



Idiopathic Intracranial Hypertension: Diagnosis and Therapeutic Approach

İdiyopatik İntrakraniyal Hipertansiyon: Tanı ve Tedavi Yaklaşımı

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Abstract

Idiopathic intracranial hypertension (IIH) is a condition of increased intracranial pressure without a secondary etiology. IIH is seen frequently in young and obese women. Headache, vision problems, and pulsatile tinnitus are the most common symptoms that lead patients to physicians. IIH requires a multidisciplinary approach because it could create permanent morbidity and its treatment plan should be individualized for each patient. The aim of this review was to provide an updated overview of IIH's pathogenesis, diagnostic criteria, and treatment strategies.

Keywords: Idiopathic intracranial hypertension, pseudotumor cerebri, primary pseudotumor cerebri, optic nerve compartment syndrome, review

Öz

İdiyopatik intrakraniyal hipertansiyon (İİH) sekonder bir nedene bağlı olmayan kafa içi basınç artışıdır. Sıklıkla genç ve obez kadınlarda görülür. Baş ağrısı, görme problemleri ve pulsatil kulak çınlaması hastaları en çok hekime götüren şikayetlerdir. İİH heterojen bulgu ve belirtileri nedeniyle aile hekimlerini ve birçok branşı birlikte ilgilendirmektedir. Tedavisi gecikirse kalıcı morbidite yaratan bu hastalıkta her olgu için kişiye özgü bir tedavi planlanmalıdır. Bu yazıda son yayınlar çerçevesinde İİH'nin etiopatogenezi ile birlikte tanı ve tedavisi gözden geçirilmiştir.

Anahtar Kelimeler: İdiyopatik intrakraniyal hipertansiyon, psödötümör serebri, primer psödötümör serebri, optik sinir kompartman sendromu, derleme

Introduction

Idiopathic intracranial hypertension (IIH) is characterized by increased intracranial pressure of unknown etiology (not due to a secondary cause) with normal cerebrospinal fluid (CSF) composition. The annual incidence of IIH is approximately 3/100,000 persons and it is usually seen in young obese women (1,2). The major morbidities are headache and vision loss if the disease cannot be diagnosed or the treatment is delayed (3).

The synonymous/interchangeable use of pseudotumor cerebri by IIH is not correct, because pseudotumor cerebri includes secondary causes of intracranial hypertension except space occupying lesions. At the present time, IIH is referred to as primary pseudotumor cerebri (4). IIH is increased intracranial pressure of unknown etiology despite all examinations. The terms "benign intracranial hypertension, meningeal hydrops and serous meningitis are no longer used.

Patients with IIH are admitted to neurologists, ophthalmologists, ear-nose-throat specialists, neurosurgeons, and

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Received/Geliş Tarihi: 05.12.2015 **Accepted/Kabul Tarihi:** 08.05.2016

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Turkish Journal of Neurology published by Galenos Publishing House.

family physicians with heterogeneous signs and symptoms. In this article, we aimed to review the current diagnosis and treatment of IIH (primary pseudotumor cerebri) within the context of recent publications.

Signs and Symptoms

Headache (92%) and transient vision loss (72%) are the most common symptoms of IIH (5,6). The headache has frontal, retro-orbital location, and is usually throbbing in nature or with pressure sensation (7). The daily persistent headache is characterized by worsening during activities such as coughing and standing (8). Allodynia is a common (50%) symptom in patients with headaches and migrainous features may be seen (9). The typical allodynia with facial nerve distribution and retroocular pain with eye movements were defined as distinguishing symptoms from other types of headache (5,9).

Except for anecdotal cases, papilledema is observed in all patients with IIH and can be detected rarely without headache (10,11). If left untreated, it may cause blindness due to progressive vision loss and optic atrophy (3). The risk factors for the development of vision loss are as follows: male sex (12), puberty (13,14), patients aged 40 years or older (15), sleep apnea syndrome (16), black race (17), and morbid obesity (18). Absence of headache, and accompanying hypertension and anemia are also associated with poor prognosis (12,19,20). Transient vision loss, blurred vision and photopsia are considered to be associated with papilledema.

There are also reported cases with unilateral or asymmetric papilledema (21,22). The mechanical pressure on the pituitary gland due to long-term increased intracranial pressure causes "empty sella" syndrome. Displacement of optic chiasma and optic nerve in the empty sella may cause vision impairment in patients. It has been suggested that papilledema can be asymmetric if this displacement occurs asymmetrically (23).

The major visual field defects are blind spot enlargement, cecentral scotoma, and concentric contractions. Blind spot enlargement is a typical defect that occurs due to optic disc swelling and displacement of peripapillary retinal receptors (choroidal folding) as a result of increased intracranial pressure. Inferior nasal visual field loss is another common visual field defect that occurs due to compression and resulting infarction of nerve axons at disk level (3).

The patients may consult ear-nose-throat specialists with pulsatile tinnitus, fullness in the ears, inability to hear low-frequency sounds, vertigo (24,25), and spontaneous otorrhea or rhinorrhea (26,27). Although spontaneous otorrhea and rhinorrhea have many causes, IIH should be kept in mind especially in overweight women with a body mass index >30 kg/m² (28). Diplopia, nausea, neck pain or back pain are other symptoms that can be seen in IIH (7,29).

Diagnostic Criteria and Differential Diagnosis

IIH diagnostic criteria were revised in 2014 in order to better distinguish secondary causes (Table 1) (30). All factors that can lead to an increase in intracranial pressure must be investigated for a diagnosis of IIH. Detailed medical history and further evaluation

is important for an appropriate treatment approach. Associated conditions in the differential diagnosis are summarized in Table 2 (31,32).

The normal CSF opening pressure measured in the lateral decubitus position is 180-200 mmH₂O. In the International Classification of Headache Disorders published by the International Headache Society (IHS) in 2013, a CSF opening pressure of over 250 mmH₂O in patients with headaches was defined as a diagnostic criterion for IIH (7). The IHS criteria do not cover patients with a CSF opening pressure of 200-250 mmH₂O and patients without headaches. In patients with a CSF opening pressure of 200-250 mmH₂O, at least one accompanying condition among pulsatile tinnitus, sixth cranial nerve palsy, papilledema, transverse venous sinus stenosis on magnetic resonance (MR) venography, partial empty sella or distention of the perioptic subarachnoid space on cranial MR imaging (MRI) was defined sufficient for the diagnosis of IIH (Table 1) (30). CSF opening pressure measurement should be performed in the lateral decubitus position prior to use of sedative drugs or initiation of pressure lowering treatment (7). CSF biochemistry and cytology should be normal.

The differential diagnosis of pseudopapilledema causes such as optic disc drusen and elevated optic nerve in hyperopia, and true papilledema must be performed by an experienced neuro-ophthalmologist. Blurring of optic nerve margins, loss of spontaneous venous pulsation, venous engorgement, elevation of optic disc, peripapillary hemorrhage and exudate or optic nerve layer infarcts are suggestive of true papilledema (Figure 1). Blood pressure measurements should be performed in patients

Table 1. Modified Dandy criteria for the diagnosis of idiopathic intracranial hypertension

1. Signs and symptoms of increased intracranial pressure
2. Absence of localizing findings on neurologic examination
3. Absence of deformity, displacement or obstruction of the ventricular system and otherwise normal neurodiagnostic studies, except for evidence of increased CSF pressure (>200 mmH ₂ O); abnormal neuroimaging except for empty sella turcica, optic nerve sheath with filled CSF spaces, and smooth-walled non-flow-related venous sinus stenosis or collapse should lead to another diagnosis
4. Awake and alert
5. No other cause of increased intracranial pressure present For CSF opening pressure of 200-250 mmH ₂ O required at least one of the following: Pulse synchronous tinnitus, 6 th palsy, Frisen grade 2 papilledema, Echography for drusen-negative and no other disc anomalies mimicking disc edema present. Magnetic resonance venography with lateral sinus collapse/stenosis preferably using auto-triggered elliptic centric-ordered technique. Partially empty sella on coronal or sagittal views and optic nerve sheaths with filled CSF spaces next to the globe on T2-weighted axial scans.
CSF: Cerebrospinal fluid

Table 2. Differential diagnosis of idiopathic intracranial hypertension

1. Estrogen-related conditions:
- Oral contraceptives,
- Pregnancy,
- Polycystic ovary syndrome.
2. Intracranial venous flow pathology:
- Congenital abnormalities that prevent venous flow,
- Dural venous sinus compression or obstruction,
- Extra-cranial pathologies that prevent cranial venous flow,
- Venous sinus thrombosis.
3. Hematologic pathologies:
- Anemia (e.g., iron deficiency, pernicious, aplastic),
- Leukemia,
- Myeloma,
- Polycythemia,
- Platelet or factor abnormalities,
- Peripheral neuropathy, organomegaly, endocrinopathy, monoclonal gammopathy (POEMS) syndrome
4. Endocrine pathologies:
- Thyroid (hypothyroidism, thyroid replacement therapy),
- Adrenal (hyperadrenalism, Cushing's syndrome, Addison's disease),
- Parathyroid (hypoparathyroidism, pseudohypoparathyroidism),
- Pituitary (acromegaly, growth hormone replacement therapy),
- Turner syndrome,
- Others
5. Infections:
- Otitis media, mastoiditis,
- Non-specific viral infections,
- Lyme disease,
- Chronic meningitis (syphilis, brucellosis, cryptococcus),
- Poliomyelitis, Guillain-Barré syndrome,
- Other viral infections (varicella, enterovirus 71),
- Other bacterial infections (frontal/paranasal sinusitis, gastroenteritis, typhoid)
6. Head trauma
7. Nutritional pathologies:
- Vitamin D deficiency,
- Malnutrition,
- Vitamin A deficiency and excess
8. Drugs and chemicals:
- Steroids,
- Tetracyclines,
- Nalidixic acid,
- Other agents (danazol, lithium carbonate, perhexiline maleate, amiodarone, penicillin, ciprofloxacin, nitrofurantoin, sulfamethoxazole, mesalamine)
9. Other diseases:
- Systemic lupus erythematosus,
- Behcet's disease,
- Renal disease,
- Cardiac and respiratory diseases,
- Sleep disorders,
- Psychiatric disorders (depression, bulimia),
- Enzyme deficiencies (galactosemia, 11-beta-hydroxylase deficiency, alpha-chymotrypsin deficiency)

The references of the Table are mentioned in the text.

with papilledema to rule out malignant hypertension, and these patients should be referred for neuroimaging regarding intracranial pathologies in the differential diagnosis. Most of patients with IIH who have papilledema are not aware of the contraction in the visual field, and visual field examination and fundus imaging by automated perimetry should be performed to monitor the disease.

The main neuroimaging findings that may accompany IIH are empty sella (70%), distention (45%), and tortuosity (40%) of the perioptic subarachnoid space, flattening of the posterior sclera (80%), protrusion of optic nerve papillae into vitreous, and transverse sinus stenosis (90%) (Figure 2, 3) (4,7,30,33,34). It should not be forgotten that these findings are not specific to IIH and other pathologies that may cause these findings must

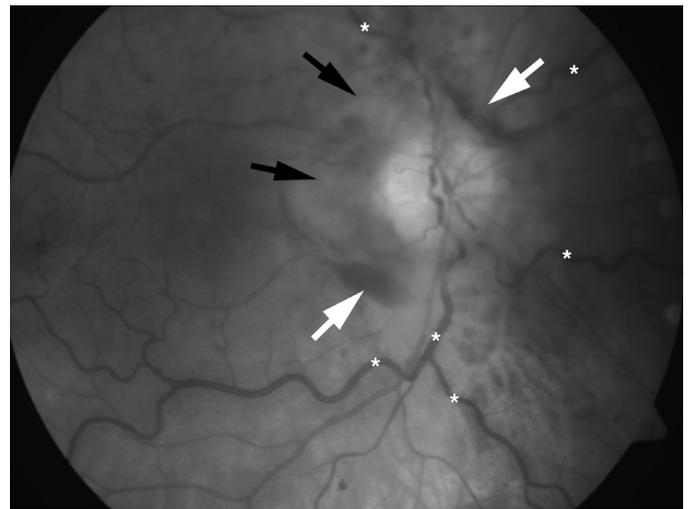


Figure 1. Papilledema in a patient with idiopathic intracranial hypertension: Blurring of optic nerve margins and elevation of optic disc, retinal venous engorgement (*), peripapillary hemorrhage (white arrows) and exudate (black arrows).

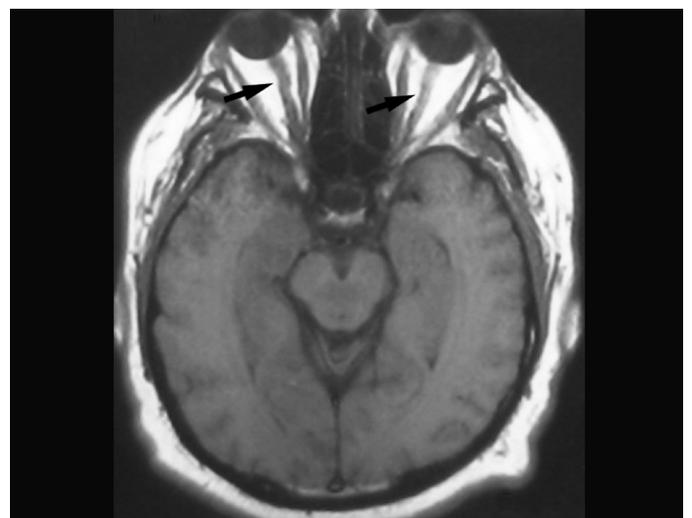


Figure 2. Bilateral optic nerve tortuosity (arrows) on axial T1-weighted magnetic resonance imaging of a patient with idiopathic intracranial hypertension.

be evaluated. MRI examination should include intravenous contrast-enhanced cranial and orbital MRI and MR venography in order to exclude possible space occupying lesions and infectious pathologies. Fat suppression sequences will provide better distinguishing of orbital and optic nerve pathologies. CSF opening pressure should be measured after making sure that there is no intracranial space-occupying lesion in patients with papilledema using neuroimaging.



Figure 3. Left transverse sinus stenosis (arrow) on magnetic resonance venography of a patient with idiopathic intracranial hypertension.

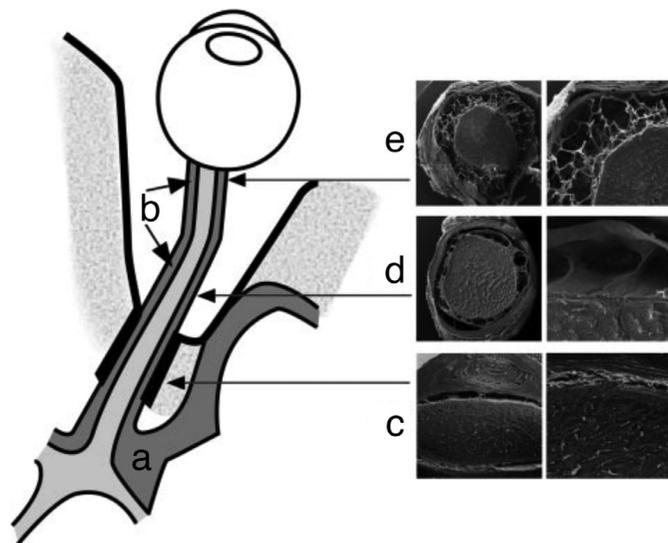


Figure 4. Schematic representation of the cerebrospinal fluid (CSF) spaces surrounding the optic chiasm (intracranial CSF space) (a) and the optic nerve (intraorbital CSF space) (b). CSF flows from intracranial subarachnoid space (a) into the orbita (b). The CSF space in the canalicular region (c) is the narrowest subarachnoid space surrounding the optic nerve. The intraorbital segment of the subarachnoid space is characterized by septae (d) and the retrobulbar segment is characterized by small trabeculae (e). Due to the CSF volume gradient, the direction of flow is directed from the intracranial subarachnoid space to the intraorbital subarachnoid space.

All patients should undergo a basic examination for pathologies listed in the differential diagnosis (Table 2) by evaluation of blood pressure, body temperature, fasting blood glucose, blood count, and serum biochemistry including liver enzymes, and renal function parameters (31,32). However, medical history will guide further investigation.

Etiopathogenesis

IIH is believed to result from irregularities of CSF production, distribution and absorption, however etiopathogenesis still remains unclear. Parenchymal edema, increased cerebral blood flow, increased CSF production, and obstruction of venous drainage have been suggested as causes (32).

Increased intracranial pressure in cases of disturbances in the hypothalamic-pituitary-adrenal axis (Addison’s disease, Cushing’s syndrome, corticosteroid use) or female sex, pregnancy, polycystic ovary syndrome, obesity, use of oral contraceptives suggests a hormonal effect in the etiopathogenesis. A neuroendocrine effect has been suggested to cause increased production of CSF by stimulation of mineralocorticoid receptors in the epithelial cells of the choroid plexus (35). This hypothesis may be illustrative in patients with hyperaldosteronism, obesity, and hypercortisolism, and in patients who are on recombinant growth hormone treatment; there was no evidence of increased production of CSF in patients without identified causes (36).

The argument that the decrease in venous drainage causes IIH remains unclear in the etiopathogenesis. Non-obstructive venous stenosis can be descriptive in head trauma, otitis media or other prothrombotic diseases (such as Behçet’s disease, systemic lupus erythematosus, Factor V Leiden mutation, antithrombin III deficiency, and hormone therapies). However, the frequent observation of comorbid prothrombotic factors such as obesity, female sex, and pregnancy complicates the clarification of this situation (32).

It was also suggested that transverse sinus stenosis in IIH might result from increased intracranial pressure rather than being a cause of the disease (37). Transverse sinus asymmetry and unilateral hypoplasia are considered normal variants in patients with normal intracranial pressure. Anatomic studies have shown that stenosis is due to trabeculae, septa or hypertrophic granulomas (38). The presence of transverse sinus stenosis following normalization of CSF pressure in patients with IIH (39), and the absence of correlation between visual field loss and the degree of stenosis (34) suggest that stenosis is a result rather than an etiologic factor.

The perioptic subarachnoid space differs from other subarachnoid spaces owing to its “cul-de-sac” anatomy and trabeculated structure (Figure 4). The optic nerve, being an extended bunch of dura-covered white matter into the orbit rather than a histologically true cranial nerve, is also in a distinctive position. The unique anatomy of the optic nerve results in direct vulnerability of the nerve in the event of intracranial space-occupying lesions, IIH, infectious and inflammatory central nervous system diseases (40).

Contrast-enhanced computerized cisternography in 3 patients with IIH revealed absence of enhancement in the perioptic subarachnoid space indicating the disruption of free circulation of CSF in subarachnoid space and thus led to the term; optic nerve

compartment syndrome (ONCS). In these 3 patients, the CSF by LP and the CSF in the optic nerve sheath was compared when performing optic nerve sheath fenestration (ONSF) for treatment. "Lipocalin-like prostaglandin D synthase (L-PGDS)" levels in the optic nerve sheath were found 2 to 7 times higher than CSF with LP according to the severity of the disease. L-PGDS is a brain-derived protein and is homogeneous in CSF. This study supports ONCS due to decreased excretion or increased production of L-PGDS in the perioptic subarachnoid space (41). Distention of the perioptic subarachnoid space, flattening of the posterior sclera, protrusion of optic nerve papillae into vitreous and even empty sella may be considered as neuroimaging findings of optic nerve compartment syndrome.

Treatment

Although the etiology has not been clarified in IIH, there are many treatment methods. The aim of medical treatment is to reduce CSF production or increase its drainage. Losing weight along with medical treatment was shown to have positive effects on headache, visual field, and papilledema (42,43). Several surgical techniques have been described in refractory patients. Treatment should be determined according to the patient and course of the disease. The goal of treatment should be preventing vision loss and headache by reducing intracranial pressure.

Acetazolamide, which is a carbonic anhydrase inhibitor that reduces CSF production from the choroid plexus, is one of the main drugs. One to four g/day acetazolamide can be used at divided doses, two times a day or three times a day. Although this drug has positive effects on papilledema and vision, it is believed to have a limited effect on the management of headaches (44). Paresthesias due to hyponatremia and hypokalemia are the most common adverse effects. In such a situation, treatment can be continued with potassium supplementation and close monitoring in the absence of other organ dysfunction. Adverse effects such as rash, crystalluria, kidney stones, bone marrow depression, thrombocytopenia, and hemolytic anemia require discontinuation of the treatment.

Topiramate, also used in the treatment of migraine, is a weak carbonic anhydrase inhibitor and is preferred due to its weight loss side effect (45,46). Topiramate has been demonstrated to be effective in the treatment of IIH and should be used in patients who are refractory to acetazolamide or who cannot use the drug due to adverse effects (46,47). Daily 100 to 150 mg topiramate dosages that were initiated at 50 mg daily divided dosages were reported effective (46).

There is no evidence that steroids are useful in the treatment of IIH. They should not be recommended because of adverse effects such as weight gain and venous stasis, and their potential to cause secondary intracranial hypertension (48). Drugs such as furosemide and mannitol have intracranial pressure reducing effects without a clear mechanism (24,49).

Diagnostic lumbar puncture (LP) may help to relieve symptoms by decreasing CSF pressure. In addition to medical treatment, LP may be performed at regular intervals depending on the patients' symptoms (48). However, recurrent LP is not usually recommended due to infection risks and uncomfortable situations. A lumbo/ventriculo-peritoneal (LPe/VP) shunt should be considered as an

option in patients who benefit from successive LPs, but not from medical treatment. Shunt operation does not provide remission in all patients and may cause surgical complications such as shunt dysfunction and infection. Patients who have benefited from surgery may again become symptomatic in approximately 2 years even though their shunts are functional (50,51,52). In a study by Rosenberg et al. (53), the authors found that the mean time to LPe shunt revision was 9 months and that 64% of all LPe shunts were replaced within 6 months in patients with IIH. While the most frequent complication of LPe shunt in IIH is shunt obstruction, the second most common complication is secondary intracranial hypotension due to CSF overshunting (53,54,55,56,57). Despite these, it is recommended as a first-line treatment in patients with headache and visual impairment (54).

VP shunts are known to have less risk of complications and revision rates compared with LPe shunts (52,58). A sufficient ventricular width is necessary for successful shunting. Framed or frameless stereotactic shunting in the presence of slit ventricles, as frequently seen in IIH, has less risk of complications (59,60). Secondary intracranial hypotension due to overshunting is observed less in VP shunts with the use of programmable valves (52,58,61). McGirt et al. (58) reported that VP shunting relieved headache in up to 95% of patients with headache. However, headache reoccur in 20% and 48% of patients within 12 and 36 months, respectively, despite a functional shunt (58). In addition to all these, it should be kept in mind that shunts are not helpful in patients without papilledema and associated long-term symptoms (58,61). Optic nerve compartment syndrome should be suspected in patients who partially benefited or did not benefit from shunt surgery.

ONSF is performed by cutting a dural and arachnoid window in the optic nerve sheath. For many years, it was performed by ophthalmologists using different techniques, mainly through orbitotomy. Associating adjacent compartments surrounding the optic nerve allows local decompression of the nerve. The improvement in vision in ONSF (80%) was shown to be better compared with other methods (38.7-47%) (62). On the other hand, this method is also associated with serious complications. Iris sphincter paresis, central retinal artery occlusion, and accommodation paresis are some of these serious complications (63,64,65,66,67,68,69). The papilledema and visual field were shown to improve even in the contralateral eye in patients with unilateral surgery (70).

In order to eliminate the risk of these serious complications, an endoscopic endonasal approach, which is a more physiologic and a minimally invasive method, was developed by neurosurgeons as an alternative to orbitotomy. Although some patients underwent ONSF with the endoscopic endonasal method (71,72), there are also patients who received optic decompression without ONSF (73,74). Endoscopic endonasal procedures may be unilateral (71,73,74) or bilateral (72). Endoscopic unilateral optic decompression is a newly defined method with low complication rates, and has positive effects on headache, papilledema, and visual field (73). The papilledema and visual field were shown to improve even in the contralateral eye in patients with unilateral surgery (73).

Transverse venous sinus stenting is another defined invasive procedure in IIH, but it is questionable as to whether the stenosis is a cause or a result (34). Therefore, the contributions of restoring venous sinus flow with this invasive method are controversial.

Research in this field is extremely new. Studies including a limited number of cases were published and successful results were reported (75,76). The long-term results of this method are unknown and some authors believe that resolving venous sinus stenosis will not provide a clinical benefit to patients (77,78,79).

Invasive procedures should be scheduled immediately in the progressive vision loss despite medical treatment. In the literature, it was stated that ONSF might be preferred in patients with evident papilledema and vision loss, and VP and LPe shunts might be preferred in patients with evident headache (50,51). However, this should not be perceived as a rule, and the treatment should be decided according to the case considering new surgical methods.

Weight gain and hormonal alterations may trigger the disease during pregnancy or may worsen the existing disease. Venous sinus thrombosis, which is commonly observed in pregnancy, must be excluded. The use of category C drugs, acetazolamide and topiramate, is not recommended in the first trimester. LP at regular intervals may be choice in these patients. Based on the fact that the growing uterus may cause shunt obstruction, ONSF should be preferred in patients who require surgical treatment.

Headache may continue after CSF pressure is normalized. In such cases, depression, anxiety, and any other types of accompanying headaches such as medication-overuse headache, migraine, tension-type headache should be questioned. Primary headaches are frequently seen in young and middle-aged women as IIH and they may worsen due to increased CSF pressure (9). The increase in the headache severity or the change in the headache character may be a symptom of shunt dysfunction or infection. Although the shunt is functional, ophthalmologic follow-up should be continued as IIH may worsen over time.

A different etiology, depending on increased CSF production, may be considered in patients who benefit from CSF-reducing drugs and interventions such as VP and LPe shunts. Decreased CSF drainage may be an etiologic factor in patients who benefit from VP and LPe shunts. Optic nerve compartment syndrome might be suspected in patients who partially benefited or did not benefit from current treatments, but further studies are needed for the elucidation of the etiopathogenesis.

Conclusion

The etiology of IIH has not yet been elucidated. The signs and symptoms of the disease vary and involve many specialties. A multidisciplinary follow-up is mandatory for all patients. An individualized treatment should be planned and all patients should be closely monitored for visual disturbances. Further scientific studies are needed for better understanding and treatment of IIH.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.S., M.O.A., Z.Y., N.H.A., Concept: N.H.A., M.O.A., Design: N.H.A., M.O.A., Data Collection or Processing: N.H.A., M.O.A., Analysis or Interpretation: Z.Y., A.S., M.O.A., N.H.A., Literature Search: N.H.A., M.O.A., Writing: N.H.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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