28 Chronic cerebrospinal venous insufficiency and meniere disease

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Meniere's disease [1] is a chronic disease that affects the inner ear and is related to the presence of endolymphatic hydrops. It is characterized by four symptoms: hearing impairment, tinnitus, sensation of fullness in the ear and relapsing dizziness.

The pathology was first described by Prospero Ménière in 1861, he was the one who identified the inner ear as the organ of our equilibrium.[1]

The diagnosis is actually done on the criteria stated by the Barany Society [2] that substitute the 1995 guidelines from the American Academy of Otology (AAO).[3] The number of categories of Meniere's disease is now reduced to the solely "definite" and "probable".

The "definite" is characterized by relapsing dizziness associated with low- to medium-frequency sensorineural hearing loss and fluctuating aural symptoms (hearing, tinnitus and/or fullness) in the affected ear confirmed by an audiometric examination. Duration of vertigo episodes is limited to a period between 20 min and 12 h. "Probable" Menière's disease is a broader concept defined by episodic vestibular symptoms associated with fluctuating aural symptoms occurring in a period from 20 min to 24 h that are reported by the patients but are not confirmed by audiometric test.

The demonstration of the endolymphatic hydrop was at the beginning only feasible on a temporal bone sample but recently, the objective diagnosis by MRI has become possible using intravenous or intratympanic gadolinium injection.[4-10]

Endolymphatic hydrops is a pathologic substrate necessary but not sufficient to determine a clinically evident disease and its responsibility in determining the cochlear and vestibular pathology is not yet demonstrated.[11-14]

The disease does not have a unanimously determined predominance, does not have a prevalence of sex, is more common in the Caucasian race,[15] almost always begins unilaterally but tends to bilateralization in a significant percentage of cases that progressively increases over the years.[16-20] There are still some uncertainties:

A) *etiology:* genetics, post-traumatic, post-inflammatory, allergic, immune and autoimmune, viral, hormonal, vascular, toxic, neoplastic (prolactinomy), etc. The origin is probably multifactorial with different incidence not always evident in each patient. It is well known the association between Menière's disease and migraine, and it has also been hypothesized that the two conditionshave a common etiopathogenetic moment.[21, 22]

B) *Pathogenesis:* classical theory attributes genesis and symptomatology to endolimphatic hydrop disease but recent theories see hydrop not as a primitive but as a secondary phenomenon of the disease. Mul-

tiple causes would work synergistically in determining a condition of cellular toxicity on non-receptive cells of the inner ear, particularly those of the vascular stroma and of the endolimphatic sac, affected by the homeostatic mechanisms of the endolinfa. C) *Therapy:* medical therapy reflects the etiopathogenetic uncertainties. No conservative medical therapy exists which shows evidence of efficacy in the control or treatment of the disease.[23] Intratimpanic therapies, conservative with steroid, or subablative chemistry with gentamicin, show some evidence of efficacy.[24] Surgical therapy: endolimphatic sac surgery,[25] labyrinthectomy [26] and selective vestibular nerve neurotomy [27] are reserved for the few cases not otherwise controlled. Certainly there is no consensus on the etiology and best treatment for Menière's disease so it is reasonable to look for new treatment strategies. In 2006, Zamboni presented for the first time the concept that a chronic disease of cerebral venous outflow could partially or totally induced neurodegenerative disease and coined the term cerebral spinal venous injury (CCSVI), associating this condition in particular with multiple sclerosis.[28] In 2009, CCSVI was recognized as a nosological entity by the Consensus Document of the International Union of Phlebology on Venous Malformations.[29] Vascular anomalies cause brain function modification of the endothelial cell function by slowing the cerebrospinal venous outflow, which in turn worsens cellular perfusion with alterations to the blood-brain barrier.[30] The slowing down of the venous outflow causes an increase in venous pressure associated with a wave reflected by the arterial system,[31] with a further increase in intravascular pressure to the capillary venous system that worsen the damage of the endothelial cells leading to small endothelial layer breaks. This causes diffusion of intravascular fluid, proteins and blood cells with local activation of inflammatory cascade, iron deposition, loss of oligodendrocytes and attraction of phagocytes, increase in interstitial fluid, and hence increased extracellular lymphatic fluid.[32-34]

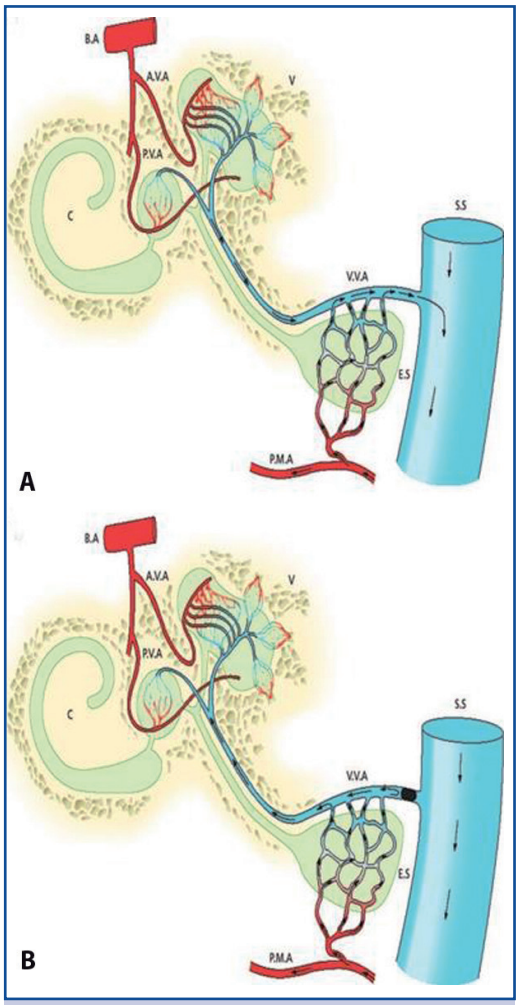

FIGURE 28.1. A) Normal blood flow in the vestibular aqueduct vein (VAV) and B) the result of a thrombosis in the very distal part of the VAV. The posterior meningeal artery (PMA) distributes blood to the microcirculation of the endolymphatic sac (ES) before it drains into the VAV; C) the blood supply to the cochlea and the vestibular apparatus (V) derives from the basilar artery (BA), anterior (AVA), and posterior vestibular artery (PVA). In (B), drainage from the VVA to the sigmoid sinus (SS) has been interrupted, reversing the flow of blood in the VAV toward the vestibular apparatus.

The evaluation of the increase in cerebral venous pressure was evaluated by mathematical models: Toro [33] developed a system based on MRI evaluations in which the stenosis of the major venous branches of the cerebral outflow causes endocranial hypertension with impact on the inner ear. There would be a stasis situation that would result in endothelial cellular toxicity with conse-

quent cellular cell damage due to iron accumulation phenomena but also to osmotic alteration of extracellular fluid components.

The cerebral anomalies may also affect the inner ear structures, which also drain into the jugular venous system. According to the model proposed by Merchant for Menière's disease,[36] the site of major interest should be the stria vascularis with its fibrocytes actively involved in the endolymphatic homeostasis. We might hypothesize that at least one of the unknown causes of cellular toxicity postulated by Merchant could be the venous stasis resulting in cellular damage to the vascular stria, which would determine alterations in the metabolism and endolimphatic homeostasis that would lead to development of hydrop.

CORRELATION BETWEEN CCSVI AND MENIÈRE DISEASE: AN HYPOTHESIS

Venous drainage of the inner ear occurs through the internal auditory vein, the cochlear aqueduct vein and the vestibular aqueduct vein, which are drained in the inferior petrosal sinus, the transverse sinus and finally in the inner jugular vein. In particular, in humans the vein of the vestibular aqueduct drains the venous blood of the utricle, the semicircular ducts, the saccule and the endolimphatic duct. The slow down of the flow at this level would increase the pressure of the inner ear veins. Friis [37] performed an interesting experimental study on the inner ear veins: he closed the aqueduct vestibular vein close to the endolimphatic sac in the guinea pigs and observed the formation of a portal flow of the inner ear and symptoms matching those described for Menière's disease. This would happen as the direction of the venous flow in the inner ear is inverted, resulting in a portal flow, where venous capillary blood falls into the arterial capillary circulation. In addition, the endolimphatic sac, as described in many papers, contains glycosaminoglycans, proteins and a natriuretic hormone, whose modifications would result in changes in the composition of inner ear fluids with negative functional effects on dark cells.[37-41]

A thrombotic obstruction of the vestibular aqueduct vein has been observed in some patients with Menière's disease at bioptic examination. The presence of microthrombi would modify the flow dynamics so explaining the fluctuating symptoms typical of Menière's disease.[40, 41]

Over the years, the persistence of slow outflow with consequent injury to the labyrinth endothelium veins would result in fibrosis of the endolimphatic sac and duct, decreased vascularization of the latter, increased local hydrostatic pressure, consequent inversion of the venous flow as predicted by the experimental model by Friis. Anatomopathological studies performed on the internal ear in MD showed that stria vascularis is atrophic and the number of vessels is highly reduced.[43, 44]

Merchant's experiment supports this hypothesis demonstrating the constant presence of endolimphatic hydrop in Menière's patients. However hydrop is not necessarily associated to the syndrome: this means that endolinphatic hydrop should be considered as a histologic marker for Meniere's syndrome rather than being directly responsible for its symptoms. The hydrop is in turn due to a primitive modification of the labyrinth homeostasis caused by cellular toxicity of type I and type II fibrocytes involved in the homeostasis of labyrinth fluids.[36] The reduced venous outflow, as demonstrated in CCSVI and in SM with concomitant CCSVI as underlined by Adams,[34] occur probably even in Menière's disease. It would affect the venous wall, increasing its permeability with formation of peripheral lymphocytic infiltrates and iron deposits which would cause cytotoxic damage to fibrocytes particularly in the highly vascularized discricts (stria vascularis). This problem in association with other causes, could lead to the development of the typical alterations and symptoms of the Menière's disease. Based on these theoretical considerations, three Italian Schools have

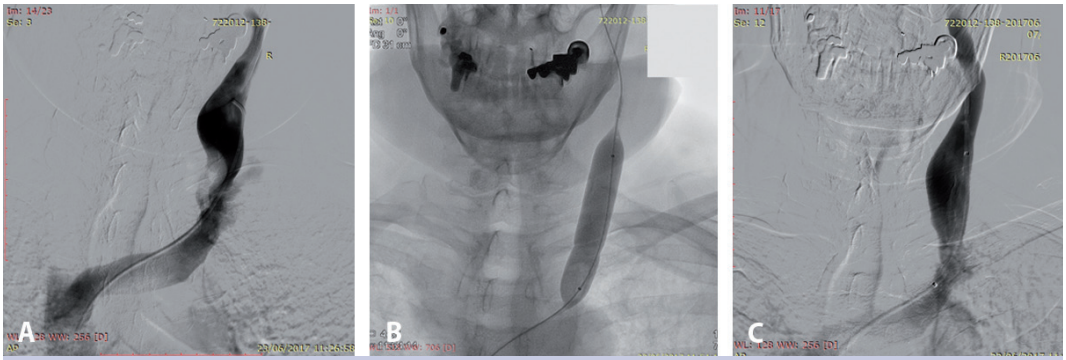

FIGURE 28.2. A) Preliminary venography; B) PTA; C) control venography.

sought and found an relationship between CCSVI and Menière's disease.[44-48]

Three methods were used to diagnose CCSVI in patients with Meniere's "definite" disease:

- duplex-ultrasound of the jugular system associated to transcranial Doppler to evaluate the deep cerebral veins and veins reflux;
- MRI angiography of the neck and intracranial circle with venous phase. This study allows a complete minimally invasive evaluation of the neck venous system, of the brachiocephalic veins and venous sinus. The main advantages are: a complete and precise evaluation of venous anomalies necessary to plan the eventual procedure, the evaluation of benign intracranial hypertension and repeatability. However there is not yet a consensus on the protocol study for CCSVI;
- phlebography with evaluation of the internal jugular veins and azygos vein.

MATERIALS AND METHODS

This study was submitted to the Campania 2 Ethic Commitee on 15 march 2013 and approved on the June 10, 2013 protocol n. 277/2013. All the treated patients included in the study signed the informed consent on the diagnostic exams and invasive procedure according to the Helsinki Declaration. Between April 2013 and December 2016, 312 patients were included in the study (189 females - 123 males). Mean age was 53.1±15.3 years. All of them had a "definite" Menière's disease, monolateral in 240 cases, bilateral in 72, according to A.A.O. 1995 criteria. The onset of symptoms varied between 1 and 28 years (Table 28.I).

All the patients were submitted to duplex ultrasound of the deep cerebral and neck veins according to the criteria of the International Society for Neurovascular Disease 2011, modified by the 2014 guidelines [49] (Table 28.II). The exam was performed also on a control population that included 102 healthy volunteers who did not have a neurologic or audiovestibular disease (54 females and 48 males).

Patients with "definite" Meniere's disease and CCSVI diagnosis were submitted to cerebral and neck MRI angiography (GE Brivo MR 355 machine1.5 T.). The MRI study protocol consist of TOF (2D) images to study arterial and venous flow dynamic and

TABLE 28.I. Demographic data of enrolled patients with MD.

Characteristic	Value
Mean age	58 (22-76)
Women	189
Men	123
Onset of illness	1-28 years before

TABLE 28.II. Ultrasound protocol for the CCSVI study: at least 2 out of 5 parameters are necessary for the diagnosis.

1	Reflux in the IJVs and/or vertebral veins (VVs) in orthostatic and supine postures; reflux was considered to be pathological when reversal flow lasted >0.88 s
2	Bidirectional flow (or reflux) in the intracranial veins and sinuses (we used the same intracranial approach and QDP system, available on our equipment)
3	B-mode abnormalities/stenosis of the IJVs: 3a) morphological stenosis: presence of severe reduction of the CSA of IJVs in the supine position (<0.3 cm2 which does not increase with Valsalva maneuver, performed at the end of the examination. 3b) hemodynamic stenosis: a significant stenosis with simultaneous presence of intraluminal defects such as webs, septa or malformed valves, and hemodynamic changes (block, reflux, increased velocity flow)
4	Flow not Doppler – detectable in IJVs and /or VVs despite numerous forced inspirations, in both sitting and supine position
5	Δ cross sectional area (ΔCSA) in the IJV: the value is obtained by measuring the difference in IJV cross-sectional area between the supine and uprigth positions The presence of Two or more criteria ensure a very high sensitivity for the diagnosis of CCSVI Furthermore, intra-observer variability was calculated, aiming at measuring the reproducibility of ultrasound evaluations and its value was 0.89 according to the ICC (intra class correlation coefficient, classified as good if over 0.80) [g].

(Proposed by Zamboni, approved by the International Society for Neurovascular Disease 2011 and modified by the 2014 guidelines).

3D contrast-enhancement MR to evaluate vascular anomalies: atresia, aplasia, truncular malformations, valve problems.

The CSA (cross sectional area) was used to evaluate the degree of stenosis of the target vessels: value <25 mm^2 at or below C3 was considered as a stenosis, on the contrary above C3 the vessel was considered stenotic for CSA <12.5 mm^2.

The inner ear was evaluated with multiplanar reconstructions before and after contrast medium.

Flebography with associated PTA of both jugular veins and azygos vein was proposed and performed to the patients with evidence of venous anomalies at duplex ultrasound and/or MRI.

The procedure was performed on 105 patients (53 females-52 males), mean age 47.4±24.43 years, 70 with unilateral Menière's disease, 35 with bilateral one, onset of symptoms was from 1 to 28 years. The 24 months follow-up was available for 50 patients. The procedural venography protocol was:

– R/L femoral percutaneous access under local anesthesia;
– 2500 IU of heparin were administered;
– selective venography of jugular veins under 3 projection using a 4 Fr Bern catheter and a 4 Fr cobra and a Terumo-stiff wire.

The main criteria adopted to define the presence of a stensosis at venography were:

– at least 50% stenosis of the diameter of the vein compared with adjacent diameter
– emptying time >6 seconds
– presence of intraluminal abnormalities
– collateral veins with faster emptying time compared with internal jugular veins or azygos.

At least 2 of these criteria should be present to confirm the diagnosis. When the stenosis was detected it was dilated for 120 seconds with a low compliant 10-20 mm balloon (Cordis Maxi L-D) for the jugular veins (the most common were the 14 mm and 16 mm balloon) and 8-12 mm balloon for the azygos vein (Cordis Power-Flex). Technical success was achieved in case of:

– residual stenosis less than 20%;
– reduced emptying time;
– disappearance or significant reduction of the collateral circulation.

The patients were discharged the day after the procedure with low weight heparin (4000-6000 IU twice a day according to their body weight) for 20 days and 100 mg/day of

mesoglycan for 12-24 months. The follow-up was performed at 1 month and subsequently every 3 months and consisted of laboratory exams (vitamins B and D, folic acid, homocysteine plasma level), duplex ultrasound of the neck and intracranial venous system, otolaryngology visit with tonal audiometric examination at the Audiology and Vestibular Disease Center of one of the referral enrolling centers. Anatomic results at 24 months were considered as the final result of the PTA procedure for CCSVI. Meniere's symptoms were evaluated as follow:

- *aural fullness:* according to patient evaluation (disappeared, reduced, not modified, worsened after PTA);
- *tinnitus:* according to patient evaluation (disappeared, reduced, not modified, worsened after PTA) and to the Dizziness Handicap Inventory evaluated before and after PTA;[50]
- *hearing loss:* evaluated with tonal audiometric examination before and after PTA (Pure Tone Average 500-3000 Hz). According to A.A.O. 1995 guidelines the exam was considered as modified (ameliorated or worsened) in case of 10 dB difference in two Pure Tone Averages;
- *dizziness:* as for acute dizziness recurrence the outcome was evaluated according to diagnostic A.A.O. 1995 guidelines, comparing the number of crisis in the 6 month before the procedure and the ones occurred between 18 and 24 months after the procedure (Table 28.III). The impact of dizziness on quality life was evaluated with the Dizziness Handicap Inventory [51] before and after PTA. All the symptoms were evaulated at least before and 24 months after PTA.

STATISTICAL ANALYSIS

Patient's demographics were evaluated with t-test; the significance of the association between "definite" Meniere's disease and CCSVI was determined by comparison with the control population with Fisher's exact test; the comparison of the initial audiologic staging was evaluated with the $\chi 2$ test. The comparison between the initial DHI and THI in the two group of patients and the pre and post-operative DHI and THI were evaluated with the Unpaired t test and so the comparison pre and post PTA Pure Tone Average. The subjective evaluation of fullness and results in terms of dizziness reduction were evaluated with the Fisher's exact test: for an easier evaluation outcome were divided in favorable (class A and B) and unfavorable (class C, D, E, F).

The results on determinants for CCSVI diagnosis before and 24 months after PTA were also evaluated with Fisher's exact test

TABLE 28.III. Vertigo attacks.

Vertigo attacks			Average attacks/month post-treatment (24 months recommended) x 100 =Control level / Average attacks/month pre-treatment (6 months. recommended)			
Control level	A	B	C	D	E	F
N. of patients	28	14	3	0	3	2
%	56%	28%	6%	6%	4%	

A O = Complete control
B 1-40 = Substantial control
C 41-80= Limited control
D 81-120: Insignificant control
E> 120 = Worsened
F Secondary treatment required due to disabling vertigo

(favorable outcome: absence of vein lesions - unfavorable outcome: persistence of vein lesions).

RESULTS

The patients with Meniere's disease and the healthy control volunteers were omogenous for age (53.1±15.34 years *vs.* 49.7±16.87; P=0.82). CCSVI diagnosis according to Zamboni criteria was present in 254 of the 312 patients with Meniere's disease (81.4%) *vs.* 12/102 of the volunteers (12.7%) (P<0.0001), with no significant differences regarding sex and age between patients with and without CCSVI. The most common ultrasound anomalies were visible intraluminal defects (criterion 3) in 90% of cases - presence of two-way flow in intracranial veins and sinuses (criterion 2) in 80%, the absence of flow both in VGIs and VVs and/or absence of flow in one projection and two-way in the other (criterion 4) in 45% of cases, while Criterion 5 (DCSA greater or unchanged at 90° and 0°) was found only in a small number of patients (3%) (Table 28.IV).

In case of monolateral Menière's disease, the largest vein lesion was always found on the side of the diseased ear, while in cases of bilateral illness, the longest onset side was always found to have more severe venous lesions. In Patients with Menière's Disease and ultrasound exam positive for CCSVI, cerebral MRI and angio MRI of the vessels of the neck and intracranial circulation were performed with venous phase study. Phlebographic examination and PTA were performed in 105 patients (53 males and 52 women) with an average age of 47 years (range 22-76 years). 70 patients were treated for unilateral illness, 35 for bilateral one.

There was a high correlation, round 90%, between ultrasound exam, MRI and flebography. Only two out of the 105 patients submitted to phlebography were not completely treated because one of the jugular veins was occluded as confirmed by intraoperative phlebography: both were partially treated by PTA of the contralateral jugular vein and azygos vein.

There was no major complication and only 5 (4,5%) minor complications occurred: 4 patients had a short-term fibrosis of the jugular vein and one a groin hematoma, treated with conservative therapy. 103 patients performed PTA on both the jugular veins and 35 also an angioplasty of the azygos.

TABLE 28.IV. The distribution of the echo-color Doppler criteria between healthy controls and patients with Ménière's disease. Data are presented as mean values (range interval), or as number and percentage.

	Healthy Controls CCSVI + 12/102 (12.7%)	Meniere Disease CCSVI + 26/312 (83.3%)	P value
Parameter 1: IJVs and/or VVs reflux	6%	55%	
Parameter 2: Intracranial veins reflux	8%	80%	
Parameter 3: IJVs stenosis a) morphological	8%	90%	
b) hemodynamic	6%	60%	
Parameter 4: Cervical veins blocked outflow	3%	45%	
Parameter 5: ΔCSA	0%	3%	

CCSVI: chronic cerebro-spinal venous insufficiency; ΔCSA: Δ Cross Sectional Area; IJVs: internal jugular veins; VVs: vertebral vein; POS.: positive.

The most involved jugular segment was J1 (60%), in 30% there was a J3 injury and in 10% a J2. In 25% of cases multiple injuries were found but only in J1 and J3. When an azygos vein stenosis was also present, it involved almost always the proximal section (90%) and only in 10% the other segments.

24 MONTHS RESULTS

1. *Results of PTA on CCSVI lesions* 24-month follow-up: out of 105 treated patients 50 completed the 24 months follow-up. Venous lesions remained unchanged in 4 patients (8%) while anatomical success was found in other 40 patients (80%). 6 patients after an initial success had a restenosis detected with ultrasound (12%).
2. *Results on of Menière's disease symptoms* The auditory capacity was overall stabilized, but did not achieve a statistically significant difference compared to the preoperative Pure Tone Average. In 6 patients, however, (12%) Pure Tone Average improvement was significant, ranging from 25 dB to 40 dB. In about 50% of the treated patients, a decrease in the number of auditory fluctuation episodes has also been reported (Table 28.IV).

Anamnestic evaluation of acute dizziness between 18 and 24 months from PTA showed a good control of vertigo (Class A + Class B) in 41/50 patients (82%), partial control (C-Class) in 6 patients, worsening in 3 patients (2 in Class E, 1 in F, treated with secondary therapy *i.e.* intratimpanic gentamicin) (Table 28.VI). Fullness was considered to be improved by 35 patients (70%), unchanged by 15, disappeared or worsened in any case (Table 28.VII). The quality of life evaluated through pre and postoperative DHI was improved in 75% of cases, unchanged in 15% and worsened in 10% cases.

TABLE 28.V. Hearing loss.

Hearing loss	PTA 0.5-3KHZ
Improved (>10 dB) In 5/25 Patients 25-40 dB	25 (50%)
Unchanged (±10 dB)	20 (40%)
Worsened (>10 dB)	5 (10%)

Note: Pure tone average is considered improved/worsened if a 10 dB difference is noted (Committee on Hearing and Equilibrium AAO-HNS, 1995)
Pre-angioplasty pure-Tone Average: 60.09 dB
Post-angioplasty pure-tone average: 50,55 dB
P=0.0031

TABLE 28.VI. Vertigo attack control.

Class A (complete control)	0
Class B (substantial control)	Jan-40
Class C (limited control)	41-80
Class D (insignificant control)	81-120
Class E (worsened)	>120

Class F (secondary treatment required due to disabling vertigo)
(Avg attacks/month post-tratment/Avg attacks/month pre-tratment) x 100 = Control Level

TABLE 28.VII. Tinnitus and fullness: subjective valuation.

	Tinnitus	Fullness
Disappeared	0	0
Improved	17 (35%)	35 (70%)
Unchanged	28 (55%)	15 (30%)
Worsened	5 (10%)	0

Changes in tinnitus and the sensation of fullness in the ear following treatment
in patients with Meniere's disease

DISCUSSION

Menière's Disease, although described for about 150 years ago, does not currently have a well defined etiology, pathogenesis, and definitive therapy with a high percentage of patients who do not respond to common therapeutic strategy. This study has shown that a high percentage of patients is affected by a modification of venous internal ear drainage due to changes in the jugular and azygos vein, whose treatment seems to offer a further therapeutic option for patients who do not respond to standard therapies.

CCSVI could therefore result in anatomical and functional alterations at the level of the non-receptive structures of the inner ear, particularly at the level of the stria vascularis, which could alter the endofacial homeostasis in a worse sense. This in addition to other cofactors could determin the outbreak of Menière's disease. The high incidence of stenosis of the veins responsible for endocranial circulatory drainage suggests that there could be a link between CCSVI and Meniere's disease and that CCSVI can be considered a further etiopathogenetic mechanism of this disease.

This study has developed new diagnostic criteria both for ultrasonographic examination and MRI of venous vessels of the neck and intracranial circulation, opening up new therapeutic horizons. Endovascular treatment of jugular and azygos veins stenosis has proved to be a low-risk procedure with long-lasting effects: at 24 months follow-up only 4 patients (8%) developed a restenosis; results on Menière's disease symptoms were favorable in a high percentage of patients, especially on dizziness, which is the most disabling factor, with improved quality of life in 75% of cases.

It should be noted that the result of PTA in the control of acute dizziness crisis is very similar to the one reported in literature with intramacular gentamicin, with two substantial differences: the first, in favour of the PTA, is that PTA poses as a "pathogenetic" type therapy, while intratimpanic gentamicin therapy is ablative, exclusively symptomatic on dizziness and with significant auditory impairment; the second, in favor of gentamicin, is that the action on the dizziness symptom is much faster with intratimpanic gentamicin, and this is why it remains the gold standard in cases where acute dizziness is a serious disabling factor for patient's quality life. The endovascular procedure, however, does not preclude and its results are not modified by other therapeutic options that can be used together if necessary.

CONCLUSIONS

In the light of our findings, one can begin to assert that the PTA of the stenosis of jugular and azygos veins may be considered a further therapeutic option for patients suffering from Menière's disease. It is probably the first time that we have a treatment that work on one of the pathogenetic mechanisms of this disease.

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