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OTOLOGY

Therapeutic strategies in the treatment of Menière's disease: the Italian experience

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Abstract

Purpose Ménière's disease (MD) is an inner ear disorder of unknown etiology, whose pathological substrate is the endolymphatic hydrops. Different treatments have been proposed; however, evidence of their effectiveness is lacking. The aim of this study was to evaluate by a questionnaire which medical and surgical treatments are used in Italy for the treatment of MD and to compare them with those proposed in other countries.

Methods An electronic questionnaire of 40 questions was formulated and sent to Italian otolaryngologist (ENT) divided into two groups: Group 1 ("generalists" 60.8%) and Group 2 ("neurotologist- NO" 39.2%).

Results One hundred and twenty five ENT replied. Treatment of the acute phase, apart from symptomatics, was based on diuretics that are prescribed by 83.5% of respondents, steroids, prescribed by 66.7%, and vasodilators, prescribed by 22%. In the intercritical phase, 87.2% of respondents recommended low-salt diet, 78.4% of respondents prescribed betahistine, and 52.8% diuretics. Statistical analysis did not show correlation neither with the declared specialization nor with the number of patients treated. In case of failure of medical treatment, IT gentamicin was suggested by 48.8% of the respondents and IT steroids by 40.8%. Statistical analysis showed that generalists prefer IT steroids and NO IT gentamicin (p 0.019). In case of failure of both medical treatment and IT treatment, vestibular neurectomy was indicated by 58.4% of the respondents, 6.4% indicated endolymphatic sac surgery, and 2.4% surgical labyrinthectomy.

Conclusion In Italy, the treatment of MD stand on a gradual approach that starts from the dietary-behavioral changes and a pharmacological therapy based on betahistine. In refractory cases, IT treatment initially with steroids and, therefore, with gentamicin allows the control in vertigo in the majority of cases. In case of failure of IT treatment, VNS is the surgery of choice.

Keywords Menière · Questionnaire · Medical therapy · Surgery

Introduction

Ménière's disease (MD) is an inner ear disorder of unknown etiology, whose pathological substrate is the endolymphatic hydrops [1]. In United Kingdom based on a sample of 500,000 people, Tyrrel et al. [2] reported a prevalence of 0.27%, while in the United States, Harris and Alexander [3] reported a prevalence of 0.19% in 60 million records. In Italy, Celestino and Ralli [4] reported an incidence of 8 new cases annually/10^5 and a prevalence of about 0.4% of the population.

The onset of the disease is typically in adulthood with a peak of incidence in the 40–60 age range. It is more common among Caucasians and women [5, 6]. Bilateral disease increases with age and duration of MD. It has been reported that in 11% of cases, the disease is bilateral at presentation [7], while patients with unilateral disease progress to

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bilateral MD in up to 35% at 10 years and 47% at 20 year follow-up [8].

In 2015, the diagnostic criteria for Menière's disease have been published after a consensus between 5 neurotological societies [9]. The main differences between the actual and the 1995 American Academy of Otolaryngology Head Neck Surgery (AAO-HNS) criteria (1) are: (1) the presence of only two categories (definite and probable MD); (2) the need to have a fluctuating hearing loss on low and medium frequencies documented by audiometric testing only in the definite MD; and (3) a time range defined for the duration of the dizziness [10].

Although there is today a consensus on the diagnostic criteria, there is not a consensus on the treatment of the disease. Several drugs have been proposed for the treatment both the acute phase, and as prophylactic treatment, however, evidence of efficacy of medical treatment is lacking [11]. Recently, during the last IFOS Congress in Paris in June 2017, an international consensus joining six experts of MD from different continents assessed the scientific literature and published a proposal on treatment of MD [12]. Another approach to evaluate the current management of MD is based on surveys. In UK, in 2005, a survey evaluated the treatment of MD among otolaryngology consultants [13], while more recently, in USA, Clyde et al. [14] questioned the members of the AAO-HNS. The aim of the present study was to evaluate by an internet-based questionnaire which medical and surgical treatments are used in Italy for the treatment of MD and to compare them with those proposed in other countries.

Materials and methods

The study was conducted at the unit of Otorhinolaryngology of the University of Bari, Italy. An electronic questionnaire of 40 questions (Annex 1) was formulated and sent via e-mail to the mailing list of the "Associazione Otorinolaringoiatri Ospedalieri Italiani—AOOI" that includes otolaryngologists working in Hospital and outpatient settings.

The questionnaire was divided into three sections: a preliminary section in which we asked the specialization and the number of patients with MD treated during the year, one section focused on the medical therapy and the last focused on therapeutic options envisaged in non-responders patients. To analyze the results, the otolaryngologist was divided into two groups according to their area of expertise: in Group 1 (defined by now "generalists"), we have grouped generalists, otolaryngologist based in outpatient departments, rhinologist and head and neck surgeons; in Group 2 (defined by now "neurotologist—NO"), we have included those doctors, whose main expertise was in the area of middle and inner ear surgery, audiology, and vestibology. Each group was then further subdivided according to the number of patients treated annually considering a cutoff of 15 patients per year.

The variables were analyzed using the Chi-square test with a p value of < 0.05. In case a statistically significant result was found, the data were re-analyzed considering the area of expertise and the number of patients treated. The Chi-square test is an approximate method valid when the frequencies are degrees; in order for it to be valid, none of the cells must have an expected frequency < 1 and at most 20% of the cells must have an expected frequency < 5. If one or both conditions occurred, we used the Fisher's exact test, ensuring better accuracy.

Results

The questionnaire was sent by email to 545 AOOI doctors and we received 125 replies (23%). The generalists represented 60.8% of the sample (76 respondents out of 125), of whom 76.3% reported to treat < 15 patients per year and 23.7% > 15 patients per year; the otologists represented 39.2% of the sample (49 respondents out of 125), of whom 42.8% reported to treat < 15 patients per year and 57.2% > 15 patients per year (Fig. 1).

Treatment of the acute phase

83.5% of respondents used diuretics in the acute phase, 66.7% steroids, and 22% vasodilators. Mannitol was the most commonly described diuretic (36%), followed by glycerol (25.2%), acetazolamide (16.2%), and hydrochlorothiazide (14.4%). Statistical analysis did not show a correlation neither with the declared specialization nor with the number of patients treated.

Treatment of the intercritical phase

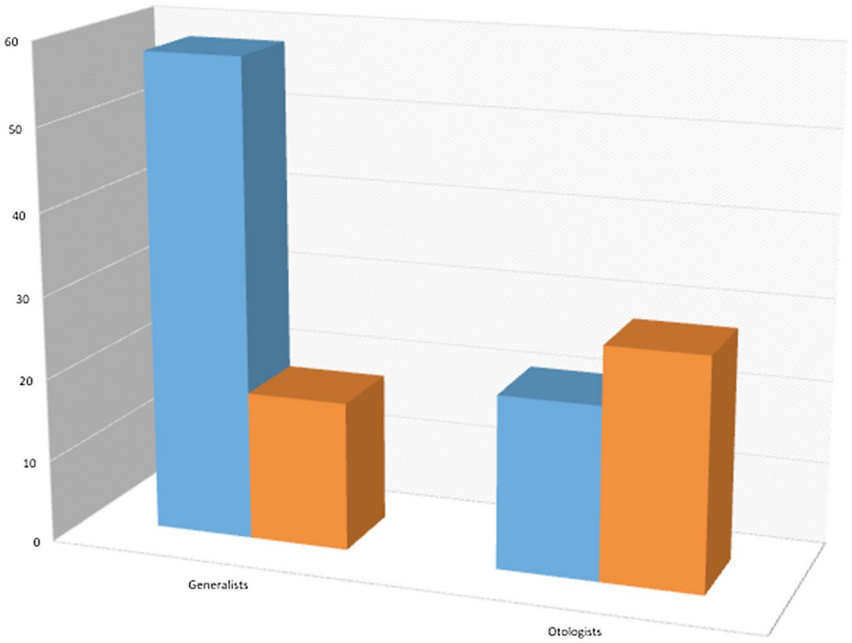
68% of the sample treat the MD patient in case of at least monthly crisis, while 32% of the sample in case of bimonthly crisis. Statistical analysis did not show a correlation with the area of specialization and the number of patients treated.

Regarding duration of treatment, 56% of respondents prescribe medical therapy for < 3 months, 31.2% for 3–6 months, and 11.2% for more than 6 months. Statistical analysis did not show a correlation neither with the declared specialization nor with the number of patients treated.

Diet

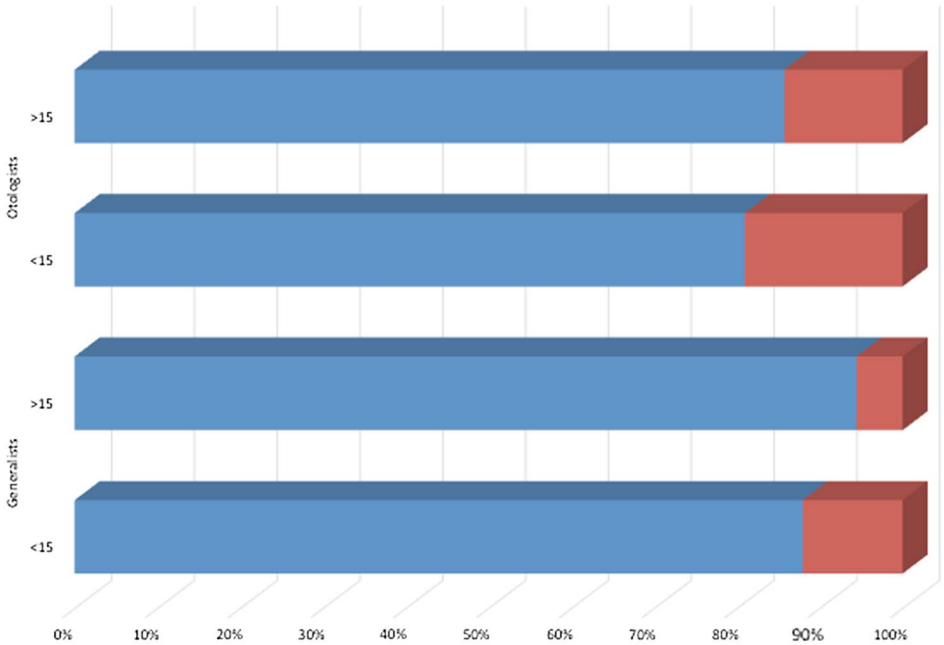
87.2% of respondents recommended low-salt diet. The statistical analysis did not show significant differences neither considering the main area of specialization nor considering the number of patients treated annually (Fig. 2).

Fig. 1 Demographic data



	Generalists	Otologists
<15	58	21
>15	18	28

Fig. 2 Low-salt diet prescription by generalists and otologists



	Generalists		Otologists	
	<15	>15	<15	>15
Yes	40,80%	13,60%	13,60%	19,20%
No	5,60%	0,80%	3,20%	3,20%

Diuretics

52.8% of respondents prescribed diuretic (59% of the generalists and 43% of NO). Acetazolamide was the most commonly prescribed drug (32.8%), followed by hydrochlorothiazide (27.1%) and the combination amiloride–hydrochlorothiazide (20%). Statistical analysis did not show a correlation neither with the declared specialization nor with the number of patients treated.

Betahistine

78.4% of respondents prescribed betahistine in the intercritical phase, the most prescribed dosage was 48 mg/day (68.37%) followed by 32 mg/day (22.45%). 82.9% of generalists prescribed betahistine (81% of those treating < 15 patients a year and 88.89% of those treating > 15 patients a year) versus 71.4% of neurotologist (66.67% of the treated patients < 15 patients annually and 75% of those treated > 15 patients a year). Statistical analysis did not show correlation neither with the declared specialization nor with the number of patients treated.

Calcium antagonists and vestibular suppressants

20% of the sample prescribe flunarizine in intercritical phase. Statistical analysis showed that NO prescribes it more frequently than the generalists (p value = 0.017); considering only specialists treating > 15 patients a year, there was no difference between NO and generalists (p value = 0.064). The differences found were, therefore, attributable to the number of patients treated per year rather than to the main working environment.

Cinnarizine was prescribed by 21.6% of the sample. NO prescribed it more frequently than generalists 86.8% (p value = 0.004). Considering only the doctors who treat > 15 patients a year with Ménière, the difference remained significant (p value = 0.038).

25.6% recommend the association cinnarizine/dimenhydrinate. Statistical analysis did not show a difference according to the working context and the number of patients treated (p value = 0.541).

An association between different drugs was prescribed by 19.4% of the sample. Statistical analysis did not show a difference according to the working context and the number of patients treated (p value = 0.541).

Intratympanic treatment

In case of failure of medical therapy, the first treatment is intratympanic (IT) injections. IT gentamicin is suggested by 48.8% of the respondents and IT steroids by 40.8%. Generalists prescribe steroids more frequently than gentamicin (48.68% versus 40.8%), while NO prescribe gentamicin more frequently then steroids (61% versus 28.6%). Statistical analysis showed a significant difference between the two groups (p = 0.019). This difference was no more significant in those treating more than 15 patients per year (p value = 0.375); in fact, both NO and generalists preferred gentamicin (Fig. 3).

In case of IT steroid use, 66.6% of the responders used Dexamethasone 4 mg/ml, 18.2% betamethasone 4 mg/ml, and the remaining 15.2% methylprednisolone.

In case of IT gentamicin, 46.7% of the responders used gentamicin 26.7 mg/ml, 43.3% used a higher concentration (40–80 mg/ml), and the remaining 10% used a lower concentration (20 mg/ml).

Surgery and other treatments

In case of failure of both medical treatment and IT treatment, vestibular neurectomy was indicated by 58.4% of the respondents, 6.4% indicated endolymphatic sac surgery, and 2.4% surgical labyrinthectomy. 29.6% of the respondents do not use invasive surgical treatments, while Meniette was prescribed by 2.63% of the generalists and by 4.08% of otologists. It should be noted that 22.45% of the NO and 34.2% of generalists do not recommend surgical treatment (Fig. 4). Statistical analysis did not show correlation neither with the declared specialization nor with the number of patients treated.

Treatment protocol

In case of failure of the medical treatment, most common protocol was: IT steroids followed by IT gentamicin and vestibular neurectomy in 32% of cases, IT gentamicin followed by vestibular neurectomy in 16% of cases, and only IT gentamicin in 14.4% of cases, IT steroids followed by IT gentamicin in 12.8% of cases.

Discussion

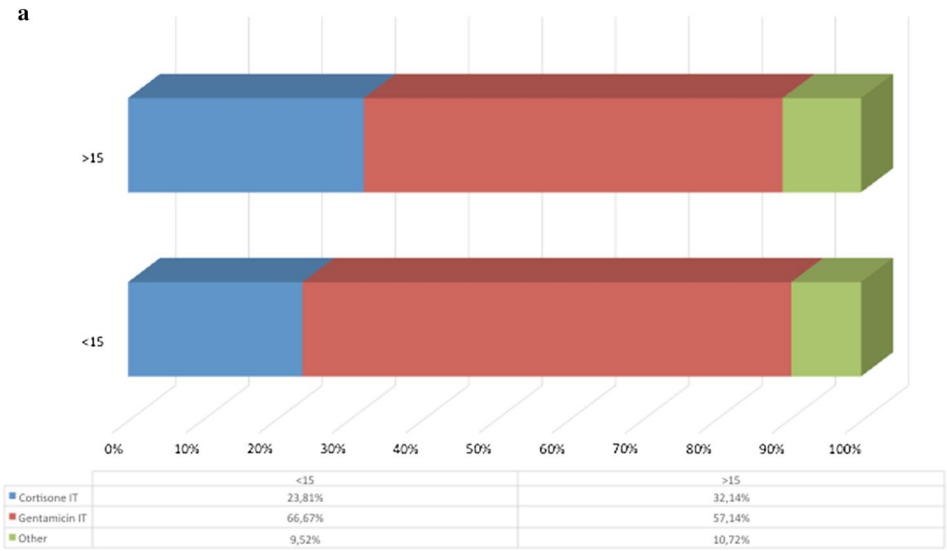
Treatment of the acute phase

Treatment of acute phase of MD is aimed at the reduction of neuronal asymmetry in neuronal input to the brainstem. Centrally acting drugs such as antihistamines with anticholinergic effects, benzodiazepines, and dopamine antagonists are all used for their symptomatic effect [11]. In the questionnaire, we asked if other drugs are used in the acute phase of MD and 83.7% of the respondents indicated diuretics and 66.7% steroids.

Among diuretics hyperosmotic solution, such as mannitol and glycerol were the most frequently used drugs. In the UK [13] and USA [14] surveys, the treatment of the acute phase was not evaluated.

Hyperosmotic solutions, apart from their use as a diagnostic test [15], have been proposed to treat fluctuating hearing loss in MD patients more than 30 years ago [16], although more than 80% of Italian ENT suggest it in the acute phase its use remains empirical.

Two-third of the respondents use systemic steroids; however, no data are present in the literature on the use of systemic steroids in the acute phase of MD. In USA, prednisone



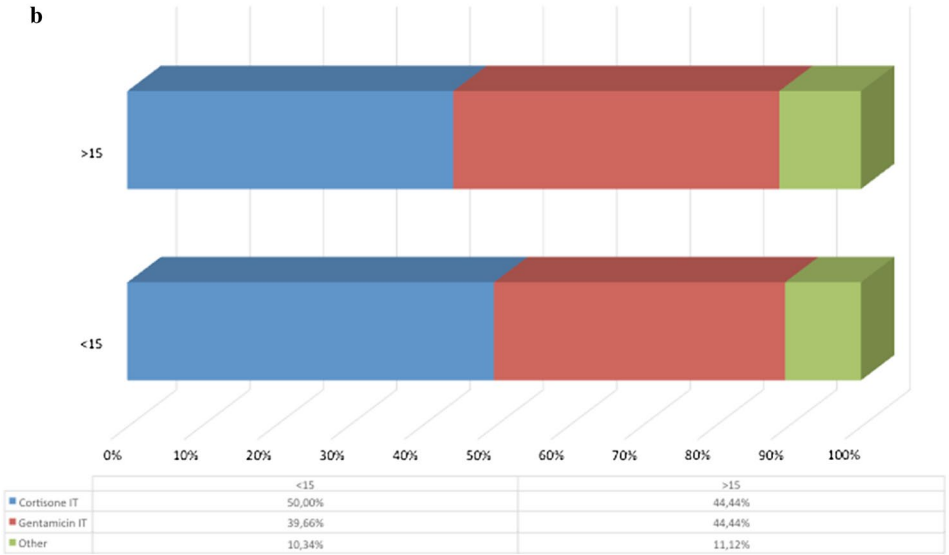


Fig. 3 Treatment of first choice in case of failure of medical therapy by neurotologists (**a**) and generalists (**b**)

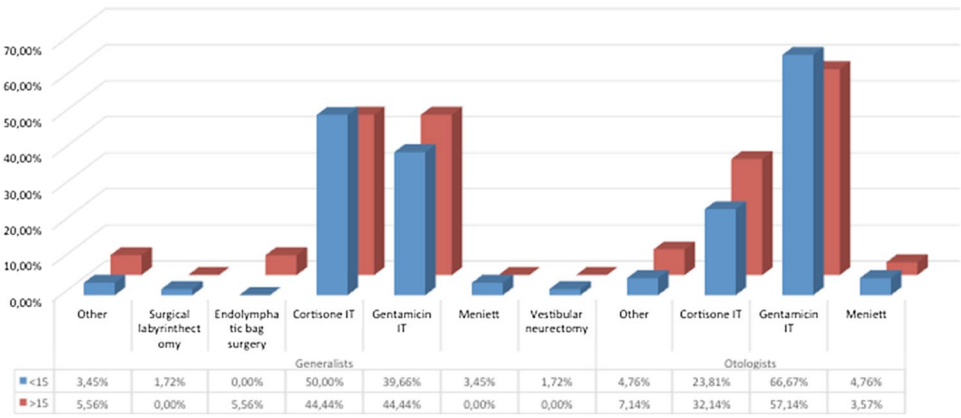


Fig. 4 Treatment of first choice in case of failure of medical therapy

was the immunosuppressant of choice, although 75% of the respondents use it "never" or "sometimes" and it is not clear if they use it in the acute phase or as a prophylactic drug [14].

Treatment of the intercritical phase

First-line treatment of MD includes diet and lifestyle changes. In particular, well sleeping, research for obstructive sleep apnea syndrome, decreasing stress, avoidance of caffeine, alcohol, and tobacco have been recently recommended by an international consensus paper [12]. Although the level of evidence is not high, the majority of otolaryngologist in Italy, USA, and UK think that salt restriction is the mainstay of MD treatment [13, 14]. As in the USA study, there was no difference between generalists and NO in their survey responses. Despite the doubts about their efficacy, dietary-behavioral changes are still today the basis of the therapy of MD patients in the intercritical phase.

Diuretics

In 2016, a systematic review of the literature identified multiple low evidence-level studies reporting that oral diuretic reduced the number of vertigo episode frequency in MD [17]. A more recent meta-analysis [18] based on three systematic reviews including 19 studies concluded that it was not clear whether diuretics were effective as medical treatment of MD.

In the present study, 52% of the respondents prescribed diuretics independently from their specialization. This percentage is lower number compared to the USA and UK studies, where diuretics were prescribed in up to 90% of cases. To date, although diuretics are recommended by an expert consensus [12], no clear evidence is found in the literature.

Betahistine

Betahistine is very popular in Europe and Australia and has been made available in the United States since 2010. Approximately 94% of the otolaryngologists in the United Kingdom prescribe betahistine to their MD patients [13], while in the USA [14], 56% otologists versus 16% of generalists recommend its use. In the present survey, 78.4% of respondents recommended betahistine at a dosage of 48 mg/day.

The efficacy of betahistine has been recently questioned in a large double blind, randomized, placebo controlled study [19]. Although high-level evidence is lacking, the use of this drug is recommended by an international consensus [12]. In addition, Casani et al. [20] have recently used the Delphi Consensus method to evaluate the use of betahistine in MD surveying 80 European experts. 87% of the experts recommended the use of betahistine in the intercritical phase with a preferred dosage of 32–48 mg/day.

Calcium antagonists

The use of calcium antagonists, alone or in association with other drugs, was recommended by 20% of respondents. The literature is scarce regarding the effects of these drugs. Teggi et al. have proposed the association between cinnarizine and betahistine both in MD patients with and without migraine [21]. Albera et al. compared the effect of flunarizine versus betahistine in a double-blind multicentre randomized study [22] and demonstrated that betahistine was more effective. Similar results were reported by Fraysse et al. [23]. The association between cinnarizine and dimenhydrinate has also been found to be superior to 12 mg/day of betahistine in a double-blind study [24].

Intratympanic treatment

Steroid injection

The use of intratympanic steroids in MD has been first proposed by Itoh and Sakata [25]. Compared to systemic steroid administration, the IT route results in higher perylimph concentration and a lower risk of side effects [26]. The effectiveness of IT steroids in vertigo control has been reported between 15 and 91% of the cases [26]. Reasons for this variability are the wide range of drugs, concentration, and protocol used; in addition, according to the AAO-HNS criteria [1], the need for further treatment is considered as a drug failure, and therefore, since patients treated with IT steroids needs repeated injections, this could be another reason for the large range in IT steroids efficacy.

In the United States [14], IT steroid injection are recommended by half of the otologists against a 10% of the generalists, while in the present study, it emerges that generalists recommend IT steroids more than neurotologist. Dexamethasone is the most commonly used drug both in USA [14] and Italy; however, recent evidence suggest that methylprednisolone may reach higher concentration in the perylimph compared to dexamethasone and is available at higher concentrations [26].

Gentamicin injection

Since its first use in 1977 [27] several studies have shown the safety and the effectiveness of IT gentamicin in the treatment of vertigo [28]. While IT steroids maintain the vestibular

function, IT gentamicin is an ablative procedure that has been shown to obtain high rates of vertigo control with minimal risk of hearing deterioration [28].

In USA [14], 87.7% of the otologists used IT Gentamicin against 24.8% of the generalists. In addition, in the present study, 61% of NO recommended IT gentamicin versus 40.8% of generalists. Almost 60% of the respondents suggest a low concentration of gentamicin between 20 and 26.7 mg/ml to optimize the effect on vertigo and reduce the risk of hearing loss [29]. Chia et al. have recently reported that the titration of gentamicin until the point of onset of ablative symptoms is the recommended method of treatment, even if many authors use the fixed-dose method [30].

Surgery

Surgical approaches in MD include conservative and ablative procedures. Endolymphatic sac (ES) surgery is a vestibular function sparing procedure that is still the first surgical options both in UK [13] and USA [14]. More than 50% of UK consultants and more than 85% US, otolaryngologists recommend ES surgery, although its use remain controversial [31]. A meta-analysis [9] has shown that endolymphatic sac surgery is effecting in relieving vertigo in 70–80% of patients, that is, similar to natural history of the disease at long-term follow-up [19].

Vestibular nerve section is a vestibular ablating procedure that has been shown to obtain higher control of vertigo and better results compared to gentamicin [27]. Since it is an invasive procedure with higher morbidity compared to IT gentamicin, it is indicated after the failure of IT and conservative procedures [12]. Although in USA [13] and UK [14] is rarely recommended, in Italy is the surgical procedure of choice, since it is recommended by 58.4% of respondents. It is interesting to note that very few otolaryngologists recommend labyrinthectomy and between 1/4 and 1/3 of them do not recommend surgical procedures.

Finally, the majority of the respondents in case of failure of medical treatment proposed the use of IT steroids, followed by IT gentamicin and finally VNS. This algorithm is similar to the expert algorithm proposed by Nevoux et al. [12], where after the first-line treatment (lifestyle counselling, low-salt diet, and medical treatment), the second line treatment is IT injections and third-line treatment is surgery.

In conclusion, in Italy, the treatment of MD stand on a gradual approach that starts from the dietary-behavioral changes and a basic pharmacological therapy based on betahistine, in refractory cases IT treatment initially with steroids and, therefore, with gentamicin allows the control in vertigo in the majority of cases. In case of failure of IT treatment, VNS is the surgery of choice.

The management of MD patients remains an unsolved problem for both generalists and otologists. The different and sometimes conflicting opinions that are highlighted in literature and, in particular, in surveys probably derive from the heterogeneity of MD patients.

Compliance of ethical standards

Conflict of interest No conflict of interests of any of the authors.

Human and animal rights statement This article does not contain any studies with human participants performed by any of the authors.

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