

## **Bridging the gap between chronic cerebrospinal venous insufficiency and Ménière disease**

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## Abstract

Ménière disease (MD) is a chronic illness of the inner ear that affects a substantial number of patients every year worldwide. Because of a dearth of well-controlled studies, the medical and surgical management of MD remains quite empirical. The main reason is that it is very difficult to investigate patients affected with *Certain MD* due to the post-mortem criterion necessary for this diagnostic grade. Although Endolymphatic Hydrops (EH) is the worldwide accepted mechanism of MD, the causes that induce it are still not clear. In fact MD has been correlated mostly to a wide and different disturbances ranging from trauma to sleep disorders. It is nowadays sufficiently demonstrated that Chronic Cerebro Spinal Venous Insufficiency (CCSVI) is very frequent in MD. Even if CCSVI may potentially induce EH through a pure *hydraulic* mechanism CCSVI, per se does not explain how the various disorders correlated with MD may interact with CCSVI and provoke EH. The aim of this review is an attempt to approach MD into the context of the more recent findings about the global brain waste clearance system, to which inner ear is anatomically and functionally connected, in order to build a reasonable model of MD pathogenesis. The major part of the diseases correlated to MD may act on the inner ear disturbing the Glymphatic (GS) and/or Brain Lymphatic System (BLS) activity. The venous system interplays with GS and BLS. In this model CCSVI is considered more than a direct cause of MD rather the anatomical predisposition to develop the disease. In this model EH, and then MD, is the consequence of a failure of the compensation of the congenital venous abnormalities, anatomical compensation as collateral pathways and/or functional compensation as GS and BLS. In this model the major part of the disturbances correlated to MD and the various treatment proposed find their appropriate placement.

## Introduction

Ménière's disease (MD) is a chronic illness of the inner ear that affects a substantial number of patients every year worldwide. In Europe the incidence is about 50-200/100.000 a year.<sup>1</sup> The disease is characterized by intermittent episodes of vertigo lasting from minutes to hours, with

sensorineural, usually fluctuating, hearing loss, tinnitus, and aural pressure. Attacks of vertigo may come on suddenly or after a short period of tinnitus or muffled hearing.

Inner ear diseases, including MD, are usually considered as *peripheral diseases* but, especially for the reasons that this paper concern, it is necessary to highlight at least three aspects that oblige the clinicians, at least under the therapeutic point of view, to approach the inner ear as a *central* organ:

inner ear structures are deeply embedded into the petrous part of the temporal bone, the unique ivory bony part of the skull: i) inner ear vascularization is provided by a long slender branch of the anterior inferior cerebellar artery (>85% cases) or basilar artery (<15% cases) through the labyrinthine artery (also named auditory artery or internal auditory artery), that accompanies the vestibulo-cochlear nerve through the internal acoustic meatus; ii) inner ear drainage is formed by the labyrinthine veins that accompany the branches of auditory artery from the vestibule and semicircular canals via the inferior petrous sinus into the Internal Jugular Veins (IJVs). MD may be classified according to the worldwide still accepted guide-lines published in 1995 by the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology – Head and Neck Surgery, into different grades of certainty (Table I).<sup>2</sup>

Because of a dearth of well-controlled studies, the medical and surgical management of MD remains quite empirical. The main reason is that it is very difficult to investigate patients affected with *Certain MD* due to the post-mortem criterion necessary for this diagnostic grade. Therefore every research is substantially conducted on patients with a lower diagnostic grade due to the impossibility to conduct control studies on *Certain MD*. Every research on MD is thus conditioned by this bias. For this reason, in our opinion, every research substantially has to be considered as an *high level speculation with a reasonable certainty grade*.

The aim of this paper is an attempt to approach MD into the context of the more recent findings about the global brain waste clearance system to which inner ear is anatomically and functionally connected in order to build a reasonable model of MD pathogenesis.

## Ménière Disease and Chronic Cerebro Spinal Venous Insufficiency

MD is substantially characterized by three symptoms, vertigo, hearing loss and tinnitus, it is generally correlated to a lot of *causes* and it is sustained by only one worldwide accepted *hydraulic* pathogenetic mechanism: the Endolymphatic Hydrops (EH). Paparella<sup>3</sup> used the notion of *lake-river-pond* to explain the occurrence of malabsorption of endolymph leading to hydrops. This notion describes the endolymphatic sac (ES) as a pond, with the vestibular aqueduct (the river) connecting it to the endolymphatic fluid space that is like a lake. When there is an obstruction near the ES or duct, a backlog of endolymphatic fluid is created, leading to hydrops. The causes of this kind of *malabsorption of endolymph leading to hydrops* are still debated.

At the beginning of our personal experiences on Chronic Cerebro Spinal Venous Insufficiency (CCSVI) we observed, quite incidentally, a possible correlation between CCSVI and inner ear disorders.<sup>4</sup> In fact, comparing Echo-Colour Doppler (ECD) findings in Multiple Sclerosis (MS) and in a controlled group of patients affected with different disorders we found only three controls out of sixty showing venous flow abnormalities: all of them had been affected by sudden hearing loss. Thus, we begun to extensively investigate CCSVI in a large sample of subjects affected with audio-vestibular disorders, including MD.

In 2013 Alpini and colleagues described a patient affected with<sup>5</sup> bilateral CCSVI and bilateral Sudden Sensorineural Hearing Loss (SSHL). In 2013 Alpini and colleagues<sup>6</sup> compared ECD arterial and venous tests in patients affected with cochleo-vestibular disturbances subdivided into three groups: Definite unilateral MD, Non-MD cochleo-vestibular impairment and patients affected with Benign Paroxysmal Positioning Vertigo (BPPV) with cochlear hearing loss. This paper showed that asymmetrical venous flow was more frequent in MD patients than in others. Successively Di Berardino and colleagues<sup>7</sup> investigated CCSVI in MD using both ECD and MRI confirming the high correlation between CCSVI and MD. This correlation is further supported by Filippo and colleagues.<sup>8</sup> Bruno and colleagues<sup>9</sup> performed Percutaneous Transluminal Angioplasty (PTA) in 20 MD CCSVI-positive patients obtaining at six-months follow-up significant improvement of

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symptoms (hearing loss and acute vertigo spells) in 19. In 2015 Bavera and colleagues presented at V ISNVD Annual Meeting in Naples a comparison of CCSVI characteristics into three groups of patients: MD, MS and other non-MD cochleo-vestibular disturbances. Incidence of CCSVI in MD and MS was, as expected, high, according to previous literature findings.<sup>10</sup> Comparing CCSVI findings in MS vs MD Authors showed that the level of venous abnormalities was different: J1 in MS and J3 in MD (Figure 1).

Venous alterations are differently distributed according to the kind of disease. Distribution is expressed in% of abnormal examinations. J3I is the most involved level in Ménière Disease (MD, 27 Definite Ménière patients); J1 is the most involved level in MS (70 Clinically Definite patients); in the group *Other Vestibular Disorders* (OVD, 51 patients) venous alterations are rare but J3 is still the most represented level. This figure has been redrawn from that presented by Bavera and colleagues at V ISNVD Meeting.

Also Filippo and colleagues<sup>8</sup> observed that MD patients showed the prevalence of proximal venous abnormalities with 76% of unidirectional venous return in the petrosal sinuses. Petrosal sinuses are directly involved in the drainage of the inner ear.

In 2016 Vannini and colleagues at VI ISNVD Meeting<sup>11</sup> presented a comparison between SSHL and MD patients regarding presence and characteristics of IJVs valves showing substantial differences in the two groups confirming, in this way, a certain disease-specificity of CCSVI.

Hence, it seems nowadays reasonable to state that CCSVI may be the anatomical background to develop EH in MD, at least in definite and probable MD patients.

### **Model of Brain Circulation In Chronic Cerebro Spinal Venous Insufficiency and its correlation with Ménière disease**

The mechanism leading from CCSVI to MD is still debated. Both Di Berardino and colleagues<sup>7</sup> and Filippo and colleagues<sup>8</sup> proposed a *hydraulic* disorder, or venous vasculitis or the microangiopathic changes usually associated with chronic venous insufficiency.

The blood–labyrinth barrier is impaired in association with the EH.<sup>12</sup> The luminal compartment of the inner ear, the endolymphatic space, is separated by the abluminal compartment, the perilymphatic space, by highly specialized epithelial cells with tight junctions. The endolymphatic space contains luminal fluid with high potassium ( $K^+$ ) concentration and low sodium ( $Na^+$ ) concentration, which provides the ionic milieu needed to sustain transduction of sound and head acceleration into VIII cranial nerve impulses. The fluid volume within the bony labyrinth remains constant. Changes in the volumes of the endolymphatic and perilymphatic compartments are responses to osmotic gradients between the compartments themselves.<sup>13</sup> Perilymph is connected fairly directly to spinal fluid pathways via the cochlear canaliculus. When spinal fluid pressure changes, perilymph pressure changes within about 10 seconds. The composition of endolymph is maintained by stria vascularis, that is the seat of  $K^+$  secretion. Stria vascularis is densely vascularized compared with the avascular Reissner's membrane and single-vessel metabolic supply of the Outer Sulcus. Reissner's membrane is thought to be primarily responsible for  $Na^+$  homeostasis of cochlear endolymph. Outer Sulcus epithelium is located in the lateral cochlear wall, it is capable of absorbing  $Na^+$  and provides a parasensory shunt for  $K^+$  efflux.<sup>14</sup> Endolymph is coupled more indirectly to Cerebro Spinal Fluid (CSF) pressure and air pressure, through membranes. One pathway is via the endolymphatic duct, to the sac, and the dural membrane. Another is via the membranes that separate the endolymphatic and perilymphatic compartments. Normally, there is little flow of endolymph either radially or longitudinally. If endolymphatic volume becomes excessive it is reabsorbed back into the stria vascularis by means of radial flow. When there is a largest volume increase endolymph move longitudinally into the ES. The ES is a blind pouch, its epithelial cells consist primarily of two types: mitochondria-rich cells and ribosome-rich cells but little is known about the ion transport properties of each cell type. ES is placed on the posterior surface of the petrous portion of the temporal bone, where it is in contact with the dura mater and perform both absorptive and secretory, as well as phagocytic and immunodefensive, functions.

In this way the underlying mechanism of EH is still debated, with some researches in favor of a purely hydraulic mechanism and others hypothesizing a control mechanism of ionic balance. Hydraulic hypothesis supports ES surgery, while Control hypothesis pharmacologic treatments.

On the other hand, several studies analyzing the temporal bone anatomy in MD patients have found consistent alterations in the arrangement of the sigmoid sinus, anteriorly or medially displaced, and Jugular Bulb Abnormalities (JBA).<sup>15</sup> For these reason Sac-Vein decompression<sup>16</sup> seems to be more effective that Sac Decompression alone.

If the role of intracranial veins in causing abnormalities of inner ear metabolism and then labyrinth function is easy to understand, more difficult is to correlate alterations of neck vein structures on cerebral venous hemodynamics.

Müller and Toro<sup>17</sup> described a mathematical model for the cardiovascular system in order to describe the complex interaction between intracranial pressure and cerebral vasculature and the Starling-resistor like behavior of the intracranial veins.

The cranial cavity is a space of fixed volume containing parenchyma, the brain, and fluids, CSF and blood, fluids functionally connected: variations in intracranial blood volume produce fluctuations of intracranial pressure and, consequently, exchange of CSF between the intracranial and spinal subarachnoid spaces. In this way<sup>18</sup> blood volume may regulate Glimphatic system.<sup>19</sup> Furthermore, variations in intracranial blood volume<sup>20</sup> may potentially influence on Brain Lymphatic System.<sup>21</sup>

Intracranial veins are flexible tubes that drain into the various dural sinuses, located in the dura madre and therefore more rigid than cerebral veins.

Starling resistor is a an experimental device in which a collapsible tube, like an intracranial vein or IJV, is connected to two rigid tubes, like the dural sinuses, at its extremities and located in a chamber of fixed volume with variable ambient pressure, like the cranial cavity.

The pressure difference that regulate cerebral blood flow (CBF) both to feed brain parechima and to drain waste products of the brain parenchima metabolism, is depending on the difference between



arterial and intracranial pressure, so called Cerebral Perfusion Pressure (CPP). CBF is considered as a flow phenomenon governed by a Sterling Resistor.<sup>18</sup>

CSF filtration from the subarchnoid space towards the dural sinuses varies linearly with the difference between intracranial pressure and superior sagittal sinus pressure.

The model proposed by the Authors indicates that the leading mechanism of Starling-resistor like behavior of intracranial veins is at the point where they join dural sinuses.

Structural, like JBA, or functional, like in CCSVI, abnormalities of the cervico-cephalic veins may impair drainage of the inferior petrosal sinuses through increased pressure or blood reflux into the sinuses.<sup>8</sup> In this way, labyrinth drainage into the petrosal sinuses through endolymphatic radial flow, by means of the cochlear and the vestibular aqueduct veins, and longitudinal flow, by means of ES, is impaired. These phenomena increase inner ear pressure, leading to EH, and/or induce alteration in  $K^+/Na^+$  balance in the inner ear fluids, provoking MD attacks.

Furthermore, since many of the venous vessels in the *scala tympani* have little or no bony covering and are essentially exposed to the perilymphatic space,<sup>22</sup> the venous system could become a route of entry for the cells participating in the inner ear inflammatory process especially if slowing or refluxing of venous flow as observed in CCSVI, prolong the persistence of toxins, autoantibodies or pathogens into the inner ear like *viruses*<sup>23-25</sup> *free radicals*<sup>26</sup> and cochlear autoantibodies, like *HSP 70*.<sup>27</sup>

MD has been correlated also to *migraine*<sup>28,29</sup> but CCSVI has been described also in chronic migraine patients.<sup>30</sup> Since, generally speaking, venous flow may be depending also on global circulating blood volume, it is possible that *hyperidric diet*<sup>31</sup> frequently proposed to MD patients, may act directly facilitating brain-inner ear venous drainage.

Some aspects of MD may be explained also without considering CCSVI. For example, lifestyle changes and *hypertension*<sup>32</sup> treatment, including *salt restriction*,<sup>33</sup> one of the most popular treatment regimen in MD and CPAP in *Obstructive Sleep Apnea Syndrome*,<sup>34</sup> may act directly on inner ear vascularization<sup>35</sup> and therefore on endolymph production, frank *hypoglycemia*<sup>36</sup> and

*hyperinsulinemia*, rather than diabetes,<sup>37-39</sup> it is known to alter  $\text{Na}^+/\text{K}^+$  inner ear pump, the same pump on which is supposed to act *Proton Pump Inhibitors*.<sup>40</sup>

Since MD has been correlated mostly to a wide and different diseases and treatments in addition to those mentioned above,<sup>41</sup> CCSVI may be considered more than a cause of MD per se, rather the anatomical predisposition to develop the disease.

The role of IJVs in MD has been extensively investigated and IJV abnormalities are substantially considered the main alteration that may condition the onset of the disease. On the other hand, IJV it is known to be the main route of venous drainage when supine. The extracranial venous circulation is strongly influenced by posture as demonstrated by Gadda and colleagues<sup>42</sup> that correlated, in a simulated model, the cross-sectional area (CSA) and the perimeter of Joint Venous Analysis (JVA) during the cardiac cycle. Authors showed that IJV is completely distended in supine position and collapsed when standing. In both postures vertebral veins drain the brain, in general, and, particularly, the brainstem and the cerebellum.

A retrospective review of MRI performed in the MD patients that we studied for the previous paper on CCSVI in MD,<sup>6,7,10</sup> showed *compensatory* hypertrophy of vertebral plexus or vertebral veins or both in all the patients that presented IJV abnormalities.

The complex connection between the inner ear and the neck<sup>43</sup> supports the idea that a disturbed labyrinth leads to a disturbance of head-to-neck position control and neck function increasing drainage difficulties through deep cervical muscles compression of the vertebral plexus. Furthermore, the idea that IJVs don't *compensate* primarily impaired vertebral drainage dysfunction had to be taken into account.

Mülle and Toro observed<sup>17</sup> flow distribution asymmetry between right and left transverse sinuses and, consequently, between left and right IJV. It is interesting to note that Simka and colleagues<sup>44</sup> showed that in MS venous malformations were more commonly found on the left side. The prevalence of left internal jugular vein malformations was 81.7% vs 64.0% on the right side. Similarly, blockages were found only in the left and not in the right brachiocephalic vein. Same

findings in MS have been recently reported by Bavera.<sup>45</sup> Herman,<sup>46</sup> in 1993 reported predominance of left ear in MD, sudden deafness, and inner ear damage. Successively, in 2014 Reiss and Reiss<sup>47</sup> confirmed the prevalence of left SSHL at least in females.

We conducted a retrospective evaluation of 135 patients (mean age 43±6 years) affected with Definite Unilateral MD. MD affected the right side in 57 and the left side in 78 with the slight left expected prevalence (57%). But, Right MD regarded 29 females (51%) while Left MD regarded only 17 males with a prevalence of 78% of females (Figure 2). In our experience the correlation between the MD side and prevalent venous abnormalities side is 87%. Therefore, our experience confirms the left prevalence either of CCSVI or MD. CCSVI is considered to be a congenital venous malformation. In adults, the IJVs that drain the brain develops from precardinal veins in the embryo.<sup>48</sup> These precardinal veins mostly join the common cardinal veins, in the area where, in an adult, the jugular valve is found. As stated by Simka and colleagues<sup>44</sup> it is plausible to imagine that this process could not always be perfect, especially on the left side, where part of the left common cardinal vein naturally involutes. Even the left prevalence is not so high as in MS this fact is at least intriguing.

Left MD present a slight prevalence (57%) but it is to highlight that the distribution of females is highly prevalent in left MD while in right MD genders are equally represented.

However, despite the side, MD has been correlated to a very wide range of very different disorders: *herpetic neuropathy*,<sup>25</sup> *autoimmune not cochlear pathologies*,<sup>49,50</sup> *metabolic disorders*,<sup>37</sup> *sleep disorders*,<sup>51</sup> *water/salt imbalance*,<sup>52</sup> *cervical disorders*,<sup>53</sup> *allergies*<sup>54</sup> and *food intolerance* with special regard to gluten sensitivity.<sup>55,56</sup>

Subject to the foregoing, it is our opinion that there is a gap between the so wide and so different disturbances connected to MD and a unique specific pathogenetic mechanism (EH). The stagnation per se due to jugular stenosis and/or intratemporal reflux or persistence of pathogens into the inner ear veins precisely due to venous stagnation does not seem to us enough.

Bearing in mind the venous cervico-cephalic drainage system into the context of the most complex waste brain clearance apparatus, constituted also by the glymphatic and the lymphatic systems, may bridge this gap.

### **Ménière disease, chronic cerebrospinal venous insufficiency and glymphatic system**

The veins of the vestibule and semicircular canals accompany the arteries, and, receiving those of the cochlea at the base of the modiolus, join to form the internal auditory veins (or veins of labyrinth) which end in the posterior part of the superior petrosal sinus or in the transverse sinus.

The common modiolar vein enters the bony channel immediately adjacent to the aqueduct to become the vein of the cochlear aqueduct, which in turn drains via the inferior petrous sinus into the IJVs. The cochlear aqueduct and the internal auditory canal communicate with the subarachnoid space<sup>57</sup> from where the CSF is driven into the Virchow-Robin spaces by a combination of arterial pulsatility, respiration, slow vasomotion and CSF pressure gradients.<sup>58</sup> The forces that drives CSF towards brain parenchyma are the same that regulates venous cervico-cephalic drainage.<sup>59</sup> As it is known, the clearance system that utilizes perivascular tunnels formed by astroglial cells is the Glymphatic System (GS).<sup>19</sup>

Consequently, due to the anatomy of its structures, the inner ear is therefore connected both to the Cervico-Cephalic venous system and the GS. The GS also facilitates brain-wide distribution of glucose, amino acids, lipids and neuromodulators.<sup>60</sup> In the same way, through the internal auditory canal, the same substance may reach the perilymphatic space. *Acetazolamide*, an inhibitor of carbonic anhydrases, is widely used in the treatment of MD<sup>61</sup> to reduce EH. However, Acetazolamide is known to have a strong effect in reducing CSF formation. We think that the connection between inner ear and GS may explain the therapeutic effects of Acetazolamide in MD: the reduction of CSF may induce a retrieval of perilymph reducing inner ear pressure.

The CSF movement into the parenchyma drives convective interstitial fluid fluxes within the tissue towards the perivenous spaces surrounding the large deep veins. The interstitial fluid is collected in the perivenous space from where it drains out of the brain towards the cervical lymphatic system.

GS functions mainly during sleep and it is largely disengaged during wakefulness.<sup>62</sup> Nakayama and colleagues<sup>51</sup> found in 35 Definite MD that total sleeping time was significantly higher than in controls. Nevertheless, they also showed, for the first time, a *poor quality of sleep* with decreased deep sleep and an elevated arousal index. Yet, major sleep disorders like Obstructive Sleep Apnea Syndrome (OSAS) were rare and not MD specific: 4 cases in MD group and 3 in controls. Hence, it is unlikely that MD is due to reduced brain oxygenation or vascular disturbances as observed in OSAS, while, in our opinion, these data support the role of a GS disturbance in MD pathogenesis, at least in patients affected with a poor quality of sleep. In the same way the role of *stress*, that is considered as a trigger of MD Attacks,<sup>63,64</sup> may be interpreted: stress increase brain levels of norepinephrine that is known to be responsible for suppression of GS.<sup>65</sup>

The supposed GS disturbance may not to be, for example, the reactive gliosis of aging because there is an inverse correlation between *age and MD* prevalence.<sup>66</sup> MD typically starts between the ages of 20 and 50. In addition, MD is not a neurodegenerative disease. Consequently, the expected GS disorders are unlikely to be linked to glia and astrocytes. It is more reasonable the involvement of the Aquaporins (AQP): they regulate the production both of CSF and endolymph. *AQP* are membrane proteins also known as water channels that form pores in the membrane of biological cells. AQP selectively conduct water molecules in and out of the cell, while preventing the passage of ions and other solutes. Some of them, known as aquaglyceroporins, also transport across the membrane other small-uncharged solutes, such as urea, CO<sub>2</sub>, ammonia and *glycerol*, depending on the size of the pore. The so-called glycerol test (GT) is a still worldwide employed test for the diagnosis of MD.<sup>67</sup> Ingestion of glycerol, 1.5 g/kg body weight, causes a transient reduction of the hearing loss in the early stage of MD. In some cases improvements occur with considerable speech discrimination gain. No glycerol effect is seen in normal or cases of cochlear deafness of other

types. The GT has been recently re-visited using the Vestibular Evoked Potentials<sup>68</sup> instead of the Pure Tone Audiometry in order to have a more objective test. The action of glycerol is purely osmotic and the effect in MD is due to a reduction of intralabyrinthine pressure by means of specific AQP. It is interesting to note though, that AQP1 is expressed both in the choroid plexuses, that produce CSF, and in the stria vascularis of cochlea, that produce endolymph<sup>69</sup> in the rats. In humans AQP1 is localized to fibrocytes and blood vessels of the underlying stroma and trabecular perilymphatic tissue:<sup>70</sup> venous vessels are connected to the perilymphatic space, thus it is more probable that glycerol acts on endolymphatic pressure through the functional connections between venous system and GS than directly on inner ear.

In *hypertension*, another putative cause of MD<sup>32</sup> vasopressine dysregulation<sup>71</sup> may be claimed and the anti-diuretic hormone results to be involved both in GS<sup>72</sup> and in EH.<sup>73</sup>

*In conclusion, we can state that a defective venous system as in CCSVI interferes with regular function of GS. When another factor of GS dysfunction occurs, like stress or hypertension or sleep/awakness cycle dysregulation, inner ear may become unable to clear waste products of its metabolism either through the subarachnoid space and GS and the river-lake-pond system blocks leading to the endolymphatic hydrops.*

### **Ménière disease, chronic cerebrospinal venous insufficiency and Lymphatic System**

A true lymphatic vascular system (LS) draining brain interstitial fluids and macromolecules has been very recently described.<sup>21,74</sup> Generally speaking, LS is constituted by a network of lymphatic vessels in the dura mater of the CNS that drains out of the skull via the foramina of the base of the skull itself alongside arteries (the major branches of the middle and anterior meningeal arteries and the pterygopalatine artery), cranial nerves (I, V, IX, X and XI) and veins. Lymphatic vessels have been observed in the dural lining of the cribriform plate, where some vessels pass through the skull into the nasal mucosa.

Dura mater lymphatic vessels drains brain ISF into deep cervical lymph nodes and experiments conducted in mice<sup>60</sup> showed that impairment of LS compromises CNS macromolecule clearance. As stated also by Zamboni<sup>75</sup> the interconnection of brain lymphatics with both the nasal mucosa and the deep cervical lymph nodes allows T-cells and viruses to easily circulate into the brain and therefore in the inner ear too.

In MD either virus infections by Herpes viruses<sup>76</sup> or autoimmune viral activation<sup>77</sup> or autoimmune diseases as thyroiditis<sup>78</sup> have been considered as probable causes of the disease. The lymphatic vessels run down toward the base of the skull along the transverse sinus, the sigmoid sinus, the retrosigmoid vein and the rostral rhinal vein. The ES, the pond into *Paparella's model*, is placed on the posterior surface of the petrous portion of the temporal bone, where is in contact with the dura mater. The endolymphatic duct and ES perform absorptive and secretory, as well as phagocytic and immunodefensive functions: the ES is capable of antigen recognition and processing for initiation of an immune response.<sup>79,80</sup>

Reflux of venous blood flow into the petrous veins, and, as a consequence along modiolar veins, may alter the capability of the endolymphatic sac to drain via the lymphatic dura vessels with an alteration of its immunocompetence of the ES inducing recurrent flogistic EH episodes.<sup>81</sup>

Another group of diseases claimed as MD cause are *allergies*, in general, food allergies, in particular. For almost a century inhalant and food allergies have been linked with MD symptoms.<sup>82</sup>

The prevalence of allergy in patients with MD is almost three times than in the general population.<sup>83</sup>

Wheat is one of the most common food allergens found in patients with MD, 68.2% according to Derebery and colleagues.<sup>84</sup> In 2010 Derebery and colleagues<sup>85</sup> defined the relation between allergy and MD. In 2012 Di Berardino and Cesarani<sup>55</sup> confirmed the relation between immune response to the acid proteins fraction of *gliadin* in MD and in 2013 Di Berardino and colleagues<sup>56</sup> reported recovery of MD after *gluten-free diet*.

Recently, Di Berardino and colleagues<sup>86</sup> in a group of 116 definite MD patients (52 Male 49,5±12 years - 63 Female 49,8±13 years) showed an incidence of 96% of atopic subjects by means of an

allergo-immunologic battery including skin tests (prick test, prick by prick and/or intradermo reaction) intestinal permeability test and nasal mucociliary clearance (NMC).<sup>87</sup> In MD NMC was significantly slowed.

It is well known the correlation between MD and nose disorders, generally read as to be sustained by *Eustachian Tube* disturbances.<sup>88</sup> In our opinion, the correlation between nose and EH pass through the LS: slowing of NMC in atopic patients may lead to slowing of allergens clearance in cervical lymphnodes and therefore a sensitization of the inner ear that become a hypersensitive target of the immune response to antigens.<sup>89,90</sup>

Venous disturbances may hamper inner ear lymphatic drainage through the perivenous lymphatic vessels. The putative correlation between cervico-cephalic venous regulation and nasal function may be sustained because the nose is not only a clearance organ but also a sophisticated conditioning system of the breathed air. It regulates both humidity and temperature of the inhaled air in order to maintain enough constant the physical characteristics of the air that reach the lungs despite the environmental conditions. This conditioning is due to the regulation of blood flow of the like-erectile tissue contained into each turbinate (three each side). As in corpus cavernosum, swelling of turbinate depends on arterial inflow and venous outflow. Congestion of the nose is also linked to body position, to be maximum on the side on which the subject is lying, head angle with respect to the trunk when supine, to be maximum when it is lower than 20°, and eventual pressure exerted on axillar vein with swelling of the same side.<sup>91</sup> Lifting the head more than 20° when sleeping on one hand facilitate nasal patency, on the other hand, it is usually suggested to a patient affected with CCSVI (so called inclined-bed-therapy). Furthermore, Eustachian Tube exercises using a small balloon to be inflate using the nose is usually suggested in MD patients in order to relieve aural fullness: this is nothing but repeated Valsalva Manouvres that de facto facilitates venous drainage from the brain to the thorax.

*In conclusion, we can state that a defective venous system as in CCSVI interferes with regular function of LS. When another factor of LS dysfunction occurs, like virus infections or allergic*



reactions or autoimmune diseases, ES may become unable to clear throughout the lymphatic vessels, the river-lake-pond system blocks leading to the inflammatory EH.

### **Bridging the gap**

The presence of Venous Disturbances in a high percentage of patients affected with Definite MD has been established. These abnormalities seem to be *disease specific* due to the specific anatomic<sup>11</sup> and functional<sup>7,8</sup> findings observed. Furthermore, it seems that venous disturbances are also and organ specific interpreting Bavera and colleagues<sup>10</sup> experience that, although the number of positive cases was very low, found J3 as the most represented dysfunctional level also in non-MD vestibular diseases. Obviously, this last observation needs to be confirmed in a largest number of patients.

This paper represents a putative model of interpreting the effects of CCSVI on inner ear under the light of brain GS and LF. From an epistemological point of view, a theory is a series of logical steps that are as valid as they are true while a model, the form of presentation we have chosen, is a series of logical steps as valid as useful. The helpfulness of our model is to allocate the various disorders and pathologies considered to be involved in MD in a logic and unitary explanation and, consequently, to facilitate therapeutic planning.

CCSVI may lead to endolymphatic hydrops through a pure *hydraulic* mechanism and therefore both an accurate case history and a complete evaluation of the patient are necessary in order to identify which compensatory circuits have been blocked to cause failure of compensation of the congenital abnormalities. On the basis of the Literature we think that the most probable blocked circuits in MD are the vertebral plexus,<sup>92</sup> the thyroid veins<sup>78</sup> and the anterior condylar confluent (ACC).<sup>93,94</sup>

Failure of compensation may regards also the Glymphatic and/or the Lymphatic System. Again, an accurate case history and a complete evaluation of the patient are necessary in order to identify why GS and/or LS are not able to compensate the venous clearance.

On the basis of the Literature we think that the most probable causes of a blocked GS in MD are sleep disorders, stress,<sup>95</sup> nicotine<sup>95</sup> and excitants abuse<sup>96</sup> water/salt balance dysregulation,<sup>97</sup> intestinal disorders.<sup>98</sup>

On the basis of the Literature we think that the most probable causes of a blocked LS in MD are virus infections,<sup>99</sup> viral reactivations,<sup>100</sup> activation of viral inner ear epitopes,<sup>101</sup> systemic autoimmune diseases,<sup>102</sup> middle ear diseases,<sup>103-105</sup> allergies,<sup>106</sup> nasal disturbances,<sup>107</sup> food intolerances.<sup>108</sup>

In conclusion, MD therapy requires accurate identification and treatment of each structural, metabolic ear, nose, throat and general diseases of the specific patient according to a model that we can define as a *Glocal Model of Meniere Disease*. This Glocal Model suggest to subdivide MD in two main groups: i) *structural MD*, in which a structural JBA may directly act impairing inner ear metabolism; ii) *combined MD*, in which two out of three brain drainage systems are impaired OR compensatory venous pathways are impaired in CCSVI-positive MD patients

Considering that PTA induces immediately a significant relief of symptoms in MS patients but requires at least three months<sup>109</sup> to obtain hearing improvement and vertigo attacks reduction in MD patients, further researches on the correlation between CCSVI and MD had to taken in account the possible causative role of the VV per se on inner ear disorders.

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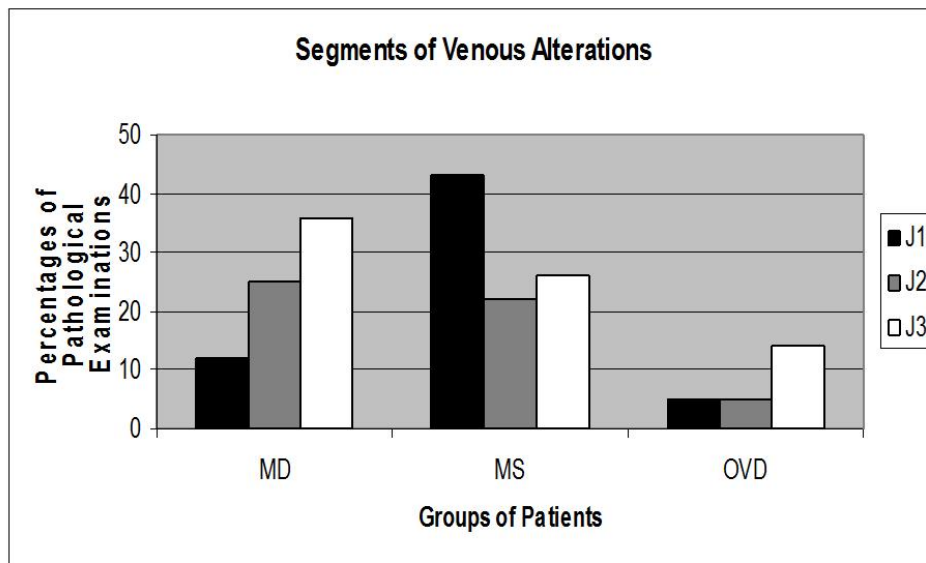


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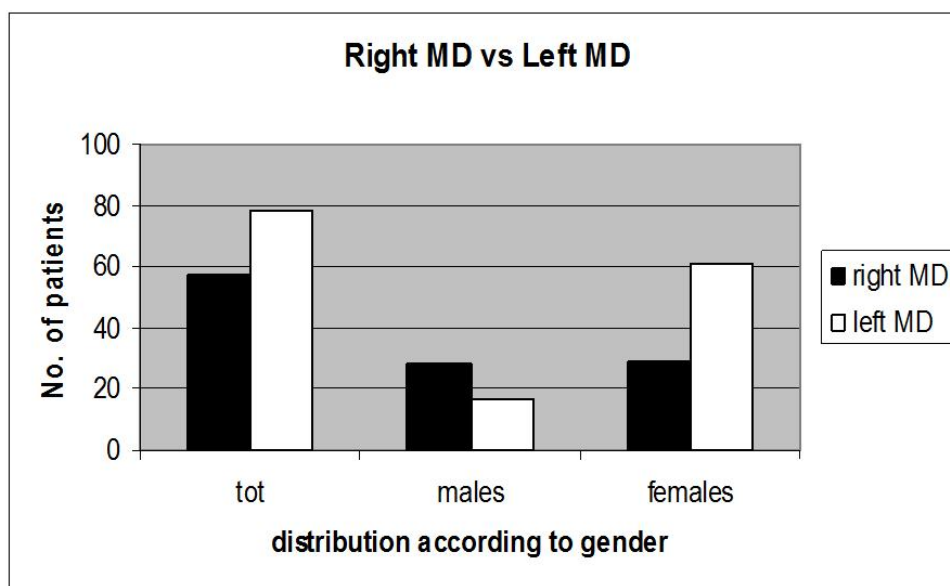
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**Figure 1. Distribution of levels of detected venous abnormalities in three groups of patients.**



**Figure 2. Distribution of side of Ménière Disease in relation with Gender.**



**Table 1. The world-wide accepted and used diagnostic Ménière Disease guide-lines. It is interesting to highlight that the grade of certainty is established to be possible only with post-mortem confirmation.**

<b>The American Academy of Otolaryngology—Head and Neck Surgery Criteria for diagnosis of Meniere's disease</b>	
The definition of the disease requires the combination of	
<ol style="list-style-type: none"> <li>1. Recurrent spontaneous and episodic vertigo. A definitive spell of vertigo lasting at least 20 min, often prostrating, accompanied by disequilibrium that can last several days; usually nausea or vomiting, or both; no loss of consciousness. Horizontal rotatory nystagmus is always present</li> <li>2. Hearing loss (not necessarily fluctuating)</li> <li>3. Either aural fullness or tinnitus, or both</li> </ol>	
The classification of the disease is graded as follows	
<b>Certain Meniere's disease</b>	Definite disease <b>plus</b> post-mortem confirmation
<b>Definite Meniere's disease</b>	Two or more definitive episodes of vertigo plus audiometrically confirmed sensorineural hearing loss, plus tinnitus, aural fullness, or both.
<b>Probable Meniere's disease</b>	One definitive episode of vertigo plus audiometrically confirmed sensorineural hearing loss plus tinnitus, aural fullness, or both; other causes excluded.
<b>Possible Meniere's disease</b>	Episodes of vertigo with no associated hearing loss or hearing loss with non-definitive disequilibrium; other causes excluded.

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