

Menière's disease and Gentamicin: preliminary results using the minimum effective dose and integrated therapy

Malattia di Menière e gentamicina: risultati preliminari con l'impiego della dose minima efficace e la terapia integrata

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Parole chiave

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Summary

Treatment of Menière's disease is aimed at restoring a normal quality of life and preserving residual hearing, in view of the increasing frequency with which the contralateral ear is affected. Conventional medical treatment (diuretics + vasoactive drugs) leads to cure in a large percentage of patients (75-95%). In intractable cases, transtympanic (intratympanic) aminoglycoside therapy, associated with various techniques, is becoming widespread as an alternative to surgery. Progressive reduction of the dose introduced into the middle ear did not prevent the onset of anacusis in several patients; the variable, unpredictable permeability of the round window membrane, the object of fundamental studies in the past, explains this complication. The Author has used gentamicin transtympanically in Menierians since 1978, and has treated a total of 105 patients. He first prescribed transtympanic gentamicin therapy that did not follow, but was integrated with conventional medical treatment in 22 intractable Menierians, by instilling the minimum effective dose, to reduce the risk of hearing impairment. Preliminary results, related to stage of disease, may be summarised as follows: improvement in the quality of life, as evaluated by the American Academy of Ophthalmology & Otolaryngology Committee on Hearing and Equilibrium questionnaire (14 patients – 63.63% – at point 1 and 8 – 36.36% – at point 2); disappearance of vertigo in 15 patients (68.18%); a minor vertigo attack in 3 and two minor attacks in 3 others not affecting quality of life; persistence of occasional unsteadiness in one patient. Hearing remained unchanged in 15 patients, improved slightly in 3 cases and worsened slightly in 2; decreased sensitivity to high tones was observed in 2 patients at the first insertion of gentamicin. According to the Author, employing integrated therapy and using the minimum effective dose of gentamicin, the risk of damage to the cochlear structures may be reduced, although not excluded, while restoring a good quality of life, even when repeat instillation is necessary.

Riassunto

La terapia della malattia di Menière si deve prefiggere un duplice scopo: il ripristino di una normale qualità della vita e la conservazione dell'udito residuo data la frequenza sempre maggiore con cui viene interessato l'orecchio controlaterale. Le cure mediche convenzionali (diuretici + "vasoattivi") permettono una percentuale elevata di guarigione (75-95%). Nei casi resistenti, in alternativa ad ogni soluzione chirurgica, si sta imponendo la terapia con aminoglicosidi per via transtimpanica (intratimpanica), attuata con diversa tecnica. La riduzione progressiva della dose introdotta nell'orecchio medio non è riuscita ad evitare in qualche paziente l'insorgenza di un'anacusia, anche alla prima introduzione; la variabile imprevedibile permeabilità della membrana della finestra rotonda, oggetto di fondamentali studi nel passato, permette di spiegare tale complicità. L'Autore ha applicato la gentamicina transtimpanica nei menierici sin dal 1978, iniziando con G. Pivotti, per un complesso di 105 pazienti, compresa questa pubblicazione. In 22 menierici (1977-novembre 2001) resistenti alle cure mediche convenzionali, per la prima volta, ha attuato la terapia con gentamicina transtimpanica non successivamente, ma contemporaneamente alla cura medica convenzionale, introducendo la minima dose efficace per ridurre il rischio di un danno alla funzione uditiva. I risultati, preliminari, riferiti allo stadio della malattia, in sintesi dimostrano: la qualità della vita (secondo il questionario del Committee on Hearing and Equilibrium della Amer Acad Otoloryngol) è migliorata in tutti i pazienti (14 al punto 1, 8 al punto 2); le vertigini sono scomparse in 15 menierici (69,18%); una piccola crisi vertiginosa in 3 di essi e due piccole crisi vertiginose in 3 di essi non sono state tali da incidere nella qualità della vita; solo un malato presenta un'instabilità non costante. L'udito è invariato in 15 (69,18%) pazienti; di poco migliorato in 3 (13,63%) e di poco peggiorato in due (9,09%); caduta sui toni alti in due (9,09%) alla prima introduzione di gentamicina. L'Autore con la terapia integrata ed usando la minima dose efficace di gentamicina, ritiene di aver ridotto, anche se non escluso, la possibilità di un danno alle strutture cocleari pur con il ripristino di una buona qualità della vita, anche nel caso occorra ripetere l'introduzione.

Introduction

ENDOLYMPHATIC HYDROPS AND MENIÈRE'S DISEASE

Menière's disease (MD)¹ has a complex pathogenesis²⁻⁸; in the juvenile, especially the bilateral forms, it is believed to be autoimmune-mediated and requires specific immunosuppressive therapy regimens^{2 9-12}.

Endolymphatic hydrops (EH) is constantly found in MD, regardless of the aetiopathogenesis^{13 14}; it has been demonstrated, histologically, in 13 out of 13 Menierians¹⁵; it has been observed also in other pathological conditions since it is the most frequent, precocious and non-specific reaction of the membranous labyrinth^{4 16}, but has been associated with MD in only one-third of the cases described in the literature.

Analysing progressive EH leads to a better understanding of the clinical features and typical course of MD^{7 17-21}.

In its early stage, EH, as is well known, is almost always limited to the anterior labyrinth, since distension occurs more easily in these structures (Reissner's membrane) and may regress spontaneously (fluctuating EH), with the disappearance of signs, both subjective (tinnitus, fullness) and objective (hypoacusia on the low pitches, air- and bone-conducted).

In the second stage, the delicate structures of the anterior labyrinth become more stiff²², and the cochlear symptoms become more evident and stabilise (chronic EH).

In the third stage, EH spreads to the entire membranous labyrinth; the structural modifications of the ampullae are responsible for the modified behaviour of the cupulae, with the onset of objective vertigo when the impaired homeostasis of fluids in the labyrinth becomes more marked.

The vertigo attacks are almost always accompanied by the typical symptoms of cochlear EH, which may appear before, during or after the attack itself ("le vertige qui fait entendre": Lermoyez) and involve not only auditory function, but also tinnitus and fullness^{23 24}.

CONVENTIONAL MEDICAL THERAPY: RESULTS

The most common medical treatment consists in administering diuretics (osmotics, dextran²⁵, isosorbide²⁶, glucose²⁷) and vasoactive drugs (xanthinol nicotinate²⁴); this enables labyrinthine homeostasis to be reconstituted in 75% to 95% of cases^{5 25 26 28 29}. Treatment must be personalised and repeated over time since MD generally develops slowly, coming for medical attention only in the acute phase or acute recurrence.

When vertigo persists, pharmacological treatment with aminoglycosides (AMGL) should be attempted prior to surgical treatment. This treatment has become progressively more widespread, as an alternative to so-called minor surgery (sacculotomy, Cody

tack, cochleosacculotomy) or more complex procedures (ultrasound radiation of the labyrinth according to M. Arslan; drainage of the endolymphatic sac, section of the vestibular nerve^{28 30-35}), and when invasive therapy has failed^{36 37}.

USE OF AMGLS, ADMINISTERED INTRAMUSCULARLY AND TRANSTYMPANICALLY (INTRATYMPANICALLY): RESULTS

The use of AMGLs, in MD, began soon after these drugs were introduced, when the incidental disappearance of vertigo and stabilization of hearing were observed in Menierians being treated for severe tuberculosis (TBC); the pioneers of this therapy have been listed in a memorandum by Schucknecht's³⁸.

The high dosages of AMGLs employed were, however, followed by persistent ataxia (thought to be due to vestibulo-cerebellar impairment³⁹), unsteadiness that made walking in the dark impossible, and oscillopsia. It was necessary to reduce the daily and total dosages; this carefully-targeted treatment was used by Langman et al.⁴⁰, and Silverstein³⁴ in bilateral Menierians, with personalised doses of streptomycin administered intramuscularly (im), a technique still considered valid even today.

Later research on AMGLs has shown that toxicity of gentamicin prevails in the structures of the posterior labyrinth³⁹⁻⁴².

TRANSTYMPANIC (INTRATYMPANIC) INJECTION OF AN AMGL SOLUTION IN UNILATERAL MENIERIANS

This treatment was first carried out by Schucknecht in 8 patients³⁹, using streptomycin; Lange^{42 43} associated Ozotin (believed to protect the cochlear structures) with streptomycin in 38 patients, which led to the disappearance of vertigo in 34 and improvement in, or stabilization of, hearing in 70%. Beck and Schmidt⁴⁴ observed disappearance of vertigo in over 90% of patients; the finding of three cases of anacusis led these Authors to reduce the doses of AMGL, while continuing to obtain positive results.

These early researcher workers demonstrated that the disappearance of vertigo was not accompanied by labyrinthine ariflexia and, therefore, attributed the favourable results to the homeostatic action on the labyrinthine fluids, by means of the dark cells.

The use of gentamicin in unilateral Menierians non-responsive to conventional treatment has become more and more frequent, and, in various statistical studies has been reported in 5%²⁸ to 20%⁴⁵ of the overall number of Menierians seeking medical help. In the groups of patients treated personally since 1978, they account for approximately 10% (in a total of 105), including those described herein.

The situation warrants a brief summary of the results achieved, drawing them from the best documented research.

Quality of life (QoL), as described by the American Academy of Ophthalmology & Otolaryngology Committee on Hearing and Equilibrium⁴⁶ improves in varying percentages since it takes into consideration all the factors involved in assuring static and dynamic equilibrium, and has only been reported in the more recent studies: “disability” in 29 out of 61 cases⁴³; 15%³³; 70% with reference to point 1 and 30% with reference to point 2 in 20 patients²⁸; 2 at point 4 and 2 at point 5 in 11 patients⁴⁵; 75.8% at point 1 and 20% at point 2 in 29 Menierians, all treated with intratympanic gentamicin³⁰.

Vertigo disappeared: in 76%⁴⁷; 90%⁴⁸; 85% of the first group^{49,50} and second group²⁴, and in 86% of the third group²⁷; in 90%³³; 56%⁵¹ 84%⁵²; 100%²⁸.

Auditory function: particular attention must be paid to this aspect. Increased mean lifespan, improved sensitivity in audiometric assessment, greater conscientiousness on the part of the medical profession have all contributed to revealing an alarming phenomenon, the growing frequency of bilaterality in MD as age advances^{40,53-55}.

Hearing remains unchanged in: 57%⁵⁶; 76%^{42,43}; 43.3% in the first⁵⁰ and second²⁴ groups, 62% in the third group²⁷; 39.3%³³; in 5 out of 69³⁶; 60%²⁸; 86.2%³⁰.

Hearing is reported as improved in: 36%⁵⁶; 5%⁴⁷; in 5 out of 29⁴⁸; 43.4% in the first⁵⁰ and second²⁴ groups and 19% in the third group²⁷; 35%³³; in 25 out of 69³⁶; 28% “unchanged or improved”⁵¹; 20%²⁸.

Hearing deteriorated in: 51.16% and in 12.5% (groups 1 and 2⁵⁶); in 9 out of 29⁴⁸; 21.7% in groups 1 and 2 and 19% in group 3^{24,27,50}; 25%³³; 22%⁵¹; in 1 case in 11⁴⁵; 20%²⁸; 10.3%³⁰.

Decreased sensitivity in perception of the high tones (over 4000 Hz), in the unanimous opinion of all the Authors, is the most important sign in evaluating initial impairment of the cochlear structures during transtympanic gentamicin therapy.

Even if it does not affect so-called “social hearing”, this finding must be assessed in order to determine the specific technique of transtympanic gentamicin therapy: the presence in 95% of the 23 cases treated by Driscoll et al.⁵² would appear to indicate a slightly excessive perfusion of the drug into the inner ear; with appropriate technical precautions, this inconvenience drops to 1 case in 29 (3.4%)³⁰.

Anacusis needs to be dealt with separately; a quasi-complete review is reported by Schoendorf et al.⁴⁵.

The regular use of high doses, at brief intervals, explains the cases of anacusis initially present in the first groups of patients: 29 out of 61^{42,43}; 7 out of 16 (44%)⁴⁸; 3 in the first 18 cases treated⁵⁰; 2 out of 20³³, to mention just a few.

His surprising to note the presence of anacusis where measures had been implemented to preserve the hearing level ascertained upon hospitalization. For example, 5 patients out of 69, of whom 25% had already undergone drainage of the sac or section of the vestibular nerve³⁶; 2 out of 20²⁸; 8 out of 11⁴⁵.

In two Menierians, anacusis appeared after a single injection of 30 mg of gentamicin³⁶, and in 2 out of 20, after the second injection²⁸.

Relative unpredictability in transtympanic gentamicin therapy is often quoted to justify the behaviour of hearing function^{42,43}.

There is agreement in the literature regarding the greater fragility of the structures of the inner ear in the presence of severe sensorineural hypoacusia, on the proportional relationship between the dose and the negative effects, which was already evident in early research^{38,39,42-44,48}, on the importance of longer intervals between injections of the drug to avoid it from accumulating in the labyrinthine fluids, in view of its long half-life^{29,57-60} and of its possible delayed effect^{58,61,62}; but these are not sufficient to account for the negative effects mentioned above.

In our opinion, further research is necessary to assess factors likely of modifying the permeability of the round window membrane (RWM), which cannot be identified prior to treatment but only afterwards, following in those cases of negative outcome.

VARIABLE PERMEABILITY OF THE ROUND WINDOW MEMBRANE

The RWM is the principal means of communication between the middle and inner ear; a secondary means is the annular ligament of the stapes⁶³.

To better understand some of the unpredictable outcomes of transtympanic gentamicin treatment it is unanimously worthwhile taking into consideration results of experimental and clinical investigations.

It is unanimously agreed that evaluation of the quantity of AMGL that has perfused into the inner ear is possible only by carefully assessing the subjective signs (modification of the fullness and tinnitus, if present; subjective vertigo during rapid head movements) as well as the objective signs (onset of “irritative” nystagmus, and, above all, performance on the high tones, due to the proximity of the basal turn of the cochlea); an audiogram at least once daily.

AMGL may be traced in the blood when it is administered intramuscularly (bilateral Menierians^{34,40}); when instilled it into the middle ear, no trace can be found in the blood serum⁴⁸.

The factors modifying RWM permeability have been studied, from an experimental and clinical point of view, in fundamental works, the knowledge of which is essential in order to understand the events that follow the introduction of gentamicin into the middle ear; these are briefly summarised here^{41 48 63 64}.

RWM permeability may be modified by numerous factors some of which are unpredictable. The most important of these are: phlogosis of the middle ear mucosa (permeability is reduced as its thickness increases⁶³); the size and shape of the niche of the round window which may also determine an accumulation of the substance instilled; the different critical levels of concentration necessary for a substance to pass the three strata; the amount of substance introduced (the volume of the middle ear varies from 0.5 to 0.7 ml⁴⁸) and its molecular weight (like gentamicin <1000); the function of the tuba; and local reabsorption in the niche of the round window.

These variables may explain some of the outcomes without resorting to "diverse individual sensitivity" to AMGLs^{42 43}; if transtympanic therapy is not successful, exploration of the round window has been proposed^{52 65}.

AMINOGLYCOSIDES AND THE INNER EAR

Once the AMGLs have penetrated into the inner ear, they bond with the melanin present in the dark cells and in the stria vascularis⁶³.

The dark cells have a dense vesicled cytoplasm, Golgi apparatus, ribosomes and an endoplasmic reticulum^{29 59 66-69}; they contain Na-K-ATPase and phospholipids with which the AMGL bonds. They play a role in the active transportation of electrolytes in the vestibular labyrinth by influencing the Na/K balance⁶⁶. Gentamicin has been shown to also have an effect on the metabolism of carbohydrates, and, therefore, affects the glucocalix coating the epithelial cells⁶⁰. These modifications are reversible upon suspending gentamicin.

In a second stage, the altered permeability of the hair cells to the Ca and Mg ions is more marked, eventually becoming irreversible and determining the destruction of the cellular membrane and the death of the cells^{31 32 57 58 60-62 66 68}.

Damage to the otoliths has also been demonstrated experimentally⁷⁰.

The elective, toxic effect of the AMGLs on the dark cells, typical of the first phase, is the most important, from a clinical point of view, since it determines a persistently reduced endolymph production^{29 48} and allows a hypothesis to be made concerning the mechanism involved in the results obtained^{32 42 43 56 64}.

One aspect to be borne in mind is the variable amount of melanin present in the inner ear; it is completely absent altogether in albinos^{62 67}; this feature may also be observed in the colour of the iris⁶⁷.

These data, on account of their clinical significance, will be further taken into consideration in the discussion.

Materials and Methods

PERSONAL CASE HISTORIES

Transtympanic gentamicin was first used by myself and G. Pivotti in 1978 in unilateral Menierians in whom objective vertigo attacks persisted after repeated cycles of conventional therapy (osmotic diuretics, chlorthalidone, glucose, and so-called vasoactive drugs).

With the first group of 28 patients⁵⁰, I followed the technique and dosages recommended by Lange⁴² and Schmidt and Beck⁵⁶, obtaining favourable results in the vertigo attacks; the onset of anacusis in three cases, even though the patients initially had an average loss of around 80 dB, led to a reduction in the doses, implemented in the second group of 34 patients²⁴, with the same percentage of favourable results.

In the third group, comprising 21 Menierians²⁷, I divided the patients according to the stage of MD reached; following the characteristic progression of the disease^{7 19-21}, I identified five stages, on the basis of auditory and vestibular function. First stage: fluctuating EH; second stage: stabilised EH, objective vertigo attacks; third stage: stabilised EH, objective vertigo attacks, vestibular hyporeflexivity; fourth stage: audiometric curve below the social hearing level, at times with a pivot around 2000-3000 Hz, objective vertigo attacks, vestibular hyporeflexivity; fifth stage: severe hearing loss, besides subintractant vertigo and vestibular hyporeflexivity.

The treatment and results obtained have been evaluated by differentiating them according to the different stages of the disease, to better reveal the mechanism of AMGL action.

The fourth group, to which the present investigation refers, includes 22 Menierians (1997-November 2001) who failed to respond to conventional medical treatment, even if repeated. The period concerns the years 1997 (5), 1998 (1), 1999 (10), 2000 (4) and 2001 (2).

Follow-up, in July 2002, was >4 years in 6 patients, >2 years in 10, 2 years in 4, and one year in 2.

Age of the patients ranges between 31 and 71 years (mean 53.54), three being 65, 70 and 71 years of age. In the patients in the fourth group, endolymphatic depletion (of the diuretics) was associated with the simultaneous injection of a small dose of gentamicin (the minimum effective dose) to improve the QoL and preserve hearing to the greatest extent possible.

TECHNIQUE

In this group of 22 vertigo patients who had failed medical therapy, we observed the following technical guidelines.

- a. Prior informed consent of the patient, following explanation of: the probable causes of failure of his/her previous medical treatment; staging of MD, to be determined by tests at intervals during follow-up; operative mechanism of transtympanic gentamicin in the course of time (usually weeks) during which it is wise to limit activities (long journeys, stress, major changes in climate or altitude, overeating, immoderation in general, etc.), advice being similar to that following surgery.
- b. Detailed medical history, in the routine manner (Lermoyez's symptom in its more extended meaning) and using the American Academy of Ophthalmology & Otolaryngology Committee on Hearing and Equilibrium questionnaire⁴⁶. Complete audiometric study, from 250 to 8000 Hz, for the definition of the endolymphatic hydrops (low tones) and degree of impairment of the cochlear receptors, even if the evaluation is made on 250-4000 Hz. Search for spontaneous vestibular signs and the response to thermal stimulation according to Veits, bearing in mind the individual and personal variations in range; static and dynamic postural tests. Evaluation of any factor, specialistic or general, which could feasibly modify static and dynamic balance.
- c. The patient is placed on his/her side on the operating table, with the contralateral half of the face turned slightly downwards to make it easier for the drug solution to reach the semipermeable membrane of the round window^{41 63 64}.
- d. Simultaneously to the mannitol IV, following topical anaesthesia of the eardrum (10% Lidocaine), a small dose of gentamicin sulphate (0.25-0.33 of a 20 mg vial in 2 ml) is instilled transtympanally under an operating microscope, with an insulin syringe and a n. 30 needle; this classic technique, is easily and rapidly performed leaving no trace in the tympanic membrane^{42 44 50}.
- e. The patient remains in this position, without moving, for exactly ten minutes; after which he/she lies down on a bed or lies back in an armchair.
- f. That same day, auditory function (tinnitus, fullness, tonal audiogram) and the static and dynamic spontaneous vestibular signs are assessed. The associated parenteral therapy (mannitol in the morning; xanthinol nicotinate in the afternoon) is continued in increasing doses for 4-5 days, during which time the patient generally remains hospitalized.
- g. If the examinations described in (f) show neither loss of hearing, nor vertigo or modified static

and dynamic vestibular signs, a second instillation of gentamicin, following the previously described procedure, is carried out $\geq 3-4$ days later, to avoid accumulation of AMGL in the labyrinthine fluids^{58 62}, and the patient remains in hospital for another 3-4 days after the second insertion, continuing the parenteral therapy. This procedure was used in 10 patients.

- h. If, on the other hand, some subjective-objective change is observed in hearing and/or the presence of spontaneous vestibular signs or if there is a vertigo attack, parenteral treatment is prolonged for 7-8 days, following the evolution of the subjective and objective symptoms (as in 12 patients). The patient is discharged and closely monitored, in case further treatment is necessary.
- i. Persistence or recurrence of vertigo attacks which affect the QoL require further hospitalisation again, for repeat treatment as described above (5 patients).
- l. The Menierian is given a direct-access telephone number to enable him/her to reach his/her doctor in case of need. The usual treatment for MD is continued at home (chlorthalidone + potassium + xanthinol nicotinate o.s.), at first daily, then, once the situation has stabilised, every other day, and thereafter, every 3 days, over a period of 3-4 months. Where necessary, routine symptomatic drugs may be used; ion, creatinine and glucose levels as well as blood pressure should be checked, periodically, by the family physician. A low-salt diet is advisable.
- m. Systematic audiovestibular assessment (6, 12, 24 months) may be performed at home but the doctor who carried out the gentamicin injection must be informed of the results. In some cases, vestibular rehabilitation may be useful to accelerate the process of vestibular compensation.

Results (Table I)

QUALITY OF LIFE

Prior to treatment: 9 patients were at point 5 (40.9%); 10 at point 4 (45.5%); 3 at point 3 (13.63%).
Following treatment: 14 patients (63.63%) were at point 1, specifically the Menierians indicated in Table 1 with numbers 2, 3, 5, 6, 8, 10, 11, 12, 14, 15, 16, 17, 21 and 22; 8 (36.36%) at point 2, specifically 1, 4, 7, 9, 13, 18, 19 and 20.

With regard to the stage of the disease: at point 1, 7 patients were in stage 2; 3 in stage 3; 4 in stage 4; at point 2, 2 Menierians were in stage 2; 2 in stage 3; 4 in stage 4.

Table I. Clinical data.

Patient/age (yrs)	Gentamicin year	Gentamicin number	follow-up	Tonal audiogram		Vertigo		Quality of life	
				before	after	before	after	before	after
1. M.A. 32	1997	2	2002	45	40	+++++	1 minor attack	5	2
2. P.P. 63	1997	2	2002	70	70	++++	–	4	1
3. V.M. 50	1997	1	2002	70	70*	++++	–	4	1
4. B.G. 42	1997	2	2002	<u>70</u>	60	+++++	2 minor attacks	5	2
5. C.N. 61	1997	3	2002	<u>50</u>	50	++++	–	4	1
6. G.L. 42	1998	2	2002	45	45	+++++	–	5	1
7. S.G. 55	1999	2+1	2002	50	50	++++	1 minor attack	4	2
8. M.L. 48	1999	1+1	2002	<u>60</u>	60	+++	–	3	1
9. T.B. 45	1999	1	2002	60	65	+++++	2 minor attacks	5	2
10. B.A. 64	1999	1	2002	60	60	++++	–	4	1
11. F.E. 50	1999	1+1	2002	60	60	+++++	–	5	1
12. F.G. 61	1999	1	2002	50	50*	++++	–	4	1
13. C.M. 65	1999	2	2002	<u>70</u>	70	+++++	2 minor attacks	5	2
14. V.D. 44	1999	1+1	2002	<u>50</u>	50	++++	–	4	1
15. N.G. 51	1999	1	2002	<u>45</u>	45	++++	–	4	1
16. R.M. 58	1999	1	2002	<u>40</u>	35	++++	–	4	1
17. V.C. 70	2000	1+1	2002	70	70	+++	–	3	1
18. S.A. 71	2000	2	2002	<u>70</u>	70	+++++	Occasional unsteadiness	5	2
19. D.A. 31	2000	2	2002	<u>50</u>	60	++++	–	4	2
20. B.A. 67	2000	2	2002	<u>70</u>	70	+++++	1 minor attack	5	2
21. M.E. 46	2001	1	2002	<u>50</u>	50	+++	–	3	1
22. B.T. 63	2001	1	2002	<u>55</u>	55	+++++	–	5	1

Tonal audiogram: from 250 to 8000 Hz; * decreased sensitivity from 4000 Hz; +++++: number of vertigo attacks in last year; underlined decibels: presence of pivot at 2000 Hz; Gentamicin (see Technique): 1: a single session; 2: two sessions at intervals during same hospitalization; 3: three sessions at intervals during same hospitalisation; +1: instillation during a second hospitalization; Quality of life: as per the Committee on Hearing and Equilibrium of the American Academy of Ophthalmology & Otolaryngology.

VERTIGO

Following treatment: 15 Menierians (68.18%) were symptomless, specifically 2, 3, 5, 6, 8, 10, 11, 12, 14, 15, 16, 17, 19, 21, 22 in Table; 8 of these were in stage 2 of the disease (5, 6, 12, 14, 15, 16, 21, 22), 4 were in stage 3 (8, 10, 11, 19), and 3 were in stage 4 (2, 3, 17).

A minor vertigo attack occurred in 3 patients (13.63%), 2 minor attacks in 3 (13.63%), and occasional unsteadiness in 1 (4.54%).

HEARING

Following treatment: unchanged in 15 patients (68.18%), corresponding to nos. 2, 5, 6, 7, 8, 10, 11, 13, 14, 15, 17, 17, 20, 21, and 22; 7 of these were in stage 2 of the disease (5, 6, 7, 14, 15, 21, 22), 3 in stage 3 (8, 10, 11), 5 in stage 4 (2, 3, 17, 18, 20); improved (less than 10 dB) in 3 patients (13.63%), in particular n. 1 in stage 2 of the disease, n. 4 in stage 4, and n. 16 in stage 2; worsened (less than 10 dB) in 2 patients (9.09%), corresponding to nos. 9 and 19, both in stage 3; loss of sensitivity in perception of

high tones in 2 patients (9.09%), in particular n. 3 in stage 4 and n. 12 in stage 2.

TINNITUS

Prior to treatment: present in all patients.

Following treatment: reduced markedly or disappeared in 9 patients (40.9%), still present in 13 (59.1%).

RECRUITMENT

Present in 19 patients (86.36%).

Following treatment: absent in 9 patients (47.36%), unchanged in 10 (52.63%).

Discussion

Reports on the use of transtympanic (intratympanic) gentamicin are constantly increasing, with regard to those Menierians in whom conventional therapy, even if intense and repeated, has been found to be ineffective; the percentage ranges from 5%²⁸ to 20%⁴⁵ of the Menierians seeking medical attention.

In the groups of patients I have treated since 1978, when I began together with G. Pivotti^{24 27 50}, up to the fourth group which is presently being described, they constitute about 10% of the total, 105 patients overall.

Transtympanic gentamicin has emerged in all of the statistical studies for its selective toxicity on the vestibular structures.

The demonstration that it was not necessary to reach labyrinthine areflexia to obtain an improvement in the quality of life and the disappearance of vertigo has led to: a) a progressive reduction of the doses of gentamicin, and number of applications^{24 27 30 42 43 56 70 71}; an increase in the interval between instillations, if more than one is necessary, to avoid the accumulation of AMGL in the inner ear, because of the long half-life of AMGL^{58 59 62}; no variation in the percentage of positive outcomes; b) the identification, both experimentally and clinically, of the superior, persistent action of AMGL, from the onset, on the secretory structures of the endolymph, in particular on the dark cells^{29 42 48 59 62}.

In almost all reports, there is a considerable frequency of “hearing remains unchanged”: it was clear from those early studies that this occurrence suggested an effect on the secretory structures of the endolymph blocking the progressive hydrops, while preserving residual cochlear function. An improvement in hearing, from 5%⁴⁷ to 28% of the patients⁷², can be explained with the reduction of EH and the presence of structures that have not yet stiffened²², while a loss of hearing may be interpreted through the interaction of several factors: stiffening of the cochlear structures, excessive perfusion of AMGL in the inner ear, and greater fragility of the sensorineural structures. A decreased sensitivity in the perception of the high pitches is, instead, the easiest to understand (and fear) because of the proximity of the RWM to the basal turn of the cochlea, although it can be exceptionally high (23 out of 25 patients, equal to 92%⁵²).

One unsolved problem, emphasized by all Authors, is the unpredictability, although rare, of the behaviour auditory function. Even in recent studies, cases of anacusis were reported where every possible measure had been taken to preserve residual hearing: Kaasinen et al.³⁶, after a single instillation of 30 mg; Leone et al.²⁸ on the second injection of a prewarmed solution of 16 mg of gentamicin. We consider as a case unto itself the cophosis in 8 out of 11 patients described by Schoendorf et al.⁴⁵, who refer to a review of the cases of anacusis reported in the literature.

Three cases of anacusis were recorded in patients in our first group (1978-1981), due to the high dosages commonly used in that period⁵⁰.

Some “surprises” may be foreseen identifying the stage of the disease present at the outset of treatment. In the third group of Menierians²⁷ and in those described in the present report, we have distinguished five stages of MD, analysing the cochlear and vestibular data (according to Shea and Ge⁷³). The results obtained are usually dealt with globally, without any reference to the stage of the disease.

The best results overall are obtained in stages 2, and 3, while patients who have reached stage 5, *ceteris paribus*, present greater lability of the cochlear structures upon instillation of gentamicin.

At this point, bearing in mind personal results as well as those reported in the literature^{24 27 50}, the problem would appear to be as follows:

- transtympanic AMGLs lead in most Menierians to cure of vertigo and improvement in QoL, without undergoing surgery;
- as MD is frequently bilateral, preservation of hearing must be safeguarded; this is correlated to the amount of AMGL reaching the inner ear.

In this fourth group, in order to reduce the amount of transtympanic gentamicin to the minimum effective dose, I instilled a small quantity of gentamicin into the middle ear while simultaneously implementing the medical therapy with diuretics and vasoactive drugs, attempting, in this way, to associate EH depletion with the reduced production of endolymph determined by the AMGL.

This fourth group of 22 patients, who have been followed up (July 2002) for >4 years (6 patients), >2 years (10 patients), 2 years (4 patients) and one year (2 patients), enables us to reach some conclusions regarding the results of this treatment.

The QoL is in line with recent research: 14 patients (63.63%) at point 1 and 8 (36.36%) at point 2 as rated by the American Academy of Ophthalmology & Otolaryngology Committee on Hearing and Equilibrium questionnaire; *cfr.* the 75.8% at point 1 and 20.6% at point 2 reported by Comacchio et al.³⁰ in 29 Menierians and the 70% “complete control” and 30% “substantial control” reported by Leone et al.²⁸ in 20 patients.

Vertigo has disappeared in 15 patients (68.18%); a minor vertigo attack was reported by 3 patients (13.63%) during follow-up, 3 patients (13.63%) reported two minor attacks, and 1 patient (4.5%) presented occasional unsteadiness.

The percentages of complete disappearance of vertigo are lower than those reported in the literature (around 90%), as in our first three groups of patients^{24 27 50}; the only exceptions are Yamazaki et al.⁴⁷, with 73% and Poe et al.⁵¹ with 56%. It is tempting to hypothesise that our reduced dose of AMGL cannot get past the variable gradient of RWM perme-

ability⁴¹; it is, therefore, necessary to repeat the instillation (as in 9 out of 22 patients) or hospitalise the patient a second time (5 out of 22).

Hearing was preserved, except for the loss of sensitivity in the perception of high pitches (6000-8000 Hz), in 2 patients (nos. 3 and 12), on their first and only instillation; this complication may paradoxically be explained by a situation of "normality" of the RWM which, being semipermeable⁴¹, usually allows gentamicin to pass easily from the middle ear to the inner ear⁶³, as its molecular weight is <1000⁴¹.

The validity of the technique proposed is borne out by the fact that hearing was not impaired, despite the 38 instillations of gentamicin performed overall during the first and second hospitalizations of the 22 Menierians, except for the loss of sensitivity on the high pitches in 2 cases (5.26%) after a single instillation.

The improvement in tinnitus (40.9%) is consistent with findings in the literature, and indicates an effect of the drug on the production of endolymph and on the complex biochemical activity of the hair cells. Careful monitoring of patients' objective data makes it possible to exclude a placebo effect⁷⁴ in transtympanic gentamicin therapy.

Conclusions

AMGLs are more and more frequently employed in Menierians not responding to conventional medical treatment (from 5% to 20%), both as an alternative to surgical procedures and in cases in which surgery has failed to give the desired results, as in 25% of those treated by Kaasinen et al.³⁶ and in all 4 patients reported by Marzo and Leonetti^{37 75}.

Anacusis is an unpredictable complication that may appear at the very first instillation of AMGL³⁶ and which may, in our opinion, be explained by the variable permeability of the RWM, which cannot be assessed, by any means, prior to treatment. A number of conditions may affect the RWM: previous otitis, the size and shape of the niche and of the RWM itself; and the molecular weight, quantity

and concentration of the substance instilled in the middle ear. The greatest risk to the structures of the inner ear is, paradoxically, posed by a normal (semipermeable) RWM, while this risk is considerably reduced when the auricular mucosa has thickened due to previous inflammation⁶³. If transtympanic (intratympanic) AMGL therapy is unsuccessful, exploration of the round window has also been proposed⁵².

Careful staging of the MD upon hospitalization of the patient is necessary to clarify the options in each case and personalise transtympanic AMGL therapy; the best results are obtained at stages 2 and 3.

Transtympanic AMGL therapy has always been implemented separately, after conventional medical treatment has failed. In this fourth group of 22 patients, my objective was to repeat the conventional therapy, even if it had not been successful, and to simultaneously instill a small quantity of gentamicin, the minimum dose presumed to be effective, in order to improve the QoL, reducing the risk of any hearing impairment as much as possible.

The persistence in time of the final hearing threshold indicates that gentamicin, even in minimum quantities, determines a histofunctional modification of the complex secretory structures of the endolymph (dark cells, stria vascularis^{42-44 59 61}).

As already been pointed out, the modified technique used in these 22 patients can be easily repeated; overall 38 gentamicin instillations were performed between the first and the second periods of hospitalization, with only 2 instances of loss of sensitivity, on the high tones, at the first injection (5.26%).

The results achieved in these patients persuaded us to continue in the application of this simple technical modification, which makes it possible to reduce the quantity of gentamicin to the minimum effective dose for the QoL, while preserving hearing, and which may be repeated if vertigo persists or recurs.

The results achieved with gentamicin have led some Authors^{42-44 72} to use this treatment also in bilateral Menierians; the technical modification described in this report may be applied in the latter cases, even if parenteral administration, at controlled daily and total dosages, is preferable³².

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