



An update on the pathophysiology of idiopathic intracranial hypertension alias pseudotumor cerebri

İdiyopatik intrakraniyal hipertansiyonun -diğer adıyla psödötümör serebrinin-patofizyolojisi üzerine bir güncelleme

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Summary

Idiopathic intracranial hypertension (IIH) is a syndrome characterized by increased intracranial pressure of unknown cause, leading to severe headache, papilledema and visual disturbances. Its former name, pseudotumor cerebri, has gained popularity recently. The strongest and most consistent risk factors of IIH are obesity and female gender. Infrequently, IIH may present in the absence of papilledema showing a headache profile similar to chronic daily headache with migrainous features. There have been several proposed mechanisms to explain the etiology of this disorder associated with various clinical conditions. In recent years, some inflammatory factors, natriuretic peptides and aquaporins have been proposed as possible contributors of the pathogenesis. On the other hand, some investigators have reported that bilateral transverse sinus stenosis is seen in the majority of IIH patients; therefore, dural sinus stent placement is used in some patients. No single theory has been able to provide a comprehensive answer, and there is no consensus about the exact cause of IIH. The aim of this review was to discuss the new insights on the mysterious pathogenesis of IIH.

Key words: Idiopathic intracranial hypertension; pseudotumor cerebri; transverse sinus stenosis.

Özet

İdiyopatik intrakraniyal hipertansiyon (İİH) şiddetli baş ağrısı, papilödem ve görme bozukluklarına yol açan, nedeni bilinmeyen intrakraniyal basınç artışı ile karakterize bir sendromdur. Eskiden kullanılan psödötümör serebri tanımı son yıllarda yeniden gündeme gelmiştir. İdiyopatik intrakraniyal hipertansiyon için en tutarlı ve en güçlü risk faktörleri obezite ve kadın cinsiyettir. Nadiren İİH'de papilödem görülmeyip, baş ağrısı migrenöz özellikler taşıyan kronik günlük baş ağrısı profili gösterebilir. Farklı klinik durumlarla birlikteliği görülen bu durumun etiyolojisini açıklamaya yönelik çeşitli mekanizmalar öne sürülmüştür. Son yıllarda, enflamatuvar etmenler, natriüretik peptitler ve akuaporinlerin patogeneze katkı olasılıkları üzerinde durulmaktadır. Öte yandan bazı araştırmacılar, İİH hastalarının çoğunda iki yanlı transvers sinüs darlığı görüldüğünü bildirmiş, bu nedenle de bazı hastalarda dural sinüslere stent yerleştirilmiştir. Görüldüğü gibi tek bir kuram bu sendromla ilgili soruları açıklamaya yetmemektedir ve İİH'nin kesin nedeni üzerinde görüş birliği sağlanamamıştır. Bu derlemenin amacı, İİH'nin gizemli patogenezi üzerine yeni gelişen görüşleri tartışmaktır.

Anahtar sözcükler: İdiyopatik intrakraniyal hipertansiyon; psödötümör serebri; transvers sinüs stenozu.

Introduction

Idiopathic intracranial hypertension (IIH) is a well-known but under-investigated clinical entity with an unsolved pathophysiologic background; hence its diagnosis and optimal management usually cre-

ates problems for clinicians. The terms “pseudotumor 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.

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However, this clinical picture is neither always benign nor related to a false tumor and therefore its terminology was changed to “idiopathic intracranial hypertension”.^[1,2] On the other hand, Friedman et al. have recently proposed that the umbrella term “pseudotumor cerebri” should be used for the patients having ICP with unclear etiology or secondary causes such as medications and other medical conditions.^[3] The pathogenesis of raised ICP in these conditions remains still unclear. Several pathophysiologic mechanisms regulating cerebrospinal fluid (CSF) pressure have been postulated. In this review, we aim to discuss the emerging new insights on the pathogenesis of IIH.

Epidemiology- clinical features

The incidence of IIH is 1-2 in 100000 population but increases to 19 in 100000 obese women of childbearing age.^[4,5] There is a clear predilection for women over men ranging from 4,3:1 to 15:1 in the literature.^[4-7] IIH may also occur in children, but obesity and female predominance appear to be less common in prepubertal children with IIH.^[8]

IIH is characterized by ICP leading to headache, papilledema, visual symptoms and signs, without any lateralizing findings in the neurological examination, and normal CSF findings.^[9] The headache attributed to IIH should be progressive with at least one of the following characteristics; daily occurrence, diffuse and/or constant (non-pulsating) and aggravated by coughing or straining.^[10] In our previous study, we showed the presence of allodynia accompanying headache in half of the patients with IIH, typically in unilateral V1 distribution. These patients with allodynia had mostly headache features similar to migraine, whereas patients without allodynia reported more frequently non-migrainous headache. Only 12 of these 46 patients with IIH had previous migraine diagnosis and 7 of the remaining patients were diagnosed previously with tension type headache. Moreover, our study supported the fact that patients with IIH often relapse or continue experiencing headaches, despite the apparent normalization of their ICP.^[11]

Infrequently, IIH may present in the absence of papilledema^[12-14] and the patients may experience a headache profile similar to chronic daily headache

with migrainous features, responding to specific antimigraine agents as well.^[15] In a recent study, these patients without papilledema had lower opening pressure when compared with those with papilledema and visual acuities were similar between two groups.^[16]

There are some intriguing clinical differences regarding visual outcome in older patients and men with IIH.^[17-19] Patients older than 50 years had fewer complaints of headache and visual disturbances^[19] and the visual prognosis was found to be better in the elderly.^[18] On the other hand, it was reported that men with IIH need to be followed up more closely regarding visual function because they may not experience or report other IIH symptoms like headache alarming the clinician.^[20] In children with IIH, headache is the most common symptom, but they also have a higher incidence of ocular motility dysfunction and cranial nerve deficits are more common in comparison to adult patients.^[21]

According to recent studies, there is also some evidence that the patients with IIH have olfactory bulb volume changes and decreased olfaction accompanying other conventional symptoms of IIH.^[22,23]

The diagnostic characteristics of this syndrome were first defined by Dandy in 1937^[24] and were later formulated as “Modified Dandy Criteria” by Smith in 1985.^[25] These criteria were revised owing to the developments in the neuro-imaging. Magnetic resonance imaging (MRI) or contrast-enhanced computerized tomography (CT) were recommended for typical IIH patients, but MRI and MR venography (MRV) were used for all others.^[26] Friedman et al., who preferred to call the syndrome pseudotumor cerebri, proposed recently updated criteria for the diagnosis which required: Papilledema, normal neurologic examination except for intracranial nerve abnormalities, neuroimaging findings including normal brain parenchyma and no abnormal meningeal enhancement on MRI for typical patients and MRI and MRV for others (contrast-enhanced CT if MRI is unavailable or contraindicated), normal CSF composition and elevated lumbar puncture opening pressure (≥ 250 mm CSF in adults and ≥ 280 mm CSF in children).^[3] They also proposed that in the absence of papilledema, the diagnosis would be suggested if at

least 3 of the following neuroimaging features were present additionally: 1) Empty sella, 2) Flattening of the posterior aspect of the globe, 3) Distention of the perioptic subarachnoid space with or without a tortuous optic nerve, 4) Transverse venous sinus stenosis.^[3]

Pathophysiology

Although recognized for more than a century, the pathogenesis of IIH remains still unclear. There are several proposed mechanisms such as parenchymal edema, increased cerebral blood volume, excessive CSF production; venous outflow obstruction and compromised CSF resorption.^[27] In recent years, possible contribution of inflammatory factors has also been proposed.^[28] No single theory has been able to provide a comprehensive answer and there is no consensus about the exact cause of IIH.

Says and Joynt reported microscopic evidence of intracellular and extracellular edema^[29] and later some MR studies also showed increased water content of the brain^[30] and water diffusion in subcortical white matter^[31] providing an indirect evidence of brain edema without further confirmation. Dandy first hypothesized that the volume of either cerebral blood or CSF might be increased in this condition.^[24] Some later reports^[32,33] supported the presence of increased cerebral blood volume in IIH using intracarotid tracer injection in anesthetized IIH patients. An excessive CSF production has also been proposed but the normal or decreased ventricular size found in IIH patients suggests that there is no increased CSF production in most of the patients.^[27] Some studies also demonstrated an abnormally increased outflow resistance, indicating a potential defect through arachnoid granulations.^[34-37]

Obesity and chronic inflammation

The strongest and most consistent risk factors of IIH are obesity and female gender; like women, men with IIH are also typically obese.^[20] Daniels et al. demonstrated a correlation between body mass index (BMI) and the risk of IIH^[38] and increased weight was found to be associated with the recurrence of the disease.^[39] Furthermore, severely obese IIH patients had more advanced papilledema and more severe visual loss than less obese patients^[40] and even a relatively small weight reduction has improved vision according to some studies.^[41]

Although obesity is clearly associated with IIH, its pathophysiologic mechanism remains undetermined. It has been suggested that obesity causing increased intraabdominal pressure could lead to reduced cerebral venous drainage.^[42] Very recently, chronic inflammation associated with obesity which can lead to a pro-thrombotic state has been proposed as one of the possible etiological factors in the development of IIH.^[28] Obesity is recognized as a proinflammatory state and is associated with increased expression of a number of adipokines and various cytokines including leptin and interleukins, macrophage chemotactic protein-1 (MCP-1/CCL2) and plasminogen activator inhibitor-1 (PAI-1). Leptin levels are found to fluctuate during an inflammatory state.^[43] 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.^[44] Ball et al. reported that significantly higher levels of CSF leptin were present in IIH patients after correcting for BMI and age, but no significant difference was found in serum leptin between the groups.^[45] However Dhungana et al. found no significant difference in CSF leptin of eight IIH patients compared with eight controls (albeit without adjusting for BMI).^[46] In a recent study which analyzed the concentrations of 14 different cytokines, IIH was found to be associated with elevated levels of IL-17 and IL-2 in the CSF, supporting the presence of an intrathecal inflammatory process.^[47]

Adipose tissue is considered as an actively secreting endocrine tissue.^[48] One of the long-standing hypotheses for the pathogenesis of IIH is abnormal vitamin A metabolism. Some studies showed that the retinol level is elevated in CSF of patients with IIH.^[49,50] Adipose tissue-derived retinol binding protein is released from adipose tissue as the name implicates and acts as a modulator of insulin sensitivity.^[49] 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 adipose tissue-produced cytokines and molecules in the pathophysiology of IIH.

Sex hormonal dysfunction

Sex hormones have been suspected as having a role in the pathogenesis of IIH because of the preferen-

tial occurrence of the disorder among post-pubertal, pre-menopausal women,^[20] and the absence of a gender preference before puberty.^[51] Despite some conflicting reports,^[52,53] the role of a sex hormone disturbance in the pathogenesis cannot be entirely ruled out. 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.^[54,55] Polycystic ovarian syndrome (PCOS) is a chronic endocrine condition leading to menstrual and ovulatory dysfunction, linked to obesity, high levels of serum leptin and low grade inflammation. The first line treatment is weight reduction which is also valuable in the management of IIH. The prevalence of PCOS in women referred because of IIH is reported to be 39%^[55] to 57%.^[54] Thus the ratio is 5 to 8 times greater than the 7% prevalence of PCOS in the general unselected population.^[56] Furthermore, IIH was found to be particularly associated with gynecoid type obesity rather than with abdominal obesity, which also emphasizes the role of sex hormonal dysfunction in the pathogenesis of IIH.^[57]

Natriuretic peptides

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.^[58] This natriuretic peptide system which is also expressed in the central nervous system 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 hemorrhage. Moreover, intraventricular administration of ANP reduces elevated ICP and CSF production in rodent models. Since two of these three NP receptors, NPR-A and NPR-C, have been located to the choroid plexus where two-thirds of the total CSF production is generated, it has been suggested that NPs may be involved in the regula-

tion of liquor dynamics. 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 BMI and may increase during weight-loss.^[58]

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.

Aquaporins and anti-neuronal antibodies

The discovery of the aquaporin (AQP) family of membrane water channels has provided new insights into the pathophysiology of brain water homeostasis. AQPs are a large family of water channels, expressed in plasma membrane of many cell types in the CNS and eye. Aquaporin 1 (AQP1) is mainly detected on epithelial cells in the choroid plexus, responsible for water secretion into the subarachnoid space.^[59] Medications could be used for IIH downregulate AQP1^[60] and several drugs such as retinoids and steroids have been shown to induce AQP1 expression suggesting the causative role of AQP1 in the pathogenesis of drug-induced IIH.^[61,62] Furthermore, AQP1 was found to be associated with weight gain in an animal model.^[63] Aquaporin-4 (AQP4) is another one of the major water channels in the brain. It 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.^[64] Many studies of transgenic mice with a complete deficiency or altered expression of AQP4 suggest a prominent role for AQP4 in cerebral water transport.^[65,66] 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.^[67] We and others could not demonstrate any association of AQP4 with IIH.^[68,69] Other studies

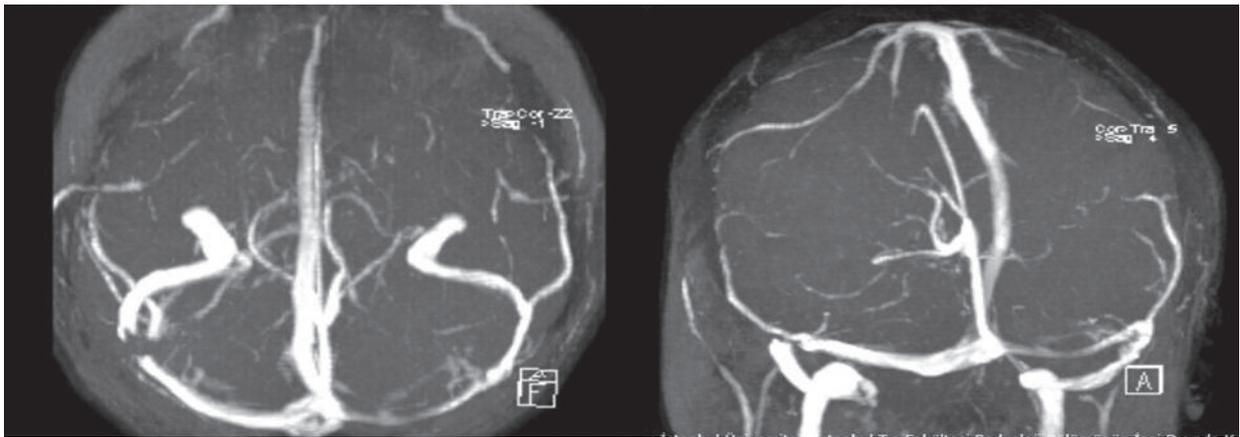


Figure 1. Standard MR-Venography of a patient diagnosed with IIH demonstrating prominent stenosis on the left transverse sinus and irregularities on the right transverse sinus.

are needed to elucidate the role of other Aquaporins and the water pump system.

Furthermore, we identified different IgG binding patterns (i.e. anti-neuronal antibodies) in the sera of several IIH patients in rates comparable to those of encephalitis patients.^[69] Our results might suggest that inflammatory 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.

New insights from neuro-imaging and bilateral transverse sinus stenosis story

Diagnosis of IIH is based on normal neuroimaging of the brain, including MRV. However there is current evidence that some patients with IIH have bilateral transverse sinus stenosis (BTSS).^[70] The transverse sinuses are well-known to be asymmetric in most individuals and an unilateral hypoplastic transverse sinus is considered a “normal variant” without any reported changes of ICP. MRV with an auto-triggered elliptic centric-ordered sequence demonstrated variable degrees of cerebral venous stenosis in most of the IIH cases compared with normal controls.^[71] Furthermore, BTSS was found to predict the presence of increased ICP in patients diagnosed with migraine or chronic tension-type headache.^[72,73] Thus, it has been proposed that the presence of transverse sinus stenosis may support the diagnosis of IIH without papilledema, as mentioned above.^[3] But, BTSS is uncommonly encountered in clinical practice, probably depending on the imaging technique and experience of the neuroradiologist (Figure 1).

There is a debate on whether such a stenosis is the cause or effect of IIH. Some authors argued that the venous sinus theory could not explain the female predominance of IIH in adults.^[74] Moreover, the clinical course, including visual field loss, was not correlated with the degree of transverse sinus stenosis.^[70] It has also been suggested that such narrowing is secondary to compression of the sinuses by the raised ICP causing outflow obstruction, which results in further venous hypertension, then decreases CSF absorption and causes further ICP.^[75,76] Furthermore, some anatomic studies suggested that these stenoses occur due to the presence of trabeculae, septae or hypertrophied granulations in the transverse sinuses.^[77,78] A positive feedback mechanism has also been proposed suggesting that venous hypertension leads to further increased ICP, independently of the initial cause of focal stenosis.^[79]

Venous sinus stenting was therefore used in some patients with conflicting results. Some investigators found that transverse sinus stent placement is effective in IIH patients and suggested it could be a new treatment option in this group.^[80-82] A review of literature including 143 IIH patients treated with venous sinus stenting revealed that most of the patients had improvement of headache, papilledema or visual acuity after this procedure,^[79] even unilateral stenting was found to be effective to reduce pressure gradients in BTSS.^[83] On the other hand, Kumpe et al. detected a new narrowing above the stent in 3 of 15 patients with a follow up by venography or venous pressure measurements.^[82] Rohr et al. reported restenosis in 3 cases associated with recurrence of

symptoms and suggested that increased ICP was the primary problem leading to venous compression. They proposed to do MRV before and after maximal CSF diversion in patients with suspected IIH, to distinguish reversible and fixed stenosis of transverse sinuses aiding in the choice of therapy-ventriculoperitoneal shunt surgery versus stent placement.^[84] In another study Rohr et al. found volume changes in the entire dural sinus system in IIH patients becoming normal after treatment and they suggested that ICP changes are linked to volume decrease of the whole sinus tree.^[85] Other studies have demonstrated improvement in these stenoses after CSF removal.^[86,87] It has also been postulated that following a relatively minor increase of ICP, a possible abnormal flexibility of transverse sinuses in this group could lead to a significant sinus stenosis and increase venous pressure unlike in normal individuals.^[88-90] Some authors concluded that medical treatment failure should be considered to decide for stenting procedure instead of the radiographic severity of the stenosis.^[70,91]

On the other hand, anatomic variants or flow artifacts of venous sinuses often make MRV interpretation difficult. Flow abnormalities in a single transverse sinus (TS) can occur in up to 30% of normal individuals.^[92] It is also worth emphasizing that one-third of the patients with BTSS had normal CSF pressure,^[73] 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, showing the lack of a direct relationship between the caliber of TS and CSF pressure.^[93]

Thus, many findings suggest that venous flow disturbances in IIH are most probably the consequence of CSF hypertension, but not its cause.^[74] However, transverse sinus stenting may be evaluated as an effective treatment option by breaking the aforementioned abnormal positive biofeedback cycle, in selected patients having medically refractory IIH.

Secondary causes, underlying factors

ICP may be secondary to several causes such as venous sinus thrombosis, medical conditions and drugs. Some investigators proposed that increased venous pressure might be the key factor in the devel-

opment of IIH because it is the unifying mechanism for all of the benign tumor-like syndromes.^[94] Cerebral venous thrombosis has been found in 11.4% of patients who were presumed to have IIH.^[95]

IIH has been associated with many etiologies such as exposition to a number of drugs (vitamin A, growth hormone, steroids, minocycline and tetracycline, sulphasalazine, etc...),^[96-102] Behçet's Disease,^[103] arteriovenous malformations,^[104] sleep disturbances including obstructive sleep apnea syndrome (OSAS),^[105,106] extracranial venous hypertension secondary to cardiac septal defect,^[107] systemic lupus erythematosus,^[108] uremia,^[109] iron deficiency anemia^[110,111] as well as some endocrine changes such as menstrual irregularities, use of oral contraceptives, hyperthyroidism and hypothyroidism.^[112,113]

It has also been argued that an underlying thrombophilic defect in patients with IIH might play a role in the pathogenesis and some small studies showed abnormalities in prothrombotic factors.^[114-116] Theoretically, at least 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.

Treatment options

IIH does not currently have a well-established management algorithm, given the paucity of studies on the issue.^[27] CSF dynamics and homeostasis in IIH are complex and incompletely understood. Obese patients are encouraged to lose weight, and acetazolamide is the first choice of medical treatment. The primary goal is decreasing ICP to preserve visual function and to eliminate headache. In IIH patients who still have headache after resolution of ICP, preventive headache medications such as topiramate, which also has mild carbonic anhydrase activity, are used in clinical practice.^[117] The therapeutic role of repeated lumbar punctures which were popular in the past is now questioned due to its difficulties for the patient and lack of evidence showing its long-lasting effects. Surgical options used in selected cases having visual loss include optic nerve sheath fenestration, CSF diversion procedures including either lumboperitoneal or ventriculoperitoneal shunting^[118] in addition to the bariatric surgery for obe-

sity^[119] and the newly introduced transverse sinus stenting as discussed above.^[81,82,120] IIH is usually a self-limiting disease but shows relapses in some of the affected patients.^[27]

Conclusion

The pathogenesis of IIH is still not fully understood. Multiple coexisting mechanisms including excessive CSF production, impaired CSF resorption, and obstructed venous outflow are likely to contribute to the pathogenesis. Increased weight clearly plays a role in the disease process, CSF pressure and the symptoms of IIH tend to fluctuate with spontaneous remissions (sometimes permanently), which are more supportive of an inflammatory process. BTSS may be a marker of increased ICP but whether it is the cause or the result of IIH remains still unsolved. Future studies are needed in order to optimize the biological understanding and reasonable treatment options of this intriguing disease.

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