

# Our Experience with the Medical Treatment of Endolymphatic Hydrops

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**Abstract:** Ménière's syndrome is an idiopathic disorder of the cochlea and labyrinth. It is caused by endolymphatic hydrops and is a relatively frequent, lifelong disorder affecting patients' quality of life and work performance. This article presents our clinical experience with the medical treatment of this disease. Patients were treated with a blend of drugs according to their condition (stage of illness and presence of associated diseases).

**Key Words:** anticoagulants; corticosteroid therapy; diuretics; endolymphatic hydrops; medical treatment; vasodilators; vestibular syndrome

Endolymphatic hydrops—Ménière's syndrome—is referred to as a labyrinthopathy of unknown etiology, with clinical features that include fluctuant sensorineural hearing loss, tinnitus, and incapacitating episodic vertigo.

## SHORT HISTORY

In 1861, Prosper Ménière described, on the basis of an autopsy study, labyrinthine hemorrhage with a clinical history that constituted tinnitus, hearing loss, and vertigo attack; imbalance; and vagal symptoms (nausea, emesis, lipothymia). On the basis of the observation that an association of auditive and vestibular symptoms was always present in affected patients, Ménière pointed out the ear as the main organ involved in this pathological process.

In 1938, Yamakawa (cited in [1]) and Hallpike and Cairns (cited in [1]) independently published their discoveries on endolymphatic hydrops in patients who developed clinical features of Ménière's syndrome; initially, they considered the hydrops to be idiopathic, owing to the lack of anatomical abnormalities that could

have justified the pathological lesions. However, as hydrops was presented, a new medical entity was introduced: Ménière's disease.

Currently, there is a tendency to confuse the two medical terms—*Ménière's syndrome* and *Ménière's disease*—in favor of Ménière's disease. In our opinion, the two entities are distinct, owing to their clinical history. *Ménière's syndrome* has a natural history of multiple attacks that vary in intensity and frequency. Initially, vestibular symptoms are the main features; in the early stage, the hearing loss might be transient, but later it becomes progressive. It may be prevented or improved by treatment. In contrast, *Ménière's disease* is characterized by a single attack followed by an important sensorineural hearing loss that does not respond to any treatment.

Throughout time, there have been different theories concerning the etiology of endolymphatic hydrops: hyperproduction of endolymph, slow resorption of endolymph, viral infections, ionic imbalance, genetic abnormalities, dietary factors, allergies, and autoimmune reactions. Though the etiology of endolymphatic hydrops does not represent the subject of this article, it is impossible to evaluate the different types of treatment without taking into consideration various causes of this entity.

The natural history of endolymphatic hydrops is characterized by remissions and exacerbations that make treatment evaluation difficult. The symptoms presented by patients allow us to identify different stages of its natural history: the prodromal stage, which is inconstant

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(several patients have noticed the increase of tinnitus intensity or anxiety attacks prior to the vertiginous crisis); the vestibular crisis; the postcrisis stage; the inter-crisis stage; and the sequela stage [2].

The clinical findings of endolymphatic hydrops include vestibular, hearing, and equilibrium symptoms and psychological and vagal symptoms. Taking into consideration the prevalence of these symptoms, we can identify different clinical forms of Ménière's syndrome: typical Ménière's syndrome; the Lermoyez syndrome (in which hearing is improved during or after a vertigo attack) [3]; Turmakin otolithic catastrophe; the cochlear form (hydrops without vertigo, with transient hearing loss); and the vestibular form (when vertigo is among the symptoms, in the absence of hearing loss).

## DIAGNOSIS

In our clinic, positive diagnosis is essentially a clinical diagnosis based on a patient's signs and symptoms. Though between crises affected patients may be asymptomatic, the presence of more than one vertiginous crisis and an audiometrically documented hearing loss in at least one attack, tinnitus, or aural fullness in the treated ear establishes the presumption of Ménière's syndrome [4].

The vestibular attack consists of rotatory incapacitating vertigo with horizontal nystagmus, aural fullness, low-frequency neurosensory hearing loss (possibly transient at the beginning and becoming progressive later), and tinnitus. In addition to the vestibular and auditory symptoms, during the vertiginous crisis affected patients may present with imbalance and vagal irritability symptoms (emesis, diaphoresis, bradycardia), confining them to bedrest and, thus, lowering their quality of life. Over time, some patients develop psychological symptoms (an anxious, depressive neurosis), which must also be considered in the diagnosis.

The investigation algorithm of this type of patient includes a series of paraclinical examinations aimed at sustaining the diagnosis and identifying in a patient health conditions that may interfere with medical treatment. The investigation algorithm consists of a complete neurootological examination; vestibular investigations (computed dynamic posturography, craniocorpography, electronystagmography [5,6]); audiological investigations (pure-tone audiometry, imitancimetry, otoacoustic emissions, brainstem auditory evoked potentials); imaging investigations (computed tomography, magnetic resonance imaging, Doppler echography, Stenvers and Schuller's x-rays, cerebral arteriography, and other examinations); laboratory investigations (glycemia, blood urea level, creatinine, hepatic enzymes, cholesterolemia, calcemia); cardiologic, ophthalmological, and neurolog-

ical examinations; and endocrinological examination. One of the most important investigations of this type is the Klokhoff test (the glycerol test), which is not only diagnostic but also therapeutic [7].

The investigation algorithm also aids in making the differential diagnosis, taking into account such other clinical entities as labyrinthitis; vestibular neuronitis; aminoglycoside toxicity; cervical spondylosis; brainstem tumors; labyrinthine concussion; labyrinthine otosclerosis; acoustic neuroma; rupture of the round-window membrane; sudden hearing loss; posttraumatic (especially if associated with a skull fracture), toxic, or pharmaceutical injury to the vestibular apparatus (alcohol, streptomycin, quinine, barbiturate, phenytoin, antihistamines); and various infections (especially herpes zoster and central nervous system syphilis).

## TREATMENT

Even today, despite technological progress, the exact cause of Ménière's syndrome remains unknown. Many new theories have been suggested regarding the syndrome's etiology. For example, one hypothesis embraces a "channelopathy" [8], based on the fact that the syndrome's evolution is sensitive to a low-sodium diet and to acetazolamide, and points to the recent discovery of multiple potassium and calcium channels in inner and outer hair cells. Another theory holds that the cause might be a genetic mutation [9]; studies have been conducted regarding the COCH gene situated on chromosome 14, and in-depth studies have focused on some genes responsible for certain human lymphocyte antigens (HLA-A3, B7, CW7, and DR2); however, the results of these studies are inconclusive.

Still another theory speaks of an autoimmune cause suspected especially in bilateral cochleovestibular dysfunction [9,10]. Affected patients have increased levels of antibodies directed against different inner-ear antigens, and such patients respond very well to corticosteroid treatment. Apparently, autoimmunity could be responsible for a small percentage of cases of bilateral Ménière's syndrome [11].

Endolymph homeostasis has also been studied, and the studies conducted thus far have raised the hypothesis that various molecules and ion channels have an important role in endolymph homeostasis [9,12]. The aquaporins were investigated, especially aquaporin 2, which is the only humorally controlled aquaporin [9]. It has an important role in the radial flow and, hence, in endolymph homeostasis.

The question of an allergic component in Ménière's syndrome has been raised [13] on the basis of proof of a link to migraine [13,14]. The higher prevalence of history of allergy in Ménière's syndrome patients with

migraine could also suggest an immunological link. However, the same study states that both migraine and Ménière's syndrome might have a multifactorial etiology and that allergy is merely a trigger.

Yet another theory posits a link between the antiphospholipid antibody syndrome and Ménière's syndrome, based on a statistically significant increase in the levels of antiphospholipid antibodies in patients with Ménière's syndrome [15]. This theory may have an impact on medical treatment, as a better response was noted in patients treated with warfarin or glucocorticoid (or both).

As stated previously, the actual cause of Ménière's syndrome has not been found. For this reason, treatment, for the time being, is symptomatic, aimed at improving the quality of life of affected patients.

In our opinion, medical treatment of Ménière's syndrome should be complex and should coincide with both the clinical stage of the disease and the patient's condition [16,17]. Though the treatment worldwide has been medical and surgical until now, we have been reluctant to resort to surgical treatment because it is considered traumatic to patients and because, owing to adequate medical treatment, we have not had any cases that would have required a surgical approach more or less destructive of the inner ear.

The main goal of medical treatment in the prodromal stage is to relax a patient and to prevent further attacks. Therefore, we explain to affected patients that when the tinnitus increases or anxiety appears (or both ensue)—announcing a new vertiginous crisis—they should self-medicate with sedatives (diazepam, 2 mg PO or alprazolam [Xanax], 0.25 mg PO) or with such anti-vertiginous drugs as Arlevert (a fixed combination of the calcium antagonist cinnarizine), 20 mg; antihistaminic dimenhydrinate, 40 mg PO, or betahistine, 16 mg PO [18–22].

A vestibular attack should be treated emergently: Medications for symptomatic relief of vertigo and nausea should be given, as this is a clinical diagnosis requiring only symptomatic care: metoclopramide, by mouth, intravenous perfusion, or intramuscularly, and diazepam, 2.5–10 mg PO, IM, or IV, repeated if necessary every 4 hours [23]. Support measures, such as intravenous rehydration (if vomiting has been severe) should be initiated as indicated, and affected patients should be hospitalized for the duration of treatment (1–3 days) until the vertigo disappears. However, few patients manage to present to the emergency clinic, because most times the vertigo is severe and incapacitating, forcing the patient to bedrest; such patients usually present to hospital after the vertigo disappears, in the postcrisis stage.

Medical treatment in the postcrisis stage is pathogenic and consists of such antihistamines as prometha-

zine (Romergan), which is given 1 hour before the intravenous perfusion or in intravenous perfusion with 5% glucose. (*Note:* Attention should be given to diabetes mellitus or hyperglycemia; in such cases, a nutritionist should be consulted to use insulin-buffered glucose or to replace the glucose with Ringer's solution or NaCl 9%.)

The effectiveness of corticosteroid (hydrocortisone hemisuccinate, 1–3 vials; 75–100 mg IV) has been suggested by our experience with sudden sensorineural hearing loss and confirmed by recent studies [24]. Despite clinical results, the pharmacological mechanism of the corticosteroids has not yet been proved. It is important that, before treatment with corticosteroids is initiated, a careful history be obtained to identify other comorbidities that might contraindicate these types of drugs.

Vasodilators (dihydroergotoxine mesylate [Hydergin, Redergin], 1–3 vials) have an important disadvantage: They are poorly tolerated by patients. As regards anticoagulants (e.g., heparin, 5,000 IU, 1–6 vials; more frequently, 3 vials), a careful medical examination must be conducted before the start of therapy with these drugs, to identify any illnesses or diseases that may represent a contraindication. The treatment must be supervised by an international normalized ratio (INR) examination every 2 days and by other coagulation tests; in case of overmedication, an antidote (protamine sulfate) is available.

We must specify that both the vasodilators and the anticoagulants are given in this case because of their action on the sanguine dynamics of stria vascularis and on normal modulation of the ionic pumps of the maculae, Reissner membrane, and stria vascularis). The treatment is limited by certain medical conditions (mitral stenosis, atrial fibrillation).

To date, multiple studies regarding the administration of diuretics orally, intramuscularly, and via intravenous perfusion have been published [16,23,25]. Though in our clinic they are rarely used, diuretic treatment must be closely monitored by assessing potassium levels and by cardiologic examination (in cases of adjusting the hypertension treatment or treating the cardiologic effects of hypokalemia).

Intravenous perfusion may be poorly tolerated by affected patients and may have as a side effect orthostatic lipothymia. For this reason, we recommend bedrest for 2 hours after ending the perfusion. If the hearing loss is mild, treatment consists of two to three perfusions; if the hearing loss is severe, five to seven perfusions is better.

It is important to mention that the dose of corticosteroids is the same every day and that, at the end of treatment, it is not necessary to decrease the dose. In the intercrisis stage, the medical treatment must maintain close-to-normal vascular status of the inner ear. Various drugs are used.

## Vasodilators

Redergin, 10 drops/12 hr for 10–20 days/mo, with B vitamins (B<sub>1</sub>, 100 mg/day; B<sub>6</sub>, 50 mg/day) for 10 days monthly works to adjust the outer-hair-cell function. This therapeutic regimen is prescribed for 8 months (3 months' treatment, 2 months' break, 3 months' treatment). The regimen is well tolerated by affected patients and does not need special follow-up. Also applicable are betahistine, 16 mg/8 hr, and Arlevert.

## Minor Diuretics

Treatment with minor diuretics should be monitored by plasmatic electrolytes assessment, especially patients' potassium levels.

## Other Types of Treatment

Some have used the Meniett device to induce intermittent overpressure locally (of which we do not approve) and transtympanic infusions of active substances [20, 26]. Over time, there have been many attempts with different substances although, at present, the studies conducted abroad focus on a few drugs [25,27–32].

Intratympanic steroid treatment is one therapeutic modality that can apply if oral therapy fails or is contraindicated. With intratympanic injections of dexamethasone (10 ml) in the middle ear, the results for long-term control of vertigo have proven to be unsatisfactory [28], partially owing to the elimination of the substance through the eustachian tube, therefore resulting in insufficient inner-ear levels. The use of intratympanic dexamethasone and hyaluronic acid in the middle ear was intended for early stages of Ménière's syndrome, before incapacitating vertigo became the main concern. The use of a round-window permeability-modulating substance (hyaluronic acid) increased the level of steroid reaching the target cells and improved hearing [30].

Dexamethasone (4 mg/ml) perfusion of the inner ear in cochlear Ménière's syndrome has improved the hearing and decreased tinnitus and pressure in the ear. Over the last decade, intratympanic gentamicin has become a major treatment modality for intractable Ménière's syndrome. Aminoglycosides cause ototoxic damage to the dark cell within the stria vascularis, thereby reducing endolymph production. Many different delivery techniques have been developed, including transtympanic injection, the Silverstein microwick, and the round-window microcatheter with continuous pump. Low-dose gentamicin perfusion through the round ear microcatheter has been shown to preserve hearing and vestibular function while obtaining effective vertigo control [25,29].

The surgical treatment of Ménière's syndrome is

available only for intractable cases, when medical treatment has failed [9,33,34]. Its most important goal is to stop the unpredictable, high-intensity, long-lasting vertigo spells by reducing or abolishing peripheral vestibular afferent stimulation (labyrinthectomy, intratympanic gentamicin, selective vestibular neurectomy). Surgery can also influence the pathophysiological process by promoting resorption (endolymphatic sac surgery with shunt implantation) or reducing the endolymph production (down-regulation of the endolymph-producing dark cells around the cupolas and in the stria vascularis by intratympanic gentamicin). Although substantial progress has been made in intratympanic gentamicin therapy, when this type of treatment fails, in other countries surgical treatment is recommended. We have no experience with surgical treatment because medical treatment allowed our patients to regain a relatively high quality of life and therefore a surgical approach has not been necessary.

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