

Idiopathic intracranial hypertension: ongoing clinical challenges and future prospects

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Abstract: Idiopathic intracranial hypertension (IIH) is an uncommon disorder characterized by increased intracranial pressure without radiological or laboratory evidence of intracranial pathology except empty sella turcica, optic nerve sheath with filled out cerebrospinal fluid spaces, and smooth-walled nonflow-related venous sinus stenosis or collapse. This condition typically affects obese women. The incidence of IIH is increasing with the rising prevalence of obesity. Persistent headache is the most common symptom. Visual impairment is a serious complication that may not be recognized by the patients. This paper reviews clinical manifestations, diagnostic challenges, and current treatments of IIH in adults. Various imaging modalities have been studied on their validity for detection of IIH and papilledema. This review also includes new studies on medical, surgical, and interventional management of this condition. Acetazolamide and topiramate are the only two medications that have been studied in randomized controlled trials about their efficacy in treatment of IIH. In patients who have severe visual impairment or progressive visual deterioration despite medical management, surgical or interventional treatment may be considered. The efficacy and complications of cerebrospinal fluid diversion, optic nerve sheath fenestration, and endovascular venous stenting reported in the last 3 decades have been summarized in this review. Finally, the prospective aspects of biomarkers and treatments are proposed for future research.

Keywords: acetazolamide, cerebrospinal fluid shunts, endovascular stenting, optic nerve sheath fenestration, pseudotumor cerebri

Introduction

Idiopathic intracranial hypertension (IIH) is an uncommon disorder of increased intracranial pressure (ICP) without radiological and laboratory evidence of intracranial pathology. Even though the clinical presentations of this condition are well-characterized, the pathogenesis remains unclear. Although obese women of childbearing age are typically affected, IIH can affect patients of any age or sex. Incidence of IIH largely varies from 0.03 to 2.36/100,000/year in total population.¹⁻⁹ As female sex and obesity are the risk factors for IIH, higher incidence was reported in female population (0.65–4.65/100,000/year)³⁻⁸ and in obese women (2.7–19.3/100,000/year).^{4,5,9} In the last decade, its incidence has been rising due to the globally increasing prevalence of obesity.⁹ Chronic headache and visual impairment are the main presentation symptoms of IIH. Quality of life is also affected by IIH, even in patients with mild visual impairment.¹⁰

Clinical manifestations

Headache is the most common symptom of IIH present in 80%–90% of patients.^{11,12} Headache is typically a bilateral frontal or retro-orbital throbbing or pressure and may

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be associated with nausea, vomiting, and transient visual obscuration. Patients often give history of worsening of headache in comparison to the headaches that they have experienced in the past. Some patients present with chronic daily headache with 12 days of headache per month on average.¹² There is no relationship between severity or frequency of headache and ICP.¹³ Sometimes, it is challenging to differentiate the headache associated with IIH from other primary headache syndromes. For example, 41% of patients with IIH reported premorbid migraine history.¹² Clinical features of chronic headache in IIH and chronic migraine are very difficult to distinguish.¹⁴ Medication-overuse headache is another condition that can mimic headache in IIH. Some IIH patients report mild-to-moderate continuous headache that can mimic the headache features in chronic tension-type headache. The diagnostic criteria for headache attributed to IIH proposed by the International Headache Society are shown in Table 1.¹⁵

IIH can cause transient visual obscurations, loss of visual acuity, visual field defects, and tunnel vision. Transient visual obscuration, which is transient loss or graying out of vision lasting a few seconds, occurs in 68% of patients

and is related to papilledema.¹² The mechanism of transient visual obscuration remains unclear. Ischemia of optic nerve head and downward herniation of the parahippocampal gyrus in the tentorial notch are the proposed mechanisms of this symptom.

Abducens nerve is the most common cranial nerve affected by elevated ICP manifesting in horizontal binocular diplopia. Sixth nerve palsy can be either unilateral or bilateral and is a false localizing sign in this condition.

Intermittent tinnitus has been reported in 52% of IIH cases.¹² This may be unilateral or bilateral, often described as a whooshing, wind-like, or a pulsatile noise. Tinnitus is explained by the compressive effect of intracranial hypertension to venous sinuses, resulting in turbulent blood flow.¹⁶ Low-frequency hearing loss and vertigo can be found in IIH patients. Prolonged interpeak latencies in auditory brainstem-evoked response was reported in one-third of patients with IIH that may be caused by compression-stretching of cochlear nerve and brainstem from intracranial hypertension.¹⁷

It is interesting to mention about the cognitive profile in IIH patients. Although, cognitive function is not routinely evaluated in patients with IIH, multiple domains of cognitive function are impaired in IIH patients, including memory, executive function, visuospatial processing, attention, motor skills, working memory, and processing speed.^{18–20} The most severe deficits were reaction time and processing speed.¹⁹ Despite significant improvement in headache, cognitive dysfunction may persist even after 3 months of treatment.¹⁹

Similar to the optic nerve, the olfactory nerve is surrounded by meningeal sheath and cerebrospinal fluid (CSF), which could also be affected by the elevation of ICP. Impaired olfactory function has been recognized in many recent studies as one of the symptoms in IIH patients.^{21–24} There was a report of morphological change of olfactory bulb volume in untreated symptomatic IIH patients.²⁵ In addition to the measurement of visual impairment, papilledema, or headache, it is interesting to study the role of olfactory nerve function and morphology in early diagnosis of IIH and as an outcome measurement after treatment of IIH.

Diagnostic challenges

Neuroimaging

Neuroimaging is helpful in excluding other causes of raised intracranial tension like space-occupying lesions. Venous sinus thrombosis can present with severe headache from intracranial hypertension secondary to impairment of CSF reabsorption, which can clinically mimic IIH symptoms. Magnetic resonance imaging (MRI) of the head and orbit with

Table 1 IHS diagnostic criteria for headache attributed to IIH

- A. Progressive headache with at least one of the following characteristics and fulfilling criteria C and D:
 1. Daily occurrence
 2. Diffuse and/or constant (nonpulsating) pain
 3. Aggravated by coughing or straining
- B. Intracranial hypertension fulfilling the following criteria:
 1. Alert patient with neurological examination that either is normal or demonstrates any of the following abnormalities:
 - Papilloedema
 - Enlarged blind spot
 - Visual field defect (progressive if untreated)
 - Sixth nerve palsy
 2. Increased CSF pressure (>200 mm H₂O in the nonobese, >250 mm H₂O in the obese) measured by lumbar puncture in the recumbent position or by epidural or intraventricular pressure monitoring
 3. Normal CSF chemistry (low CSF protein is acceptable) and cellularity
 4. Intracranial diseases (including venous sinus thrombosis) are ruled out by appropriate investigations
 5. No metabolic, toxic, or hormonal causes of intracranial hypertension
- C. Headache develops in close temporal relation to increased intracranial pressure
- D. Headache improves after withdrawal of CSF to reduce pressure to 120–170 mm H₂O and resolves within 72 hours of persistent normalization of intracranial pressure

Abbreviations: IHS, International Headache Society; IIH, idiopathic intracranial hypertension; CSF, cerebrospinal fluid.

intravenous contrast and magnetic resonance venography (MRV) are the modalities of choice to exclude any structural lesions prior to IIH diagnosis. Several radiologic signs are suggestive of IIH; however, none of them are pathognomonic for this condition.

Intracranially, empty or partially empty sella sign and decreased pituitary height are commonly seen in IIH. Sella turcica is a saddle-shaped depression in the sphenoid bone where the pituitary gland is situated. Prolonged intracranial hypertension enlarges bony structure of pituitary fossa with minimal effect on the pituitary size, which contributes to the partial empty appearance of sella turcica in MRI.^{26,27} Herniation of subarachnoid space to the anterior portion of sella turcica diaphragm is the hypothesis of empty or partially empty sella sign in IIH. Enlargement of sella area provided high sensitivity (100%) and specificity (90%) in differentiating IIH from normal controls.²⁷ The area of the pituitary gland has been reported to be very sensitive (100%) for detecting posttreatment changes.²⁷

Narrowing of trigeminal cave, an arachnoid pouch containing CSF and trigeminal ganglion, is a novel finding reported in IIH.²⁸ Apart from effect on sella turcica, bone erosion and remodeling secondary to chronic intracranial hypertension may result in widening of the bony canals of the skull base. Enlargement of the foramen ovale demonstrated high specificity (81%), but low sensitivity (50%) in diagnosis of IIH.²⁹ The jugular foramen and hypoglossal canal were also reported to be enlarged in IIH.^{30,31}

Enlargement of CSF space or spontaneous CSF-filled outpouchings of the dura (meningoceles) resulting from chronic intracranial hypertension may be the supportive findings in diagnosis of IIH.³¹ These enlargements have been reported in the Meckel's cave, the oculomotor nerve sheath, and the CSF spaces around the abducens nerve.^{31,32}

Stenosis of the transverse sinus is another common finding in IIH, which can lead to venous outflow obstruction. Stenosis within dural sinus system has been reported in 30%–93% of IIH patients.³³ The volume of the entire dural sinus system is also decreased in IIH patients.³⁴ Stenosis of transverse and sigmoid sinuses detected by MRV are considered as a reliable neuroimaging marker of IIH with high sensitivity (93%) and specificity (93%).³⁵ Even though a study reported that transverse sinus stenosis still persists after lumbar puncture (LP),³⁶ cerebral sinus diameter and dural sinus volumes are significantly increased after normalization of ICP in IIH independent of resolving of transverse sinus stenosis.^{34,37} It is still inconclusive whether venous sinus stenosis is a causative factor or a consequence of intracranial

hypertension. Acute CSF volume reduction by CSF diversion or single LP can decrease stenosis of venous sinuses. On the contrary, stenting of transverse sinus stenosis can improve intracranial hypertension. These findings suggest that venous sinus stenosis and intracranial hypertension may have a circular loop relationship.^{38,39}

Intraorbital imaging shows enlarged optic nerve sheath, posterior globe flattening, or optic nerve head protrusion. Transorbital ultrasonography is a reliable and noninvasive imaging technique to detect enlargement of the optic nerve sheath diameter (ONSD) with satisfactory sensitivity (90%) and specificity (84%) at a cutoff value of 5.8 mm in detection of IIH. In another study, ONSD >5.5 mm predicted CSF pressure ≥ 20 cm H₂O with both sensitivity and specificity of 100%.⁴⁰ Another study showed that ONSD >5 mm can detect ICP >20 cm H₂O with sensitivity of 88% and specificity of 93%.⁴¹ Optic disc elevation can also be detected by ultrasound.⁴² MRI is another reliable imaging modality for the detection of increased ONSD with sensitivity of 72%–80% and specificity of 96%.⁴³ ONSD decreases after LP within 30 minutes, while optic disc protrusion requires longer treatment time for reduction.^{44–46}

Flattening of the posterior globe in MRI is highly specific, but not sensitive, in detection of IIH.⁴³ A study reported 100% specificity of this finding, indicating that it strongly supports the diagnosis of IIH.⁴⁷ It is important to emphasize that even though these findings on imaging provide reliability in differentiating IIH from a normal population without intracranial hypertension, they are not specific for IIH. These signs can also be found in patients with intracranial hypertension from other identifiable causes.^{48,49} For example, empty/partially empty sella sign, flattening of the globes, and dilatation/tortuosity of the optic nerve sheath were reported in 65%, 42%, and 16% patients with cerebral venous thrombosis, respectively.⁴⁸

Ophthalmological examination

Compression of optic nerve and optic nerve ischemia are the two major theories explaining papilledema caused by elevated ICP in IIH.⁵⁰ Papilledema is one of the hallmarks for diagnosis of IIH. Even though, papilledema is commonly symmetric or only mildly asymmetric, significant asymmetry may be found in some patients and can be explained by difference in size of bony optic canals or variation of trabecular meshwork in subarachnoid space surrounding optic discs.^{51,52} Unilateral papilledema is not commonly reported.^{53,54}

Fundoscopy examination is very important to evaluate this condition. Frisén's⁵⁵ criteria has been widely accepted for grading severity of papilledema. It is very important to dif-

ferentiate true papilledema from pseudoedema, which is the physiologic variant, or benign changes of the optic disc. Findings from funduscopy examination showed that the presence of retinal or choroidal folds is a pathognomonic sign of true papilledema. However, this finding was seen only in 23% of the patients with true papilledema. The combination of four features from funduscopy examination, including the swelling of the peripapillary retinal nerve fiber layer, peripapillary hemorrhages, papilla elevation, and congestion of peripapillary vessels, provides very good validity in differentiating true papilledema from pseudoedema (accuracy 93%, sensitivity 95%, and specificity 89%).⁵⁶

Optical coherence tomography is a noninvasive imaging tool used to evaluate optic nerve status including the severity of papilledema either by measuring fast retinal nerve fiber layer thickness or total retinal thickness.⁵⁷ High-resolution three-dimensional T2-weighted imaging performed at submillimeter slice thickness can effectively detect papilledema.⁵⁸ In diffusion-weighted imaging, hyperintensity of optic nerve head at diagnosis of IIH was found to be correlated with the severity of papilledema.⁵⁹ Macular thickness is significantly reduced in patients with resolved chronic papilledema, which is also correlated with severity of visual field loss. Macular thickness may be an indicator of ganglion cell loss in IIH patients with papilledema.⁶⁰

Idiopathic intracranial hypertension without papilledema

Idiopathic intracranial hypertension without papilledema (IIHWOP) is the variant of IIH, which was reported in 5.7% of IIH patients in one study.⁶¹ IIHWOP is found in 10%–14% of patients with chronic daily headache who fulfilled the criteria for migraine.^{14,62} In patients with migraine, 6.7% had bilateral transverse sinus stenosis, of which 67.8% had IIHWOP.⁶³ In a similar manner, bilateral transverse sinus stenosis was found in 9% of patients with chronic tension-type headache, and 69.2% of these patients had IIHWOP.⁶⁴ IIHWOP must be considered in patients with chronic daily headache with evidence of sinus stenosis and unresponsiveness to medical management. MRV can detect venous sinus stenosis which is a strong predictor for intracranial hypertension in such patients. LP should be done to confirm the diagnosis.^{65,66}

Lumbar puncture

LP is classically contraindicated in the setting of elevated ICP. However, this procedure is routinely performed in IIH either for diagnostic or for therapeutic purposes. Real-time ONSD reduction and opening of the collapsed transverse

sinuses were observed after a bedside LP.^{45,67} Long-standing clinical remission is not uncommon within a single or few sessions of LP.⁶⁷ Amount of removed CSF or a dural hole during single LP may not be the only explanations for long-standing clinical remission. This finding may be explained by the circular loop relationship between CSF and cerebral venous pressure. Removal of CSF by LP is compensated by enlargement of cerebral venous diameters resulting in cerebral venous pressure reduction and enhancing CSF outflow which can promote further venous enlargement.³⁹

It is important to note that LP is not a harmless procedure in IIH patients. To date, two cases of tonsillar herniation after LP were reported in IIH patients with preexisting low-lying cerebellar tonsil and worsening metabolic acidosis.^{68–70}

Current management

The primary goal of treatment of IIH is to prevent visual loss and decrease headache and other symptoms associated with intracranial hypertension. Routine follow-up by neuroophthalmologist or ophthalmologist is very essential for reassessing visual status and degree of papilledema. Weight reduction counseling and medical management are generally sufficient in most patients. Surgery is required only in patients who have severe visual loss, progressive visual loss, or intractable headache despite aggressive medical management. Aggressive weight reduction is necessary in obese patients. Gastric bypass surgery has been demonstrated to improve visual outcomes and reduce ICP in IIH cases with morbid obesity.^{71,72}

Although there are many options for the treatment of IIH, the most recent Cochrane review reported that there is insufficient information to generate an evidence-based management for IIH.⁷³

Pharmacotherapy

To date, acetazolamide and topiramate are the only two medications that have been studied in randomized controlled trials for their treatment efficacy in adults with IIH. The efficacy of other medications is only supported by case reports or case series. For example, there was a case series reporting the efficacy of combination of acetazolamide and furosemide in eight children in 1994.⁷⁴ Corticosteroid was reported to be effective in the short-term in patients who presented with severe papilledema and severe visual loss. However, steroid withdrawal and its side effect on weight gain are precipitating factors for worsening IIH in long-term use. A summary of the trials of acetazolamide and topiramate in treatment of IIH in adults are discussed in the following sections.

Acetazolamide

Acetazolamide inhibits carbonic anhydrase enzyme in the choroid plexus resulting in decreased CSF production and pressure. It is considered as the first-line medication for IIH. The side effects of acetazolamide generally include paresthesia of extremities, loss of appetite, transient myopia, and metabolic acidosis.

The Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) IIH study groups carried out the first multicenter, double-blinded, randomized controlled trial of the efficacy of acetazolamide in 165 patients with IIH and mild visual loss who received low-sodium and weight reduction diet at 6-month period.⁷⁵ The use of acetazolamide with a low-sodium and weight reduction diet moderately improved a visual field defect compared to diet alone. Papilledema and visual-related quality of life were significantly improved in acetazolamide group. Moreover, patients in acetazolamide group also had significant reduction in weight, with an average reduction of 7.5 kg. The effect of acetazolamide on visual function was found more frequently in patients with high-grade papilledema. The dose of acetazolamide used in this trial was maximal at 4 g/d (mean: 2.5 g/d). Even though, the finding was statistically significant, the less-than-expected difference of visual field improvement between two groups made the authors caution that “the clinical importance of this improvement remains to be determined.”

Topiramate

Topiramate is an anticonvulsant, which has been previously reported to be effective in the treatment of IIH.^{76–78} There was an open-label, randomized study to compare the efficacy of topiramate (20 patients) and acetazolamide (20 patients).⁷⁹ The doses of topiramate and acetazolamide ranged from 100–150 mg/d to 1–1.5 g/d, respectively. This study demonstrated no significant difference in visual field improvement between these two groups at the end of the months 3, 6, and 12. Relief of headache and improvement of papilledema were comparable between two groups. The improvement in headache was seen after 3.75 months in the topiramate group and 3.30 months in the acetazolamide group. This is the first open-label, randomized study on the efficacy of topiramate on the treatment of IIH. However, the number of subjects was small (total: 40 subjects in this study). A larger multicenter, double-blinded, randomized controlled trial would be the next step to confirm the efficacy of topiramate in IIH.

The mechanism of topiramate in IIH treatment is explained by its mild effect on carbonic anhydrase inhibition.

The common side effects of topiramate are distal paresthesia, concentration difficulty, weight loss, and nephrolithiasis. Rare cases of acute angle-closure glaucoma and myopia were reported.^{80–82} As topiramate is a prophylactic medication for other forms of headache including migraine, it may be particularly effective in IIH patients without papilledema or in IIH patients with migraine who have intractable headache after resolution of papilledema.⁸³

Surgical management

Generally, surgical intervention is indicated in IIH cases with severe optic neuropathy or medical treatment failure that are vision-threatening. Surgical intervention for IIH includes CSF diversion and optic nerve sheath fenestration (ONSF).

CSF diversion

CSF diversion by a ventriculoperitoneal shunt (VPS) and lumboperitoneal shunt (LPS) are the most widely used methods to divert CSF from the ventricle or subarachnoid space to peritoneal space. Ventriculoatrial shunt (VAS) is another alternative method to divert CSF from ventricle to right atrium.

LPS has the advantage of avoiding an intracranial approach, thus decreasing the incidence of surgery-related intracranial complications such as intracranial infection and subdural hemorrhage. However, it can cause cerebellar tonsillar descent leading to iatrogenic Chiari malformation. Other complications of CSF diversion are shunt infection, catheter migration, shunt obstruction, and overdrainage. LPS has a higher complication rate than VPS.⁸⁴ Moreover, LPS often requires more revision and greater overall cost than VPS.^{84–87}

In terms of clinical outcomes, LPS improved headache in 71%–92% of IIH patients who experienced progressive visual loss or were not responsive to medical treatment.^{84,88} However, recurrent headache was usually found during the follow-up period.^{85,89} Visual acuity was improved by LPS in 42%–91% of patients.^{84,86} Visual field and papilledema were also improved after the procedure. VPS and VAS were less studied than LPS in their role of IIH treatment. These procedures are also effective in improving headache and visual function in patients with IIH. Headache was improved in 60%–90% of the patients after the procedure.^{84,86} VPS and VPA effectively improved visual functions and papilledema. Visual acuity improved in 40%–100%, while papilledema resolved in 56%–87% of cases.^{84,86,89,90} Image-guidance is recommended for placement of VPS.^{91,92}

A recent case series including five patients with IIH refractory to standard peritoneal therapy reported the role of lumbopleural shunt to divert CSF. The complications of this procedure were pleural effusion, hydrothorax, and pneumothorax. The average survival time of the lumbopleural shunt was 48 months (ranged from 2 to 178 months). However, the clinical improvement of IIH was not reported in this study.⁹³ Fluoroscopy-guided percutaneous placement of catheter in the perimedullary cistern is reported as an alternative CSF diversion method in two IIH patients with multiple proximal shunt failure.⁹⁴

In conclusion, most of the studies reported similar clinical outcomes (headache, visual function) between LPS and VPS/VAS. However, LPS has a higher shunt revision rate associated with increased shunt obstruction. Table 2 summarizes the studies on the CSF diversion in IIH treatment.

Optic nerve sheath fenestration

ONSF is another surgical intervention to reduce papilledema-related visual loss. This procedure is used primarily to reduce CSF pressure on retrolaminar part of the optic nerve. However, it may not decrease ICP. Thus, this method is preferred in IIH patients who mainly experience visual symptoms. The majority of studies also emphasized the visual outcomes (visual acuity, visual field, and papilledema) more than outcome on headache reduction.

In terms of efficacy, ONSF demonstrates very satisfactory outcomes. Improvement or stabilization of visual acuity and visual field are reported in a very wide range, from 60% to 100%, of cases depending on the criteria of each study. Papilledema was improved in 71%–100% of patients after the procedure. Even though ONSF locally decrease CSF pressure surrounding an optic nerve with very minimal effect on the overall ICP, improvement of headache was reported after this procedure in 13%–90% of cases. Table 3 summarizes the outcomes of ONSF in IIH.

In the past, there was a suggestion that, in case of bilateral visual loss or papilledema, CSF diversion can decrease the need for bilateral ONSF. However, some studies also reported the improvement of bilateral papilledema and visual function after unilateral ONSF.^{95–98} In comparison to CSF diversion, ONSF is less invasive and does not require leaving any foreign body in the central nervous system. The rate of infection is minimal. The majority of complications are often minimal and transient, which include diplopia, anisocoria, and corneal drusen. Major complications were rarely reported, including central retinal artery occlusion, acute angle-closure glaucoma, iatrogenic traumatic optic neuropathy, and infectious

optic neuropathy.^{99–102} In the early postoperative period, fluid collection adjacent to the dural window site occurs in majority of the patients, but this disappears in the late period.^{96,103} Protracted postsurgical blindness can occur after ONSF, and patients subsequently recover in some cases.¹⁰⁴

Endovascular venous stenting

Venous stenosis is detected in a significant number of IIH patients. It is still unclear whether venous stenosis directly causes intracranial hypertension due to impaired cerebral venous return or is the consequence of vascular compression from long-standing intracranial hypertension. Previous studies demonstrated that fixing the stenosis by endovascular stenting decreased venous pressure gradient and ICP in subgroup of IIH patients who have a venous pressure gradient across the stenosis.^{105–108} Even in bilateral stenosis, unilateral stent is sufficient to decrease the venous pressure gradient.¹⁰⁵ In terms of cost, there is no cost difference between the initial insertion of stent or CSF shunting. However, considering the high revision rate of CSF shunting, venous stenting costs significantly less than CSF shunting.¹⁰⁹

From the pooling analysis of nine retrospective studies (total 174 cases), this procedure provided satisfactory outcomes during the mean follow-up period of 23 months.^{105–108,111–114} Among 129 patients who had headache, 99 patients (77%) had improvement or resolution of headache after the stent insertion. Of 54 patients documented to have visual problem, visual acuity was improved or stabilized in 48 patients (89%) and papilledema was resolved or improved in 109 from 117 patients (93%). Of the 51 patients who presented with pulsatile tinnitus, it was resolved in 48 patients (94%) after stent placement. Table 4 summarizes the outcomes of endovascular venous stenting in IIH.

The common complications of venous sinus stenting are ipsilateral headache in 20%–100% of cases; this resolves within few days after the procedure. Intracranial hemorrhage is a serious complication that is rarely seen after the procedure (4%–6%). Proximal stent stenosis was found in some studies with unclear etiology.^{105,110} In contrast to an arterial stenting, in-stent stenosis is very rare in venous sinus stenting. Aspirin and clopidogrel are generally required for 3–4 days prior to the procedure and are continued for 3–6 months after the placement before clopidogrel is discontinued.^{105,110}

Various cutoff points for mean pressure gradients have been postulated in different studies ranged from 4 to 10 mmHg prior to the procedure. Some studies did not consider this pressure gradient.^{105,106,108,110,112} Further research is needed to identify the

Table 2 Outcomes and complications of CSF diversion in IIH

Studies	Type of diversion	Number of cases	Follow-up (months)	Clinical outcomes			Revision rate and complication
				Headache	Visual acuity	Visual field	Papilledema
Fonseca et al ⁹⁰	VPS (37%) VAS (63%)	19	34	NR	47% improved, 32% stable, 21% worsened	Improvement of mean deviation from -15.80 to -9.23 dB	Revision rate =42% Complications: shunt infection (5%)
Huang et al ¹¹⁹	VPS	17	21	Overall outcomes were 53% improved, 29% stable, 6% worsened, and 12% indeterminate	Statistical improvement of VA on both eyes, but no significant improvement of VF	87% complete resolution 13% stable at grade I	Nonfunctioning VPS 20%, 35%, and 53% at 1, 2, and 3 years, respectively
Yadav et al ⁸⁸	LPS	24	51	92% improved	56% improved, 27% stable, and 17% worsened in VA	Resolution 35%, 52%, and 56% at 6, 12, and 24 months, respectively	Revision rate =8% Complications: overdrainage (63%)
Sinclair et al ⁸⁹	LPS (92%) VPS (8%)	53	24	32%, 23%, and 21% remission at 6, 12, and 24 months, respectively	No data on VF or papilledema outcomes	No significant improvement	Revision rate =51% within 7.5 months in average and 85% within 1 year
Tamaris et al ⁸⁴	LPS (83%) VPS (17%)	29	29	71% improved in LPS 60% improved in VPS	Significant improvement at 6 and 12 months (not at 24 months)	Resolution 35%, 52%, and 56% at 6, 12, and 24 months, respectively	Complications: obstruction (44%), disconnection (19%), and migration (7%)
Abubaker et al ⁸⁶	LPS (72%) VPS (28%)	25	48	83% improved in LPS 90% improved in VPS	42% improved in LPS 40% improved in VPS	NR	Revision rate =40% in LPS and 22% in VPS within 14.3 months in average
Ushewokunze et al ¹²⁰	LSS	23	24	83% improved in LPS 90% improved in VPS	91% improved in LPS 100% improved in VPS	100% improved in LPS 100% improved in VPS	Complications: 24% in LPS and 11% in VPS (shunt infection, obstruction, overdrainage, and migration)
McGirt et al ⁸⁵	LPS (69%) VPS/VAS (31%)	42	49	57% had only transient improvement which subsequently required VPS/LPS 44% had sustained and permanent improvement, required no further intervention 95% improved immediately with recurrent headache in 36 months	100% improved in VPS	88% improved in LPS 86% improved in VPS	Revision rate =60% in LPS and 30% in VPS within 7 months in average
				Risk factors for recurrence of headache were papilledema (RR: 5.2) and long-term symptoms (RR: 2.5)			Complications: migration, obstruction, shunt infection, and overdrainage in LPS. Chronic subdural hematoma in VPS
							Complications: overdrainage (65%), back pain and sciatica (39%), CSF leak (13%)
							Risk of revision increased 2.5-fold in LPS compared with VPS/VAS
							Shunt obstruction was 2.5-fold higher in LPS. Similar risks of overdrainage, migration, and infection between LPS and VPS/VAS

Abbreviations: CSF, cerebrospinal fluid; IIH, idiopathic intracranial hypertension; VPS, ventriculoperitoneal shunt; VAS, ventriculoatrial shunt; NR, not reported; VA, visual acuity; VF, visual field; LPS, lumboperitoneal shunt; LSS, lumbar subcutaneous shunt; RR, relative risk.

Table 3 Outcomes and complications of optic nerve sheath fenestration in IIH

Studies	Number of cases	Follow-up (months)	Clinical outcomes			Revision rate and complication	
			Headache	Visual acuity	Visual field	Papilledema	
Fonseca et al ⁹⁰	14	17	NR	50% improved, 29% stable and 21% worsened	Improved mean deviation from -23.50 to -17.29 dB	71% complete resolution	No revision
Sencer et al ²¹	10	28	57% improved	78% improved	89% improved	78% improved or resolved	No revision
Moreau et al ⁹⁹	236 (455 eyes)	19	NR	17% (eyes) improved 79% (eyes) stable 4% (eyes) worsened	63% (eyes) improved 34% (eyes) stable 3% (eyes) worsened	NR	Revision rate =7% (patients) Complications: ocular misalignment (6%) and corneal dellen (0.8%)
Alsuhaibani et al ⁹⁵	78	12	NR	Improved in both operated (P=0.005) and unoperated eyes (P=0.026)	Improved in both operated (P=0.017) and unoperated eyes (P=0.009)	Improved in both eyes at 0.5, 3, 6, and 12 months (P<0.0001)	NR
Nithyanandam et al ¹²²	5 (10 eyes)	3	NR	40% (eyes) improved 60% (eyes) stable	90% (eyes) improved 10% (eye) stable	NR	Overall complications included transient pupillary atony (13.4%), transient diplopia (3.4%), and early orbital cellulitis
Yazici et al ⁹⁶	17 (26 eyes)	32	47% improved or completely relieved	96% improved in visual function		100% (eyes) resolved or improved.	Ischemic optic neuropathy in 1 patient
Banta and Farris ¹⁰¹	86 (158 eyes)	20	13% improved	94% (eyes) stable or improved 6% (eyes) worsened	88% (eyes) stable or improved 12% (eyes) worsened	NR	Revision rate =7% (patients) Complications: diplopia (35%), dellen (7%), anisocoria (7%), orbital apex syndrome (1%), and traumatic optic neuropathy (0.6%)
Goh et al ¹²³	29 eyes	16	NR	14% (eyes) improved 76% (eyes) stable 10% (eyes) worsened	48% (eyes) improved 38% (eyes) stable 14% (eyes) worsened	NR	Revision rate = 14% (patients) No report on the complications
Kelman et al ⁹⁷	17 (21 eyes)	17	90% improved	97% (eyes) improved or stabilized	95% improved	100% improved	No repeat surgery required Complication: central retinal artery occlusion (1%)
Corbett et al ⁹⁸	28 (40 eyes)	6	65% improved or relieved	30% (eyes) improved 55% (eyes) stable 15% (eyes) worsened	55% (eyes) improved 27% (eyes) stable 18% (eyes) worsened	86% improved	Complications: tonic/atonic pupil (40%), retrobulbar hemorrhage (2.5%)
Sergott et al ¹²⁴	23	22	76% immediately improved	100% improved	100% improved	NR	Complications: transient diplopia (4%), dellen (4%)
Knight et al ¹²⁵	5	NR	NR	60% improved	60% improved	100% improved	Postoperative visual loss (10%)

Abbreviations: IIH, idiopathic intracranial hypertension; NR, not reported; CSF, cerebrospinal fluid.

Table 4 Outcomes and complications of cerebral sinus endovascular stent in IIH

Studies	Number of cases	Age (years)	Follow-up (months)	Clinical outcomes				Criteria for stent	Mean pressure gradient (mmHg)		Complications
				Headache	Visual acuity	Visual field	Papilledema		Pre-stent	Post-stent	
Ducruet et al ¹⁰	30	33	22	19/27 improved (overall symptoms) Patent of stents in 27/27 at the mean 22 months follow-up period				Stenosis (>50%) with a pressure gradient of >10 mmHg	NR	NR	Common femoral artery pseudoaneurysm (3%)
Radvany et al ⁰⁵	12	39	16	7/12 improved or resolved	11/12 improved or stable	19 of 24 (eyes) improved	11/12 improved	Stenosis with a pressure gradient of ≥ 4 mmHg	12.4	1.2	Transient retro-orbital pain (100%)
Fields et al ⁰⁶	15	34	14	10/15 improved	13/14 improved or stable	NR	15/15 resolved	Stenosis with a pressure gradient of ≥ 10 mmHg	24	4	Femoral pseudoaneurysm (7%)
Kumpe et al ⁰⁷	18	38	44	10/12 improved or resolved	15/15 improved or stable	NR	15/16 resolved	NR	22.5	2.6	Intracranial hemorrhage (6%)
Albuquerque et al ¹¹	15	32	20	12/15 improved	Patent of stents in 14/14 at the mean 12.5 months follow-up period			Stenosis >50%	NR	NR	Retroperitoneal hematoma (6%)
Ahmed et al ¹²	52	34	24	35/43 improved	9/13 improved	23/30 improved	46/46 improved	Stenosis with a pressure gradient of >8 mmHg	19	0.6	Ipsilateral frontal headache, intracranial hemorrhage (4%)
Bussière et al ⁰⁸	10	34	20	10/10 improved or resolved	NR	NR	8/10 resolved	Stenosis with a pressure gradient of ≥ 10 mmHg	24.6	11.25	Ipsilateral headache (20%)
Donnet et al ¹³	10	41	17	8/10 improved or resolved	9/10 improved		10/10 resolved	NR	19.1	NR	None
Higgins et al ¹⁴	12	33	14	5/12 resolved, 2/12 improved, 5/12 unchanged or resolved	5/12 improved, 2/12 improved, 5/12 unchanged or resolved	5/12 unchanged	4/8 improved or resolved	NR	NR	NR	Ipsilateral headache, transient hearing loss (17%), unsteadiness (8%)

Abbreviations: IIH, idiopathic intracranial hypertension; NR, not reported.

Table 5 Long-term outcomes of the intervention to visual function and headache when follow-up > 1 year

Procedures	Number of studies	Number of cases	Follow-up (months)	Clinical outcomes				
				Headache improvement (range)	Visual acuity improvement (range)	Visual field improvement (range)	Papilledema improvement (range)	Revision rate of procedure (range)
Optic nerve sheath fenestration	8	432	20	26% (13%–90%)	42% (17%–100%)	72% (48%–100%)	92% (79%–100%)	6.5% (5%–21%)
CSF diversion	7	209	39	55% (21%–92%)	56% (40%–93%)	77% (64%–100%)	70% (56%–87%)	44% (8%–85%)
Cerebral sinus endovascular stent	9	174	23	77% (58%–100%)	89% (69%–100%)	79% (77%–79%)	93% (50%–100%)	NA

Abbreviations: CSF, cerebrospinal fluid; NA, not applicable.

optimum gradient and severity of venous stenosis amenable for the selection of patients for endovascular stenting.

In IIH patients with focal venous sinus stenosis, emphasis on the management of sinus stenosis by stenting is a new emerging treatment option providing very satisfactory clinical outcomes and low rate of complications or revision.

Future prospects

Biomarkers or diagnostic development

The pathogenesis of IIH remains unknown. Some studies demonstrated the presence of oligoclonal bands in IIH patients that is associated with vision loss.¹¹⁵ Patients with IIH had significantly higher serum levels of TNF- α , IFN- γ , IL-4, IL-10, IL-12, and IL-17 in comparison to multiple sclerosis patients and normal controls. IL-2, IL-4, IL-10, IL-17, and IFN- γ levels in CSF were higher in IIH patients compared to patients with multiple sclerosis or nonorganic/noninflammatory neurologic conditions.¹¹⁶ These findings may support the immunologic role in pathogenesis of IIH.^{115–117}

There is a study aimed at identifying the CSF proteome in IIH patients as the new biomarkers. Six proteins were upregulated in IIH, namely, sterol regulatory element-binding protein 1, zinc- α -2-glycoprotein, immunoglobulin heavy constant α -1, α -1-antitrypsin, serotransferrin, and haptoglobin. Four proteins were downregulated in IIH, including hemopexin, angiotensinogen, vitamin-D-binding protein, and transthyretin. Angiotensinogen was the first protein validated in the study, and it was found that downregulation of angiotensinogen may contribute to the increased CSF production, which subsequently causes IIH. The study of other proteins may provide more knowledge on the new biomarkers for diagnosis of IIH. Moreover, these proteins may be the target for therapeutic intervention.¹¹⁸

Conclusion

IIH is an uncommon disorder characterized by symptoms and signs of intracranial hypertension without radiologic or

laboratory evidence of intracranial pathology. This condition typically affects young-to-middle-aged females with obesity. Visual impairment and severe headache are the major concerns in this condition; thus, the primary treatment purpose is to prevent visual dysfunction and reduce headache severity. Counseling about weight reduction is the initial treatment approach in all obese patients. LP is a diagnostic tool for evaluation of elevated ICP. Medical management is generally the first line of treatment and is adequate in the majority of patients. Acetazolamide and topiramate are the only two medications that have been studied in randomized controlled trials and showed significant improvement of headache and visual outcomes. Acetazolamide is the first-line medication in most patients. In patients with severe optic neuropathy or those who fail medical therapy, surgical management, either CSF diversion or ONSF, and endovascular venous stenting of transverse sinus stenosis are the next available options which have demonstrated satisfactory outcomes on visual function and headache. Table 5 summarizes the long-term outcome of visual function and headache of each intervention in the treatment of refractory IIH. There are many challenges that need to be explored in future research on the diagnosis and treatment of IIH. Many biomarkers have been demonstrated to relate to IIH pathogenesis and may be the targets in the future research. In addition, more prospective, randomized controlled trials are needed to establish a treatment guideline for IIH.

Disclosure

The authors report no conflicts of interest in this work.

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