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Review

Cerebrospinal fluid (CSF) and idiopatic intracranial hypertension (IIH): a critical review

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Abstract

Pseudotumor cerebri is a syndrome that results from increased intracranial pressure. The main symptoms are headache, vision disturbances, and pulsatile tinnitus. Definitive diagnosis requires the presence of clinical and/or radiological signs of intracranial hypertension, high opening pressure on lumbar puncture (LP), and normal CSF constitution. Several studies have evaluated new contributions of CSF in the clinical evaluation and the in understanding of the pathophysiology of pseudotumor cerebri. Such studies have included the analysis of inflammatory biomarkers, adipokines, proteomic analysis, and CSF flow studies. In this review, we present the main results obtained so far and critically discuss the present status and the potential role of research involving the CSF in this condition. Based on current knowledge, it is possible to conclude that CSF research with new biomarkers has not yet provided information that can be employed in clinical practice at this moment. However, a better understanding of the constitution and dynamics of CSF circulation in patients with pseudotumor cerebri has brought some information about this condition and can potentially improve our knowledge about this condition in the future.

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Introduction

Pseudotumor cerebri is a syndrome that results from increased intracranial pressure. The condition can be primary, when no cause is identified, being called idiopathic intracranial hypertension (IIH); or secondary, when there is a defined etiology. Secondary cases are associated with medication use (eg, growth hormone, some antibiotics, vitamin A, retinoids, and lithium) and systemic diseases (eg, Addison's disease, hypoparathyroidism, severe anemia, Behcet's disease, thrombophilia, cerebral venous thrombosis, and uremia).[1] The most common clinical features are headache, visual abnormalities, and pulsatile tinnitus. Visual abnormalities may include blurred vision, visual field defects, binocular diplopia, and loss of visual acuity.[2] A definite diagnosis requires the presence of papilledema and elevated opening pressure on lumbar puncture (LP).[3] In the absence of clinical signs of intracranial hypertension, including papilledema and/or abducens nerve palsy, magnetic resonance imaging (MRI) findings reflecting increased intracranial pressure may fulfill diagnostic criteria.[4] The therapeutic options include reducing weight, medications such as acetazolamide and topiramate and, in selected severe cases, some interventional therapies such as ventriculoperitoneal shunts, optical nerve sheath fenestration, and intracranial venous sinus stenosis stenting.[5]

IIH has no known etiology, and most cases are seen among obese female of childbearing age. An imbalance between cerebrospinal fluid (CSF) production at the choroid plexus and reduced absorption at the arachnoid granulations and an increased venous pressure have been suggested as possible mechanisms underlying the disease.[2] The way in which obesity and female sex hormones are related to these CSF hydrodynamic alterations is not yet known.[6] There are several lines of research seeking to better understand the causes of this dysregulation of CSF dynamics, but no definitive answer has been found so far. Considering the proximity of CSF with the brain and optic nerves it seems reasonable to search for CSF related biomarkers as potential markers of this brain disease, either as diagnostic markers, or as pathophysiological markers of the underlying the disease.

Methods

In this review we will address "Pseudotumor Cerebri" or "Idiopathic Intracranial Hypertension" and its relationship with "Cerebrospinal Fluid" or "Inflammation" or "Glymphatic System". The process of collection and selection of published papers included a search of the PubMed/Medline for all peer-reviewed articles to date with a combination of key words, including "idiopathic intracranial hypertension," "pseudotumor cerebri", and "cerebrospinal fluid", and after that a third search with "inflammatory markers", "inflammation", "adypokines", "glymphatic system", "cerebral lymphatic", and "CSF flow", from Jan, 1990 to July, 2022. Other references from the articles that were identified in the initial search were also selected and reviewed for extraction of additional information or points of view.

Routine CSF evaluation

Elevated opening pressure on LP is essential for the diagnosis of IIH. For a precise pressure recording, the patient should be relaxed and lying in the lateral decubitus position with legs extended or slightly flexed, but not compressing the abdomen.[7] Sitting position, anxiety, and pain can give falsely elevated values.[8,9] CSF pressures may vary along the day and sometimes repeating the LP may be required.[9]

The upper limit of normal for opening pressure in adults is 20 cmH2O. Overweight patients have a higher upper limit of normal so that the diagnostic criteria establishes that an opening pressure of 25 cmH2O or higher is required for IIH diagnosis.[10,11] Higher upper limits have been proposed for young children, particularly in overweight or sedated children.[8] The current diagnostic criteria establish the limits of 28 cmH2O for overweight or sedated children, and 25 cmH2O in children who are not sedated or overweight.[8,12,13]

The CSF composition (protein, cells, glucose, and lactate), as well as additional routine CSF studies for microbial agents, CSF cytology, antibody and antigen testing is normal in patients with IIH.[1] Even within normal limits, the total CSF protein concentration was correlated with the opening pressure. One study showed that an increase of 1 cm in CSF opening pressure was associated with a small but statistically significant decrease in CSF total protein (-0.18 mg/dL).[14]. In the same study a multivariable analysis showed that increased CSF opening pressure and CSF total protein were independently associated with visual findings.[14] Other studies also found a relationship between raised opening pressure and the visual prognosis of IIH. Effective treatment of this condition with acetazolamide is associated with a reduction in opening pressure and an improved visual prognosis.[15-18] Therefore, CSF opening pressure in not only a diagnostic but also a prognostic marker in IIH.

Inflammatory markers

Systemic inflammation has been associated with pseudotumor cerebri.[18] An example is the occurrence of pseudotumor cerebri in children with multisystem inflammatory syndrome (MIS-C).[19] This is a life-threatening inflammatory immune response associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[19] Most patients present with hypotension, shock, gastrointestinal, cardiovascular, and mucocutaneous symptoms. Neurologic findings may occur and include headache and papilledema, with potential vision loss. Acetazolamide has been used in such cases with good results. Other inflammatory diseases have also been associated with pseudotumor cerebri.[20,21]

The contribution of inflammatory mechanisms and changes in cytokine levels have been proposed as one of the pathophysiological mechanisms of this disorder. One study found that one-third of IIH patients showed various patterns of oligoclonal bands (OCBs). The presence of OCBs only in CSF independently of serum OCBs suggest the occurrence of a humoral immune response in the intrathecal compartment.[22] Several studies have described higher CSF cytokines and chemokines concentrations. Interleukins (IL) IL-17, IL-4, IL-2, IL-10, interferon (IFN), tumor necrosis factor (TNF-a), macrophage chemotactic protein-1 (MCP-1/CCL2), C-C motif chemokine ligand 2, 7, and 8 (CCL2, CCL7, and CCL8), plasminogen activator inhibitor-1 (PAI-1) were found to be raised in CSF in patients with IIH.[23-26] Gene expression signatures showed activation of inflammatory genes and microRNAs with activation of several miRNAs involved in this response, such as miR-9 and miR-16, that are upregulated in CSF and plasma of IIH patients.[27]

Whether immunological mechanism is related with elevated CSF pressure and how could it participate in IIH pathogenesis remains to be clarified. Although several inflammatory markers concentrations are increased in IIH when compared to controls without IIH, there is a large overlap of the values, and it is not possible to establish reliable cut-offs for the diagnostic use of these dosages. Another important and opened question is if IIH patients might benefit from immunosuppression or immunomodulation. More studies are needed in this regard.

Adipokines

Adipose tissue was traditionally considered to be an energy storage organ, but it is now recognized as having a key role in the integration of systemic metabolism by secreting numerous proteins, referred to as adipokines. The increased adipose tissue mass seen in obesity is associated with alteration in adipokine production as over expression of TNF- alpha, Il-6, PAI- 1, and under expression of adiponectin in adipocite tissue. The pro-inflammatory status associated with these changes has been associated with the atherosclerotic process and type 2 diabetes. Conversely, the reduction of adipose tissue mass reduces TNF-alpha, IL-6, and PAI-1, increases adiponectin, and is associated with improved insulin sensitivity.[28,29]

Leptin is a hormone secreted by adipose cells and enterocytes that inhibits hunger thus diminishing fat storage in adipocytes. In obesity there is a decreased sensitivity to leptin, resulting in an ability to detect satiety. Leptin levels correlate with adipose mass, indicating the occurrence of leptin resistance. Obese individuals have high levels of leptin without anorexic responses. Leptin increases the production of pro-inflammatory cytokines, therefore, leptin acts as a pro-inflammatory adipokine. In addition to leptin, many other adipokines promote upregulation of pro-inflammatory state and contributes to metabolic dysfunction. In addition to the numerous pro-inflammatory adipokines, adipose tissue also secretes some anti-inflammatory factors, such as adiponectin.[30,31]

IIH occurs predominantly among young women with obesity, therefore, it is reasonable to search for a connection between the metabolic and inflammatory changes associated with obesity and the increase in intracranial pressure. A serum increase in leptin levels was found in some studies. One study found that CSF and serum leptin were significantly higher in patients with IIH compared to controls after correction for age, gender, and body mass index (BMI), suggesting that leptin might be important in the pathophysiology of IIH and that obesity in IIH may occur because of a hypothalamic leptin resistance.[32] Further studies also found increased serum leptin but did not reproduce this finding of an increased CSF leptin levels.[6,33] Other adipokines were not found to be altered in serum samples of patients with IIH.[6,34] Increased leptin secretion occurs in IIH but a causal relationship between the adipose tissue metabolic abnormalities and adipokines secretion and raised intracranial pressure in IIH is not clear at this moment.

Proteomics

Proteomic analysis (proteomics) refers to the systematic

identification and quantification of the complete set of proteins (the proteome) of a biological system (cell, tissue, organ, biological fluid, or organism) at a specific point in time. Mass spectrometry is the technique most often used for proteomic analysis. Proteomics is useful for disease diagnosis, prognosis and to monitor the disease development, having a vital role in drug development as target molecules. Proteomics is one of the most significant methodologies to understand the gene function and the pathogenesis of the diseases.[35]

Two studies performed CSF proteomic analysis in patients with IIH. One of them the authors used CSF samples of IIH obese and non-obese patients. In this study four proteins were demonstrated to be differentially produced in the CSF of obese compared with non-obese patients with IIH. The proteins were osteopontin, nerve growth factor inducible (VGF), fibrinogen c-chain, and chromogranin-A. Osteopontin is an inflammatory secreted by macrophages at inflammation sites where it mediates monocyte adhesion, migration, and differentiation, as well as phagocytosis. VGF is a polypeptide that is induced by neurotrophic factors and is involved in neurite growth and neuroprotection. It has been implicated in the control of feeding behaviour, facilitation of nutrient uptake and regulation of gastric contractility, regulation of energy balance and the control of feeding behaviour. Chromogranin-A is a neuroendocrine mediator that is increased in obese patients relative to non-obese subjects. Fibronectin is a synaptic plasticity marker that may be involved in hypothalamic regulation of feeding behavior and body weight. The authors speculate that proteins involved in inflammation, neuroendocrine mediators, and brain plasticity proteins may be detected in CSF and may play a role in obesity development be related with IIH.[36]

Another study evaluated CSF proteomics of IIH patients and compared with controls without IIH. Four proteins were downregulated in IIH: hemopexin, angiotensinogen, vitamin D–binding protein, and transthyretin. The authors suggest a possible association of angiotensinogen with IIH pathology. Renin and angiotensin are synthesized by brain neuronal and glial cells and renin-angiotensin system (RAS) influence cerebral blood flow autoregulation. The choroid plexus has receptors for angiotensin II as well as high concentrations of renin and angiotensin-converting enzyme (ACE). Downregulation of the RAS in IIH could contribute to an increased CSF production. Hemopexin is synthesized in the brain by ventricular ependymal cells but its potential role in IIH remains to be established. Vitamin D–binding protein has immune regulatory functions implicated in chronic inflammatory CNS disease. Transthyretin has been described in previous studies investigating the CSF proteome in inflammatory as well as neurodegenerative diseases. The authors postulate that RAS of the brain may offer new targets for diagnostic and therapeutic intervention in IIH, but larger studies are still necessary to confirm this hypothesis.[37]

The hypotheses generated by the studies deserve further confirmation since the CSF proteomic studies in IIH since studies are still very scarce and the results are not convergent in terms of which proteins are altered in the CSF of IIH patients.

CSF flow markers

Recent evidence has shown that CSF and interstitial fluid are continuously interchanged. This exchange is facilitated by the influx of CSF along the periarterial space. CSF is conducted into the Virchow-Robin spaces from the subarachnoid space, and subsequently into the brain parenchyma. This movement is facilitated by the aquaporin 4 (AQP4) water channels expressed in the astrocytic feet surrounding the cerebral vasculature. Interstitial fluid is then collected in the perivenous space and drained out of the brain into the cervical lymphatic system. This fluid flow system with rapid exchange of CSF and interstitial fluid is called glymphatic system.[38]

The dynamics of the glymphatic system was first characterized in 2012 in animal models in which fluorescent markers were injected into the CSF, via cisterna magna. CSF has been shown to rapidly enter the brain along the cortical pial arteries. This entry does not occur in a diffuse and random way in the parenchyma, but through a specific periarterial pathway that surrounds vascular smooth muscle cells delimited by perivascular astrocytic terminal feet. Subsequently, the injected markers rapidly exit the brain through the central deep veins. This movement is an energy-requiring process driven by multiple mechanisms, such as 1) the constant and continuous production of CSF by the choroid plexus, 2) respiration, 3) the pulsation generated by the smooth muscle cells. Corroborating this last mechanism, the experimental administration of dobutamine, an adrenergic agonist, which significantly increases the pulsatile effect, results in greater passage from the CSF into the brain parenchyma.[39]

Some authors have postulated a role for glymphatic system dysfunction in the development of IIH.[40-45] One hypothesis is that transverse sinus stenoses play a role in the development of intracranial pressure by determining

a decrease in the pressure gradient between the venous system and the subarachnoid space.[41,42] Different degrees of sinus stenoses would explain the different degrees of intracranial hypertension. By this hypothesis IIH could result from a restriction of the venous CSF outflow pathway with a congestion of the glymphatic system. This hypothesis finds some theoretical support in the fact that compression of the jugular veins results in increase of venous pressure that increases the CSF pressure between 0.9 to 2.2 cm H2O.[46] This might explain why patients with sinus stenosis are at higher risk of developing the disease. However, this theory does not explain the pathogenesis of IIH in patients without morphological changes in the transverse sinuses.

Another hypothesis is that an impaired CSF absorption by the arachnoid granulations (AG) or an increase in CSF production could favor congestion and overflow of the glymphatic system. Impaired AG function can be caused by meningeal inflammatory conditions. Since obesity is a pro-inflammatory state with greater concentration of inflammation markers that could recruit perivascular leukocytes in the CNS, increasing BBB permeability and reducing AG absorption increasing glymphatic system congestion.[43] Also, adipose tissue may release retinol proteins that enhances expression of AQP1 that increases CSF production.[43]

Another evidence of glymphatic system dysfunction contribution to IIH pathogeneses comes from pathological studies. Electron microscopy of brain tissue obtained from tissue banks demonstrated altered mitochondrial morphology in perivascular astrocytic feet of IIH patients when compared with controls. Abnormalities at the glia-vascular interface, where AQP4 water channels are expressed, may theoretically determine CSF flow disturbance in IIH patients.[47] Another study showed higher AQP4 expression at vascular perivascular astrocytic feet. The increased perivascular aquaporin-4 expression in astrocytic feet may represent a compensatory mechanism to enhance brain fluid drainage.[43] It is therefore possible that pathological changes at the cellular level within the brain may be implicated imbalance of the dynamics of the CSF.

Some methods, mainly magnetic resonance imaging (MRI), have been used to evaluate the glymphatic system/neurofluid dynamics. Intravenous injection of gadolinium has been used to evaluate the correlation between glymphatic function and blood-brain barrier function. Enlarged perivascular spaces were associated with compromised blood-brain barrier integrity, increased turnover through the system, and delayed gadolinium leak into the CSF after intravenous injection. Attempts have also been made to evaluate glymphatic system activity using diffusion images. A limited diffusion capacity along the perivascular space was shown in IIH. Other methods potentially able to trace CSF flow such as phase-contrast method, time-spatial labeling inversion pulse MRI, phase-contrast method and four-dimensional phase-contrast have also been tested showing some potential correlations with IIH. Even with these attempts of correlating IIH with CSF flow MRI findings, no imaging techniques have yet been established that clearly reveal the dynamics of the glymphatic system and neurofluids.[48] Future developments in imaging techniques may provide information with potential clinical utility in these cases.

Conclusion

The examination of CSF opening pressure is an important element in establishing the diagnosis of IIH. Although the conventional analysis of CSF does not provide additional diagnostic contributions besides raised opening CSF pressure, the present review showed that a better understanding of the constitution and of the dynamics of CSF circulation may bring relevant contributions to the understanding of this condition, justifying further studies in this regard. The development of new technologies for the study and assessment of the CSF microenvironment and CSF flow dynamics, whether laboratorial or neuroimaging, may help to better understand the complex relationships between the metabolic, hydrodynamic, and neurological dysfunctions of IIH.

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