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Otology

Chronic cerebrospinal venous insufficiency in patients with Ménière's disease

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Abstract
To analyze the presence of chronic cerebrospinal venous insufficiency parameter and vascular abnormalities, in the internal jugular veins (IJVs) and/or vertebral veins in sitting and supine posture, in patients with Meniere's disease compared to healthy general population. A prospective study on 32 patients affected by definite Ménière was performed from February 2012 to January 2013. All subjects underwent an echo-color Doppler examination of the cerebrospinal venous flow. 21 of the 32 Menieric patients showed a statistically significant reflux in the intracranial veins versus healthy (65.6 vs 25%; $P < 0.001$). A high prevalence of IJVs stenosis with hemodynamic changes (increased velocity or absence of flow) was observed (66.7 vs 33.3%; $P < 0.05$). The other parameters considered did not show statistically significant differences among the two groups. The results obtained showed a vascular pattern of cerebrospinal venous system present in patients affected by definite Meniere. This vascular impairment significantly affects the vascular areas more directly involved in the venous drainage of the inner ear. Thus venous stasis may be considered a further pathogenetic mechanism for development of Meniere's disease.
Keywords
Ménière's disease CCSVI

Introduction

Ménière's syndrome (MS) is an inner ear disorder characterized by a symptom complex of episodic vertigo, fluctuating hearing loss, tinnitus, and aural fullness. There are various conditions that can cause MS, both congenital and acquired. Nevertheless, there is an idiopathic group for which no causes have been determined which, in this context, will be referred to Meniere's disease (MD). The incidence of MD is difficult to determine because of its specific characteristics: that is, occasional subtle onset, fluctuating symptoms, and long period of remission, hence the difficulty in establishing the diagnosis. Studies from Germany and USA estimate the incidence of MD in the relative populations as being 120 per 100,000 people and 190 per 100,000 people, respectively [1, 2]. In 1995, the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology-Head and Neck Surgery published guidelines for defining, reporting, and

interpreting results of the treatment of MD [3]. The diagnosis of definite MD is based on clinical history and the presence of the four main symptoms. People with MD experience incapacitating vertigo, often with nausea and vomiting, typically lasting hours, tinnitus, pressure in the head or ear during vertigo spells, audiological evidence of fluctuating low-frequency and/or progressive sensorineural hearing loss.

As implied by its definition, MD's true etiology and pathophysiology remains incompletely understood. The underlying mechanism for these symptoms is thought to be an endolymphatic hydrop originated from a disturbance in the relationship between ion transport, endolymph composition and volume. Several pathological mechanisms have been proposed, such as: hypoproteinemia, blockage of the outlet from the endolymphatic space through the sac duct or excretory insufficiency of the sac epithelium [4–6]. In rare cases, posterior fossa meningioma can involve endolymphatic sac resulting in endolymphatic hydrop and a constellation of symptoms suggestive of Meniere disease [7]. Moreover, Ménière's disease with pulsatile tinnitus has been observed in patients with a high and medial jugular bulb undergone to a complete mastoidectomy. Attacks of vertigo were reported as disabling preoperatively (92 %) versus 1 (8 %) after surgical treatment. Tinnitus had been reported in all patients preoperatively and decreased in intensity in 4 (31 %) and disappeared in 3 (23 %) after surgery [8].

One of the least explored causes is the mechanism whereby the disturbance in the microcirculation of the stria vascularis might be involved. Godlowski hypothesized that an elevation of the hydrostatic head pressure at the arterial end of the microcirculation in stria vascularis in case of Ménière's disease will increase the force which drives fluid from the capillaries into the endolymphatic space. In such an event the hydrostatic pressure within the endolymph will rise only if the excess fluid is not eliminated at an equal rate back into the blood at the venous end of the stria vascularis. The venous drainage of the inner ear is carried out by the vein of cochlear aqueduct (anterior and posterior vestibular veins) and the cochlear vein [Axelsson's common modiolar vein] [9] and the vein of vestibular aqueduct (the vein of ampulla and superior, lateral and posterior canal). The venous blood empties either directly into the inferior and superior petrosal sinus or internal jugular vein [10].

Based upon both the anatomy of venous inner ear drainage and the pathogenic mechanism suggested by Godlowski, an existing excess of endolymphatic volume could be secondary to a chronic reduced or altered venous drainage of the anterior and posterior vestibular veins and/or of the cochlear veins into the venous cerebrospinal system (IJVs).

In 2006, Zamboni introduced the concept that chronic impaired venous outflow of the central nervous system is associated with multiple sclerosis (MS), coining the term of chronic cerebrospinal venous insufficiency (CCSVI). The diagnosis of CCSV requires the evaluation of five ultrasound parameters that assess both neck and head venous blood flow and anatomy [11–13]. CCSVI is diagnosed if a patient has an abnormality in two or more of the five parameters. There is controversy about the frequency and role of CCSVI in patients with multiple sclerosis and whether the frequency differs between patients with and those without multiple sclerosis. Data obtained from recent studies seems to not support the CCSVI concept [14, 15].

Is it possible to hypothesize that CCSVI for congenital anatomical alterations or functional acquired alterations represents a predisposing factor for developing inner ear disorders as Ménière's disease? The aim of this study was to evaluate the venous drainage of the neck and head in 32 patients affected by definite Ménière and compare the results with a healthy control group matched for age and sex.

Materials and methods

The study group consisted of 32 patients (13 men and 19 women, mean age 50 years ± 9.1 SD) affected by definite Ménière's disease admitted to the Department of Sensory Organs of University "Sapienza" of Rome. The presence of all four following symptoms was the criteria for inclusion in

the present study: sensorineural hearing loss, fullness, tinnitus and vertigo. Pure tone audiometry, vestibular assessment and a questionnaire regarding the duration of the symptoms, the number of episodes of vertigo in the last year and associated diseases were all performed. The healthy control group consisted of 97 patients (42 men and 55 women, mean age 38.9 years ± 14.2 SD) in general good health with no history of ear, neurological or vascular diseases.

Ultrasound evaluation of cerebrospinal venous outflow

All subjects underwent an echo-color Doppler (ECD) of the cerebrospinal venous flow. A single expert ultra-sonographer performed all ECD evaluations to reduce bias. The examination was performed with the patients in the sitting and supine positions. The morphology of the IJVs was assessed by means of high resolution B-mode ultrasounds (ECD equipped with 2.5 and 7.5–10 MHz probes and Qualite Doppler Profile system—QDP) and hemodynamics, adopting the diagnostic criteria recently approved in a consensus conference [*16*]. Venous anatomical abnormalities that we tried to find were septa/valve malformations (S/M) and membranes (MM) able to influence the venous hemodynamics of cerebral veins in these patients. These included S/M as valvular abnormalities able to create a blood flow obstacle within IJVs-brachiocephalic/anonymous trunk junction and MM as a membrane occluding a vein, according to Ciccone et al. [*17*] work recently published. Furthermore, hemodynamic parameters considered in this study are as follows [*18*–*21*].

(1)
Reflux in the IJVs and/or vertebral veins (VVs) in orthostatic and supine postures; reflux was considered pathological when reversal flow lasted more than 0.88 s.

(2)
Reflux in the intracranial veins. Reflux is defined as a reversal of flow direction during the inspiratory and expiratory phase during normal breathing with mouth closed. The transcranial color-coded duplex sonography study was carried out using the transcondylar window which assesses the direction of flow in the petrosal sinuses.

(3)
B-mode abnormalities/stenosis of the IJVs:
(3a)
Morphological stenosis: presence of severe reduction of the Cross Sectional Area (CSA) of IJVs in the supine position (<0 3 cm2 which does not increase with Valsalva maneuver, performed at the end of the examination; Fig. 1).

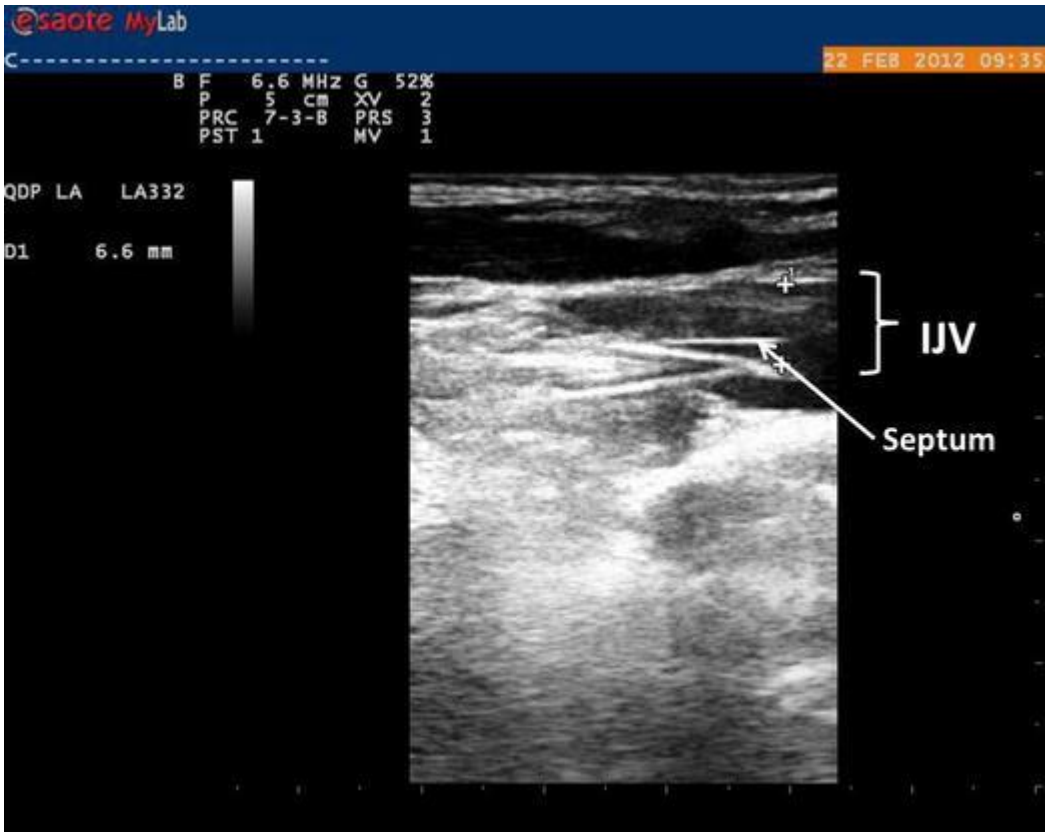

Fig. 1
Morphological internal jugular vein stenosis

(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) Fig. 2

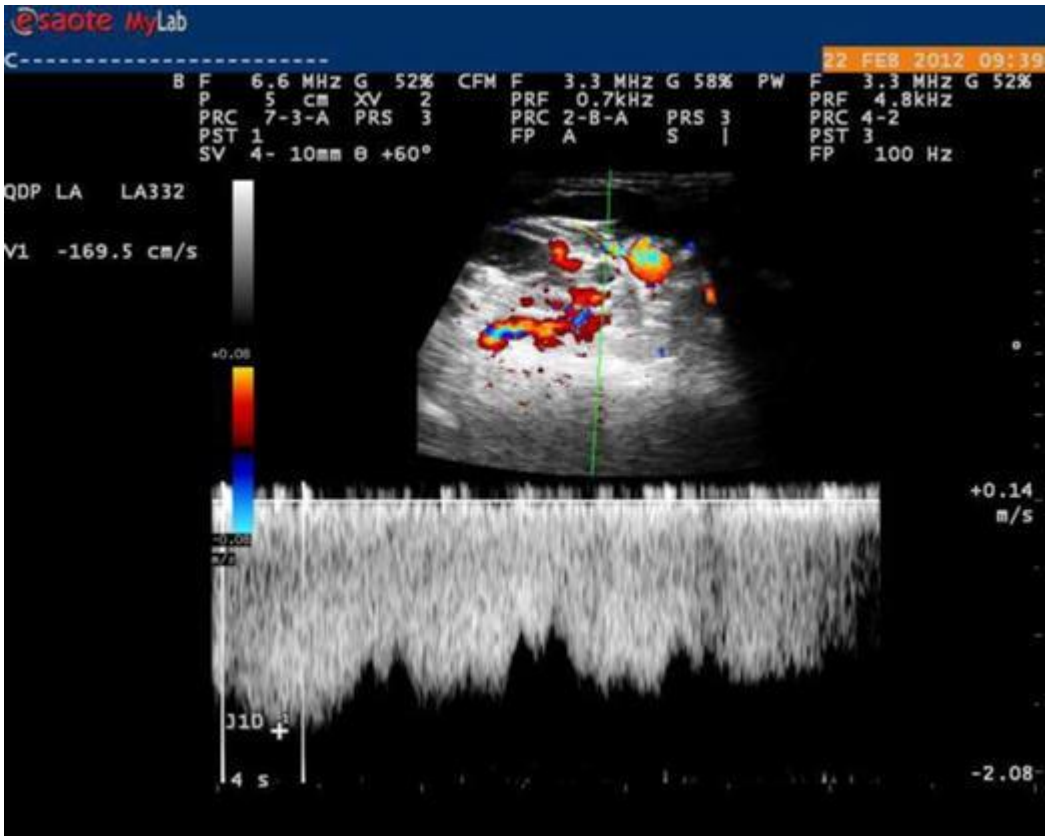

Fig. 2
Hemodynamic internal jugular vein stenosis
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(4)
Flow not Doppler–detectable in IJVs and/or VVs despite numerous forced inspirations, in both sitting and supine position.

(5)
Negative Δ CSA (ΔCSA) in the IJV: the value is obtained by measuring the difference in IJV cross sectional area between the supine and upright positions.

The presence of two or more criteria ensures a very high sensitivity for the diagnosis of CCSVI [*22*]. Furthermore, intra-observer variability was calculated, aiming at measuring the reliability of ultrasound evaluations and its value was 0.89 according to the intra class correlation coefficient (ICC) >0.80 [*23*].

Statistical analysis

The data are given as mean values ± standard deviation (SD), and categorical variables as frequencies and percentages. Between-group comparisons were made using analysis of variance (ANOVA). Frequencies were compared using the Chi-squared. P value of <0.05 was considered to be statistically significant. The statistical analysis was carried out with Statistics 6.1 software (Stat. Soft Inc., Tulsa, OK, USA).

Results

Out of a total number of 41 patients, thirty-two affected by definite MD (19 women and 13 men) were included in the study group. Twenty-one of these patients (65.6 %) were positive for CCSVI at the ECD examination of the cerebrospinal venous flow, whilst 11 patients (35.4 %) proved to be negative. The healthy control group consisted of 97 subjects (55 women and 42 men) and only 24 (25 %) showed positivity for CCSVI. Demographic and clinical characteristics of the patients are summarized in Table 1.

Table 1

Demographics and clinical characteristics in the healthy controls and in patients with MD

	Healthy controls total: 97 (%)	**Meniere disease total: 32 (%)**	**P value**
Age (years)	48.9 ± 8.1	(50 ± 9.1)	Ns
Men	42 (43)	13 (40)	Ns
Women	55 (57)	19 (60)	Ns
CCSVI POS (%)	24 (25)	21 (65.6)	<0.001
S/M and MM.	36	67	<0.001

Data are presented as mean values (range interval), or as number and percentage

MD Ménière's disease, CCSVI chronic cerebrospinal venous insufficiency, S/M Septa/Membranes, MM membrane occluding a vein, POS, positive

In the current study, the female: male ratio was 1.46:1. The mean duration of MD was 74 months. The duration of MD was 64 months in CCSVI positive and 114 months in CCSVI negative patients. The number of vertigo attacks in the course of the last year was five in the CCSVI positive patients and two in the CCSVI negative ones.

The ECD results (Table 2) showed no statistical significant differences between MD and control group concerning criteria 1, 4, and 5. A statistical significant difference ($P < 0.001$) was observed for criteria 2 and 3b. The criteria 2 (intracranial veins reflux) was positive in 76.2 % of MD (16 patients) compared with 12.5 % (3 patients) in the control group. The criteria 3b (stenosis of IJV and hemodynamic changes) was positive in 66.7 % of MD (14 patients) and 33.3 % of control subjects (8 patients) ($p < 0.05$). In addition, the stenosis of the internal jugular vein ipsilateral to the ear affected was observed in 20 MD patients (62 %) with CCSVI positive diagnosis.

Table 2

The distribution of the echo-color Doppler criteria between healthy controls and patients with MD

	Healthy Controls CCSVI POS.: 24 (25 %)	**Meniere Disease CCSVI POS.: 21 (65.6 %)**	**P value**
Parameter 1: IJVs and/or VVs reflux	12 (50)	13 (61.9)	NS
Parameter 2: Intracranial veins reflux	3 (12.5)	16 (76.2)	<0.001
Parameter 3: IJVs stenosis a) morphological	13 (54.2)	13 (61.9)	NS
b) Hemodynamic	8 (33.3)	14 (66.7)	<0.05
Parameter 4: Cervical veins blocked outflow	12 (50)	12 (46.1)	NS
Parameter 5: ΔCSA	0 (0)	0 (0)	NS

Data are presented as mean values (range interval), or as number and percentage

MD Ménière's disease, CCSVI chronic cerebrospinal venous insufficiency, ΔCSA Δ cross sectional area, IJVs internal jugular veins, VVs vertebral vein, POS positive

Discussion

The original concept that hydrops arise owing to an imbalance between endolymphatic secretion in the cochlea and endolymph resorption by endolymphatic sac has seemed increasingly unlikely and alternative theories have evolved. Salt has shown that in guinea pigs the composition of endolymph is maintained by the stria vascularis [*24*]. The stria vascularis controls the influx of water and modifies the ionic content. Normally there is little flow either radially or longitudinally, and the endolymph is a biologic puddle. If volume of endolymph is excessive, it is reabsorbed back into the stria vascularis (radial flow). Only under exceptional circumstances, such as when there is a large volume increase, does the endolymph move longitudinally into the endolymphatic sac (longitudinal flow). The balance of endolymph is maintained by the radial mechanism alone and rarely has to call upon the endolymphatic sac mechanisms to provide longitudinal flow [*25*]. The present study is based on the assumption that the radial resorption of the endolymph is then drained from the venous vascular system of the inner ear based primarily on two venous systems as cochlear and vestibular aqueduct veins that drain themselves in the inferior petrosal sinuses before emptying into the internal jugular vein. The hypothesis supported in this work was to determine whether the venous drainage of the inner ear in patients with Ménière's is compromised by venous stenosis or regurgitation that does not allow physiological endolymphatic drainage. The ultrasound study of venous district of MD patients showed a 65 % positivity of CCSVI compared to 25 % observed in the healthy. MD patients have a chronic venous insufficiency head-neck which is significantly higher than that reported from the control group. In particular the analysis of the second hemodynamic parameter, relative to the vascular intracranial reflux, showed a significant difference in the two groups. We observed that patients showed a prevalence of 76 % compared to 12.5 % in the control group. In MD patients the petrosal sinuses, more directly involved in the drainage of the inner ear, show the presence of a venous return which is not unidirectional as usually occurs physiologically. It highlights the presence of a substantial amount of venous blood stagnating in the compartment. The analysis of the third ultrasound parameter studied (jugular vein hemodynamic stenosis) was also significant and showed the simultaneous presence of intraluminal defects such as webs and septa or malformed valves, and hemodynamic changes of extracranial veins. Also patients suffering from MD showed a statistically significant stenosis of the internal jugular vein ipsilateral to the ear affected compared to the control group. The findings would seem to suggest two possible different physio-pathogenetic mechanisms that do not necessarily have to be considered as alternatives to each other. The first is that the predisposition to modified hemodynamics of the extracranial veins would lead to a critical level of accumulation of endolymph in basal conditions which could still be compensated. The presence of CCSVI in MD patients in acute phase, in whom there has been a sudden increase in volume of the endolymph (factors related to inflammatory, infectious, immunological, traumatic, with or without associated emotional factors) [*26*–*29*], could not allow an adequate venous drainage. In these patients, the hemodynamic aforementioned predisposition becomes important in the case of an increased functional necessity of the inner ear affected. The second suggestive theory about the origin of endolymphatic hydrops is based directly on venous vasculitis, which has a mechanism similar to that occurs in other vascular areas of the body. Following this hypothesis, under conditions of turbulent or inverted flow, the interaction of blood cells with the endothelium gives rise to the formation of plugs leukocytes, platelet adhesion and activation of proteolytic enzymes with subsequent degradation of the tissue [*30*, *31*]. The chronic venous stasis would have a direct action on the vascular endothelium of the stria, with the consequent reduction of the exchange or the active transport of ions between the stria and endolymphatic space at medium scale. This modification of the endolymphatic fluid would produce an increase in volume of the endolymph with consequent cochlear hydrops. The first hypothesized mechanism might be more directly involved in the early stages of the disease justifying the presence of the classic MD symptoms, that is fluctuating hearing loss, vertigo and tinnitus followed by inter-critical periods of well-being. The second mechanism may act at a later stage, justifying the natural evolution of the disease and the establishment of a moderate to severe hearing loss and absence of vertigo. The presence of an inverse correlation between duration of MD and CCSVI positive would

be a further confirmation of the greater importance of the role that could have the cerebral hemodynamic changes during the first years of the disease.

Conclusions

The study was aimed by evaluation of ultrasonographic criteria for the diagnosis of CCSVI and showed a statistically significant positivity for two criteria (2 and 3b) in MD patients.
The results obtained showed that CCSVI could be considered a new ultrasound vascular pattern of cerebrospinal venous system present in patients affected by definite MD. This vascular impairment significantly affects the vascular areas more directly involved in the venous drainage of the inner ear. Even though the diagnosis of CCSVI does not require the use of CT or MR images to confirm the presence of the criteria highlighted by ultrasonography the location of the jugular bulb on CT scan or MRI, the predominance of sigmoid sinus on T2MRI should be studied to exclude vascular abnormalities that in rare cases have been observed in MD patients.
The venous stasis of the head and neck veins may be considered a further etiopathogenetic mechanism which adds to many other already known and that define MD as a multifactorial disease. Further studies are needed to confirm and validate these results and to eventually suggest new surgical or medical therapies.

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Conflict of interest
None.

References

1.
Radtke A, von Brevern M, Feldmann M, Lezius F, Lempert T, Ziese T, Neuhauser H (2008) Screening for Meniere's disease in the general population—the needle in the haystack. Acta Otolaryngol 128:272–276PubMedCrossRef
2.
Harrys JP, Alexander TH (2010) Current-day prevalence of Meniere's Syndrome. Audiol Neurotol 15:318–322CrossRef
3.
(1995) Committee on hearing and equilibrium guidelines for the diagnosis and evaluation of therapy in Meniere's disease. American Academy of Otolaryngology-Head and Neck Foundation, Inc. Otolaryngol Head Neck Surg, 113:181–185
4.
Shambaugh GE Jr (1966) Surgery of the endolymphatic sac. Arch Otolaryngol 83(4):305–315PubMedCrossRef
5.
Williams HL Jr (1965) A review of the literature as to the physiologic dysfunction of Meniere's disease: a new hypothesis as to its fundamental cause. Laryngoscope 75(11):1661–1689PubMed
6.
Godlowski Z (1972) Hyperosmosis of endolymph as primary pathogenic mechanism of Meniere's Disease and its clinical management. Acta Otolaryngol Suppl 299:1–36PubMed
7.
Coelho DH, Roland JT Jr, Golfinos JG (2008) Posterior fossa meningiomas presenting with Ménière's-like symptoms: case report. Neurosurgery 63(5):E1001. doi:10.1227/01.NEU.0000327883.36668.B4 (discussion E1001)PubMedCrossRef
8.
Couloigner V, Grayeli AB, Bouccara D, Julien N, Sterkers O (1999) Surgical treatment of the high jugular bulb in patients with Ménière's disease and pulsatile tinnitus. Eur Arch Otorhinolaryngol 256(5):224–229PubMedCrossRef

9.
Axelsson A (1988) Comparative anatomy of cochlear blood vessels. Am J Otolaryngol 9(6):278–290PubMedCrossRef
10.
Mazzoni A (1990) The vascular anatomy of the vestibular labyrinth in man. Acta Otolaryngol Suppl 472:1–83 (Review)PubMedCrossRef
11.
Zamboni P (2006) The big idea: iron-dependent inflammation in venous disease and proposed parallels in multiple sclerosis. J R Soc Med 99(11):589–593PubMedCrossRef
12.
Diaconu CI, Conway D, Fox RJ, Rae-Grant A (2012) Chronic cerebrospinal venous insufficiency as a cause of multiple sclerosis: controversy and reality. Curr Treat Options Cardiovasc Med 14(2):203–214PubMedCrossRef
13.
Zamboni P, Galeotti R, Menegatti E (2009) Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. J Neurol Neurosurg Phychiatry 80:392–399CrossRef
14.
Valdueza JM, Doepp F, Schreiber SJ, van Oosten BW, Schmierer K, Paul F (2013) What went wrong? The flawed concept of cerebrospinal venous insufficiency. J Cereb Blood Flow Metab 33(5):657–668. doi:10.1038/jcbfm.2013.31 PubMedCrossRef
15.
Comi G, Battaglia M, Bertolotto A, Sette MD, Ghezzi A, Malferrari G, Salvetti M, Sormani M, Tesio L, Stolz E, Zaratin P, Mancardi G; the CoSMo Collaborative Study Group (2013) Observational case-control study of the prevalence of chronic cerebrospinal venous insufficiency in multiple sclerosis: results from the CoSMo study. Mult Scler, [Epub ahead of print]
16.
Zamboni P, Morovic S, Menegatti E, Viselner G, Nicolaides AN (2011) Screening for chronic cerebrospinal venous insufficiency (CCSVI) using ultrasound—recommendations for a protocol. Int Angiol 30(6):571–597PubMed
17.
Ciccone MM, Galeandro AI, Scicchitano P, Zito A, Gesualdo M, Sassara M, Cortese F, Dachille A, Carbonara R, Federico F, Livrea P, Trojano M (2012) Multigate quality Doppler profiles and morphological/hemodynamic alterations in multiple sclerosis patients. Curr Neurovasc Res 9(2):120–127PubMedCrossRef
18.
Valdueza JM, Schmierer K, Mehraein S, Einhaupl KM (1996) Assessment of normal flow velocity in basal cerebral veins. A transcranial Doppler ultrasound study. Stroke 27:1221–1225PubMedCrossRef
19.
Lepori D, Capasso P, Fournier D, Genton CY, Schnyder P (1999) High-resolution ultrasound evaluation of internal jugular venous valves. Eur Radiol 9:1222–1226PubMedCrossRef
20.
Radak D, Kolar J, Tanaskovic S, Sagic D, Antonic Z, Mitrasinovic A, Babic S, Nenezic D, Ilijevski N (2012) Morphological and hemodynamic abnormalities in the jugular veins of patients with multiple sclerosis. Phlebology 27(4):168–172. doi:10.1258/phleb.2011.011004 (Epub 2011 Sep 8)PubMedCrossRef
21.
Simka M, Kostecki J, Zaniewski M, Majewski E, Hartel M (2010) Extracranial Doppler sonographic criteria of chronic cerebrospinal venous insufficiency in the patients with multiple sclerosis. Int Angiol 29(2):109–114PubMed
22.

Nicolaides AN, Morovic S, Menegatti E, Viselner G, Zamboni P (2011) Screening for chronic cerebrospinal venous insufficiency (CCSVI) using ultrasound: recommendations for a protocol. Funct Neurol 26(4):229–248PubMed
23.
Laupacis A, Lillie E, Dueck A, Straus S, Perrier L, Burton JM, Aviv R, Thorpe K, Feasby T, Spears J (2011) Association between chronic cerebrospinal venous insufficiency and multiple sclerosis: a meta-analysis. CMAJ 183(16):E1203–E1212. doi:10.1503/cmaj.111074 (Epub 2011 Oct 3)PubMedCrossRef
24.
Salt AN, Plontke SK (2010) Endolymphatic hydrops: pathophysiology and experimental models. Otolaryngol Clin N Am 43(5):971–983. doi:10.1016/j.otc.2010.05.007 (Review)CrossRef
25.
Gibson WPR, Kaufmann Arenberg I (1991) The circulation of endolymph and a new theory of the attacks occurring in Ménière's disease. In: Kaufmann AI (ed) Inner ear surgery. Kugler Publications, The Hague, pp 17–23
26.
Friedman RA, Ryan AF (1999) The molecular mechanism and genetics of Meniere disease. In: Harris JP (ed) Meniere's disease. Kugler Pubblications, The Hague, pp 356–369
27.
Takeda T, Takeda S, Kakigi A, Okada T, Nishioka R, Taguchi D, Nishimura M, Nakatani H (2010) Hormonal aspects of Ménière's disease on the basis of clinical and experimental studies. ORL J Otorhinolaryngol Relat Spec 71(Suppl 1):1–9 (Epub 2010 Feb 24)PubMed
28.
van Cruijsen N, Jaspers JP, van de Wiel HB, Wit HP, Albers FW (2006) Psychological assessment of patients with Menière's disease. Int J Audiol 45(9):496–502PubMedCrossRef
29.
McCabe BF (1979) Autoimmune sensorineural hearing loss. Ann Otol Rhinol Laryngol 88(5 Pt 1):585–589PubMed
30.
Nicolaides AN (2005) Chronic venous disease and the leukocyte-endothelium interaction: from symptoms to ulceration. Angiology 56(Suppl 1):S11–S19 (Review)PubMedCrossRef
31.
Masutani H, Takahashi H, Sando I (1992) Stria vascularis in Mèniere's disease: a qualitative histopathological study. Auris Nasus Larynx 19(3):145–152