

# The Prevalence of Chronic Cerebrospinal Venous Insufficiency in Meniere Disease: 24-Month Follow-up after Angioplasty

Aldo Bruno, MD, Marisanta Napolitano, MD, PhD, Luigi Califano, MD, Giuseppe Attanasio, MD, Vincenzo Giugliano, MD, Pier Paolo Cavazzuti, MD, Marika Viccaro, MD, Eleonora Masci, MD, Diego Mastrangelo, MD, Francesca Salafia, MD, Salvatore Mazzone, MD, Benedetto Bernardo, MD, Laura Cagnoni, MD, Roberto Filippo, MD, PhD, Marco De Vincentis, MD, PhD, and Antonio Greco, MD, PhD

## ABSTRACT

**Purpose:** To evaluate relationship between Meniere disease (MD) and chronic cerebrospinal venous insufficiency (CCSVI) using ultrasound, magnetic resonance (MR) imaging, and venography and to evaluate the effectiveness of angioplasty of the internal jugular vein (IJV) and azygos vein (AV) in reducing symptoms of MD.

**Materials and Methods:** Patients with a confirmed diagnosis of MD unresponsive to standard treatment underwent duplex ultrasound and MR imaging to diagnose CCSVI. Healthy volunteers were also studied to evaluate CCSVI in asymptomatic subjects. Patients with CCSVI and MD underwent venography and percutaneous transluminal angioplasty (PTA) of IJV and AV.

**Results:** There were 182 patients with no clinical benefit from standard treatments evaluated. CCSVI was diagnosed in 175 (87.5%) patients with MD. Venography was performed in 69 patients to confirm the diagnosis of CCSVI. In 80% of these patients, PTA of the IJV and/or AV was effective for treating signs and symptoms of MD. In the healthy cohort, CCSVI was observed in only 12% of subjects.

**Conclusions:** These results suggest a possible etiologic relationship between CCSVI and MD that warrants further investigation.

## ABBREVIATIONS

AV = azygos vein, CCSVI = chronic cerebrospinal venous insufficiency, IJV = internal jugular vein, MD = Meniere disease

From the Vascular Surgery Division (A.B., D.M., B.B.) and Radiology Department (V.G.), Gepos Clinic Telesse Terme, Via Roma 82100, Telesse Terme (BN), Italy; Hematology Unit (M.N.), Palermo University, Palermo, Italy; Departmental Unit of Audiology and Phoniatrics (L.Cal., F.S., S.M.), A.O.G. Rummo (G. Rummo Hospital Group), Benevento, Italy; Head and Neck Department (G.A., R.F.), Umberto I Polyclinic, Rome, Italy; ENT Department (P.P.C.), Maggiore Hospital, Bologna, Italy; and Sense Organs Department (M.V., E.M., L.Cag., M.D.V., A.G.), Sapienza University, Rome, Italy. Received May 12, 2016; final revision received October 17, 2016; accepted October 22, 2016. Address correspondence to A.B.; E-mail: [dottaldobruno@gmail.com](mailto:dottaldobruno@gmail.com) and [aldobruno@webmail.it](mailto:aldobruno@webmail.it)

None of the authors have identified a conflict of interest.

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*J Vasc Interv Radiol* 2016; XX:■■■-■■■

<http://dx.doi.org/10.1016/j.jvir.2016.10.019>

Meniere disease (MD) affects the inner ear and is characterized by dizziness, hearing impairment, tinnitus, and a sensation of fullness in the ear (1,2). The disease occurs in approximately 0.5 per 100,000 people (1,2). Although Ménière described the disease for the first time in 1861 (3), the mechanism leading to MD to date still is not fully understood. Diagnostic guidelines from the American Academy of Otolaryngology in 1985 and 1995 defined MD as an idiopathic syndrome of endolymphatic hydrops (1,2,4). Several factors have been advocated to contribute to the etiology of MD, including genetic predisposition, autoimmune disease, inflammation, blocked drainage and increased endolymphatic fluid production, endocrine system abnormalities, viral infection, dietary deficiencies, vascular system abnormalities,

and trauma (2,4,5). These factors, individually or in various combinations, may lead to endolymphatic hydrops (2,4–6). MD is associated with a recurrent clinical course characterized by acute attacks of vertigo and fluctuations in hearing ability that are more obvious in the early stages of the disease and can negatively affect the patient's quality of life, particularly during acute episodes (5–7). The diagnosis is usually simple; the most common differential diagnosis is neuroma of the eighth cranial nerve (1,2,7). At the present time, there is no definitive treatment for MD (8–11). In the last decade, morphologic changes in the veins draining blood from the brain and spinal cord of patients with multiple sclerosis have been observed, with consequent slowing of the blood flow and the development of collateral circulation. This condition has been identified as chronic cerebrospinal venous insufficiency (CCSVI) (12–14). Blood flow alterations also could represent a concurrent etiologic factor for MD onset. This hypothesis derives from previously reported vascular histologic abnormalities affecting the stria vascularis (15,16) and endolymphatic sac (17,18) of patients with MD.

The aim of the present study was to evaluate whether CCSVI could be a predisposing factor for developing MD. Duplex ultrasound in combination with transcranial Doppler is considered to be the most suitable method for diagnosis of CCSVI (12,19–21). In 2009, an endovascular angioplasty protocol was proposed for the treatment of these lesions to improve cerebral venous outflow (22); however, the efficacy of the procedure is still debated in the scientific community (23). Therefore, a secondary purpose of the present study was to assess the effectiveness of percutaneous transluminal angioplasty (PTA) for treating symptoms of MD.

## MATERIALS AND METHODS

This experimental study was approved by the Ethics Committee of the Italian National Health Service, “Comitato Etico Campania Nord,” and it was performed in accordance with the guiding principles of care. From April 2013 to December 2015, patients with a confirmed diagnosis of MD were enrolled; patients included 109 women and 72 men with a mean age of 46 years (range, 34–76 y) (Table 1). MD was diagnosed according to the 1995 and 2015 American Academy of Otolaryngology criteria. The onset of MD in patients ranged from 28 years to 2 years prior. All patients underwent duplex ultrasound of the neck veins and intracranial venous circulation according to the criteria of the International Society for Neurovascular Disease Consensus of 2011 (20) and modified by guidelines published in 2014 (21). Duplex ultrasound was also performed on healthy volunteers (mean age, 49 y; range, 30–75 y) who did not have a neurologic or audiovestibular disease (control population). In patients with MD and

**Table 1.** Demographic Data of Enrolled Patients with MD

Characteristic	Value
Mean age, y (range)	46 (34–76)
Women	109
Men	72
Smokers	48 (26.5%)
Body mass index > 25	34 (18.7%)
Alcohol intake	51 (28.1%)
Oral contraception	18 (0.9%)

MD = Meniere disease.

positive CCSVI by ultrasound evaluation, magnetic resonance (MR) imaging was performed with a 1.5T clinical MR imaging system (Brivo MR355; GE Healthcare, Fairfield, Connecticut). Venography of the internal jugular vein (IJV) and azygos vein (AV) was also performed in patients with CCSVI.

The main criterion adopted to define stenosis of the IJV or AV at venography was at least 50% stenosis of the vein compared with the diameter of an adjacent segment of the vein. Stenosis was confirmed if  $\geq 2$  of the following additional criteria were met: (i) emptying time of > 6 seconds in all vein projections; (ii) intraluminal abnormalities (web, septa, valvular abnormalities); (iii) collateral veins with a faster emptying time compared with IJV or AV. When a stenosis was diagnosed, endovascular treatment (PTA) was performed. The following PTA protocol was applied (22): (i) percutaneous right/left femoral access under local anesthesia; (ii) administration of 2,500 IU of heparin sodium; (iii) selective venography of the IJV in 3 views using a 100-cm 4-F Ber 2 hydrophilic catheter (Cordis Corporation, Miami Lakes, Florida) and selective venography for the AV using a 100-cm 4-F Cobra catheter (Cordis Corporation), both mounted on a 0.035-inch hydrophilic guide wire (Cordis Corporation). Drainage time of the IJV and AV was evaluated. Dilation was performed with a low-compliance PTA catheter and a 10- to 20-mm balloon (Maxi LD; Cordis Corporation) for the IJV and a 10- to 12-mm balloon (Maxi LD) for the AV using inflations assisted by an inflation device for 120 seconds at 4–8 atm.

At discharge, low-molecular-weight heparin was prescribed at a therapeutic dosage (6,000 IU 2 $\times$ /d) for 20 days followed by mesoglycan at a dosage of 100 mg/d for 12–24 months. The following criteria were adopted to define the resolution of stenosis after PTA: resolution or marked improvement (> 80%) of vein stenosis, normal outflow, and disappearance of collateral venous circulation. Regular follow-up visits, including laboratory assays (vitamin B, vitamin D, folic acid, and homocysteine plasma levels), duplex ultrasound, and ear, nose, and throat examination at the Audiology and Vestibular Disease Center of one of the referral enrolling centers, were scheduled 1 month after treatment and once every 3 months thereafter. Dizziness was

evaluated according the Dizziness Handicap Inventory (24) and using the formula proposed in the 1995 American Academy of Otolaryngology guidelines (1,2). Tinnitus was evaluated with the Tinnitus Handicap Inventory (25). A quality-of-life questionnaire was also administered.

Data were analyzed by *t* test, and the significance of the association between CCSVI and established MD was determined by comparison with the control population using Fisher exact test. IBM SPSS Statistics for Windows version 20 (IBM Corporation, Armonk, New York) was used to analyze the data.

## RESULTS

Duplex ultrasound of the neck veins and intracranial venous circulation revealed  $\geq 2$  parameters positive for CCSVI in 162 patients (162 of 181; 89%), particularly on the side affected by MD. Changes consistent with CCSVI were reported in only 12 of 102 (12%) healthy volunteers in the absence of signs or symptoms attributable to a neurodegenerative disease or MD. MR imaging was performed only in patients with ultrasound scans positive for CCSVI and before performing venography. In bilateral MD cases, the very narrow lesions were on the side initially diagnosed with MD; however, the other side was also affected by lesions that slowed blood outflow in 100% of cases. AV involvement was present in 21 patients (29%). In 2 cases, obstruction of 1 IJV that could not be recanalized occurred. In 90% of cases, ultrasound, MR imaging, and venography findings corresponded.

The endovascular procedure was performed in 67 (31 men and 36 women; mean age, 47 y; age range, 35–73 y) of the 69 patients scheduled to undergo treatment. Patients had unilateral MD in 45 cases and bilateral MD in 24 cases. Total occlusion of 1 of the IJVs was found in 2 patients, making treatment inappropriate. In these 2 cases, occlusions were in the medial section of the IJV (J2). The IJV lesion was mostly (60%) found close to the brachiocephalic section of the IJV (J1), whereas it was close to the carotid bifurcation (J3) in 20% of cases and in both sections in the remaining 20% of cases. PTA provided generally good results with improved blood flow, reduction of collateral vessels, and reduction of stenosis in 75% of patients. In 25% of patients, good results were observed only in 1 of the IJVs. No major complications and only 2 cases of minor complications were recorded: 1 inguinal hematoma and 1 case of fibrosis of 1 IJV after PTA, diagnosed with ultrasound scans at the 1-month follow-up visit. Fibrosis of 1 IJV was cured with medical therapy using clopidogrel and salicylates. All patients were discharged the day after the procedure.

Of the 67 patients who underwent the procedure, 30 have been followed for 24 months as of this writing. At 2 years after the endovascular procedure, the feeling of fullness in the ear was improved in 70% of patients and

unchanged in 30% (Table 2). Hearing capacity was improved in 50% of patients, unchanged in 40%, and worsened in 10% (Table 3). At 24 months of follow-up, dizziness showed a significant improvement: it was reduced or had disappeared in 85% of patients and was unchanged or worsened in 15% (Table 4). Tinnitus improved in only 35% of patients, was unchanged in 55%, and worsened in 10% (Table 2). Questions regarding quality of life after PTA revealed an improvement in 76.6% (23 of 30) of patients. At 24 months of follow-up, only 3 cases of restenosis on ultrasound had occurred. One of these patients experienced worsening of clinical symptoms of MD. All 3 patients with restenosis refused to undergo a second endovascular procedure.

## DISCUSSION

MD is a disabling disease, in particular for patients who are unresponsive to standard treatments. A high percentage of cases of MD has been associated with lesions in the IJV and AV, such as malformations or stenosis, followed by a reduced cerebral venous outflow (26–28). The present study has evaluated vascular abnormalities in MD and tried to offer an alternative therapeutic option to otherwise untreatable subjects. The experience gained during this study allowed us to perform a more accurate ultrasound and endovascular assessment of the cerebral venous circulation in patients with MD, the characteristics of which were thus far unexplored. In this investigation, vascular abnormalities were confirmed by MR imaging and venography studies.

PTA of the IJV and AV was an effective and very low-risk procedure for the treatment of CCSVI in MD. With pharmacologic antithrombotic therapy, IJV thrombosis was not observed immediately or long after the

**Table 2.** Subjective Evaluation of Tinnitus and Fullness

	Tinnitus	Fullness
Disappeared	0	0
Improved	10 (35%)	21 (70%)
Unchanged	16 (52%)	9 (30%)
Worsened	4 (12%)	0

**Table 3.** Hearing Loss

Hearing Loss	PTA 0.5–3 kHz
Improved (> 10 dB)	15 (50%)*
In 15/30 Patients 25–40 dB	
Unchanged ( $\pm$ 10 dB)	12 (40%)
Worsened (> 10 dB)	3 (10%)

Note—Pure-tone average is considered improved/worsened if a 10-dB difference is noted (1). Pure-tone average was 60.09 dB before angioplasty and 50.55 dB after angioplasty ( $P = .0031$ ). \*In 7/15 patients, improvements were 25–40 dB.

Table 4. Vertigo Attacks

Vertigo attacks	Average attacks/month post-treatment (24 months recommended × 100 = control level)					
	A	B	C	D	E	F
Control level						
No. patients	17 (56%)	9 (30%)	2 (8%)	0 (0%)	1 (3%)	1 (3%)

Note—Control levels are defined as follows:

A: 0 = complete control

B: 1–40 = substantial control

C: 41–80 = limited control

D: 81–120 = insignificant control

E: > 120 = worsened

F: Secondary treatment required owing to disabling vertigo

\*American Academy of Otolaryngology–Head and Neck Surgery Committee on Hearing and Equilibrium, 1995–2015 (1).

procedure. PTA of the IJV and AV safely managed signs and symptoms of MD up to 24 months after treatment. Preliminary treatment outcomes persisted 24 months after the procedure and improved quality of life of patients. The observed positive effects of PTA on several important parameters support the hypothesis of an etiologic link between CCSVI and MD that warrants further investigation.

In conclusion, studies of patients with MD and CCSVI treated with PTA are needed with long-term follow-up to evaluate the duration of therapeutic results regarding signs and symptoms of MD and to assess combination with current therapeutic options. The central role of ear, nose, and throat specialists should continue to be recognized in the specific management of MD.

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