

BILATERAL TRANSVERSE SINUS STENOSIS IS NOT A CRITICAL FINDING IN IDIOPATHIC INTRACRANIAL HYPERTENSION SYNDROME, BECAUSE IT COULD NOT EXPLAIN THE FULL-BLOWN PATHOLOGY!

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The terms “pseudo-tumor cerebri” and “benign intracranial hypertension” were originally applied to patients with **increased intracranial pressure** (ICP) in whom no tumor was found and whose course was believed to be benign. However, this clinical picture is neither benign nor a false tumor and therefore terminology was changed to idiopathic intracranial hypertension (IIH). IIH is characterized by ICP leading to **headache, papilledema, visual symptoms** and signs, without any localizing signs, and normal CSF. Less commonly, IIH may present in the absence of papilledema.

The incidence of IIH is 1-2 in 100,000 general population but increases to 19 in 100,000 **obese women** of childbearing age. There is a predilection for women over men from 8:1 to 4.3:1 in the literature. IIH may also occur in children, interestingly with an equal incidence in boys and girls. There were some clinical differences regarding visual outcome in men and older patients with IIH.

The pathogenesis of IIH remains still unclear, although it has been recognized for more than a century. There are several **proposed mechanisms** such as parenchymal edema, increased cerebral blood volume, excessive cerebrospinal fluid (CSF) production; venous outflow obstruction or compromised CSF resorption. And lastly possible contribution of inflammatory factors has been proposed. No single theory has been able to provide a comprehensive answer currently and there is no consensus about its cause. Some investigators proposed that increased venous pressure might be the key factor in the development of IIH because it is the unifying mechanism for all of the benign tumor-like syndromes; others suggest that increased resistance to absorption of CSF through arachnoid granulations could be responsible. Cerebral venous thrombosis has been found in 11.4% of patients who were presumed to have IIH and IIH has been associated with many etiologies such as **exposition to a number of drugs** (minocycline and tetracycline, growth hormone, steroids and vitamin A, among others), acquired or congenital prothrombotic states, **Behçet’s Disease**, arteriovenous malformations, sleep disturbances including obstructive sleep apnea syndrome (**OSAS**), extracranial venous hypertension secondary to **cardiac septal defect**, iron deficiency anemia, **systemic lupus erythematosus**, uremia, as well as some **endocrine changes** like menstrual irregularities, use of oral contraceptives, hyperthyroidism and hypothyroidism.

Diagnosis of IIH is based on normal neuroimaging of the brain, including **magnetic resonance venography** (MRV), documented increased ICP (> 250 mm H₂O), and a normal CSF examination. There is currently considerable evidence that the majority of patients with IIH carry **bilateral transverse sinus stenosis** (BTSS), although there is debate on whether such a stenosis is a cause or effect of the condition as some authors suggest such narrowing is secondary to the raised ICP. MRV with an autotriggered elliptic centric-ordered sequence demonstrated variable degrees of cerebral venous stenosis in most of the cases compared with normal controls. Venous sinus stenting was therefore used in some patients with conflicting results. Although venous dysfunction is probable, its exact cause remains obscure. Flow artifacts or anatomic variants of venous sinuses often make MRV interpretation difficult. Moreover flow abnormalities in a single transverse sinus (TS) can occur in up to 30% of normal individuals, whereas flow abnormalities of both TS are uncommon and when encountered on imaging, the patients should perhaps be investigated for elevated CSF pressure according to Bono et al. Furthermore Bono et al. reported that one-third of the patients with BTSS had normal CSF pressure, suggesting that BTSS is only one of the contributing factors involved in IIH. Moreover BTSS, as revealed by MRV, persists in patients with IIH after normalization of CSF pressure, suggesting the lack of a direct relationship between the caliber of TS and CSF pressure. Thus, many findings suggest that venous flow disturbances in IIH are most probably the consequence of CSF hypertension, not its cause.

Treatment of IIH is divided into medical and surgical therapy to prevent blindness. According to some studies, even a relatively small weight reduction has improved vision. The strongest and most consistent risk factors of IIH are obesity and female gender, which do not have any apparent association with BTSS.

The pathophysiologic **mechanism of obesity and increased ICP** is undetermined. Very recently, chronic inflammation associated with obesity has been proposed as one of the possible etiological factors in the development of IIH. Obesity is recognized as a proinflammatory state and is associated with increased expression of a number of **adipokines and cytokines** including **leptin**, interleukin-6 (IL-6), macrophage chemotactic protein-1 (MCP-1/CCL2) and plasminogen activator inhibitor-1 (PAI-1). In a study by Lampl et al., significantly elevated serum leptin levels in obese patients with IIH were found compared with both obese and non-obese controls. Ball et al. reported that significantly higher levels of CSF leptin were present in IIH patients after accounting for BMI and age, but no significant difference in serum leptin was found between the groups. Dhungana et al found no significant difference in CSF leptin of eight IIH patients compared with eight controls (albeit without adjusting for BMI). Given the strong predilection of IIH for obese young women, larger studies are warranted to elucidate the true role of CSF vs. serum leptin and other cytokines in the pathophysiology of IIH.

Many patients give a history of menstrual irregularities and there have been case reports linking IIH to the use of oral contraceptive pills and also polycystic ovarian disease. Despite some conflicting reports, the role of **sex hormone disturbance** in the pathogenesis of the condition cannot be entirely ruled out.

It has been argued that an **underlying thrombophilic defect** of the condition cannot be entirely ruled out. It has been argued that an **underlying thrombophilic defect** of the condition cannot be entirely ruled out. It has been argued that an **underlying thrombophilic defect** of the condition cannot be entirely ruled out. It has been argued that an **underlying thrombophilic defect** of the condition cannot be entirely ruled out. Theoretically, in some

patients, IIH could be due to microthrombi impeding CSF drainage but not demonstrable on imaging. Therefore the role of thrombotic factors in IIH needs to be investigated by larger studies.

Another important recent study by Skau et al. evaluated the **natriuretic peptide system** as a possible cause of disturbed ICP autoregulation in 40 patients with IIH. This natriuretic peptide system which is also expressed in the central nervous system (CNS) comprises a family of structurally related neuro-peptides (NP) with antagonizing properties against the renin–angiotensin–aldosterone system. The more well-known **atrial natriuretic peptide (ANP)** and **B-type natriuretic peptide (BNP)** are released primarily from cardiomyocytes in response to increased wall-tension and promote natriuresis and diuresis. In contrast, **C-type natriuretic peptide (CNP)** is released from various tissues, including **endothelial cells**, and acts as a paracrine relaxant of vascular tone. Increased concentrations of NPs in CSF have been shown in intracranial hypertension, i.e. subarachnoidal haemorrhage. Moreover, intraventricular administration of ANP reduces elevated ICP and CSF production in rodent models. Since two of three NP receptors, NPR-A and NPR-C, have been located to the choroidal plexus where two-thirds of the total cerebrospinal fluid (CSF) production is generated, it has been suggested that NPs may be involved in liquor dynamic regulation. Plasma levels of **proCNP were significantly lower in IIH patients** and levels of **proBNP were significantly lower** in IIH patients compared with those of controls. More interestingly, the plasma concentrations of these neuropeptides are inversely associated with body mass index (BMI) and may increase during weight-loss.

Considering the association between peripheral NP production and obesity, and the proposed ICP regulatory actions of NPs, it is tempting to hypothesize that there is a link between IIH and NP concentrations.

Endothelial dysfunction is known to be an early event in obesity, present even in the absence of hypertension or hyperglycemia. This dysfunction is defined as loss of normal homeostatic function of the endothelium, partly secondary to reduce NO bioavailability, resulting in abnormal vasomotor activity and inflammation. The renin–angiotensin system is one of the factors considered to be involved in this dysfunction. Due to CNP's antagonizing actions of the renin–angiotensin system, CNP may also be involved in the obesity-related endothelial dysfunction. The discovery of the **aquaporin (AQP)** family of membrane water channels has provided new insights into the pathophysiology of brain water homeostasis. Aquaporin-4 (AQP4) has been presumed to play an important functional role in the transport of water in and out of the brain, due to its wide distribution within the CNS, including the choroid plexus and ependymal cells of the ventricles and its critical localization in astrocytic foot processes along the blood-brain barrier and brain-CSF interface. Many studies of transgenic mice with a complete deficiency or altered expression of AQP4 suggest a prominent role for AQP4 in cerebral water transport. AQPs are a large family of water channels, expressed in plasma membrane of many cell types in the CNS and eye. AQP4 seems to play a significant role in the development of cytotoxic edema and the absorption of excess brain water resulting from vasogenic edema. However, these important preclinical results have not been translated to human clinical diseases, except the association with neuromyelitis optica (NMO). Another recent study suggested that brain lesions in some patients with NMO spectrum disorder may be accompanied by vasogenic edema due to AQP4 autoimmunity-related water flux impairment. However, we and the others could not demonstrate any association of AQP4 with IIH. Other studies are needed to elucidate the role of other Aquaporins and water pump system in IIH.

Furthermore, we identified different IgG binding patterns (i.e. **anti-neuronal antibodies**) with the sera of **several IIH patients** in rates comparable to those of encephalitis patients. Our results might suggest that inflammatory pathogenic mechanisms are in play at least in some IIH patients and thus further investigation of potential neuronal target autoantigens, is warranted to fully understand the pathophysiology of IIH.

Both CSF pressure and the symptoms of IIH tend to fluctuate, with spontaneous remissions and —sometimes permanently, which are clear evidences against a simple mechanical obstruction. On the other hand, some patients experience a chronic disabling course with headache for years that limits their capacity to work and to participate in social life. Experimental pathophysiological studies are needed in order to optimize the biological understanding and therapy of this disease of theories.

In conclusion, it is not reasonable to believe that only BTSS could explain the mysterious pathogenesis of IIH in a simple way. Therefore I defend the view that even though this finding is important in IIH, it is not of critical importance.