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REVIEW

Novel Approaches to the Treatment of Idiopathic Intracranial Hypertension

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Abstract

Purpose of Review Idiopathic intracranial hypertension (IIH) typically affects women of childbearing age, is associated with recent weight gain, and can result in debilitating headache as well as papilledema that can cause vision loss. There have been advances in the medical and surgical treatment of affected patients with IIH that can improve outcomes and tolerability of therapy.

Recent Findings Medical treatment with agents that lower intracranial pressure through pathways other than carbonic anhydrase inhibition are being developed, and medically-directed weight loss as well as bariatric surgery now may be considered as primary therapy. New surgical options including venous sinus stenting have shown efficacy even with cases of severe vision loss.

Summary Our treatment options for IIH patients are becoming more diverse, and individualized treatment decisions are now possible to address specific components of the patient's disease manifestations and to lead to IIH remission.

Keywords Papilledema · Intracranial Pressure · Headache · CSF Diversion · Optic Nerve Sheath Fenestration · Venous Sinus Stenting

Introduction

Idiopathic intracranial hypertension (IIH), a disorder of elevated intracranial pressure (ICP) without an identified cause, may cause pressure-related headache and papilledema, either of which can cause significant morbidity [1]. This disorder represents a subset of patients with pseudotumor cerebri syndrome, the umbrella term for disorders of high ICP [2]. IIH may occur at any age but is most common in women between 15 and 45 years of age. Although IIH occurs equally in pre-pubertal males and females, it has a strong female predominance after puberty [3]. IIH has a general incidence of 2.1 per 100,000, and it may occur in as many as 20 per 100,000 persons at highest risk [4, 5]. Elevated body weight and recent weight gain have been found to be strongly associated with IIH development, and forthcoming data (abstract presented at the annual meeting of the American Academy of Ophthalmology in November 2023) suggest that the rise in overweight and obesity rates in the United States has led to increased IIH incidence. While obesity is the most consistently identified risk factor, other contributors to the development of IIH include minocycline and related antibiotics as well as excess vitamin A intake [6–8]. At one time, oral contraceptive (OCP) use was suggested to be a potential risk factor for IIH development, and more recent work has demonstrated that modern OCPs, with hormonal doses much lower than in the past, do not appear to increase the occurrence of IIH [9•]. In children, mastoiditis and other middle ear disorders may lead to IIH [10], although it is not clear that these cases do not represent occurrences of cerebral venous sinus thrombosis and thus not a truly idiopathic high ICP disorder.

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Diagnosis

Patients may be diagnosed with IIH because they present with symptoms of elevated ICP such as positional headache (often worst upon awakening), transient visual obscurations, pulse-synchronous tinnitus, diplopia, or peripheral or central vision loss. Others are found to have papilledema on routine eye examination and have a paucity or even absence of symptoms [11, 12]. In either case, the diagnostic criteria for IIH (Table 1) must be satisfied by clinical examination and further testing to exclude alternative causes of ICP elevation (tumor, venous sinus thrombosis, CSF inflammation, etc.) [3]. In most cases, the patient must have papilledema for a definite diagnosis of IIH to be given [3]. When bilateral optic disc edema is present and especially when vision loss is out of proportion to the degree of swelling (i.e. central vision loss should not occur with mild optic disc edema), other entities like autoimmune optic neuritis must be considered. MRI in these cases may show optic nerve enhancement unlike in IIH, and opening pressure on LP is typically normal [2]. Confirmation of a correct diagnosis of IIH should occur, especially when a diagnosis has been given based upon radiographic features (empty sella turcica, optic nerve sheath abnormalities, putative posterior globe flattening, and others that are associated with but not specific for elevated ICP) or clinical symptoms of headache or pulse synchronous tinnitus alone [13•,14,15,16•]. Analysis of brain MRI done for reasons other than suspected IIH showed that 30% of such patients have one or more of these abnormal findings, yet papilledema was present only when 3 or more of these signs were present [16•,17]. Lumbar puncture (LP) opening pressure also should be obtained, with cerebrospinal fluid analysis being performed to exclude an inflammatory or infectious cause of raised ICP. If the opening pressure is normal but papilledema is present, a diagnosis of IIH may be given tentatively. Repeat LPs rarely are indicated to confirm a diagnosis or to confirm IIH recurrence when new symptoms occur. Published evidence shows that LP opening pressure may remain elevated in some patients even after remission of clinical symptoms and signs, including papilledema [18].

Medical Management

Acetazolamide and Topiramate

Once the diagnosis of IIH is made, treatment is instituted to address both papilledema, which can lead to permanent vision loss, and headache, which can be disabling and have a negative impact on quality of life and daily functioning. Strategies to manage headache and to reduce papilledema are used in parallel, as the approach to each concern may be independent of the other. In mild cases with mild or no vision loss, medical therapy to lower intracranial pressure often is used in concert with weight loss. A prospective, randomized, double-masked placebo-controlled clinical trial comparing the efficacy of acetazolamide versus placebo when combined with weight loss in patients with mild vision loss from IIH showed that patients using acetazolamide had a greater improvement in visual field mean deviation as well as more rapid resolution of papilledema [19–21]. Lumbar puncture after 6 months of treatment confirmed that ICP was lower in patients treated with acetazolamide [21]. However, headache outcomes were comparable between the groups and did not demonstrate that acetazolamide was an effective headache therapy in these subjects with IIH [22•]. This observation, as well as clinical experience, has led to the co-management of patients with IIH by neuro-ophthalmologists and headache specialists so that the papilledema and headache may be addressed most effectively and, often, independently.

Table 1 Diagnostic criteria for idiopathic intracranial hypertension (IIH)

Required criteria when papilledema is present	A. Normal neurological exam (cranial nerve abnormality allowed) B. MRI/MRV without findings of mass/structural lesion, hydrocephalus, or pathologic enhancement C. Elevated CSF opening pressure (for age) on lumbar puncture D. Normal CSF composition
Required criteria with unilateral or bilateral sixth nerve palsy	Same as for papilledema
Suggestive MRI criteria that support diagnosis in the absence of papilledema or sixth nerve palsy (must have ≥ 3)	Same criteria as above for papilledema plus: A. Empty sella turcica B. Posterior globe flattening C. Enlarged perioptic subarachnoid space (w/wo tortuosity) D. Distal transverse venous sinus stenosis

Adapted from ref. 3

In some cases where papilledema is mild, vision loss is minimal or absent, and headache is the primary concern, topiramate may be prescribed as a sole medical therapy that can be effective for headache management and lead to weight loss that will reduce papilledema. The weak carbonic anhydrase inhibition produced by this medication is probably insufficient to reduce ICP sufficiently to have a therapeutic effect, although no direct evidence to support or reject this hypothesis exists. An open label study comparing clinical outcomes in a series of IIH patients treated with either acetazolamide or topiramate found that subjects in both groups had improved symptoms and signs with no statistical difference; however, the patients taking topiramate experienced greater weight loss [23].

Other Medications

In cases where maximally tolerated doses of acetazolamide (up to 4 g daily, divided) are insufficient to treat the papilledema and vision loss, furosemide and other diuretics have been used as second line agents [24]. The efficacy of these agents is variable, and the mechanism of action in a disorder of ICP elevation is not clear. A physician must be cautious in prescribing acetazolamide and furosemide simultaneously, as significant hypokalemia may occur through augmented diuresis and potassium excretion.

Animal studies have shown that glucagon-like receptor 1 (GLP-1) receptor agonists can lower intracranial pressure by reducing CSF production independent of carbonic anhydrase inhibition. In a model of chemically-induced ventricular scarring and destruction of arachnoid outflow pathways, the GLP-1 agonist exenatide prevented ventricular enlargement while control animals developed hydrocephalus [25]. GLP-1 agonists, which as a class are primarily indicated for the treatment of type II diabetes, also have been observed to promote weight loss through appetite reduction and early satiety [26]. Since weight loss is expected to lead to IIH improvement in most patients, this effect was potentially confounding in terms of therapeutic efficacy and outcomes. However, these data suggested that exenatide could lower ICP through a direct pathway rather than indirectly from weight loss, and a phase 3 clinical trial of an exenatide formulation (Presendin, Invex Therapeutics, Sydney, Australia) for IIH treatment was initiated [27]. This trial was suspended shortly after its global initiation because recruitment was limited by very stringent inclusion and exclusion criteria. A recent open label comparative case series of IIH patients given treatment with the GLP-1 agonist semaglutide or liraglutide in additional to usual medical care (including weight loss counseling and acetazolamide) found that significant (≥ 10% of body weight) weight loss was much more common in the semaglutide/liraglutide treated patients vs. control patients receiving usual care [28••]. Mean headache days also were fewer in the semaglutide/liraglutide group, while papilledema improvement occurred in both cohorts and was not different between them [28••].

Medical therapy to lower ICP by increasing CSF outflow also is being studied and developed. CSF outflow occurs through both the arachnoid granulations and the nasal lymphatic vessels [29–31], and the latter drainage pathway may be especially important in patients with elevated ICP. Lymphatic contractility can be enhanced with a number of pharmaceutical agents, and prostaglandin analogues are particularly effective in some cases. Preclinical research on the use of topical prostaglandin analogues used in glaucoma treatment demonstrated enhanced nasal recovery of a CSF tracer molecule with both acute and longer-term nasal drug application [32]. Human clinical trials are being planned to evaluate the safety and efficacy of intranasal latanoprost in reducing ICP.

Surgical Treatment

Invasive procedures typically are reserved for cases in which maximally tolerated medical therapy, usually acetazolamide, is inadequate to halt vision loss and to improve papilledema. However, there has been increasing recognition and acceptance of the need to perform urgent surgery in patients who present with rapid disease onset. This manifestation of IIH has been termed "fulminant," and the precise definition of how rapidly the disease is progressing or what the initial severity must be to warrant immediate surgery remains subjective and unsupported by prospective evidence. Case reports and small case series have supported the use of any of the three surgical procedures discussed below. Indeed, there is a dearth of evidence demonstrating superiority of one surgical method over another in general. In other cases, the urgency for surgical is lessened, although timing again remains controversial and is often determined by other factors such as surgeon or facility availability, patient preference, and regional practice patterns. The decision to pursue surgery is based upon severity of visual field loss on perimetry (automated perimetry more reproducible than kinetic in most cases), loss of central visual acuity not attributable to macular edema (optical coherence tomography often helpful in these cases), and the rate of progression in either of these measures [2, 33–38].

"Fulminant" IIH

It is estimated that fewer than 5% of IIH patients will present with rapidly progressive vision loss, often with severe headache, that can lead to irreversible optic nerve injury if not treated quickly. When patients present in this manner, it is essential that secondary causes of elevated ICP such

as cerebral venous sinus thrombosis, CSF inflammation or infection, and intrathecal malignancies among others be excluded, as that can affect the timing and choice of available treatments. Once the diagnosis of IIH is confirmed and vision loss is documented clinically (augmented by perimetry as well as fundus photography and/or optical coherence tomography), surgical intervention is undertaken as quickly as feasible [7, 33–39]. In some cases, inpatient lumbar CSF drainage may be used as a temporizing measure to reduce ICP before surgical treatment is performed [36, 40, 41]. Even with timely intervention, visual outcomes in patients with fulminant IIH remain mixed, with numerous case reports and series demonstrating permanent vision loss even to the level of no light perception despite early surgical and medical interventions being performed [33, 42].

Optic Nerve Sheath Fenestration

Creating a dural opening in the retrobulbar optic nerve sheath to relieve papilledema has been a surgical option for over 150 years, first described by DeWecker in 1872 [43]. CSF that is normally trapped within the optic nerve sheath complex is released into the orbit and reabsorbed by the tissues through ill-defined pathways. Surgery can be performed via several approaches, with the medial transconjunctival approach being most popular in a recent survey of oculoplastic surgeons [44]. Access to the optic nerve also can be obtained via an incision through the superomedial eyelid crease; anatomically, this approach may be more direct although it involves retraction of the superior ophthalmic vein and eyelid fat pads [45]. A lateral orbitotomy approach also may be used, either with or without creating a bone flap; this technique is not used frequently by most surgeons since it requires more superficial and deep dissection [46]. A superomedial transconjunctival approach was described recently in a large case series in which it appears to be quicker than the typical medial approach (because extraocular muscles are not disinserted) and safe [47•]. No head-to-head comparison of the techniques has been performed, and choice of a particular procedure is dependent upon surgeon experience and preference.

Outcomes of optic nerve sheath fenestration have been compared to outcomes of CSF diversion/shunting (see below) with no significant difference found for improvement in either visual acuity or visual fields [48, 49]. The fenestration may close over time, and techniques such as applying mitomycin C to the nerve sheath prior to incision have been described [50] but not widely adopted. Repeat fenestration may be performed but can be challenging because of scarring from the initial surgery.

CSF Diversion/Shunting

Both lumbar and ventricular shunts are used in the treatment of IIH patients with the goal of lowering intracranial pressure and improving both papilledema and headache. CSF is drained either into the peritoneal space (either lumbar or ventricular) or into the pleural cavity or right atrium (ventricular), and flow may be regulated through placement of a fixed or adjustable valve [51–53]. Antisiphon devices also may be used to prevent overdrainage of CSF and symptoms of low CSF pressure. Historically, lumboperitoneal (LP) shunts were favored because of relative ease of placement and potentially lower morbidity than ventricular placement in a patient with normal or small ventricles. Improved intraoperative surgical navigation tools and surgeon experience have increased the popularity of ventriculoperitoneal (VP) shunt placement, and there are conflicting data regarding the relative failure rates and need for revision when comparing VP and LP shunts [54, 55]. The peritoneal end of either shunt may become occluded by fat or other abdominal structures, and shunt revision for this occurrence or for disconnection along the shunt tubing pathways is not uncommon. Recent evidence suggests that having a shunt placement protocol in place to ensure appropriate patient selection, valve use, and surgical technique especially for distal catheter placement results in a greater success rate, lower infection rates, and a lesser need for subsequent shunt revision [56–58].

It has been theorized that optic nerve sheath fenestration may lead to a more rapid resolution of papilledema than shunting can, but there are no prospective data to demonstrate if this is true or not. In fact, the use of temporary external lumbar drainage for fulminant IIH as noted above would indicate that lowering CSF pressure remote to the optic nerves may still relieve pressure within the nerve sheath and at the optic nerve head. In a subset of patients, CSF trapping or sequestration within the optic nerve sheath may occur and prevent pressure equalization with the rest of the CSF space [59, 60]. In these cases, optic nerve sheath fenestration may be required even after shunt placement [61]. Conversely, shunting after failure of papilledema to improve with ONSF has been reported to lead to papilledema resolution [62].

Cerebral Venous Sinus Stenting

The most recent innovation in the treatment of patients with IIH involves endovascular treatment of cerebral venous sinus stenoses that are believed to be pathogenic in many IIH patients. A focal narrowing of the distal transverse sinus can be seen in more than 90% of patients with

IIH and does not occur merely because of obesity [63, 64]. The stenosis may occur initially because of elevated CSF pressure itself causing collapse of the venous sinus wall, often adjacent to an arachnoid granulation. Some stenoses thus appear to be reversible by lowering the intracranial pressure (i.e. by short term lumbar puncture or drainage or by CSF shunting), but many persist despite CSF pressure reduction and represent a fixed stenosis that will increase cerebral venous pressure and thus intracranial pressure as well [65]. As with ONSF and shunting, venous sinus stenting should be reserved for patients whose IIH cannot be controlled with medical therapy and/or weight loss. It is tempting to consider venous sinus stenting as a lower risk procedure because it does not involve open surgery; however, it is still an invasive procedure that may infrequently cause vascular occlusion or intracranial hemorrhage [66]. Treated patients also must take dual antiplatelet therapy for several months post procedure and typically remain on aspirin (or another antiplatelet agent if aspirin is not tolerated) for life. The results of venous sinus stenting have been reported in a number of retrospective studies [67–79] and at least one prospective study [39] of IIH patients needing a surgical intervention. A randomized clinical trial has been initiated in the United States to compare the efficacy of venous sinus stenting versus shunting in IIH patients who have moderate to severe visual field loss and active papilledema without uncontrolled headache. Venous sinus stenting may be an adjunctive treatment after ONSF if papilledema does not improve as quickly as anticipated [37, 80]. Since patients must be on antiplatelet therapy for months after stenting, it can be difficult to perform a secondary surgical procedure (ONSF or shunt) after stenting is done, and a team-based approach to the management of IIH patients who may need procedural intervention will ensure that an individualized decision is made for each patient [38].

Surgical Weight Loss

Bariatric surgery for IIH has been used clinically for many years after a small retrospective case series reported that signs and symptoms of the disease improved or remitted post-surgery [81]. More recently, a randomized clinical trial of 66 IIH patients with BMI $\geq$ 35 kg/m^2 who received either standard medically-directed weight loss or bariatric surgery showed that weight loss and ICP reduction were greater in the surgery group and that quality of life measures had larger levels of improvement in the surgery group [82••]. The improvement in both objective and patient-reported measures was more durable with surgery than conventional weight loss. A recent systematic review reinforced these findings and proposed that all women with IIH who have a BMI $\geq$ 35 kg/m^2 be considered for bariatric surgery to address their IIH related symptoms and to reduce the likelihood of disease recurrence [83, 84].

Table 2 Treatment options for papilledema in idiopathic intracranial hypertension (IIH)

Medical	Acetazolamide Methazolamide Topiramate Furosemide Other thiazide diuretics
Surgical	Optic nerve sheath fenestration Ventriculoperitoneal shunt Ventriculoatrial shunt Lumboperitoneal shunt Bariatric surgery
Neurointerventional	Cerebral venous sinus stenting
In development	GLP-1 agonists Intranasal prostaglandin analogues

Conclusions

IIH prevalence has continued to rise globally in concert with obesity rates in adult and pediatric populations. While the threshold weight/body mass index after which IIH rates increase may vary in different parts of the world, the disease manifestations do not vary significantly. The areas of concern for both patients and their physicians are the disabling features of the associated headache and the potential for permanent vision loss from papilledema. A number of treatment options exist (Table 2), and selection is primarily guided by the severity of papilledema and the visual status. The majority of IIH patients can achieve relief of symptoms and resolution of papilledema with weight loss (with or without medication to lower ICP in the short term), and recent data would favor proceeding to bariatric surgery in patients with higher BMI. When papilledema worsens and vision loss is occurring, then surgical treatment of the elevated ICP directly (ONSF, CSF shunting) or indirectly (venous sinus stenting) should be pursued to protect the optic nerve from permanent injury. The timing and urgency of surgical intervention has not been defined clearly in the literature, with a general medical consensus holding that sooner intervention is favored once vision loss is confirmed. There is still a lack of prospective data comparing the relative efficacy of medical and surgical techniques in the treatment of vision loss from IIH, and in the absence of such data, clinicians must use judgement and multidisciplinary consultations (neuro-ophthalmology, neurology, ophthalmology, neurosurgery, interventional neuroradiology, and others) to determine the appropriate treatment for a given IIH patient.

Author Contributions PSS was the sole author of this work and made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; drafted the work or revised it critically for important intellectual content; approved the version to be published; andagree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests Dr. Subramanian reports grants and personal fees from Invex Therapeutics, outside the submitted work; In addition, Dr. Subramanian has a patent Intranasal application of latanoprost to lower intracranial pressure pending.

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