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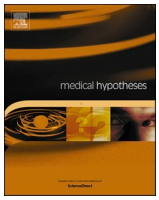

Venous outflow impairment in the posterior Cerebellum: A new pathogenic perspective on Chiari Malformation type I

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ABSTRACT

Chiari Malformation type 1 is defined as the prolapse of the cerebellar tonsils downward into the cervical canal. Known since the late 19th century, it has always lacked a clear etiological explanation and an evidence-based treatment. The comprehension of brain physiology and anatomy has evolved increasingly fast with contributions from different fields of science. Particularly, cerebrospinal fluid functions and movements, along with the venous contribution to neural physiology, are emerging concepts that are providing new insights into pathologies not yet fully described or understood. We propose a new pathogenic theory for Chiari Malformation type 1, based on the latest concepts of cerebrovascular physiology. Cerebellar tonsil herniation could result from regional edema caused by an impairment in venous drainage through the posterior paravertebral venous complex. This could provide an explanation with Goel's report about atlantoaxial instability as the cause of tonsillar prolapse and is consistent both for cases with a small posterior fossa and for cases that don't fit that classical definition. Further studies are needed to better assess the internal and external validity of this theory.

Introduction

Hindbrain structure herniation downward into the cervical canal was first described by John Cleland in 1883 after post-mortem examinations [1]. Eight years later, Hans Chiari, an Austrian pathologist, published an iconic paper titled "*Concerning Alterations in the Cerebellum Resulting from Cerebral Hydrocephalus*" [2]. Since then, a clear definition and widely shared classification have been lacking [1]. It is generally believed that Chiari Malformation (CM) Type 1, by far the most common form, has a different etiology from other types, which are more clearly "malformatives" *sensu strictu*. However, to date, no specific and singular cause has been identified. Its prevalence is estimated to be around 0.24–3.6 % of the population according to radiological studies [3]. Criteria for the diagnosis of CM-1 include cerebellar tonsil herniation greater than 3–5 mm below the foramen magnum level. However, metrics are not always definitive: there are symptomatic patients with < 3 mm prolapse [4] and asymptomatic patients with well-documented radiographic criteria for CM-1 [5]. Clinical manifestations of CM include exertional headaches, difficulty swallowing, vomiting, dizziness, neck pain, unsteady gait, poor hand coordination, numbness of the hands and feet, and speech problems [6].

Most importantly, a defined pathogenic mechanism is still missing, leading to several hypotheses, more or less coherent and consistent.

Previous Theories.

- In 1965 Gardner [7] proposed, in his hydrodynamic theory, that forebrain hydrocephalus during uterine life pushes the tentorium downward, resulting in a small posterior fossa (PF), which cannot accommodate the growing hindbrain that descends into the cervical canal. Accompanying syringomyelia is the result of the water hammer effect of cerebrospinal fluid (CSF) suddenly spurted by choroid plexus pulsations.
- Bernard Williams postulated, in 1980 [8], that birth injuries were the main causes of CM-1, given the compression of the soft skull causing downward displacement of the hindbrain. Particularly in these cases, cerebellar tonsils act as a one-way valve for CSF in the subarachnoid

Abbreviations: CM, Chiari Malformation; CSF, Cerebrospinal Fluid; ISF, Interstitial Fluid; ICF, Intracellular Fluid; IJV, Internal Jugular Vein; VVP, Vertebral Venous Plexus; SCS, Suboccipital Cavernous Sinus; SVP, Suboccipital Venous Plexus; MS, Marginal sinus; ACV, Anterior Condilar Vein; LCV, Lateral Condilar Vein; PCV, Posterior Condilar Vein; IIH, Idiopathic Intracranial Hypertension; JEDI, Jugular Entrapment and Dilated Ventricle; CCSVI, Chronic Cerebrospinal Venous Insufficiency; CVJ, Cranio Vertebral Junction; VA, Vertebral Artery; PF, Posterior Fossa.

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space: every increase in intra-abdominal pressure pushes CSF upward into the cranium, and the misplaced tonsils prevent it from flushing back to the spinal canal. This movement creates a pressure differential between cranial and spinal spaces, with a sucking effect and further hindbrain herniation. Additionally, CSF flows from the fourth ventricle down into the obex, creating syringomyelia. Once inside the medulla, CSF itself enlarges the cavity by "sloshing" upward and downward in response to epidural vein pressure variations [9].

- More recently, Marin-Padilla et al. [10] have linked CM and axial skeletal defects to a primary paraxial mesodermal insufficiency induced by vitamin A. In hamsters, a single dose of vitamin A during the early gestational period (8th day) induces skeletal malformations, including underdevelopment of the basiocciput, resulting in downward displacement of the tentorium and a crowded PF that leads to hindbrain prolapse, similar to Gardner's theory.
- During the last decade, Atul Goel et al. have proposed a reverse approach to the problem of CM. They postulate that the pathogenic *primum movens* is atlantoaxial instability, and thus cerebellar tonsil prolapse is a physiological response of the organism to protect the medulla from mechanical trauma [11]. They report significant clinical and radiological improvement after surgery for atlantoaxial fixation [12]. Other authors advocated atlanto-axial instability as a cause for symptomatic CM-1 in adult patients [13].

Here we propose a possible new explanation of CM-1 pathogenesis based on the latest advancements in craniospinal vein physiology and a reinterpretation of acquired principles of functional anatomy.

The hypothesis

Premises.

- Monro-Kelly Principle

The Monro-Kelly law describe the fixed-volume nature of the intracranial space and introduce the principle that arterial inflow must be matched by venous outflow due to brain incompressibility [14].

- CSF Physiology

The CSF system is inherently dynamic, a notion reinforced by the discovery of the glymphatic system in 2012[15], which revised the classical model of CSF flow [16]. This system facilitates exchange between intracellular fluid (ICF, 60–70 %), interstitial/extracellular fluid (ISF, 20 %), blood (10 %), and CSF (10 %) across endothelial and ependymal interfaces [17]. Driven by pressure gradients, this exchange results in ISF reabsorption into the venous system and cervical lymphatics [17,18]. Glymphatic functions include the clearance of interstitial catabolites and electrolyte regulation; however, its full physiological and pathological roles remain under investigation. Dysfunctions in this system have been implicated in multiple sclerosis [19], Alzheimer's disease, Parkinson's disease, Ménière's disease, and migraines [20].

- Venous embryology, anatomy and physiology

The cerebral venous system originates from the primitive meninx as a network of irregular cavities that eventually differentiate into defined venous structures [21]. Cerebral venous outflow follows two primary pathways: anteriorly via the internal jugular vein (IJV) and posteriorly via the vertebral venous plexus (VVP). The latter has been historically underestimated despite evidence of its significant anatomical, embryological, and physiological relevance. During early fetal life, blood from the growing parenchyma primarily drains through the PF complex. At the 11th week, the occipital sinus starts developing from the torcular and rapidly increases to 5–7 venous channels connecting to the vertebral plexus via the already well-developed marginal sinus [22]. At this stage, multiple collateral veins form through the skull for better extracranial drainage. Meanwhile, the transverse sinus balloons and enlarges to accommodate the increasing blood flow from the telencephalon. Interestingly, the jugular bulb still isn't formed, and the flow through the IJV, although detectable from the 35-mm stage of the embryo, is minimal. Additionally, a narrow segment can be identified at the junction between the sigmoid sinus and the IJV [22]. The jugular bulb is not formed during gestation but develops later during the first two years of life. Okudera et al. [22] propose that the enlargement of the bulb occurs as a consequence of the hammering effect of ascending negative pulse waves from the atrium after the child adopts an erect posture, creating a negative brain–heart differential pressure.

PF venous drainage is typically classified into three groups [23]:

- *Superior group*: Draining the superior cerebellum and mesencephalon into the vein of Galen.
- *Anterior group*: Draining brainstem, precentral cerebellar fissure, and cerebellar hemispheres into the superior petrosal sinus.
- *Posterior-inferior group*: Draining posterior cerebellar structures into the transverse sinus or torcular.

At the craniovertebral junction (CVJ), intra- and extracranial venous systems are intricately interconnected. Key anatomical structures include (Fig. 1):

- *Suboccipital cavernous sinus* (SCS), surrounding the V3 segment of the vertebral artery [24].
- *Suboccipital venous plexus* (SVP)[25].
- *Cervical VVP*.
- *Marginal sinus* (MS).
- *Anterior, lateral, and posterior condylar veins* (ACV, LCV, PCV), providing intra-extracranial venous anastomoses.
- *Mastoid and occipital emissary veins*.

Cerebral venous drainage is influenced by posture and thoracoabdominal pressure. Epstein [26] demonstrated in primate models that venous drainage preferentially occurs via the IJV in supine or high-pressure conditions, whereas in upright, spontaneously breathing states, the IJV collapses and venous flow is redirected through the VVP. These findings have been corroborated by ultrasound imaging [27] and biomechanical simulations [28].

- Interaction between Glymphatic and Venous system: CCSVI and IIH

The interplay between the glymphatic and venous systems has profound pathological implications. Disrupted cerebral venous outflow elevates IJV pressure, increasing resistance to cerebral venous drainage and transmitting hypertension to dural sinuses and parenchymal veins.

Idiopathic Intracranial Hypertension (IIH), predominantly affecting obese females, is characterized by elevated intracranial pressure in the absence of identifiable causes. It presents with symptoms such as papilledema, visual impairment, headache, tinnitus, and neck pain. There is growing evidence that IIH results from cerebral venous hypertension, often due to obesity-induced elevated thoracic-abdominal pressure [29] or venous sinus stenosis [30]. Treatments addressing venous hypertension, such as weight loss or venous stenting, have shown therapeutic efficacy. Moreover, IIH appears to involve glymphatic dysfunction, leading to ISF accumulation, a condition that could be seen as a "*glimphedema of the brain*" [31].

Chronic cerebrospinal venous insufficiency (CCSVI) encompasses a spectrum of disorders with impaired cerebral venous outflow [18]. Conditions such as Ménière's disease, transient monocular blindness, and Alzheimer's disease have been associated with IJV stenosis [32]. Impaired venous drainage compromises glymphatic clearance, fostering

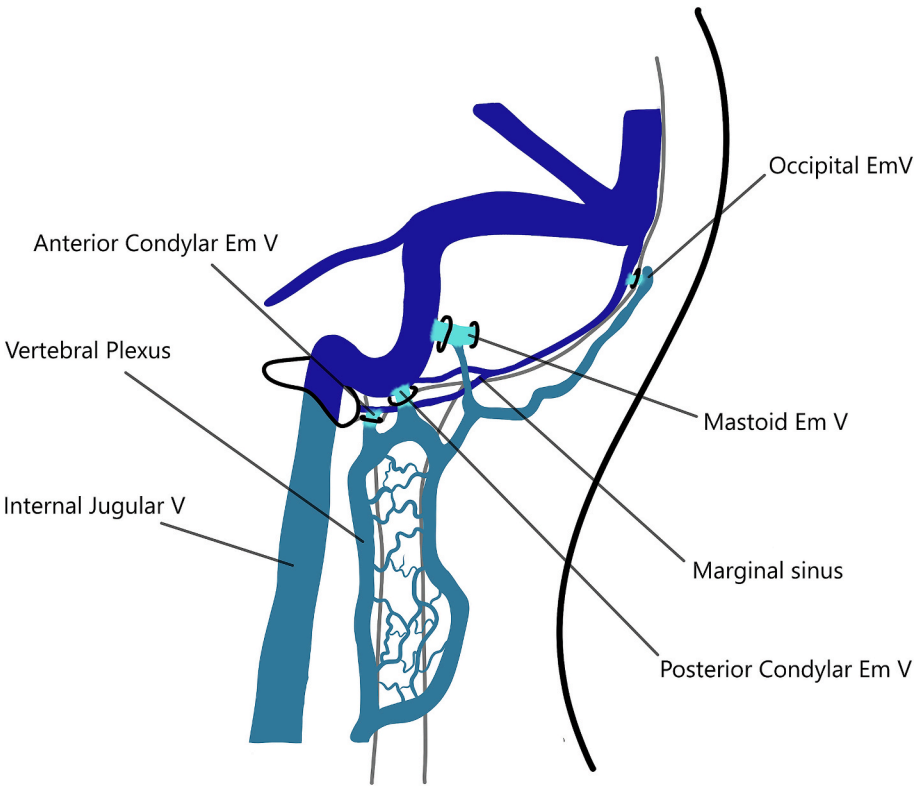

Fig. 1. Key anastomosis at the CVJ.

neuroinflammation and neurodegeneration [33].

Building on these bases, which include the most recent anatomical and physiological evidence described above, we propose a novel pathophysiological hypothesis for the development of CM-1. Specifically, we suggest that cerebellar tonsil descent may result from regional parenchymal edema secondary to impaired venous outflow in the posteroinferior cerebellar compartment. This venous drainage impairment may have multiple etiologies, both intraluminal (e.g., stenosis, thrombosis) and extrinsic (e.g., extravascular compression, elevated thoracoabdominal pressure). As described, venous hypertension disrupts the physiological pressure gradients that drive CSF and ISF clearance via the glymphatic system. When this clearance is compromised, ISF accumulates in the parenchyma, resulting in localized edema. Over time, this promotes mechanical displacement of tissue and may initiate or exacerbate chronic neurodegenerative changes. From a mechanistic perspective, this process parallels the pathogenesis of IIH: an extracranial increase in venous resistance leads to intracranial venous hypertension, impaired CSF/ISF reabsorption, and subsequent parenchymal fluid accumulation. In the context of CM-1, the anatomical confinement of the PF and its specific venous architecture—especially the connections through the CVJ and the condylar-emissary system—make this region particularly susceptible to such disturbances (Figs. 2 and 3).

Evolution of the hypothesis

Our hypothesis could bring together elements from different previous theories. As observed by Goel, atlantoaxial instability has a close link to CM-1, and its treatment is effective. It is noteworthy, given the extreme vascular importance of the CVJ, as depicted above, for venous outflow. Micro-movements caused by instability, congenital or acquired, can act as compressive forces for the SCS and nearby structures.

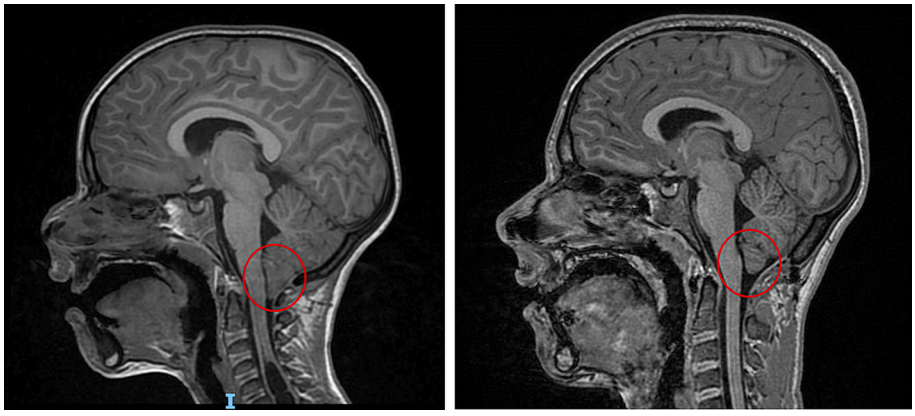

Fig. 2. Left) T1 pre-op: blurring of cortical-subcortical distinction and sulci disappearence, as observed in edematous tissues. Right) T1 post op: cortical-subcortical distinction and observable sulci with CSF.

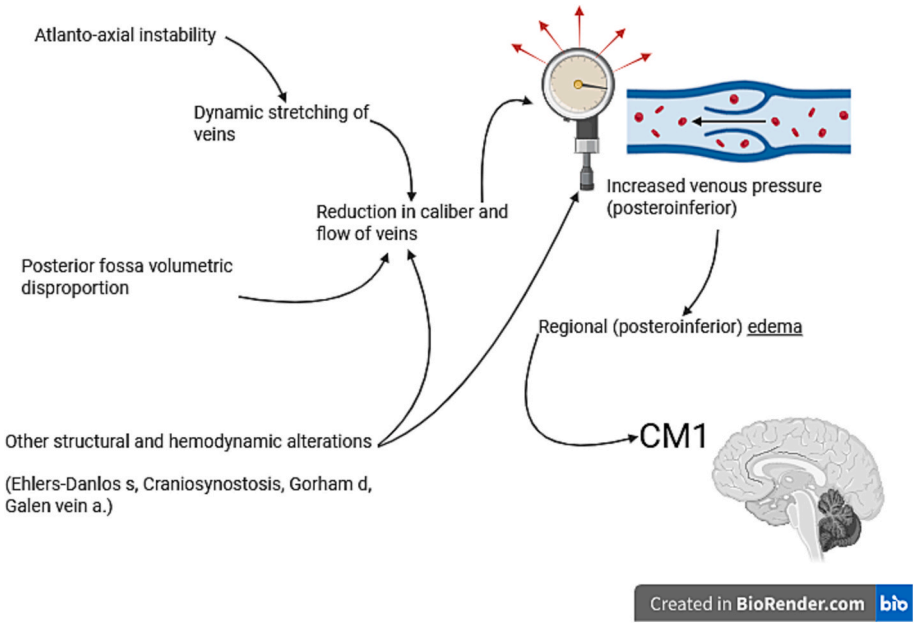

Fig. 3. Schematic representation of the proposed model. Created in https://BioRender.com.

This causes an increase in venous outflow resistance of the posteroinferior compartment and ISF accumulation in the tributary territories. On the other hand, fixation restores physiological flow through the posterior cerebral venous pathway and permits a regression in tonsillar prolapse.

Girard et al. [34] in 1994 described 8 cases of Vein of Galen Malformation in infants with associated CM-1. They observed that tonsillar prolapse was reversible if adequate venous drainage is reconstituted through embolization, and thus suggested that in some other conditions, "*Chiari I malformations may be secondary to early hydrovenous dysfunction of the posterior fossa*".

Usually, PF dimensions have been advocated as a possible cause of CM-1 due to the crowding of structures and consequent descent of tonsils. However, Shuman et al. [35], in one of the latest reviews to date on the topic, failed to find a clear correlation between morphometric parameters and CM-1 in the literature, even if further studies with Artificial Intelligence application are still ongoing. On the other hand, PF volumetric disproportion and venous outflow impairment should not be viewed as mutually exclusive mechanisms. Rather, they may represent two interrelated components of a unified pathophysiological continuum.

The observation that BMI is not linked to tonsillar position [36] does not contradict our hypothesis, as obesity-related upstream venous hypertension may contribute to venous stasis and focal cerebellar edema, but typically requires concomitant predisposing factors—most notably insufficient collateral venous drainage—consistent with the fact that IIH also occurs in non-obese individuals, implying additional venous outflow anomalies.

Nwotchouang et al [5] found that tonsillar ectopia that meet the radiological criteria for CM-1 is fairly common (1–3 %) in an asymptomatic population of children and young adults. As noted by Okudera [22], the anatomy of the venous outflow system undergoes significant changes during childhood, with a progressive reduction in both the number and caliber of venous drainage pathways. This developmental remodeling suggests that, in the pediatric population, the capacity for venous compensation is inherently greater due to the presence of more abundant and redundant venous routes. Moreover, during childhood less-developed neck muscles could result in less venous compression compared to adulthood. Although empirical data on this specific aspect are lacking, it is reasonable to hypothesize that this higher compensatory potential may help maintain physiological equilibrium even in the presence of anatomical alterations typically associated with CM-1. Such a mechanism could explain the relatively high prevalence of positive radiological criteria for CM-1 observed in asymptomatic pediatric patients. In these cases, the structural changes identified by imaging may not yet reach a threshold sufficient to disrupt neural tissue function.

Developmental anomalies leading to a hypoplastic or morphometrically constrained PF can inherently alter the organization and maturation of the regional venous network. These structural constraints may result in underdeveloped venous channels, reduction in luminal caliber, and decreased flow capacity.

Furthermore, PF crowding increases mechanical stress on key intra- and extracranial venous anastomoses—particularly the condylar venous system—at the CVJ. This localized compression can impair the drainage capacity of emissary veins and venous plexuses that serve as compensatory outflow pathways when IJV flow is reduced, such as during upright posture or elevated thoraco-abdominal pressure. As a result, parenchymal venous hypertension may develop, promoting interstitial fluid accumulation, regional edema, and tissue displacement. Therefore, a small PF may not only be a primary morphogenetic factor in CM-1 but also a contributing cause of secondary venous congestion, linking the structural and hemodynamic hypotheses. This integrated model provides a broader understanding of how congenital morphometric alterations and acquired venous dysfunction can synergistically lead to the downward displacement of the cerebellar tonsils.

The hypothesis that CM-1 may arise from impaired posterior venous drainage is supported by a broader range of conditions in which secondary venous or skeletal abnormalities influence cerebellar tonsillar herniation. One of the most illustrative examples can be found in syndromic craniosynostosis (e.g., Apert, Carpenter, Crouzon, Jackson-Weiss, Pfeiffer, and Saethre-Chotzen syndromes), where cranial base malformations and altered cranial development can simultaneously lead to increased PF crowding and venous drainage abnormalities. Park et al. [41] proposed the term "squeezed-out sinus syndrome" to describe the presence of prominent emissary transdiploic veins functioning as collateral pathways when intracranial dural sinus patency is compromised in patients with complex craniosynostosis. Recent studies have shown that aberrant venous drainage patterns are associated with increased ventricular size and elevated ICP in patients with Apert and

Crouzon syndromes [42,43]. Furthermore, Cinalli et al [44] demonstrated that following posterior cranial vault distraction and foramen magnum decompression in cases of syndromic craniosynostosis, there was expansion of the dural sinuses and a reduction in aberrant diploic venous emissaries, accompanied by significant improvement in tonsillar herniation and syringomyelia.

Another notable example is described by Coulter et al.[45], who investigated CM-1 associated with Gorham's disease of the skull base. Gorham's disease is characterized by progressive osteolysis, which may induce structural and hemodynamic alterations at the CVJ. The study reports cases in which these changes resulted in a Chiari-like presentation, suggesting that external factors such as venous disruption may contribute to the development of cerebellar tonsillar descent. Other authors have also reported similar cases of acquired CM-1, with or without associated intracranial hypotension or meningitis [46,47,48].

This case aligns with our hypothesis, as venous insufficiency at the posterior cranial fossa could similarly lead to regional edema, increasing intracranial pressure and ultimately contributing to tonsillar herniation. Such findings reinforce the concept that CM-1 may not solely arise from intrinsic PF morphometry but also from acquired or secondary venous anomalies.

Histological alterations in resected tonsils are generally linked to chronic ischemia and trauma and are not always present [37]. The main described changes are Purkinje cell loss, Bergman gliosis, atrophic cerebellar cortex, meningeal fibrosis, and internal granular layer loss. Cystic degeneration can be seen quite often [38]. Although these are not the typical findings in cerebral edema, it has been proven that histology is not the best method to assess brain tissue edema [39]. Moreover, literature lacks specific studies regarding cellular changes in CCSVI. It is interesting to note that inflammation is not one of the main alterations, unlike what is observed in neurodegenerative processes like multiple sclerosis [40].

Hypothesis Testing

To validate this hypothesis, it is essential at first to identify indirect signs of regional edema in the cerebellar tonsils, which may reflect impaired venous drainage. To this end, we are conducting a radiological study comparing pre- and post-operative imaging in CM-1 patients, with a focus on detecting both direct and indirect markers of localized edema (see as an example Fig. 3). These include structural and signal changes associated with altered venous outflow or CSF dynamics [49]. Artificial intelligence–based pattern recognition algorithms are being employed to enhance the detection and quantification of these imaging features. This study is designed to provide preliminary radiological evidence of the proposed venous contribution to cerebellar tonsillar descent.

In parallel, we are exploring complementary approaches that could offer more direct mechanistic insights. For example, a hybrid physical-computational model simulating venous circulation in the PF—accounting for anatomical constraints—could help elucidate the role of anterior and posterior compensatory pathways in maintaining venous outflow. Moreover, advanced flow quantification techniques could be applied in vivo to measure perivascular cerebellar flow [50], offering functional data on local hemodynamic behavior. Collectively, these strategies are intended to provide both structural and physiological evidence to support, refine, or challenge the proposed pathophysiological model of CM-1 based on compromised venous drainage.

Implications

By clarifying the pathophysiological underpinnings of CM-1, our hypothesis may open the door to a new paradigm in both diagnosis and treatment. Specifically, it could support the development of dedicated MRI sequences optimized for the evaluation of venous flow, along with advanced techniques for quantifying perivascular fluid dynamics. These tools may enable a shift from traditional, anatomy-based classifications toward a functional categorization grounded in measurable physiological disturbances. Such a framework would not only enhance diagnostic precision but also guide therapeutic strategies aimed at restoring effective compensatory venous circuits, thereby directly targeting the dysfunctional mechanisms driving symptomatology. From a surgical perspective, for example, current procedures primarily aim to "create more space" for the compressed neural structures. To some extent, the effectiveness of this approach has been demonstrated. However, from a physiological standpoint, the underlying mechanisms remain unclear. It is not fully understood why these procedures are effective or which specific pathophysiological factors they target. As it stands, different surgical techniques—such as PF decompression and C1–C2 stabilization—have both demonstrated efficacy based on available clinical data. A deeper understanding of the pathophysiological mechanisms underlying CM-1 development could inform new surgical strategies—for example, facilitating compensatory venous outflow pathways rather than simply decompressing the PF.

Furthermore, this model may offer meaningful insights into the broader landscape of craniospinal physiology—normal and pathological alike—providing physicians with a more comprehensive understanding of cerebrovascular and cerebrospinal fluid interplay in both CM and related conditions.

Conclusion

In our novel pathogenic theory, we suggest that CM-1 tonsillar herniation could be the result of regional cerebellar edema deriving from impaired venous outflow through the posterior-inferior venous group. This statement is coherent with clinical, anatomical and radiological observations previously made by several authors, and with the latest concepts regarding cerebrovascular physiology and glymphatic system. Even if this paradigm adequately recollects different phenomena and gave them new meanings, it still has to be tested specifically and externally validated, so further studies both clinical and preclinical are needed to assess its coherence and consistency.

Ethical Statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. The manuscript does not contain any sensitive or identifiable data related to individual patients.

Funding Declaration

The authors did not receive support from any organization for the submitted work.

CRediT authorship contribution statement

Pasquale De Bonis: Writing – review & editing, Investigation, Conceptualization. **Giorgio Mantovani:** Writing – review & editing, Writing – original draft, Methodology, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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