Idiopathic Intracranial Hypertension from Benign to Fulminant: Diagnostic and Management Issues

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Abstract

Idiopathic intracranial hypertension (IIH) primarrily affects obese women of childbearing years and is commonly associated with headaches, pulsatile tinnitus, and vision changes. Though most patients have a "benign" course, it can lead to significant morbidity, including blindness. The treatment approach is based on severity of visual impact and includes weight loss, intracranial pressure lowering medications, and sometimes surgery, such as spinal fluid diversion, optic nerve sheath fenestration, or venous sinus stenting. More studies are needed to determine when surgery is most appropriate and which surgical procedure provides maximal benefit with the least risk.

Keywords: Benign, diagnosis, fulminant, headache, IIH, management, treatment

Introduction

Idiopathic intracranial hypertension (IIH) often presents with headache, pulsatile tinnitus, transient visual obscurations and is a condition of unknown etiology. It most commonly affects obese women of childbearing age, and given the rise in obesity, is becoming more prevalent. IIH was once referred to as benign intracranial hypertension, though this terminology has fallen out of favor, due to the devastating effects it can have on vision and quality of life.[1] Diagnosis requires the presence of optic disc edema and/or cranial nerve six palsy, normal brain imaging with the exception of signs of elevated intracranial pressure, confirmation of elevated intracranial pressure with normal cerebral spinal fluid (CSF), and an otherwise normal neurological exam.[2,3] Treatment includes weight loss, medical management, and, in severe cases, surgical intervention. The following is a literature review discussing current concepts in diagnosis and management of mild to severe IIH.

Pathophysiology

The etiology of IIH remains unknown, though theories tend to center around over production of CSF, impaired CSF resorption, and elevated intra-abdominal pressure causing decreased venous return from the head.[4] Recent studies have more closely examined the relationship between intracranial venous hypertension and intracranial pressure (ICP).[5] Elevated Lumbar puncture (LP) opening pressure has been shown to be highly predictive of elevated intracranial venous pressure.[6] In fact, a proposal was made to change the name from IIH to chronic intracranial venous hypertension syndrome.[7] Four theories are proposed for etiologies of elevated intracranial venous pressure: elevation in central venous pressure without venous sinus stenosis (driven by obesity or cardiopulmonary disease), venous sinus stenosis, a combination of these two, or venous thrombosis.[6,7] Transverse sinus stenosis is found in up to 93% of patients with IIH.[8] Venous stenosis may be caused by intrinsic lesions, such as large arachnoid granulations obstructing venous outflow or extrinsic compression from elevated ICP.[9] There is evidence for a positive feedback loop where an inciting event induces elevated ICP (i.e. sleep apnea induced nocturnal ICP elevation) and, in an anatomically predisposed individual, extrinsic stenosis occurs at the transverse sinus.[5] Treatment with venous sinus stenting specifically targets this pathophysiology. Recently, the venous sinuses are further implicated as impairing lymphatic and glymphatic drainage of the CSF.[10] Whatever the cause, recent evidence suggests that there is also a metabolic syndrome as well as cardiovascular risk associated with many individuals and this may have an adverse effect on an individual's longevity.[11]

Symptoms and Signs of IIH

The most common symptoms reported in the IIH treatment trial (IIHTT), a prospectively collected series, included

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headache (84%), transient visual obscurations (68%), back pain (53%), pulse synchronous tinnitus (52%), dizziness (52%), photophobia (48%), neck pain (41%), subjective vision loss (32%), and diplopia (18%).[12]

In the IIHTT, the average LP opening pressure was 343.5 mm CSF and there was no correlation between severity of visual field deficits on formal visual field testing and papilledema grade or LP opening pressure. The most concerning complication of IIH is vision loss, which is most often reversible, but can be severe in 10% of patients.[12] Arcuate defects, enlarged physiologic blind spots and diffuse constriction can be seen on formal visual field evaluation. Diplopia can be a result of unilateral or bilateral cranial nerve six palsies from elevated ICP.[13]

Risk Factors in IIH

Though the etiology of IIH remains unknown, there are risk factors associated with the condition. The most common risk factors are female sex and being overweight or having recent weight gain. There are multiple metabolic conditions that can contribute to IIH/pseudotumor cerebri syndrome. Common ones include hypothyroidism, systemic lupus erythematosus, anemia, hypoparathyroidism, among others. Medications can contribute to elevated intracranial pressure, including tetracyclines, vitamin A derivatives, lithium, steroid (particularly withdrawal from steroids). Oral contraceptives are often continued in women with IIH, as there is limited evidence that these are causative.

Diagnosing IIH

The modified Dandy criteria for diagnosis of IIH have traditionally been used for diagnosis, though updates have occurred.[2,3,14,15] Requirements include symptoms of elevated ICP, no structural etiology for elevated ICP identified on intracranial imaging, CSF opening pressure of at least 25 cm H_2O with normal composition, and a normal neurologic exam, with the exception of optic disc edema and/or abducens nerve palsy. Probable IIH can be diagnosed if the opening pressure is between 20 and 25 cm H_2O and there are at least 3 of the 4 signs of elevated ICP identified on head imaging.[3] Imaging signs suggestive of elevated ICP include flattening of the posterior globe, optic nerve sheath distention or tortuous optic nerves, empty sella, and transverse venous sinus stenosis [Figure 1].[3] If a secondary etiology is identified, for example tetracycline use, venous sinus thrombosis, or a metabolic derangement, then the condition is no longer idiopathic and the terminology secondary pseudotumor cerebri syndrome should be used. Fulminant IIH is diagnosed when the typical signs and symptoms of IIH occur acutely (rapid progression within four weeks) and result in severe vision loss [Figure 2]. Clinical recognition of vision threatening papilledema is critical to saving vision.

IIH without papilledema (IIH WOP) can be a diagnostic challenge and overdiagnosis may expose patients to unnecessary medications and surgical procedures. In 2013, revised diagnostic criteria were created to reduce misdiagnosis of IIH WOP.[3] Elevated opening pressure of greater than 25 cm H_2O in adults and greater than 28 cm H_2O in sedated, obese children can occur in up to 10% of the normal population. No individual radiologic feature is diagnostic of elevated ICP; however, having three out of four signs of elevated ICP (listed above), is nearly 100% specific.[16] Reduced pituitary gland height is a sensitive (80%), but not specific (64%) marker of elevated ICP. Flattened pituitary was found in 80% of patients with IIH with papilledema, though was also found in 36% of normal controls.[3] Seventy-eight percent of patients with IIH with papilledema had venous sinus stenosis.[3] Flattened posterior globe and transverse-sigmoid sinus stenosis are among the more specific findings, though posterior globe flattening is prone to subjectivity.[3] Visual loss in IIH WOP does not usually occur and if present, may be functional.[17]

Medical Treatment of IIH

Treatment of IIH is directed toward lowering ICP, preserving vision, and managing symptoms, such as headache. Three approaches to treatment include weight loss, medications, and surgical approaches.

a. **Weight reduction:** Weight loss of 6–10% body weight from the time of diagnosis has been thought to improve signs and symptoms of IIH, though a recent study showed that weight loss of 24% may be needed.[18,19] Maintenance of weight loss is essential, as rebound weight gain is a significant risk of recurrence of IIH.
b. **Medications:**
    a. **Acetazolemide:** The IIHTT studied the use of acetazolamide plus weight loss versus weight loss alone in patients with mild vision loss. Use of acetazolamide, up to 4 g/day, showed greater improvement in visual field, CSF opening pressure, papilledema, and quality of life.[12]
    b. **Topiramate:** Topiramate is also used for treatment of IIH, as it has carbonic anhydrase inhibitor properties similar to acetazolamide. Topiramate is more effective for the treatment of headache compared to acetazolamide and has a beneficial side effect of weight loss.[20-22] In a healthy rat model, topiramate was shown to significantly lower ICP, while acetazolamide did not.[20,23] Acetazolamide and topiramate have similar side effects of paresthesia, fatigue, and increased risk of kidney stones, while topiramate may have more predisposition to cognitive impairment.
    c. **Diuretics:** Diuretics, such as furosemide, chlorthalidone, and amiloride can also be used to lower ICP.
    d. **Others:** Octreotide, a somatostatin analogue has also been reported as helpful.[24] See Table 1 for treatments for IIH to reduce pressure.

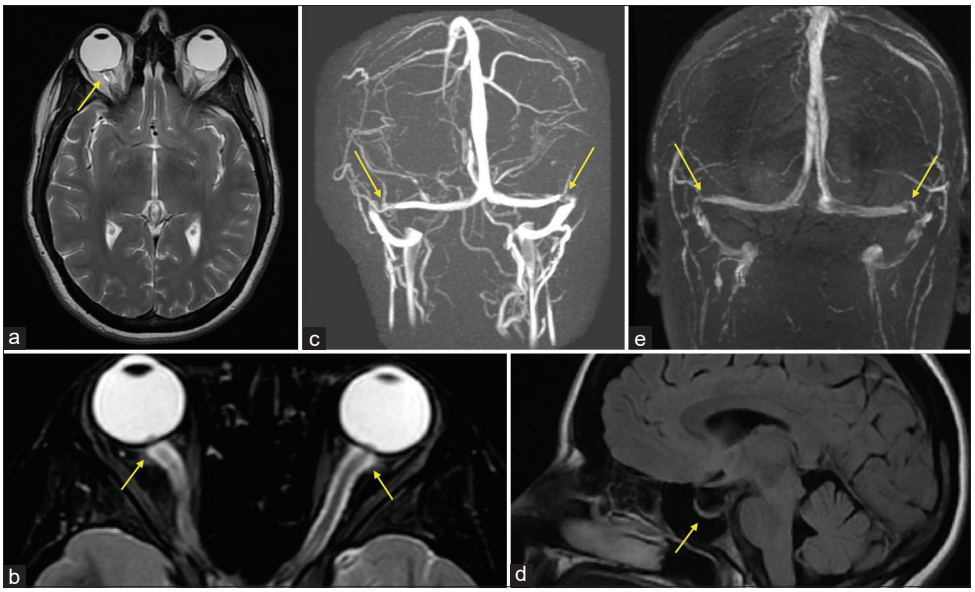

Figure 1: MRI findings suggestive of elevated intracranial pressure: (a and b) Distention of the optic nerve sheath with posterior globe flattening and protrusion of the optic nerve into the globe (yellow arrows); (c and e) stenosis of the transverse-sigmoid sinus junctions (yellow arrows); (d) pituitary flattening (yellow arrow)

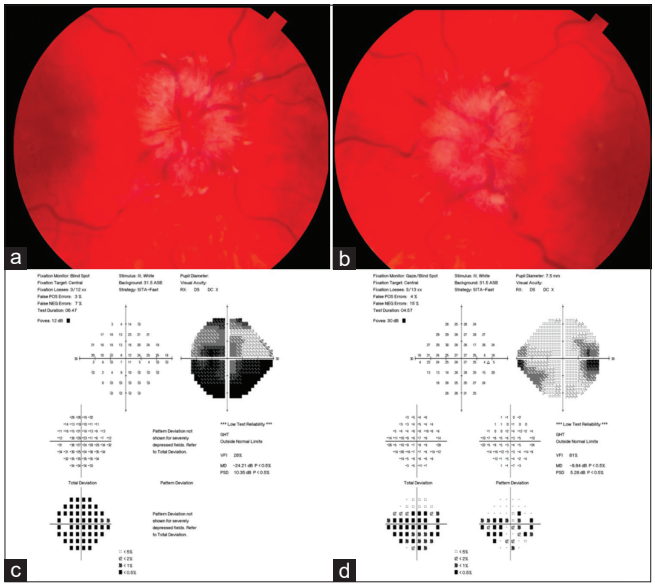

Figure 2: Color fundus photographs of a 17-year-old girl with fulminant IIH. The right eye (a) and left eye (b) display grade IV optic disc edema, peripapillary hemorrhages, cotton wools spots, and tortuous vessels. Humphrey Visual Field testing revealed severe vision loss in the left eye (c) and moderate to severe vision loss in the right eye (d)

Table 1: Medications used to lower intracranial pressure and acutely treat IIH

Medication	Dose
Acetazolamide	500 mg twice daily Up to 4000 mg/day, in divided doses
Topiramate	Starting at 25 mg at night Increasing by 25 mg up to 200 mg/day, in divided doses
Methazolamide	150–300 mg total daily in divided doses
Zonisamide	100 mg daily Up to 200 mg (limited data on dosing for IIH)
Chlorthalidone	25-50 mg daily
Furosemide	20 mg daily; titrate up to 40 mg twice daily and potentially up to three times daily
Octreotide	0.3—1.0 mg subcutaneously daily for 6-8 months

Surgical Treatment of IIH

For cases of IIH refractory to medical management, situations of medication non-compliance, or fulminant IIH, surgical options exist. Patients are considered refractory, if moderate to severe vision loss (perimetric mean deviations worse than -6 dB) does not improve or continues to worsen with maximal tolerated medical management. We do not favor surgical intervention for headaches alone, in the absence of vision loss. Surgeries include optic nerve sheath fenestration (ONSF), CSF diversion (ventriculoperitoneal or lumboperitoneal shunts), venous sinus stenting (VSS), and bariatric surgery.[25] There are limited evidence-based recommendations on the surgical management of IIH and decisions on the most appropriate surgical management largely depend on local expertise. The Surgical Idiopathic Intracranial Hypertension Treatment Trial (SIGHT) aimed to compare medical versus surgical treatment (ONSF or ventriculoperitoneal shunt) of moderate to severe IIH, however, was discontinued early due to failure to recruit participants.[26]

Optic nerve sheath fenestration

Optic nerve sheath fenestration involves opening the retro-orbital optic nerve sheath to reduce the pressure in the subarachnoid space immediately behind the globe. The retro-orbital optic nerve sheath is accessed via a

medial transconjunctival, superomedial transconjunctival, superomedial transcutaneous upper eyelid, or a lateral orbitotomy approach.[27]

Kalyvas *et al*.[25] reviewed 818 patients who underwent 1365 ONSF procedures. Complications occurred in 145 out of 724 patients, with serious complications accounting for only 2.2% of these (3rd or 6th nerve palsies, strabismus requiring surgery, orbital cyst, traumatic optic neuropathy, conjunctival abscess). An additional intervention, such as CSF diversion or VSS was needed in 17% of 700 patients, primarily to achieve headache control, despite an initially successful ONSF. A retrospective chart review to assess 6-month outcomes after unilateral ONSF was performed.[28] Results showed both structural (papilledema grade) and functional (visual field) improvement in the operated and non-operated eyes. Improvement in the contralateral eye has been observed after ONSF and could be explained by a general decrease in intracranial pressure.[29,30] This hypothesis is supported by research showing improvement in headache after unilateral ONSF and greater improvement in headache after bilateral ONSF.[25,28,31]

CSF diversion

CSF diversion is primarily performed via ventriculoperitoneal or lumboperitoneal shunting (VPS and LPS, respectively). A focused review of VPS (142 patients) in IIH showed improvement in visual acuity in 58% and visual fields in 67% of patients. Headaches were improved in 91%, while improvement in papilledema occurred in 91%. The 12-month VPS failure rate was 40.6%.[25] The same study evaluated LPS in 157 patients with IIH. Visual acuity improved in 70% and visual fields in 72% of cases. Headaches improved in 98%, while papilledema improved in 87% of patients. Shunt revision was performed in 35% of patients while the LPS 12-month failure rate was 38%.[25] Unfortunately, headaches often recur after VP and LP shunts.[32]

In fulminant IIH, a temporary CSF diverting measure can be performed with a lumbar drain.[33,34] In some cases, this may allow medical management to take effect and surgical procedures to be avoided. In others, surgical procedures may still be required. The authors' institution has created a vision-threatening papilledema protocol that allows for emergent admission for lumbar drain and close monitoring of visual function with a virtual visual field device.[35] This has prevented the need for surgical procedures in some patients, while allowing time for surgical planning in others.

Venous sinus stenting

An important finding in patients with IIH is transverse-sigmoid dural venous sinus stenosis. It is unclear whether this is a cause or effect of elevated ICP, though studies have shown that stenting of this stenosis provides a therapeutic reduction in ICP.[36] Prior to deploying a venous sinus stent, a cerebral venogram is performed and the trans-stenotic pressure gradient is measured. A pressure gradient of at least 4–10 mmHg is considered sufficient to proceed to stent placement.[25]

The review by Kalyvas *et al*.[25] assessed 825 patients who underwent VSS. Three percent of patients had symptom relapse with evidence of restenosis leading to venous sinus re-stenting or subsequent intervention. The 12-month estimate of VSS failure rate was 13%. Minor complications occurred in 9%, while major complications affected 2% of patients. Major complications included various forms of intracranial hemorrhages, obstructive hydrocephalus, and death.

Bariatric surgery

The strong association of obesity and IIH makes weight loss essential for long-term treatment. While not indicated as the main treatment in cases of fulminant IIH, due to time needed to achieve weight loss, various versions of bariatric surgery can be utilized in non-vision threatening IIH.[25] Patients undergoing bariatric surgery versus a community weight loss program were shown to have greater reduction in ICP, disease remission, and greater quality of life. Additionally, bariatric surgery was shown to be more cost-effective in the long-term compared to a community weight loss program alone.[19,37,38] These findings have implications when considering insurance coverage of bariatric surgery for patients with IIH.

Headache in IIH and Its Treatment

Headache is very common (84%)[12] in patients with IIH and many (41%) of these patients have an underlying history of migraine—more than the general population (18% in women). The International Classification of Headache Disorders (ICHD-3) describes headaches related to IIH as a new or significant worsening (two-fold increase in frequency or severity) of headaches in the setting of symptoms and clinical and radiographic signs consistent with IIH.[39] The phenotype of the headache was studied in the IIHTT and found to be migraine or probable migraine in 58%, tension-type in about 28% and 51% had medication overuse headache.[40] From the IIHTT we learned that the quality of life correlated with the Headache Impact Test-6 (HIT-6), meaning as the headache worsened, so did the quality of life and visual quality of life. The headache disability did not correlate with the opening pressure (baseline or at six months), body mass index (BMI), weight loss, papilledema grade, or visual field loss. Further, there was no difference in the opening pressure between those with or without headache![12]

Treatment of the headache is frustrating, because even if the vision improves with diet and weight loss, the headache frequently does not.[12] So, what is the best treatment for headache associated with IIH? While acetazolamide is often the front-line treatment for IIH and reducing intracranial pressure, it is not always successful at treating the headache. Topiramate is often chosen since it both inhibits carbonic anhydrase to some extent, as well as prevents migraine.[38,39] Other medications have been tried, including CGRP monoclonal antibodies,[41] intravenous indomethacin,[42] and onabotulinum toxin.[43]

In general, the accepted practice in treating the headache associated with IIH is to use a diuretic like acetazolamide plus

Table 2: Preventive treatments used for headache in IIH

Medication	Additional considerations
Topiramate	Excellent first choice due to migraine prevention and promotes weight loss; possible teratogenicity
Beta-blockers	First-line for migraines, though do not use in patients with asthma
Tricyclic antidepressants (amitriptyline, nortriptyline)	Be mindful of weight gain
Zonisamide	Similar to topiramate, though it has less evidence; promotes weight loss
Gabapentin	Be mindful of weight gain
Valproate	Be mindful of weight gain; teratogenicity
Non-steroidal (indomethacin)	Be mindful of gastrointestinal issues
Calcitonin gene-related peptide (CGRP) monoclonal antibodies (erenumab, fremanezumab, Galcanezumab, eptimizumab)	Have evidence for prevention of migraine headache in IIH
Onabotulinum toxin	Given every three months; follow chronic migraine protocol
"Gepants" (rimegepant and atogepant)	Used as both acute and preventative treatments

a migraine preventative. Many of the preventive medications have side effects that are unfavorable to individuals with IIH including tricyclics and valproate which both cause weight gain. See Table 2 for preventive treatments of headache in IIH.

While we tend to reserve invasive procedures for the treatment of visual loss, headaches can be reduced somewhat as well. Lumbar puncture itself can transiently reduce the pressure and sometimes help headache severity by 71% but this is not long lasting.[44] CSF shunting procedures similarly can reduce headaches for a while; however, in many of the larger studies, shunt complications and revisions occurred, while headaches did not always respond or later recurred.[32] Optic nerve sheath fenestration can reduce headache by about half in clinical studies, but long-term effectiveness is not known. Venous stenting has more recently been proposed as a treatment for IIH, and 70% do have reduced headaches, but this treatment still remains unproven.[44] Recently, bariatric surgery was found to reduce intracranial pressure and reduce headache when individuals lost 24% of body weight.[19]

Conclusion

IIH most commonly occurs in obese women and is a condition of unknown etiology leading to elevated intracranial pressure. Recent studies indicate the potential for elevated intracranial venous pressures, though the etiology is likely multifactorial. Though vision is preserved in most patients, about 10% of patients can have significant vision impairment. Additionally, quality of life and visual quality of life are impacted by IIH. Three arms of treatment include weight loss, carbonic anhydrase and diuretic medications, and surgeries, such as ONSF, CSF diversion, VSS, and bariatric surgery. Continued research is needed to further elucidate the pathophysiology to better direct treatment and improve outcomes and quality of life.

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Conflicts of interest

There are no conflicts of interest.

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