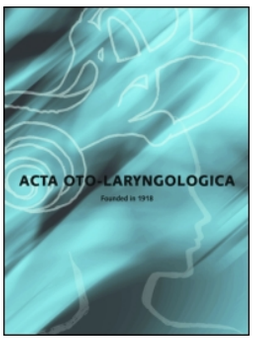

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ORIGINAL ARTICLE

Chronic cerebrospinal venous insufficiency as a cause of inner ear diseases

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ABSTRACT

Conclusion: The present study confirms a correlation between chronic cerebrospinal venous insufficiency (CCSVI) diagnosis and Ménière's disease (MD). CCSVI could be considered a new ultrasound vascular pattern of the cerebrospinal venous system in patients affected by definite MD. Conversely, the present results showed that CCSVI cannot be considered a pathogenic mechanism for idiopathic sudden sensorineural hearing loss (ISSNHL).

Objectives: The aim of this study is to investigate the correlation between CCSVI and MD and to evaluate if CCSVI can be considered a risk factor also for ISSNHL. Moreover, this study seeks to establish if, even with a different timing of onset and natural history, MD and ISSNHL may share a common pathogenic mechanism.

Method: One hundred and eighty-two patients affected by definite MD, 60 patients affected by ISSNHL, and 100 healthy control patients were enrolled in this study. All subjects underwent an echo-color Doppler (ECD) of the cerebrospinal venous flow.

Results: One hundred and fifty-two patients affected by definite MD (83,5%) and 13 patients affected by ISSNHL (21.6%) were positive for CCSVI at the ECD examination of the cerebrospinal venous flow. The healthy control group consisted of 100 subjects and only 21 (21%) showed positivity for CCSVI.

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Cochlea; jugular vein; hydrops; sudden deafness; Meniere disease; echo-color Doppler

Introduction

Sudden sensorineural hearing loss (ISSNHL) and Meniere's disease (MD) are neuro-otologic disorders affecting the inner ear, whose pathogenic mechanism has not been conclusively established.

ISSNHL has been defined as an acute form of hearing loss of greater than 30 dB in at least three contiguous test frequencies that arises over less than 72 h. ISSNHL is diagnosed by exclusion after having ruled out known causes of hearing loss. The causes of ISSNHL are unknown. The most reliable theories for the etiopathogenesis include viral infection, intra-labyrinthine membrane rupture, perilymphatic fistula, and autoimmunity. Additionally, occlusive arterial disease, whether thrombotic, embolic, or spastic, plays a role in some ISSNHL [1].

MD is a chronic inner ear disease defined by the presence of endolymphatic hydrops and clinically characterized by the presence of four symptoms: unilateral or bilateral fluctuating hearing loss, tinnitus, aural fullness, and episodic vertigo.

Recently new diagnostic criteria for Menière's disease have been formulated by the Classification Committee of the Bárány Society [2]. This classification replaces criteria formulated in 1995 [3] by AAO and includes only two categories: definite Menière's disease and probable Menière's disease.

The endolymphatic hydrops appears as the pathological substrate necessary but not sufficient to produce clinically evident disease. However, the true etiology and pathophysiology of MD remain unclear [4] and the hydrops have not been conclusively shown to be responsible for the entire cochlear and vestibular symptoms [5]. A recent study demonstrated that venous stasis of the head and neck veins may be considered a further etiopathogenetic mechanism [6]. Inner ear venous drainage occurs primarily through the internal auditory vein, cochlear aqueduct vein, and vestibular aqueduct vein that drain into the superior petrosal sinus, trasversal sinus, and the superior bulb of the internal jugular vein. In humans, the vestibular aqueduct vein empties the venous flow of the utriculus, semicircular canals, endolymphatic duct, and sac [7]. Based upon both the anatomy of venous inner ear drainage and the pathogenic mechanism for MD suggested by Godlowski [8] and by Merchant et al. [9], an existing excess of endolymphatic volume could be secondary to a chronic reduction or altered venous drainage into the venous cerebrospinal system of the anterior and posterior vestibular veins and/or of the cochlear veins. In 2006, Zamboni [10] introduced the concept that chronic impaired venous outflow of the central nervous system is associated with multiple sclerosis (MS), coining the term 'chronic cerebrospinal venous insufficiency' (CCSVI) [11].

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The diagnosis of CCSVI requires the evaluation of five ultrasound parameters that assess both neck and head venous blood flow and anatomy [12]. 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 without multiple sclerosis. Data obtained from recent studies instead seems to support a possible relationship between CCSVI and MD [6]. The aim of this study is to investigate the correlation between CCSVI and MD and to evaluate if CCSVI can be considered a risk factor for ISSNHL as well. Additionally, we seek to establish if, even with a different timing of onset and natural history, MD and ISSNHL may share a common pathogenic mechanism.

Materials and methods

One hundred and eighty-two patients affected by definite MD and 60 patients affected by ISSNHL were enrolled in this study. All patients were admitted to the Department of Sensory Organs of the 'Sapienza' University of Rome from July 2014 to October 2015. The healthy control group consisted of 100 patients in general good health with no history of ear, neurological, or vascular diseases. Demographic and clinical characteristics of patients are summarized in Table 1. Out of a total of 60 patients with ISSNHL there were 21 down-sloping audiometric curves, 23 pantonal curves, four up-sloping curves, and 12 audiometric curves defined as 'others' (severe-to-profound hearing loss).

Ultrasound evaluation of cerebrospinal venous outflow

All subjects underwent an echo-color Doppler (ECD) of the cerebrospinal venous flow. To reduce biases, all ECD evaluations were performed by a single expert. 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, by adopting the diagnostic criteria recently approved in a consensus conference [12]. The main venous anatomical abnormalities that were considered were septa/valve malformations (S/M) and membranes (MM) capable of affecting the venous hemodynamics of the cerebral veins in these patients. These included S/M, such as valvular abnormalities able to create an obstacle to blood flow within IJVs-brachiocephalic/anonymous trunk junction, and MM, such as a membrane occluding a vein [13]. The hemodynamic parameters considered in this study are as follows [14,15]:

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: presence of severe reduction of the Cross-Sectional Area (CSA) of IJVs in the supine position ($<0.3\,cm^2$), which does not increase after performing the Valsalva maneuver at the end of the examination; or 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. Negative D CSA (DCSA) 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. Furthermore, the reliability of the ultrasound evaluations was confirmed by the high value (0.89) of the intra-observer correlation coefficient [16].

Statistical analysis

The data is reported as mean values ± standard deviation (SD) for continuous variables, and as frequencies and percentages for categorical variables. Between-group comparisons were carried out by analysis of variance (ANOVA). Frequencies were compared using the Chi-squared test. A p-value $<.05$ was considered to be statistically significant. The statistical analysis was carried out with Statistics 6.1 software (Stat. Soft Inc., Tulsa, OK).

Results

Table 2 summarizes the distribution of the echo-color Doppler results among healthy controls, patients with MD, and patients with ISSNHL

one hundred and fifty-two patients affected by definite MD (83,5%) and 13 patients affected by ISSNHL (21.6%) were positive for CCSVI at the ECD examination of the cerebrospinal venous flow. The healthy control group consisted of 100 subjects and only 21 (21%) showed positivity for CCSVI.

There is no difference in the incidence of CCSVI between ISSNHL and Healthy Controls ($p = 0.9$). Parameter 5 of the

Table 1. Demographics and clinical characteristics in the subjects enrolled in the study.

	MD ($n = 182$)	ISSNHL ($n = 60$)	Healthy controls ($n = 100$)
Age (years)	52 ± 9.2	49.2 ± 8.6	51.3 ± 8.4
Men	73 (40.1%)	27 (45%)	39 (39%)
Women	109 (59.9%)	33 (55%)	61 (61%)

MD: Ménière's disease; ISSNHL: idiopathic sudden sensorineural hearing loss.

Table 2. Distribution of the echo-color Doppler results among healthy controls, patients with MD, and patients with ISSNHL.

	Healthy Controls	MD patients	ISSNHL patients	*p*-value between MD CCSVI + and ISSNHL CCSVI+
CCSVI POS	21/100 (21%)	152/182 (83.5%)[a]	13/60 (21.6%)	>.001
Parameter 1: IJVs and/or VVs reflux	5 (23.8%)	100 (65%)[a]	4 (30.7%)	>.001
Parameter 2: Intracranial veins reflux	3 (14.3%)	121 (80%)[a]	3 (23%)	>.001
Parameter 3: IJVs stenosis	7 (33.3%)	136 (90%)[a]	5 (38.4%)	>.001
Parameter 4: Cervical veins blocked outflow	2 (9.5%)	68 (45%)[a]	2 (15.4%)	>.001
Parameter 5: ΔCSA	1 (4.7%)	4 (3%)	3 (23%)[a]	>.001

Data are presented as number and percentage. MD: Menière's disease; CCSVI: chronic cerebrospinal venous insufficiency; ΔCSA: Delta cross-sectional area; IJVs: internal jugular veins; VVs: vertebral veins; POS: positive.
[a]Statistical significance.

Table 3. Audiological characteristics of ISSNHL patients positive for CCSVI.

Audiometric curve profile	CCSVI+
Down-sloping ($n = 21$)	2 (9.5%)
Pantonal ($n = 23$)	8 (34.7%)[a]
Up-sloping ($n = 4$)	1 (25%)
Severe–profound ($n = 12$)	2 (16.6%)

[a]Statistical significance.

ECD was the only one to show a statistically significant difference between the ISSNHL and Healthy control groups.

MD patients show a statistically significant difference in the incidence of CCSVI + compared to both the ISSNHL and healthy control groups ($p < .001$).

Parameters 1–4 of the ECD showed a statistically significant difference in MD patients with CCSVI + compared to both ISSNHL and healthy controls.

A statistical analysis was also performed on the audiometric curve of patients with ISSNHL positive for CCSVI, showing a significant difference in the occurrence of moderate pantonal audiometric curve (Table 3).

Discussion

The study was aimed at determining whether the venous drainage of the inner ear in patients affected by ISSNHL is compromised by venous stenosis or regurgitation, as previously demonstrated in patients affected by MD [6].

The results confirm the close correlation between MD and CCSVI. Accordingly, 83.5% of patients affected by MD were positive for CCSVI at the ECD examination of the cerebrospinal venous flow, compared to 21% in the healthy control group. The two most frequently positive criteria were IJVs stenosis (90%) and intracranial venous reflux (80%). The close correspondence between the side of the vascular lesion, and the side where menieric symptoms are greater and last longer, further supports the notion of a possible correlation between the two diseases. These results are in agreement with previously published data, obtained on a smaller sample of patients [6].

In 2007, Friis and Qvortrup [17] demonstrated that, following the obstruction of the vestibular aqueduct vein in rats, the venous blood drained from the endolymphatic sac may enter a portal circulation in the inner ear, causing the capillary venous blood to enter the capillary arterial circulation. The presence of a portal shunt in the inner ear could cause disturbances in endolymph homeostasis and potentially similar symptoms, as seen in MD. Over the years, a chronic persistence of slow cerebrospinal venous flow and the resulting lesions of labyrinthic veins endothelium could cause a fibrosis of the endolymphatic sac and duct. This would in turn result in a reduction of their vascularization and a concomitant increase in local hydrostatic pressure, with a complete inversion of venous flow, as theorized by Friis and Qvortrup. This mechanism would cause an increase of the cerebral venous pressure with a slowing of venous outflow, as predicted by mathematical models [18]. At the same time, stasis would be toxic to the endothelium by mechanisms such as iron overload, osmotic alteration of the extracellular fluids, etc., ultimately resulting in reduced functionality. These cerebrovascular alterations could also affect other inner ear districts, which also drain into the jugular venous system. As theorized by Merchant et al. [9], the most affected anatomic regions should be the stria vascularis and its fibrocytes that are actively involved in endolymphatic homeostasis. Therefore, it can be theorized that at least one of the unknown causes of toxicity postulated by Merchant et al. could be venous stasis, resulting in cellular damage of the stria vascularis, with consequent metabolic and endolymphatic disorders that lead to endolymphatic hydrops. CCSVI could then cause anatomical and functional changes in non-receptor structures of the inner ear, particularly in the vascular stria. Such alterations could alter endolymphatic homeostasis and, in the presence of additional cofactors, could contribute to the onset of Meniere's disease. This cascade of events does not seem to be involved in an acute disease such as ISSNHL, where the etiopathogenetic mechanism seems to be associated with isolated events (viral infection, ischemia, intra-labyrinthine membrane rupture, perilymphatic fistula, etc.). Accordingly, our results show no statistically significant alterations in venous drainage of the inner ear in patients affected by ISSNHL. Moreover, there were no statistically significant differences between patients with up-sloping audiometric curves and MD patients, even if the former hearing loss is more similar to the endolymphatic hydrops condition. In our study, only the moderate pantonal curve showed significant incidence in patients with CCSVI + (Chi-squared =9.462 with 3° of freedom; the two-tailed *p*-value =.024). Nevertheless, these results need to be confirmed in a larger cohort, since the distribution in four sub-samples based upon different audiometric curves reduces the number of patients for statistical analysis. Additionally, there were no common characteristics among ISSNHL patients with a diagnosis of CCSVI. CCSVI was present in 21% of patients in the healthy control group,

with no history of ear, neurological, or vascular diseases, and this result was similar to patients affected by ISSNHL (21.6%).

Conclusions

The study confirms a correlation between CCSVI diagnosis and MD, even greater than previously reported (83.5% vs 65.6%) [6]. CCSVI could be considered a new ultrasound vascular pattern of the 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. Conversely, the present study demonstrates a lack of association between CCSVI and ISSNHL. Accordingly, CCSVI cannot be considered a pathogenic mechanism for ISSNHL.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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