .9913). In the IT group, the mean PTA was 51.4 dB both at T0 and T24 (p = .9954). No statistically significant changes were found in both groups, between T0 and T24. Furthermore, no statistically significant changes were found between the two groups at T0 (p = .6257) and at T24 (p = .6076).

3.2. Vertigo spells

The mean number of vertigo spells in both groups and the EI are shown for each patient in Table 2.

The EI after 18 months of therapy was 41.07 in the SPC group and 83.15 in the IT group (p = .0017). The EI after 24 months of therapy was 39.61 in the SPC group and 91.76 in the IT group (p = .0111).

When comparing EI score within groups, in the SPC group the EI decreased after 24 months compared with EI after 18 months of therapy although not significantly (p = 0,9336), while it increased in the IT group (p = 0,5482).

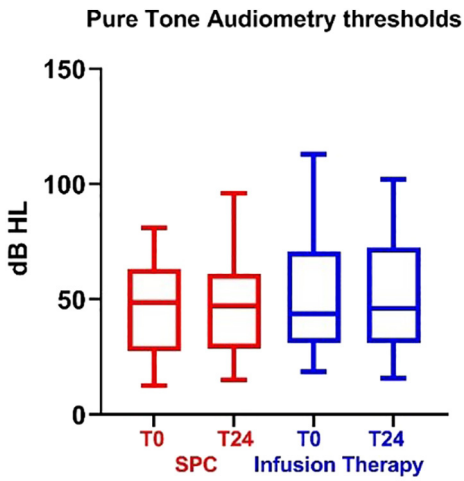

Fig. 1. Pure tone audiometry (PTA) thresholds in the specially processed cereals (SPC) group and in the infusion therapy (IT) group before and after 24 months of treatment.

When dividing patients into classes and comparing the two groups according to the AAO-HNS criteria after 18 and 24 months, in the SPC group three patients had a class improvement (23.07%), six had no class change (46.15%) and four had a class worsening (30.76%). All three patients (100%) who had a class improvement had an improvement of two classes. In the four patients who had a class worsening, three patients had only one class worsening (75%) and one patient worsened of two classes (25%).

In the IT group, one patient had a class improvement (7.69%), eighth had no class change (61.53%) and four had a class worsening (30.76%). The only patient who had a class improvement had an improvement of a single class. All four patients who had a class worsening had a worsening of a single class.

3.3. Questionnaires

Results of self-administered questionnaires for hearing (HHIA), tinnitus (THI) and quality of life (FLS) at T18 and T24 are shown in Figs. 2 and 3.

The mean HHIA score was 49.4 at T0 and 38.1 at T24 (p = .3323) in the SPC group and 57.4 at T0 and 61.8 at T24 (p = 0,6970) in the IT group. No statistically significant changes were seen in both groups between T0 and T24. Also, no significant differences were found between the two groups at T0 (p = .4859) and at T24 (p = .1085).

The mean THI score in the SPC group was 58 at T0 and 25.07 at T24, with a significant reduction at T24 (p = .0131). In the IT group, the mean THI score was 66.9 at T0 and 60.8 at T24 (p = .5826). No significant differences were found between the two groups at T0 (p = .4723), while a significant difference was found at T24 (p = .0027).

The mean FLS score in the SPC group was 4.6 at T0 and 3.2 at T24 with a statistically significant reduction (p = .0093); in the IT group, the mean FLS score was 4.6 at T0 and 4.8 at T24 (p = .7621). No statistically significant changes were seen in these groups between T0 and T24. Furthermore, no significant differences were found between the two groups at T0 (p = 1) while were found at T24 (p = .0033).

When comparing FLS questionnaire at T0 and T24 (Table 3), in the SPC group seven patients reported an improvement of their QoL (53.84%), five reported no change (38.46%), and one complained a deterioration in QoL (7.69%). In the IT group, two patients have noted an improvement of their QoL (15.38%), eight reported no changes (61.53%), and three reported a deterioration (23.07%). The treatment impact on QoL is summarized in Fig. 4.

4. Discussion

In this study, our therapeutic protocol has been evaluated for 24 months according to the AAO-NHS recommendations. In a previous study published by our group, an identical sample of patients was evaluated over a period of only 12 months [31]. A longer follow-up period has the undoubted advantage to evaluate if therapy remains effective and if results are stable over the time.

Regarding vertigo spells, EI in the SPC group significantly decreases already after 18 months; this result is confirmed even after 24 months of therapy. In our opinion, this result is particularly interesting since in the first study period, i.e. at 12 months, the efficacy on vertigo was limited, only showing an improvement trend, without reaching statistical significance. In the present study, the SPC group showed good results in terms of reduction of vertigo spells (Table 2) providing indications for the duration of therapy.

THI score was already significantly decreased in the SPC group after 12 months [31], showing a reduction of discomfort in these patients. This score confirms a sensible decline even after 24 months of therapy, as shown in Fig. 5. On the other side, no significant changes were found in the IT group. These results suggest that the severity and intrusiveness of tinnitus should not be considered as a steady state but susceptible to

Table 2
Mean of vertigo attacks before starting therapy, after 18 months and after 24 months of therapy calculating also efficacy index (EI) and class of belonging according to the AAO-HNS criteria.

Patient no.	X (6 months before T0)	Y (T18)	Z (T24)	Y/X × 100	Class	Z/X × 100	Class
1 SPC	2	1	0	50	C	0	A
2 SPC	1	1	2	100	D	200	E
3 SPC	3	1	1	33	B	33	B
4 SPC	6	2	1	33	B	17	B
5 SPC	3	0	0	0	A	0	A
6 SPC	2	0	1	0	A	50	C
7 SPC	3	0	0	0	A	0	A
8 SPC	3	2	0	66	C	0	A
9 SPC	4	1	2	25	B	50	C
10 SPC	2	1	1	50	C	50	C
11 SPC	5	2	1	40	B	20	B
12 SPC	3	3	1	100	D	33	B
13 SPC	8	3	5	37	B	62	C
1 IT	14	9	11	64	C	78	C
2 IT	9	8	9	89	D	100	D
3 IT	2	2	2	100	D	100	D
4 IT	3	1	0	33	B	0	A
5 IT	5	2	3	40	B	60	C
6 IT	14	13	15	93	D	107	D
7 IT	4	3	2	75	C	50	C
8 IT	7	9	11	129	E	157	E
9 IT	15	18	16	120	D	106	D
10 IT	6	5	9	83	D	150	E
11 IT	12	12	16	100	D	133	E
12 IT	20	16	18	80	C	90	D
13 IT	8	6	5	75	C	62	C

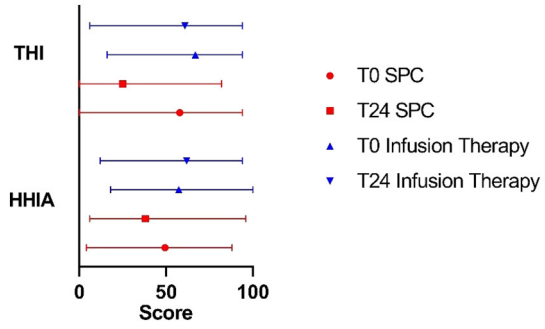

Fig. 2. Hearing Handicap Inventory for Adults (HHIA) and Tinnitus Handicap Inventory (THI) at T0 and T24 in both groups.

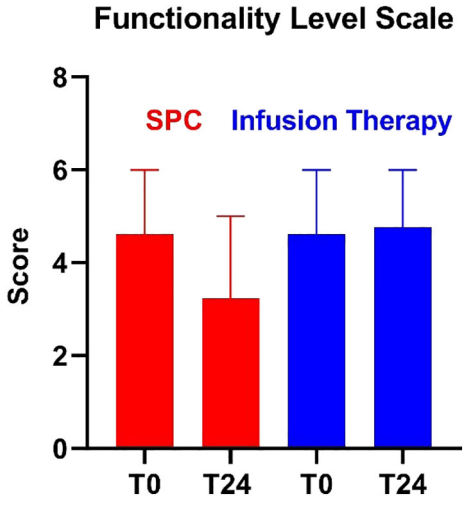

Fig. 3. Functionality Level Scale (FLS) at T0 and T24 in both groups.

fluctuate in severity during the course of disease. Likewise, this further improvement in the THI score in our longer follow-up could be an indirect consequence of the aforementioned effect on vertigo attacks. In fact, as vertigo improves, the annoyance of tinnitus is also reduced. On the other hand, the reduction of the mechanisms that generate EH positively affects both vertigo and tinnitus, the most disturbing symptoms for MD patients.

QoL also plays a central role in the management of MD patients. The FLS questionnaire showed an improvement in daily activities in patients in the SPC group compared to those in the IT group, with statistically significant overall scores. In our 24-month evaluation, this aspect

Table 3
Functionality Level Scale (FLS) at T0 and T24 for the specially processed cereals (SPC) group and infusion therapy (IT) group.

Patient no.	Functionality level scale T0	Functionality level scale T24
1 IT	5	5
2 IT	5	5
3 IT	1	3
4 IT	5	4
5 IT	5	5
6 IT	5	5
7 IT	5	5
8 IT	5	6
9 IT	6	6
10 IT	2	3
11 IT	6	6
12 IT	6	5
13 IT	4	4
1 SPC	5	1
2 SPC	2	3
3 SPC	6	3
4 SPC	6	3
5 SPC	3	3
6 SPC	5	4
7 SPC	5	5
8 SPC	4	3
9 SPC	5	1
10 SPC	5	2
11 SPC	5	5
12 SPC	4	4
13 SPC	5	5

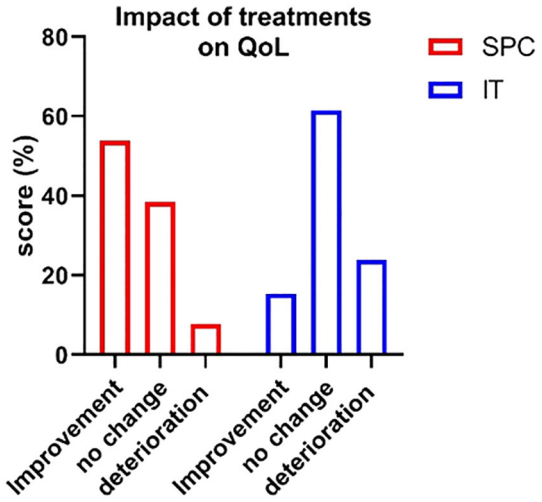

Fig. 4. Impact of treatment on Quality of Life at T24.

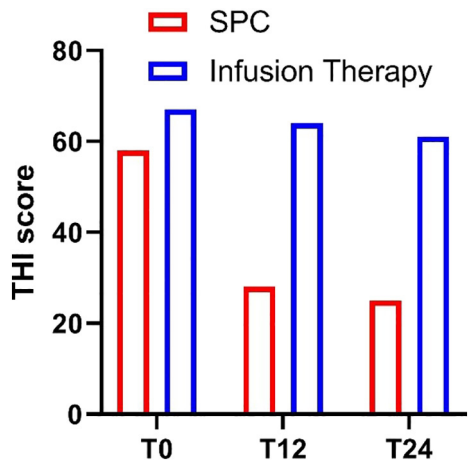

Fig. 5. Tinnitus Handicap Inventory (THI) trend at T0, T12 and T24.

became particularly significant, confirming the trend already showed in the previous 12-month evaluation [31]. We believe that is aspect is very important, because QoL can influence, as much as in a vicious circle, the appearance or the tolerability of the other MD symptoms. Our results are in accordance with previous studies [22,23] that reported an improvement of the functional level in a significant percentage of patients, as well as in randomized double-blind placebo-controlled trials [20,22].

Lastly, neither of the two groups achieved significant PTA improvements, as already documented in our 12-month evaluation [31] and as reported in other experiences in the literature [20,24]. Similarly, no subjective hearing modification was reported by patients in both groups at the HHIA questionnaire.

4.1. Study limitations

The present study has several limits. The main limitation is that we did not include a control group, as it was not possible for the study project to have a randomized double-blind controlled trial. Secondly, the small cohort of patients enrolled may have influenced the statistical power of our analysis. Last, the comparison treatment group was treated with a therapy regimen that is not widely accepted or employed; therefore, the comparison results should be interpreted with caution. More research is needed to confirm the effectiveness of SPC in MD patients.

5. Conclusion

Our preliminary results suggest that the use SPC in MD should be considered, as the outcomes in terms of number of vertigo spells, tinnitus severity and QoL in our patients were stable or improved. As expected, no effects on hearing thresholds were noted in both groups. Our results, although biased by several limitations and preliminary, are encouraging for the use of AF to decrease the frequency and intensity of vertigo attacks in patients affected by unilateral MD. However, larger prospective studies with better control arms are needed to validate these preliminary results.

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Research involving human participants and/or animals

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee of the University of Catanzaro “Magna Graecia” and the University of Salerno and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

CRediT authorship contribution statement

Pasquale Viola: Conceptualization, writing original draft preparation.
Davide Pisani: Methodology and data curation.
Alfonso Scarpa: Conceptualization, writing reviewing and editing.
Claudia Cassandro: Formal analysis and visualization.
Carla Laria: Software and visualization.
Teodoro Aragona: Resources and supervision.
Marco Ciriolo: Methodology and visualization.
Lucrezia Spadera: Software and validation.
Massimo Ralli: Writing reviewing and editing.
Michele Cavaliere: Formal analysis and visualization.
Maurizio Iengo: supervision and resources.
Giuseppe Chiarella: Methodology, resources and supervision.

Declaration of competing interest

The authors declare that they have no conflict of interest.

References

[1] Lopez-Escamez JA, Carey J, Chung W, et al. Diagnostic criteria for Menière’s disease. J Vestib Res 2015;1:1–7.
[2] Naganawa S, Nakashima T. Visualization of endolymphatic hydrops with MR imaging in patients with Meniere’s disease and related pathologies: current status of its methods and clinical significance. Jpn J Radiol 2014;32(4):191–204.
[3] Salt AN, Plontke SK. Endolymphatic hydrops: pathophysiology and experimental models. Otolaryngol Clin North Am 2010;43(5):971–83.
[4] Paparella MM. Methods of diagnosis and treatment of Meniere’s disease. Acta Otolaryngol Suppl 1991;85:108–19.
[5] Ralli M, Greco A, Altissimi G, et al. Vestibular schwannoma and ipsilateral endolymphatic hydrops: an unusual association. Int Tinnitus J 2017;21(2):128–32.
[6] Russo FY, Ralli M, De Seta D, et al. Autoimmune vertigo: an update on vestibular disorders associated with autoimmune mechanisms. Immunol Res 2018;66(6):675–85.
[7] Ralli M, D’Aguanno V, Di Stadio A, et al. Audiovestibular symptoms in systemic autoimmune diseases. J Immunol Res 2018:5798103.
[8] Scarpa A, Cassandro C, De Luca P, et al. Therapeutic role of intravenous glycerol for Meniere’s disease. Preliminary results. Am J Otolaryngol 2020;41(4):102498. https://doi.org/10.1016/j.amjoto.2020.102498.

[9] Crowson MG, Patki A, Tucci DL. A systematic review of diuretics in the medical management of Meniere's disease. Otolaryngol Head Neck Surg 2016;154(5):824–34.
[10] Phillips JS, Westerberg B. Intratympanic steroids for Meniere's disease or syndrome. Cochrane Database Syst Rev 2011;7:CD008514. https://doi.org/10.1002/14651858.CD008514.
[11] Pullens B, van Benthem PP. Intratympanic gentamicin for Meniere's disease or syndrome. Cochrane Database Syst Rev 2011;3:CD008234.
[12] Clyde JW, et al. Current management practices in Meniere's disease. Otol Neurotol 2017;38(6):e159–67.
[13] Hussain K, Murdin L, Schilder AG. Restriction of salt, caffeine and alcohol intake for the treatment of Meniere's disease or syndrome. Cochrane Database Syst Rev 2018;12:CD012173.
[14] Nakashima T, et al. Meniere's disease. Nat Rev Dis Primers 2016;2:16028.
[15] Scarpa A, Ralli M, Cassandro C, et al. Low-dose intratympanic gentamicin administration for unilateral Meniere's disease using a method based on clinical symptomatology: preliminary results. Am J Otolaryngol 2019 Nov - Dec;40(6):102289.
[16] Scarpa A, Ralli M, De Luca P, et al. Therapeutic strategies in the treatment of Meniere's disease: the Italian experience. Eur Arch Otorhinolaryngol 2020 Jan 7. https://doi.org/10.1007/s00405-019-05774-1.
[17] Teggi R, Carpini SD, Zagato L. Endolymphatic hydrops and ionic transporters: genetic and biohumoral aspects. J Neurol 2019;266(Suppl. 1):47–51. Sep.
[18] Chiarella G, Petrolo C, Cassandro E. The genetics of Ménière's disease. Appl Clin Genet 2015;8:9–17. Jan 8.
[19] Hanner P, Jennische E, Lange S. Antisecretory factor: a clinical innovation in Ménière's disease? Acta Otolaryngol 2003;123(6):779–80. Aug.
[20] Hanner P, Rask-Andersen H, Lange S, Jennische E. Antisecretory factor-inducing therapy improves the clinical outcome in patients with Ménière's disease. Acta Otolaryngol 2010;130(2):223–7. Feb.
[21] Ulgheri C, Paganini B, Rossi F. Antisecretory factor as a potential health-promoting molecule in man and animals. Nutr Res Rev 2010;23(2):300–13. Dec.
[22] Leong SC, Narayan S, Lesser TH. Antisecretory factor-inducing therapy improves patient-reported functional levels in Meniere's disease. Ann Otol Rhinol Laryngol 2013;122(10):619–24. Oct.
[23] Ingvardsen CJ, Klokker M. Antisecretory therapy with no improvement in functional level in Ménière's disease. Acta Otolaryngol 2016;136(3):232–5.
[24] Hanner P, Jennische E, Lange S, Lönnroth I, Wahlström B. Increased antisecretory factor reduces vertigo in patients with Ménière's disease: a pilot study. Hear Res 2004;190(1–2):31–6. Apr.
[25] Gibson WP, Arenberg IK. Pathophysiologic theories in the etiology of Meniere's disease. Otolaryngol Clin North Am 1997;30(6):961–7. Dec. [Review].
[26] Laurenius A, Wängberg B, Lange S, Jennische E, Lundgren BK, Bosaeus I. Antisecretory factor counteracts secretory diarrhoea of endocrine origin. Clin Nutr 2003;22:549–52.
[27] Johansson E, Lange S, Lönnroth I. Identification of an active site in the antisecretory factor protein. Gut 1997;41:642645.
[28] Johansson E, Jonson I, Bosaeus M, Jennische E. Identification of flotillin-1 as an interacting protein for antisecretory factor. Regul Pept 2008;146:303–9.
[29] Johansson E, Lonnroth I, Lange S, Jonson I, Jennische E, Lonnroth C. Molecular cloning and expression of a pituitary gland protein modulating intestinal fluid secretion. J Biol Chem 1995;270(35):20615–20.
[30] Bjorck S, Bosaeus I, Ek E, Jennische E, Lonnroth I, Johansson E, et al. Food induced stimulation of the antisecretory factor can improve symptoms in human inflammatory bowel disease: a study of a concept. Gut 2000;46(6):824–9.
[31] Scarpa A, Ralli M, Viola P, et al. Food-induced stimulation of the antisecretory factor to improve symptoms in Meniere's disease: our results. Eur Arch Otorhinolaryngol 2020;277(1):77–83. Jan.
[32] Newman CW, Weinstein BE, Jacobson GP, Hug GA. The Hearing Handicap Inventory for adults: psychometric adequacy and audiometric correlates. Ear Hear 1990;11(6):430–3.
[33] Passi S, Ralli G, Capparelli E, Mammone A, Scacciatelli D, Cianfrone G. The THI questionnaire: psychometric datafor reliability and validity of the Italian version. Int Tinnitus J 2008;14(1):26–33.
[34] Moschen R, Fioretti A, Eibenstein A, et al. Validation of the Chronic Tinnitus Acceptance Questionnaire (CTAQ-I): the Italian version. Acta Otorhinolaryngol Ital 2019;39(2):107–16. Apr.
[35] Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Meniere''s disease American Academy of Otolaryngology-Head and Neck Foundation. Inc Otolaryngol Head Neck Surg 1995;113(3):181–5.