Cerebral venous outflow abnormalities and inner ear: an underestimated piece of the puzzle?

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Chronic Cerebrospinal Venous Insufficiency (CCSVI) is a medical disorder initially documented by Zamboni, which is distinguished by the impeded drainage of cerebrospinal fluid through the extracranial venous system. This obstruction mostly arises from the constriction or blockage of veins located in the cranial region and neck. This syndrome has the potential to result in the development of collateral circles, venous reflux, and iron accumulation within the central nervous system.[1,2]

In 2011, a set of five ultrasonography parameters were identified and published, which precisely indicate anatomical and functional changes in the venous blood flow within the neck. These parameters were essential in establishing the distinct characteristics associated with CCSVI. The most suitable approach for investigating CCSVI involves the assessment of venous flow using echo-enhanced Doppler, in conjunction with transcranial Doppler. This combined method enables the evaluation of both deep cerebral veins and potential reflux.

The role of CCSVI has been investigated as a potential etiological component in the development of many neurological and/or neurosensory conditions, including Multiple Sclerosis (MS).[2-4] Nevertheless, in recent years, some investigations have also established a potential correlation between CCSVI and Inner Ear Disorders (IED). The venous drainage of the inner ear primarily consists of three veins: the cochlear aqueduct vein, also referred to as the cochlear canaliculus vein; the vestibular aqueduct vein; and the labyrinthine vein, alternatively known as the internal auditory vein. The venous drainage occurs via the inferior petrous sinus, which ultimately connects to the Internal Jugular Vein (IJV).[5-9] In a preliminary investigation conducted by Menegatti *et al.*,[4] it was shown that individuals diagnosed with both MS and IED had a greater prevalence of CCSVI as measured by abnormal IJV function, in comparison to a control group consisting of individuals without any known health conditions. The authors have provided evidence to support the notion that both groups had a notably larger occurrence of valvular system in the IJV compared to healthy participants. Furthermore, it was observed that these patients exhibited a malfunctioning valvular system, characterized by a higher prevalence of monocuspid valve.

Undoubtedly, Meniere's Disease (MD) has garnered significant attention from the scientific community as one of the most prominent manifestations of CCSVI. MD is a clinical disorder distinguished by symptoms such as vertigo, sensorineural hearing loss, and tinnitus, as evidenced by several scholarly sources.[7-12] At present, the genesis of MD remains uncertain. Among the several explanations proposed, one of the most widely recognized in the academic literature is the hypothesis suggesting that MD may be attributed to the inner ear's excess accumulation of endolymph, leading to the development of a condition known as Endolymphatic Hydrops (EH). According to some reports, the presence of an obstruction in the extracranial venous outflow may eventually lead to intracranial venous hypertension; this, in turn, can impede the reabsorption of Cerebrospinal Fluid (CSF), resulting in an elevation of CSF pressure. Consequently, these changes in pressure could give rise to variations in endolymphatic and perilymphatic pressures. Some authors have also attributed the hydropic ear to a dysregulation/impairment of the inner ear blood flow,[7,13] particularly reporting that a venous obstruction may cause changes in the inner ear microcirculation, consequently hampering the function of the stria vascularis, and therefore of the outer and inner hair cells, as well as of the saccular, utricular and ampullary hair cells.[13]

Interestingly, it has been suggested that the presence of distinct ultrasonography CCSVI vascular patterns may be associated with the manifestation of different clinical disorders, such as MS and MD. In the disease known as CCSVI the duration of blood flow via the neck is extended primarily as a result of functional stenosis caused by either the inadequate opening of faulty jugular valves or muscular entrapment. The MS pattern is distinguished by stenosis in the J1 segment (located at the confluence with the brachio-cephalic venous trunk), alterations of the trunk in the J2 segment (associated with the ipsilateral thyroid lobe), a higher occurrence of alterations in the medial-distal J1-J2 segments, and the presence of compensatory collaterals along with the vertebral venous system. The MD pattern is distinguished by the presence of modified trunks in the J3 region, specifically in the superior segment located at the carotid bifurcation and the mandibular angle. Additionally, there is a higher occurrence of medial-proximal modifications in the J3-J2 region, together with vertebral venous hyperplasia, without any other observable collateral vessels.[8] According to the available literature,[1,2] Percutaneous Angioplasty (PTA) has demonstrated excellent

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outcomes as the sole treatment for MD, making it the only IED to be effectively managed by this approach. Specifically, in 2014, Bruno *et al.* conducted a PTA procedure on the IJV and azygos vein in patients with both MD and CCSVI. Their study reported favorable outcomes in terms of the severity of symptoms and the rate of recurrence.

The potential involvement of cerebral venous outflow abnormalities could also be considered in the pathogenic mechanism of further neurosensory diseases, including other IED disorders; in this way, some authors have also considered a possible link between CCSVI and Sudden Sensorineural Hearing Loss (SSNHL).[5,14] The etiology of SSNHL remains unknown and continues to be a subject of ongoing scholarly discourse. The vascular hypothesis (the impairment of the cochlear microcirculation) is widely supported as one of the potential etiological factors contributing to the development of this disease. Due to this rationale, certain researchers have also explored a potential correlation between severe SSNHL and CCSVI. The initial research findings indicate an elevated occurrence of CCSVI in individuals with severe SSNHL compared to those without the condition, as evidenced by some studies.[4,5,15] Despite the intriguing and encouraging first findings, the current body of literature lacks a substantial number of publications that assess the true impact of venous outflow blockage on the development of SSNHL.

Furthermore, in recent studies, a possible correlation has been established between CCSVI and recurrent Benign Paroxysmal Positional Vertigo (BPPV).[6] The etiology of recurrent BPPV, as with other inner ear disorders, remains unknown for now. Nevertheless, some investigators have proposed the notion of inner ear microcirculation impairment as a potential mechanism. It is possible to hypothesize that a slowed venous drainage may damage the inner ear at different sites; if the damage is prevalent at the level of the stria vascularis, this could cause MD, while if the injury is prevalent at the level of the utricular macula, this could cause damage to the neuroepithelium and subsequent otolithic detachment generating recurrent BPPV.[1,4]

In summary, our current understanding of the pathophysiology of IED remains limited.[15-19] Given the intricate nature of the inner ear circulation and the challenges associated with its in vivo assessment using current diagnostic methods, drawing definitive conclusions regarding the role of inner ear microcirculation in these disorders remains challenging. Enhancing our comprehension of the correlation between venous blood flow and IED could be very important for advancing our understanding of the pathophysiology of IED and subsequently assessing prospective targets for therapeutic intervention.

References

1. Zamboni P. The big idea: Iron-dependent inflammation in venous disease and proposed parallels in multiple sclerosis. J. R. Soc. Med. 2006;99:589–93.
2. Zamboni P, Galeotti R, Menegatti E, et al. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry. 2009;80:392-9.
3. Zamboni P, Morovic S, Menegatti E, et al. Screening for chronic cerebrospinal venous insufficiency (CCSVI) using ultrasound-recommendations for a protocol. Int Angiol. 2011;30:571-97.
4. Menegatti E, Tessari M, Vannini ME, et al. High resolution M-mode evaluation of jugular vein valves in patients with neurological and neurosensory disorders. Curr Neurovasc Res. 2017;14:316-22.
5. Ciorba A, Tessari M, Mazzoli M, et al. Cerebral inflow and outflow discrepancies in severe sudden sensorineural hearing loss. Curr Neurovasc Res. 2018;15:220-5.
6. Ciorba A, Tessari M, Natale E, et al. Cerebral outflow discrepancies in recurrent benign paroxysmal positional vertigo: focus on ultrasonographic examination. Diagnostics (Basel) 2023;13:1902.
7. Alpini DC, Bavera PM, Di Berardino F, Barozzi, S., et al. Bridging the gap between chronic cerebrospinal venous insufficiency and Ménière disease. Veins and Lymphatics 2016;5:1-8.
8. Bavera PM, Di Berardino F, Cecconi P, et al. Chronic cerebrospinal insufficiency in multiple sclerosis and meniere disease: same background, different patterns?. Veins and Lymphatics 2017;6:1-4.
9. Toro EF, Borgioli F, Zhang Q, et al. Inner-ear circulation in humans is disrupted by extracranial venous outflow strictures: Implications for Ménière's disease. Veins and Lymphatics 2018;7:1-12.
10. Frau GN, Pagani R, Maronato F, et al. The role of omohyoid muscle entrapment of the internal jugular vein and is surgical transection in Ménière's disease and other inner ear disorders. Veins and Lymphatics 2019;8:1.
11. Müller LO, Zhang Q, Contarino C, et al. Multi-compartment mathematical model for cerebrospinal fluid mechanics coupled to the systemic circulation: application to transverse sinus stenosis. Veins and Lymphatics 2019;8:1.
12. Bruno A, Califano L, Mastrangelo D, et al. Chronic cerebrospinal venous insufficiency in Ménière's disease: diagnosis and treatment. Veins and Lymphatics 2014;3:1-4.
13. Foster CA, Breeze RE. The Meniere attack: an ischemia/reperfusion disorder of inner ear sensory tissues. Med Hypotheses. 2013;81(6):1108-15.
14. Alpini D, Bavera PM, Di Berardino F, Barozzi S, Cesarani A. Bilateral sudden sensorineural hearing loss and chronic venous cerebrospinal insufficiency: a case report. Phlebology. 2013;28:231-3.
15. Tessari M, Ciorba A, Mueller LO, et al. Jugular valve function and petrosal sinuses pressure: a computational model applied to sudden sensorineural hearing loss. Veins and Lymphatics 2017;6:1-6.
16. Zamboni P, Menegatti E, Conforti P, et al. Assessment of cerebral venous return by a novel plethysmography method. J Vasc Surg. 2012;56:677-85.
17. Veroux P, Giaquinta A, Perricone D, et al. Internal jugular veins out flow in patients with multiple sclerosis: a catheter venography study. J Vasc Interv Radiol. 2013;24:1790-7.
18. Zamboni P, Galeotti R, Menegatti E, et al. A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency. J. Vasc. Surg. 2009;50:1348–58.
19. Zamboni P, Galeotti R, Salvi F, et al. Effects of Venous Angioplasty on Cerebral Lesions in Multiple Sclerosis: Expanded Analysis of the Brave Dreams Double-Blind, Sham-Controlled Randomized Trial. J Endovasc Ther. 2020;27:1526602819890110.