Chronic cerebrospinal venous insufficiency in Ménière's disease: diagnosis and treatment

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Abstract

The purpose of this study was to evaluate by the means of Doppler ultrasound and phlebography the relationship between Ménière's disease (MD) and chronic cerebrospinal venous insufficiency (CCSVI) and to test whether angioplasty is effective in improving symptoms. Phase 1: 50 patients diagnosed with definite MD (American Academy of Otolaryngology 1995) who had gained no benefit from routine therapy, underwent echo-enhanced color Doppler sonography using the Zamboni protocol to check for CCSVI. One-hundred healthy subjects matched for age and gender acted as controls. Phase 2: in 20 of echo-color Doppler positive Ménière's cases we performed a venogram and the diagnosis of associated CCSVI was confirmed. These patients were simultaneously treated by angioplasty of the internal jugular vein, then re-tested respect the baseline scales of MD. Out of a total of 50 patients with MD, an ultrasound diagnosis was made of CCSVI in 45 patients (90%). In the healthy population CCSVI is found in only 3% of cases (P<0.001). Twenty patients were given venograms that confirmed the CCSVI diagnosis. Finally, percutaneous transluminal angioplasty (PTA) proved to be effective in 90% of patients, with significant improvement of several scales of vestibular function at six months follow-up. There is a significant prevalence of CCSVI in patients with MD and treatment with PTA seems useful because of an improvement in symptoms and vestibular function recorded in the majority of patients.

Introduction

Ménière's disease (MD) is an inner ear disease characterized by dizziness, hearing loss, tinnitus and a feeling of fullness, with a prevalence of 0.5/100,000 of the population.[1-3] In Scandinavian countries the incidence is 430 cases per million population, with the highest percentage being found in England with 1000 cases per million population. Five thousand people are estimated to be affected by the disease in Italy.[4] Although it was first described in 1861 by Prospero Ménière,[5] at present the etiology is still uncertain; one of the most likely causes is an inability of the inner ear to absorb endolymph, leading to endolymphatic hydrops.[1-3]

In 1995, the Committee on Hearing and Equilibrium Guidelines For the Diagnosis and Evaluation of Therapy in Ménière's Disease stated that: *Ménière's disease is a clinical disorder defined as the idiopathic syndrome of endolymphatic hydrops*.[6]

MD is characterized by dizziness, tinnitus and hearing loss often associate with a feeling of fullness of the ear; it has a relapsing clinical course. Acute dizzy spells may last from minutes to hours, with a negative impact on the patient's quality of life, particularly during the acute vertiginous crisis.[1-3,7] Onset is usually unilateral, but over the years the disease may also affect the other ear; in long term follow up, bilateralization is reported in approximately 40% of cases, the majority in the first 5 years.[2,3,8] Hearing ability between attacks is recovered in the early stages, but gradually deteriorates over the years, generally with hearing loss stabilizing at levels between moderate and severe.[1-3,8.]

With regard to the pathophysiology of MD, many assumptions have been made including: i) genetic predisposition; ii) autoimmunity; iii) inflammation; iv) blocked drainage/increased endolymphatic production; v) alteration of the endocrine system.

But also: i) neuro-vegetative abnormalities; ii) viral infection; iii) dietary deficiencies; abnormal vascular system; iv) trauma, which may lead, individually or collectively, to endolymphatic hydrops.[3,7,8,9]

The onset is typically between the third and fourth decade of life, and diagnosis is usually easy;[1,3,8,10,11] the main initial differential diagnosis is a neuroma of the 8th cranial nerve.[9,11] Initially, sensory hearing loss fluctuates. Instrumental diagnosis relies on tonal and vocal audiometric examination, vestibular examination of auditory evoked potentials, vestibular evoked myogenic potentials, electrocochleography, glycerol test and inner ear computed tomography (CT) scan to rule out dehiscence of the bony capsule of the labyrinth or perilymphatic fistulas, as well as possible structural alterations; magnetic resonance imaging (MRI) brain scan focused on the acoustic facial bundle excludes neuroma of the 8th cranial nerve.[1,2,8-10,12-14]

CT scan and 3-Tesla MRI show narrowing and shortening of the vestibular aqueduct in test patients, which might suggest a morphological modification of the isthmus.[8,14]

At the moment there is no definitive cure for MD.[1,6,8] In 2006 it was reported that patients with multiple sclerosis (MS) showed a high frequency of a modification of the veins that drain blood from the brain and the medullary apparatus, with a slowing down of the flow and the formation of collateral circulation.[15-19] This condition, whose pathophysiological significance is not yet entirely clear and not accepted by everybody,[20] has been identified as chronic cerebrospinal venous insufficiency (CCSVI).[15-18]

Especially in the brain, such vascular abnormalities, slowing venous outflow, would appear to modify the mechanism of the cell adhesion molecules regulating the endothelial barrier function. This phenomenon could be due to increased permeability of the blood-brain barrier. The resulting inflammation may cause the activated endothelium to secrete pro-inflammatory cytokines, with secondary transformation of monocytes into antigenic elements, triggering an autoimmune reaction against myelinated nerve cells.[16,19-22]

Among the numerous methods proposed for the diagnosis of CCSVI, the most appropriate is the evaluation of venous flow by echo-enhanced Doppler, combined with transcranial Doppler, which also allows an assessment of the deep cerebral veins and any reflux. Zamboni therefore established an ultrasound protocol for identifying the 5 characteristic parameters of CCSVI:[21,23-27] i) evidence of two-way flow in one or both of the internal jugular veins (IJV) and/or in the vertebral veins (VV) in both positions (supine and upright), or bi-directional flow in one position with the absence of flow in the other; ii) evidence of two-way flow in the intracranial veins and sinuses; iii) visibility of intraluminal defects (flaps, septa or valvular defects) associated with hemodynamic changes (blocks, reflux or acceleration) and/or reduction of IJV in the

supine position to 0.3 cm/2°; iv) no evidence of flow in both the IJV and VV and/or absence of flow in one position and two-way flow in the other; v) CSA (cross-sectional area) of IJV enlarged or unchanged both at 90° and 0°.

This article reports a first phase study on the ultrasound diagnosis of CCSVI in patients with MD. So far in the literature only four papers have examined this correlation.[28-31]

In 2009, Zamboni proposed endovascular treatment for these lesions by angioplasty in order to improve cerebral venous outflow.[32] In recent years, percutaneous transluminal angioplasty (PTA) procedures on neck veins and the azygos vein of patients with multiple sclerosis has become wide spread, producing good results and low morbidity,[32-34] while fueling debate and controversy in the scientific community.[33]

This article reports also on our preliminary experience in the diagnosis and endovascular treatment of CCSVI in patients with MD.

Materials and Methods

The diagnosis of Ménière's disease was made using the diagnostic scale based on clinical criteria proposed by the American Academy of Otolaryngology (AAO) in 1995.[6]

From April 2013 to December 2013 we observed 50 patients, 35 females, 15 males, aged 32 to 68 years, with an average age of 46 years, suffering from definite Ménière's disease according to AAO 1995.[6,11] Patients were diagnosed at several Italian specialized Otolaryngology and Audiology Centers. Tonal and speech audiometry was performed, along with tympanometry, vestibular examination (*bed-side* test to detect spontaneous nystagmus, head shaking evoked nystagmus, vibration evoked nystagmus, positional and positioning nystagmus; caloric stimulation according to the Fitzgerald-Hallpike technique); auditory brainstem responses; vestibular evoked myogenic potentials.

Audiological staging followed the AAO 1995 guidelines: Stage 1: ≤25 dB four tone average; Stage 2: 26-40 four tone average; Stage 3: 41-70 four tone average; Stage 4: >70 four tone average. The four tone average considers audiometric levels at 0.5, 1, 2, and 3 kHz.

The severity of vertigo in Ménière's disease was assessed using the *functional level scale,*[6] from 1 (*My dizziness has no effect on my activities at all*) to 6 (*I have been disabled for 1 year or longer*).

All patients had poor response to conventional treatment therapies (betahistine, steroids, diuretics, loop diuretics, osmotics, vasoactive drugs, etc.), with persistent dizziness, spells of acute vertigo, hypoacusis, ear fullness and tinnitus.

The patients underwent echo-color Doppler of the veins of the neck and intracranial venous according to the Zamboni protocol; the examination was also performed on 100 age-matched healthy patients, with no evidence of neurological or audiovestibular disease.

Twenty patients, 13 women and 7 men, were given phlebograms and endovascular treatment with bilateral PTA of the internal jugular vein and an assessment of the azygos vein that was treated with PTA in only three cases.

Six months after the endovascular procedure, patients were sent for follow-up to the Audiology Unit of the *G. Rummo* Hospital, for an audiovestibular assessment, through pure tone and speech audiometry and bed-side vestibular examination.

Endovascular procedure

PTA of the internal jugular vein was carried out as per the standard surgical protocol of our hospital for the treatment of CCSVI associated with multiple sclerosis: i) percutaneous right or left femoral approach under local anesthesia with lidocaine 2%; ii) direct or ultrasound-guided puncture of the common femoral vein; iii) insertion of an 8 Fr or 9 Fr introducer; iv) administration of 2500 IU of heparin sodium; v) selective venography of the internal jugular veins in three projections with an assessment of emptying times using 100 cm 4 FR BER hydrophilic catheters (or alternatively, 4Fr Cobra catheter for the azygos vein) mounted on a stiff 260 cm hydrophilic guide wire; vi) after obtaining confirmation of the presence of the lesion by echo-color Doppler, we took the PTA dilatation catheter with 10 to 20Fr low-compliance balloon attached to a power-assisted inflation-device applied for 120 seconds at 4-8 Atm; vii) hemostasis was by compression; viii) at discharge, patients were prescribed low molecular weight heparin at therapeutic doses (bemiparin sodium: 7500 IU/day) for 20 days and subsequently mesoglycan: 100 mg/day for 12-24 months.

Statistical analysis

Differences between pre- and post-operative Four Pure Tone Average and between pre- and post-operative frequency of spells of acute vertigo were assessed through the Unpaired T-test, considering a P value of <0.05 as significant, and a confidence interval of 95%. The difference in the presence of CCSVI parameters in patients suffering from MD *versus* the control population was assessed via 2-way Contingency table analysis, considering a P value of <0.05 as significant.

Results

Audiological staging

Twenty-five patients were Stage 4; 23 were Stage 3; 2 were Stage 2. Of the 20 patients who underwent PTA, 11 were Stage 4, 8 were Stage 3, and 1 was Stage 2, with a pre-operative four pure tone average of 65+/-12.68 db nHL. The mean speech discrimination was 80% both in the whole group and in the subgroup of 20 patients who underwent PTA.

Functional staging

Twenty-two patients were functional level #3; 10 were functional level #4; 9 were functional level #5; 8 were functional level #2; 1 was functional level #6. Of the 20 patients who underwent PTA, 10 were functional level #3; 6 were functional level #4; 3 were functional level 5; 1 was functional level #6.

The mean number of spells of acute vertigo in the period six months before treatment was 8.9+/-4.08.

The echo-color Doppler examination of the venous vessels of the neck and intracranial venous evidenced in 45 cases out of fifty the presence of 2 or more positive parameters for CCSVI on the side affected by MD, and in 20 cases also on the healthy side. In patients with MD bilateral lesions were revealed in the jugular and in three cases also in the azygos vein. No hypoplasia of the jugular vein was detected.

In the control population, abnormalities compatible with CCSVI were detected by Doppler ultrasound in only three patients (3%) and none had a diagnosis or symptoms of neurodegenerative disease or MD (P<0.001).

There was a correlation between the ultrasound diagnosis and the phlebogram in 90% of cases.

In all cases it was possible to perform the endovascular procedure as scheduled. No major complications or morbidity were reported, and no disability after intervention. All patients were discharged the day after the procedure.

At follow-up 6 months after the PTA, 19 patients reported an improvement in both symptoms and hearing level, and fewer spells of vertigo and tinnitus. One patient did not show any significant improvement in hearing ability, but reported a subjective improvement in tinnitus and the sensation of ear fullness.

The post-operative four pure tone average was 55.7+/-13.79 dBnHL; the difference between pre- and post-operative four pure tone average is statistically significant (P=0.03, confidence interval 95%); speech intelligibility improved from a pre-operative average value of 80% to a post-operative value of 90%.

The mean number of spells of acute vertigo decreased from 8.9 +/-4.08 in the six months

before treatment , to 0.1 +/- 0.3 in the six months after treatment, *i.e.* only 2/20 patients reported a single spell of acute vertigo (P<0.001).

Upon re-assessment of the functional level, 9 patients were functional level #2; 10 were functional level #3; 1 was functional level #4.

One patient presented with a re-stenosis of one of the jugular veins, although the symptomatic benefit persisted.

The echo-color Doppler follow-up according to the Zamboni method at 1, 3 and 6 months showed a recurrence in only one case, but without the loss of the benefit gained. There were no cases of auditory and vestibular symptoms returning to pre-surgical levels.

Discussion and Conclusions

Phase 1 of the present study showed confirms a significant high prevalence of CCSVI screened by Doppler ultrasound in MD as compared to healthy controls.[28-31]

After the confirm of CCSVI with catheter venography in a subgroup of Ménière's patients with lesions of the IJV and azygos vein, similar to those characteristic of MS (CCSVI), with slowing of the cerebral venous outflow, we consider venous drainage as a risk factor of major importance in view of the seriousness of the disease.

The results of our preliminary study confirm that PTA of the internal jugular and azygos vein is an effective procedure. Experience in treating arterial and venous lesions certainly plays a decisive role; the standardization of the method also minimizes the risk of major complications and results in a lower relapse rate than other case studies.

In this study no post-procedural thrombosis of the IJV occurred, neither at short nor longer term follow-up. The absence of such a serious complication is related to the drug therapy used and reported above: no drug-related side effects were reported.

This experience has led to a re-assessment of the vascular venous circulation of the neck and brain that until now was almost completely disregarded. Since this assessment had not previously been performed in Ménière's Disease patients, and since abnormal flow is not found in normal subjects, it certainly offers new treatment prospects.

We therefore believe that endovascular angioplasty of the internal jugular and azygos veins in patients with Ménière's disease is a safe procedure associated with the current treatment, in cases where there are diagnostic criteria, and recognize the fundamental role of the specialist and ENT expert in the management of this disease.

Improvements in subjective dizziness, num-ber of spells of acute vertigo, ear fullness and tinnitus, as well as improved hearing and vocal discrimination allow us to consider our results encouraging. However, the major limitation of our second phase study is the short follow-up.

AAO[6] suggests that *the frequency of definitive attacks for the period 6 months before treatment should be compared with the interval occurring between 18 and 24 months after treatment... characterization of treatment response for an individual patient should not be made until the patient has been observed for 24 months after treatment.* We were unable to comply with the last point due to the short follow-up, therefore we must consider our current results as non-definitive.

Consequently, it will be essential to extend the length of the follow-up of treated patients for a at least two years in order to assess the persistence of the therapeutic effects on the symptoms of MD and to apply the criteria for therapeutic validity proposed by the AAO in 1995.

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