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IDIOPATHIC INTRACRANIAL HYPERTENSION: GLYMPHOEDEMA OF THE BRAIN

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Running title: IIH: brain glymphoedema

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ABSTRACT

Background : During the last decade, our understanding of cerebrospinal fluid (CSF) physiology has dramatically improved thanks to the discoveries of both the glymphatic system and of lymphatic vessels lining the dura mater in human brains.

Evidence acquisition : We detail the recent basic science findings in the field of CSF physiology and connect them with our current understanding of the pathophysiology of idiopathic intracranial hypertension (IIH).

Results : Transverse sinus stenoses appear to play a major causative role in the symptoms of IIH, as a result of a decrease in the pressure gradient between the venous system and the subarachnoid space. However, the intracranial pressure (ICP) can be highly variable amongst different patients, depending on the efficiency of the lymphatic system to resorb the CSF as well as on the severity of transverse sinus stenoses. It is likely that there is a sub-clinical form of IIH and that IIH without papilledema is probably under-diagnosed among patients with chronic migraines or isolated tinnitus.

Conclusions : IIH can be summarized in the following pathological triad: Restriction of the venous CSF outflow pathway - Overflow of the lymphatic CSF outflow pathway - Congestion of the glymphatic system. In order to better encompass all the stages of IIH, it is likely that the Dandy's criteria need to be updated, and that perhaps renaming IIH should be considered.

BACKGROUND

During the last decade, our understanding of cerebrospinal fluid (CSF) physiology has dramatically improved thanks to the discoveries of both the glymphatic system and of lymphatic vessels lining the dura mater in human brains. While the characterization of CSF physiology is probably one of the most challenging projects in neuroscience, it is likely that these recent (and future) findings will have major clinical implications. The CSF circulation and the cerebrovascular system (including arteries, veins and lymphatics) seem to be more intimately related than previously suspected. Given ongoing work in this area, it is likely that our understanding of the overall picture will probably evolve further in the near future. In particular, it is likely that we will gain a better understanding of the clinical and radiological features of idiopathic intracranial hypertension (IIH) in the broader context of these basic science findings [1,2]. This, in turn, will probably lead to significant clinical and therapeutic advances. In this paper, we detail the recent basic science findings in the field of CSF physiology and connect them with our current understanding of the pathophysiology of IIH.

EVIDENCE ACQUISITION

- The Glymphatic System

In 2012, Iliff et al. identified the glymphatic system as “a brain-wide pathway for fluid transport, which includes the para-arterial influx of subarachnoid CSF into the brain interstitium, followed by the clearance of interstitial fluid along large-caliber draining veins” [3]. This process is preferentially activated during sleep[4], and is driven by a combination of arterial pulsatility, respiration, and pressure gradients [5,6]. The exchange of water molecules between the three compartments of the brain (i.e. the blood, the CSF and the brain parenchyma) is mediated by water-channel transporters called Aquaporins (AQP).

CSF is continuously produced by the choroid plexuses, which are expansions of the ependymal epithelium in the ventricles [7]. The total constant volume is 150-160 mL in humans, and this volume is renewed approximately four times per day [8]. CSF production is mediated by osmotic- and pressure-gradients that drive the movement of water and ions from the blood to the ventricular lumen [4]. The exchange of water molecules from the blood to CSF is mediated by AQP-1, which is located in the apical membrane of the choroid plexus epithelial cells [9]. From the ventricles, the CSF then exits through the foramina of Magendie and Monro to reach the subarachnoid space [4]. Alternatively, CSF may exit the ventricles via trans-ependymal spread to reach the perivascular spaces of the brain. This trans-ependymal spread pathway is especially apparent during cases of obstructive hydrocephalus. From the subarachnoid spaces, CSF then enters the periarterial spaces, travelling from the cortex toward the deep white matter along the courses of the pial and perforator arteries [4]. Along with other metabolites, CSF is then filtered and driven from the periarterial space to the brain parenchyma [4]. The transport of water from CSF to the brain is mediated by another water-transporter, AQP-4 [3]. This water channel is expressed in astrocytic endfeet that ensheath the brain vasculature [3]. This continuous movement of CSF from the periarterial space into the brain parenchyma then drives convective bulk parenchymal fluid flow toward the perivenous spaces surrounding the large cortical veins [3]. Following this, the method of resorption of CSF from the perivenous spaces is still unclear. Two CSF outflow pathways have been described in humans: the venous outflow pathway and the lymphatic outflow pathway.

- **CSF outflow**

While the venous CSF outflow pathway has historically been considered as the only way of resorption of CSF, the recent discovery of the dural lymphatics in humans (as distinct from

the brain parenchymal glymphatic system outlined above) has been another major paradigm shift[10]. In order to better describe the CSF outflow pathways, we first need to clearly distinguish two physiological roles of CSF: a mechanical role (which plays a role in the regulation of ICP), and a metabolic one (which plays a role in clearance of brain metabolites).

- The *venous* CSF outflow pathway

It was historically believed that the venous resorption of the CSF occurs across the arachnoid villi and granulations. These anatomical structures are traditionally described as focal areas of protrusion of the subarachnoid space across the dura matter into the lumen of the dural sinuses. These “avascular granulations” also play a mechanical role of regulation of the ICP, as the flow of CSF across the granulation is dependent on the pressure gradient between the subarachnoid space and the venous blood of the dural sinus. In the light of the recent scientific findings concerning the glymphatic system, it seems that another type of granulations – the so-called “vascular granulation” - has probably been wrongly neglected over time. Previous pathological [11,12] and radiological studies [12,13], support that some arachnoid granulations may enter the dura mater to reach the lumen of the venous sinuses in close association with a major cortical vein. These “vascular granulations” could represent an anatomical and physiological connection between the perivenous space (draining the ISF from the glymphatic system) and the venous blood of the dural sinus [12]. Vascular granulations may therefore be involved in the excretion of the brain metabolites as one final exit pathway of the glymphatic system. The intrinsic molecular mechanisms of this filtration are however still unknown.

- The *lymphatic* CSF outflow pathway

It was long believed that the CNS did not have a lymphatic drainage system. Ironically, an Italian anatomist called Paola Mascagni described meningeal-related lymphatic vessels in a

landmark anatomical text in 1787, but her findings were discounted by the scientific community for more than 200 years[14]. In 2015, the presence of functional lymphatic vessels lining the dural sinuses was eventually demonstrated in murine brains [15,16] . Two years later, Absinta et al went on to image these dural/meningeal lymphatics in both primates and humans [17]. They also seem to be involved in the clearance of the CSF (or ISF) from the glymphatic system[15,18], and also in the regulation of the ICP (through a direct reabsorption of the CSF from the subarachnoid space) [16]. Other work by Hoon Ahn et al, showed that CSF drains preferentially through a basal outflow pathway, with CSF tracers draining via skull base meningeal lymphatics to the deep cervical lymph node system. Anatomically, the lymphatic system of the brain could therefore be described as a drainage network extending from the dural sinuses to both eyes, tracking above the olfactory bulb, following the dural arteries and veins into the dura matter [15,16]. The dural lymphatics finally join the skull base, discharging the CSF into the sheaths of the cranial nerves. The CSF is eventually excreted into the deep cervical lymph nodes and the systemic lymphatic circulation [19].

RESULTS

In the light of these scientific findings, the radiological signs of IIH can be summarized in the following pathological triad (Fig. 1) [1]:

- 1/ Congestion of the glymphatic system
- 2/ Overflow of the lymphatic CSF outflow pathway
- 3/ Restriction of the venous CSF outflow pathway

- **IIH: congestion of the glymphatic system**

Several radiological studies indicate that IIH is associated with an increase in CSF in the perivascular spaces of the brain and in the subarachnoid space, suggesting a congestion of the glymphatic system. Since the skull represents a fixed volume, the excess of CSF in the glymphatic system results in increased intracranial pressure. The first radiological observations of IIH were based on CT-scans and showed a reduction of ventricular size, suggesting that IIH was due to cerebral swelling [20]. This interstitial edema was confirmed later with MRI diffusion techniques and with 3D-volumetric MRI sequences [21]. Alperin et al. showed a significant increase in extra-ventricular CSF and interstitial fluid volumes in patients with IIH, when compared to a matched cohort of patients without IIH.

- **IIH: overflow of the lymphatic CSF outflow pathway**

Imaging evidence of excess CSF along the sheaths of cranial nerves is one of the cardinal signs of IIH. Most typically this is found along the optic nerve sheaths, however the sheaths of other cranial nerves can also be enlarged. This may be a consequence of the accumulation of CSF along the sheaths of the cranial nerves. This excess of CSF appears to be related to the engorgement of the lymphatic CSF outflow pathway[22,23]. For example, erosion of the cribriform plate (which may result in idiopathic CSF leak) may be the consequence of the chronic overflow of CSF around the olfactory bulbs [24]. Other cardinal imaging signs of IIH are also likely related to an excess of CSF along the relevant nerve sheaths. These imaging signs include widening of the foramen ovale and Meckel's cave dilatation (CSF excess in the trigeminal nerve sheaths), enlargement of the third cranial nerve sheaths in the cavernous sinus [25], [26] and enlargement of Dorello's canal (indicating excess CSF in along the sheaths of CN VI). Finally, meningoceles of the temporal bone, mostly located at the petrous apex or Meckel's cave near the continuation of the nerve sheaths of the acoustic and facial

nerves also point to an excess of CSF along these nerves. These can also lead to CSF leaks [27].

- **Restriction of the venous CSF outflow pathway**

More than 90% of patients with IIH have transverse sinus (TS) stenoses, which are usually located bilaterally at the junction between the vein of Labbé and the transverse sinus [28]. Those stenoses can result in increased cerebral venous pressure (CVP), leading in turn to a less efficient venous CSF outflow pathway as a result of equalization of the pressure gradient between the subarachnoid space and the venous blood of the dural sinuses. Although TS stenoses are probably the main precipitating factor in the occurrence of clinical symptoms in IIH - and the resolution of symptoms after venous stenting gives support to this hypothesis - the cause of these stenoses remains unclear. However, it is likely that a molecular impairment of CSF filtration at the venodural junction may be responsible for the formation of TS stenoses. We presume that the metabolic and hormonal factors associated with IIH (obesity, hormones, drugs...) may be involved in this molecular trigger.

Two types of venous sinus stenoses have been described in IIH: intrinsic and extrinsic [29]. An intrinsic stenosis can be defined radiologically as a short-segment stenosis secondary to the presence of a sub-arachnoid granulation inside the sinus[30]. Conversely, an extrinsic stenosis can be defined as a long-segment sinus stenosis without an endoluminal abnormality. Patients with intrinsic stenoses are often older than patients with extrinsic stenoses [29]. In patients with intrinsic stenoses, the efficiency of the venous blood-CSF barrier can be impaired as outlined above. Paradoxically, the initial development of an arachnoid granulation may initially slightly delay the manifestation of IIH by increasing the exchange area between the CSF and the venous system. The lymphatic outflow pathway may also initially compensate for the decreased efficiency of the venous CSF pathway. However, as it

enlarges the arachnoid granulation can eventually cause a mechanical obstruction in the venous sinus which will then lead to increased pressure in the dural sinuses, and thus to IIH symptoms as a result in impairment of the CSF venous outflow pathway.

Extrinsic stenoses on the other hand affect younger patients than intrinsic stenoses. Two mechanisms may be involved in their formation. The first one is a direct compression of the transverse sinus by the congested brain and CSF, suggesting that intracranial hypertension is the cause of LS stenoses. This theory is supported by the disappearance of such extrinsic stenoses after removal of CSF [31], and by their propensity to reform adjacent to the stented zone after stenting [32]. De Simone et al. have hypothesized that the dural sinuses in IIH are hyper-collapsible, to try to explain the mechanism of formation of extrinsic stenoses [33].

CONCLUSIONS

Transverse sinus stenoses appear to play a major causative role in the symptoms of IIH. The suppression of the pressure gradient between the venous system and the subarachnoid space can in turn lead to further inefficiency of the already impaired venous outflow pathway. Thus, the lymphatic outflow pathway becomes the only CSF outflow pathway of the brain, and the overflow of the CSF along the sheaths of the cranial nerves results in the classical clinical and radiological signs of IIH. The ICP may be highly variable amongst different patients, depending on the efficiency of the lymphatic system to resorb the CSF as well as on the severity of TS stenoses. This may explain why the radiological signs of IIH are frequently found in patients with chronic headache or isolated pulsatile tinnitus without papilledema or raised intracranial pressure. It is likely that there is a sub-clinical form of IIH in these patients, i.e. in patients with a degree of CSF outflow impairment but in whom the signs and symptoms do not yet meet the criteria for IIH. It is therefore likely that IIH without papilledema (IIWOP), (i.e. with normal or near-normal ICP) is probably under-diagnosed among patients

with chronic migraines or isolated tinnitus [34]. We suggest including the radiological signs in the next revision of the diagnostic criteria of IIH while putting less value on the ICP value. This may be helpful to try and better capture the benign stages of this radio-clinical syndrome. Papilledema and raised intracranial pressure could probably therefore be considered as the most severe stage of the disease, while headache and pulsatile tinnitus with normal ICP (and without papilledema) could be considered as benign stages of IIH. In order to avoid semantic misunderstandings and to better encompass all the stages of IIH, it is likely that the Dandy's criteria need to be updated, and that a rename of IIH has to be considered.

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FIGURE LEGENDS

Figure 1 : The cascade of Idiopathic Intracranial Hypertension (IIHWOP: idiopathic intracranial hypertension without papilledema, IIH: idiopathic intracranial hypertension, ICP: intracranial pressure)

Figure 2: Radiological signs of Idiopathic Intracranial Hypertension. Figure 1A and 1B: T2-weighted MRI in coronal view showing the excess CSF along the sheaths of the optic nerves (Fig. 1A, blue arrows) and of the IIIrd cranial nerves (Fig. 2B, blue arrows), a petrous apex meningocele (Fig. 2B, green arrow) and the CSF leak across the cribriform plate (Fig. 2A, yellow arrows). Figure 2C: CT scan in bone window showing the erosion of the cribriform plate (green arrow). Figure 2D: MR venography showing the bilateral transverse sinus stenoses (red arrows).



