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Idiopathic Intracranial Hypertension (Pseudotumor Cerebri): Recognition, Treatment, and Ongoing Management

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OPINION STATEMENT

Idiopathic intracranial hypertension (IIH, pseudotumor cerebri) is a syndrome of elevated intracranial pressure of unknown cause that occurs predominantly in obese women of childbearing age. It is a diagnosis of exclusion and, therefore, other causes of increased intracranial pressure must be sought with history, imaging, and cerebrospinal fluid examination before the diagnosis can be made. IIH produces symptoms and signs of increased intracranial pressure, including papilledema. If untreated, papilledema can cause progressive irreversible visual loss and optic atrophy. The treatment approach depends on the severity and time course of symptoms and visual loss, as determined by formal visual field testing. The main goals of treatment are alleviation of symptoms, including headache, and preservation of vision. All overweight IIH patients should be encouraged to enter a weight-management program with a goal of 5% to 10% weight loss, along with a low-salt diet. When there is mild visual loss, medical treatment with acetazolamide should be initiated. Other medical treatments can be added or substituted when acetazolamide is insufficient as monotherapy or poorly tolerated. When visual loss is more severe or rapidly progressive, surgical interventions, such as optic nerve sheath fenestration or cerebrospinal fluid shunting, may be required to prevent further irreversible visual loss. The choice of intervention depends on the relative severity of symptoms and visual loss, as well as local expertise. At present, the role of transverse venous sinus stenting remains unclear. Although there are no evidence-based data to guide therapy, there is an ongoing randomized double-blind placebo-controlled treatment trial, investigating diet and acetazolamide therapy for IIH.

Keywords

Idiopathic intracranial hypertension; Treatment; Recognition; Management; Pseudotumor cerebri; Papilledema; Vision loss; Acetazolamide; Topiramate; Optic nerve sheath fenestration; Cerebrospinal fluid shunting

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INTRODUCTION

Idiopathic intracranial hypertension (IIH) is a syndrome of increased intracranial pressure (ICP) of unknown cause that occurs most often in obese women of childbearing age, but can also occur in children, men, and older adults. It is characterized by symptoms and signs of increased ICP; common symptoms include headache, visual loss, diplopia, and pulsatile tinnitus, whereas common signs include papilledema, visual field defects, and sixth nerve palsy. IIH is a diagnosis of exclusion (see Table 1 for the modified Dandy diagnostic criteria) and, therefore, other causes of increased ICP need to be excluded with imaging (ideally MRI brain and MRV head) and lumbar puncture before the diagnosis can be confirmed. Treatment with certain medications (e.g., vitamin A derivatives, tetracyclines, and lithium) and cerebral venous sinus thrombosis can cause an indistinguishable clinical picture; such conditions must be excluded before IIH can be diagnosed, because they require a different treatment approach (e.g., those with increased ICP due to medications often improve following withdrawal of the offending agent).

Headache is the most common symptom reported by IIH patients at presentation [1, 2]. A prospective study revealed that many IIH patients are awakened by the headache and often suffer from daily headaches [3]. The headache often slowly increases in intensity and, contrary to traditional teaching, is pulsatile in nature in over 80% of patients [3]. Although the headache may be holocranial, about 70% of patients also report a focal component to their headache (e.g., occipital or retro-orbital pain) [3]. If the headache is due to the elevated ICP, it can dramatically improve with a decrease in ICP (e.g., after lumbar puncture). However, many IIH patients have other coexisting headache disorders (e.g., migraine, analgesic overuse headache, rebound headache) [4] and, consequently, the headache might not respond well to treatments that decrease ICP. Such patients often require treatment with conventional agents for headache prophylaxis to achieve symptom control [4].

Visual symptoms are common in IIH patients and are usually due to papilledema. Papilledema is the most common sign and is usually symmetric, but can be highly asymmetric or unilateral in about 10% of patients. Patients with papilledema often report transient visual obscurations, which are brief episodes of visual loss that are precipitated by postural changes and Valsalva-like maneuvers, with rapid recovery of vision back to baseline within seconds. Papilledema can also cause progressive visual field loss and optic atrophy, if untreated. Enlargement of the physiologic blind spot, coupled with a nasal step defect, is the earliest visual field change to occur. If papilledema is persistent or severe, there can be nasal (often inferonasal) defects, arcuate defects, and severe visual field constriction. Visual acuity is not usually affected until the visual field loss is advanced and, consequently, the visual field loss can go unnoticed by the patient until advanced. Formal visual field testing (e.g., automated static or manual kinetic perimetry) and consultation with an ophthalmologist or neuro-ophthalmologist is therefore essential to guide management decisions.

The main goals of treatment are alleviation of symptoms and preservation of vision. The approach used in a particular patient depends on the severity and time course of their symptoms and visual loss, as determined by perimetry. The diagnostic lumbar puncture often results in a transient improvement in symptoms, but rarely a lasting remission. Obese patients should be encouraged to lose a modest amount of weight. Potential contributing factors (e.g., obstructive sleep apnea) should be treated. A variety of medical and surgical treatments can be considered when symptoms and visual loss are more than mild, although no randomized controlled trials have confirmed the efficacy of these treatments. When there is mild visual field loss, medical treatment with acetazolamide should be initiated. Other medical treatments can be added or substituted when acetazolamide is not sufficient as

monotherapy or poorly tolerated. When visual field loss is more severe or rapidly progressive, surgical treatments (e.g., optic nerve sheath fenestration or cerebrospinal fluid shunting) should be considered to prevent irreversible visual loss. The choice of procedure depends on local expertise, as well as the relative severity of symptoms and visual field loss. The roles of emerging treatments, such as transverse venous sinus stenting, remain unclear and such treatments require further evaluation in clinical trials. Regardless of the treatment strategy used, all IIH patients require careful follow-up, as IIH is a chronic disease.

TREATMENT

Diet and lifestyle

- Obesity and recent weight gain are well known to be associated with IIH [5, 6, Class II]. **Weight loss** should therefore be routinely recommended for all obese IIH patients. A recent prospective study of obese IIH patients found that weight loss leads to reduced symptoms, signs, and ICP [7•, Class III]. The findings of several studies suggest that only a modest amount of weight loss (5% to 10% of total body weight) is required to bring about an improvement in symptoms and signs [8-10, Class IV]. In patients with minimal symptoms, signs, and visual loss, a weight management program with a low-salt diet and lifestyle changes, including an exercise program, is a reasonable initial treatment strategy. However, weight loss alone may be inadequate. In such cases, other treatments should be initiated simultaneously.

Pharmacologic treatment

- Pharmacologic treatments can be considered for patients with mild to moderate disease.
- Acetazolamide is the mainstay of treatment, but other medications, such as topiramate and furosemide, can be considered when acetazolamide is poorly tolerated or insufficient when given as monotherapy.
- Steroids are no longer routinely recommended, but can be considered for short-term treatment of patients with a fulminant presentation while awaiting surgical intervention.

Acetazolamide—Acetazolamide, a carbonic anhydrase inhibitor, is thought to decrease cerebrospinal fluid production and thereby decrease ICP, leading to improved symptoms and signs of IIH. However, a treatment effect has not yet been confirmed; a recent randomized trial of acetazolamide versus no treatment was inadequately powered to detect a treatment effect [11, Class II]. A large, multicenter, randomized controlled trial is currently underway in the US, comparing the efficacy of weight loss and placebo with weight loss and acetazolamide for mild to moderate IIH [12].

Standard dosage: There is no standardized dosing regime for acetazolamide. A reasonable starting dose is 500mg two times daily, gradually titrating up to a maximum of 4g daily in twice-daily doses. Dosage increases may be limited due to dose-dependent side effects.

Contraindications: Known hypersensitivity, including sulfur allergy. Acetazolamide use is contraindicated in patients with liver failure, due to the increased risk of producing hepatic encephalopathy. Acetazolamide is relatively contraindicated in patients with a history of renal stones. Acetazolamide is a category C drug in pregnancy, although two studies suggest that it is safe to use during the second and third trimesters of pregnancy in IIH patients [13, 14, Class IV].

Main drug interactions: Side effects can be increased with concurrent use of salicylates. Side effects from cyclosporine, quinidine, and phenytoin can increase when acetazolamide is administered concurrently.

Main side effects: Side effects are common. Patients should be warned that, as the medication takes effect, they will experience paresthesias, altered taste sensation (especially for carbonated beverages), and lethargy that may be transient; these symptoms are usually not severe enough to necessitate a dosage reduction. Renal stones can occasionally complicate treatment. However, a prior history of renal stones is not a contraindication for acetazolamide treatment. Furthermore, the development of renal stones is not an absolute indication to stop treatment; acetazolamide can be continued concurrently with treatment directed toward the renal stones [15, Class IV]. If acetazolamide is continued, the patient should have periodic renal ultrasound studies to monitor for the development of new renal stones.

Special points: Methazolamide, a faster-acting carbonic anhydrase inhibitor, can be tried when the side effects of acetazolamide are intolerable [16, Class IV].

Cost / cost effectiveness: Acetazolamide is available as a generic. The cost is approximately \$30 for 100 tablets.

Topiramate—Topiramate is most commonly used for treatment of primary headache disorders and can also be considered for the treatment of IIH, especially when headache is prominent. On the basis of a small, randomized treatment trial, it appears to have similar efficacy to acetazolamide for treatment of mild to moderate IIH [17, Class II]. Topiramate is a weak carbonic anhydrase inhibitor and often causes some weight loss as a side effect [17, Class II], suggesting that it might be more suitable for treatment of IIH than other agents used for headache prevention.

Standard dosage: There is no standardized dosing regimen for topiramate. It can be started at 25mg once daily and titrated up to 100mg twice daily, depending on benefit and side effects.

Contraindications: Known hypersensitivity. Topiramate use is contraindicated in patients with liver failure and is relatively contraindicated in patients with a history of renal stones. It is a category D drug in pregnancy.

Main drug interactions: Topiramate interacts with carbonic anhydrase inhibitors, valproate, and drugs that cause decreased sweating (including anticholinergics).

Main side effects: Side effects are common and include paresthesias, drowsiness, lethargy, and decreased appetite. Renal stones occasionally complicate treatment. Since angle-closure glaucoma can sometimes develop with topiramate treatment, patients who develop eye pain, eye redness, and changes in vision should seek an immediate ophthalmic evaluation.

Special points: Although combined treatment with acetazolamide can significantly increase the risk of side effects, especially renal stones, addition of low-dose topiramate (e.g., 25mg twice daily) can sometimes be helpful for treating headache that is not sufficiently controlled with acetazolamide alone. If the patient develops renal stones, one of the medications should be discontinued and alternative headache treatment options should be explored.

Cost / cost effectiveness: Topiramate is available as a generic. The cost is about \$40 for 100 tablets.

Furosemide—Furosemide, a loop diuretic, can be administered alone or in combination with acetazolamide when acetazolamide alone is inadequate [18, Class IV].

Standard dosage: Only a low dose of furosemide (e.g., 20mg or 40mg once or twice daily) is required in most patients.

Contraindications: Known hypersensitivity. Furosemide should be used with caution in patients with hepatic failure and renal impairment or failure. Furosemide is a category C drug in pregnancy.

Main drug interactions: Salicylate and lithium toxicity are more likely when these drugs are used concurrently with furosemide. The risk of ototoxicity is increased when furosemide is used in combination with aminoglycosides. The risk of hypotension and renal impairment is increased when furosemide is used together with angiotensin converting enzyme inhibitors and angiotension II receptor blockers.

Main side effects: Common side effects include dehydration, rash, and tinnitus. If severe, dehydration can cause postural hypotension and renal impairment or failure. Hypokalemia is a common side effect and, consequently, potassium supplements are usually necessary. Irreversible hearing loss can occur with higher doses.

Special points: Serum potassium concentration should be monitored to ensure that potassium replacement is adequate.

Cost / cost effectiveness: Furosemide is available as a generic and is inexpensive.

Steroids—Steroids were commonly used for treating IIH in the past, but cause significant long-term side effects, such as weight gain, that are undesirable in IIH patients. Furthermore, withdrawal of steroids can cause rebound intracranial hypertension [19, 20, Class IV]. Thus, steroids should not be used routinely for IIH treatment. High-dose intravenous steroids can, however, be useful for short-term treatment of patients with fulminant disease while a more definitive intervention (e.g., optic nerve sheath fenestration or cerebrospinal fluid shunting) is awaited [21, 22, Class IV].

Standard dosage: Methylprednisone can be given at a dose of 1g per day, while definitive intervention is awaited.

Contraindications: Steroids are relatively contraindicated in patients with hypertension, diabetes, congestive cardiac failure, renal failure, active infections, osteoporosis, peptic ulcer disease, and psychosis. Methylprednisone is a category C drug in pregnancy.

Main drug interactions: Hepatic inducers (e.g., phenytoin and rifampin) can increase the clearance of methylprednisolone, whereas hepatic inhibitors (e.g., ketoconazole) can inhibit it. Seizures can occur when methylprednisone is used concurrently with cyclosporin.

Main side effects: Side effects are myriad and well documented. Common short-term side effects include insomnia and mood disturbances, such as euphoria and depression. Rare, but important, short-term side effects include avascular necrosis. Other steroid side effects, such

as osteoporosis, impaired glucose tolerance, and sodium retention, occur mostly with long-term treatment.

Cost / cost effectiveness: Corticosteroids are available as generics and are inexpensive.

Interventional procedures

Lumbar puncture—IIH symptoms (e.g., headache) often improve following the diagnostic lumbar puncture. In most cases, the improvement is transient, but occasional patients can have a lasting remission following a lumbar puncture [23, Class IV]. Repeated lumbar punctures have been used for treatment for IIH, but should no longer be considered standard treatment as they are often technically difficult and poorly tolerated. Nevertheless, a lumbar puncture can be a useful temporizing measure in patients with an acute exacerbation of symptoms or a fulminant presentation [21, Class IV].

Standard procedure—The lumbar puncture is usually performed with the patient in the lateral decubitus position, although it is often easier to enter the subarachnoid space with the patient seated. Following injection of a local anesthetic agent (e.g., lidocaine), a spinal needle is inserted into a lower lumbar (e.g., L4/L5) intervertebral space. A long spinal needle may be required in very obese patients. The opening pressure should be measured using a manometer held at the level of the left atrium, prior to the removal of a large volume (e.g., up to 30mL) of CSF.

Contraindications—Lumbar puncture is contraindicated in patients with an intracerebral mass or obstructive hydrocephalus, due to the increased risk of herniation; such abnormalities should have been excluded by the imaging performed during the initial work-up. Lumbar puncture should be performed with caution in patients with coexisting Chiari malformation, due to the risk of causing lower brainstem compression. Lumbar puncture is contraindicated in patients taking anticoagulants, due to an increased risk of bleeding.

Complications—The most common complications associated with lumbar puncture include local discomfort and low-pressure headache. Low-pressure headache often improves with conservative treatment (e.g., caffeine). However, when persistent for more than 2 or 3 days, CSF blood patch is often required.

Special points—Lumbar puncture can be performed using fluoroscopic guidance in obese patients, especially when bony landmarks are difficult to establish.

Surgery

- Surgical intervention is required when other treatments have failed to prevent progressive vision loss or when the disease onset is fulminant. The two commonly used surgical treatments are CSF diversion (e.g., ventriculo-peritoneal and lumbo-peritoneal shunting) and optic nerve sheath fenestration (ONSF). The choice of procedure depends on local expertise, as well as the patient's symptoms and signs. When both are available, ONSF may be preferable in IIH patients with vision loss due to papilledema who have relatively mild or no other symptoms of increased ICP, whereas shunting may be preferable in patients with visual loss, papilledema, and significant symptoms of increased ICP.
- Bariatric surgery is an emerging treatment that can be considered for morbidly obese IIH patients in whom attempts at weight loss have been unsuccessful [24, 25, Class IV].

Cerebrospinal fluid (CSF) shunting

CSF shunting produces a rapid reduction in ICP and thereby brings about a rapid improvement in symptoms and signs [26-30, Class IV]. The two procedures most commonly performed are lumbo-peritoneal (LP) and ventriculo-peritoneal (VP) shunting. Although VP shunting is more difficult and usually requires a stereotactic approach, as IIH patients do not have enlarged ventricles, it is preferred due to its lower complication rate [31, 32, Class IV].

Standard procedure—CSF shunting is performed under general anesthesia and involves inserting shunt tubing into the lateral ventricle (for VP shunting) or lumbar subarachnoid space (for LP shunting). The tubing is then passed subcutaneously so that the distal end empties into the peritoneal cavity (or venous system). Most CSF shunts are fitted with programmable valves, such that shunting only occurs once a certain CSF pressure is reached.

Contraindications—Shunting is contraindicated when there is active infection in any of the areas where the shunting tubing is to be placed. Shunting is contraindicated in patients taking anticoagulants, due to increased risk of bleeding.

Complications—Complications are common; many patients develop shunt infections, shunt obstruction, or migration of the shunt tubing. Since shunt failure occurs in about half of cases, shunt revisions are commonly required [27-30, Class IV]. Over-shunting and intracranial hypotension can occasionally occur, but are less common since the introduction of programmable shunt valves.

Special points—CSF shunting should not be routinely offered for treatment of headache in IIH patients with no papilledema, given the high complication rate and the fact that many IIH patients have coexisting headache disorders that do not improve with lowering of ICP. In a series with long followup, only half of those shunted for IIH had headache relief at 36 months [32, Class IV].

Optic nerve sheath fenestration (ONSF)

ONSF produces a rapid reduction in the pressure on the optic nerve head, leading to reduced papilledema and improved visual function in the operated eye [33-37, Class IV]. The papilledema and visual function in the fellow eye can occasionally improve, although many patients with bilateral papilledema require bilateral sequential ONSF [34, Class IV]. A fluid collection is seen adjacent to the fenestration site initially following the surgery, suggesting that the initial improvement occurs due to the formation of a fistula [38, Class IV]. However, fibrous tissue forms after a few months, suggesting that scarring at the fenestration site might prevent transmission of the CSF pressure gradient to the retrolaminar portion of the optic nerve, thereby preventing recurrence of papilledema [38, Class IV]. Nevertheless, occasional patients continue to lose vision following ONSF [39, Class IV]. As ONSF does not decrease ICP, it may not be effective in alleviating other symptoms and signs of increased ICP [40, 41, Class IV]. Consequently, weight loss efforts and medical treatments should be maintained following the surgery.

Standard procedure—With the patient under general anesthesia, an orbital approach is used to identify the retrolaminar portion of the optic nerve. The dural sheath is fenestrated, either by creating a window defect or a series of slits, to create a fistula between the subarachnoid space and orbital cavity. There is often a gush of CSF into the orbit when the fenestration is performed.

Contraindications—Contraindications to ONSF include infection at the surgical site and anticoagulation use.

Complications—Complications are usually minor if the surgeon is experienced. A tonic pupil can occur if the ciliary nerves are damaged. Transient or permanent visual loss can occur if there is trauma to the optic nerve or its vascular supply [42-44, Class IV].

Special points—ONSF should not be performed if there is no papilledema or if visual field loss is minimal.

Assistive devices

- Prisms can be effective in the management of diplopia in primary position in IIH patients with sixth nerve palsy.

Prisms

Usage—Prisms are used to optically compensate for misalignment of the eyes in primary position of gaze. The power of prism is determined by measurements obtained during the strabismus examination. If the amount of misalignment changes depending on gaze position, prisms will not compensate for diplopia in all positions of gaze.

Special points—Patients should be prescribed a Fresnel (temporary) prism, unless the ocular misalignment is long-standing and stable.

Cost / cost effectiveness—A Fresnel prism costs about \$20, but ground-in prisms can add more than \$100 to the cost of glasses.

Other treatments

- Potential exacerbating factors, such as anemia and obstructive sleep apnea, should be addressed, although there are no trial data to confirm that doing so improves symptoms and signs of IIH.

Emerging therapies

Venous sinus stenting

Transverse cerebral venous sinus stenoses are a common finding in patients with IIH [45, 46, Class III-IV]. Their origin and functional significance remains controversial. It has been postulated that patients with increased ICP develop the stenoses due to external compression of the venous sinus. Indeed, the stenoses sometimes resolve when ICP is reduced by lumbar puncture or shunting [23, 47, 48, Class IV]. Modeling studies have suggested, however, that stenting of these stenoses might reduce cerebral venous pressure, leading to increased CSF absorption, reduced ICP, and improved symptoms and signs, even if the stenoses are caused by increased ICP [49]. Supporting this hypothesis are the findings of case studies and series, in which patients have undergone endovascular stenting of these stenoses, with subsequent normalization of ICP and resolution of symptoms and signs [50-55, Class IV]. However, potential complications are serious and, thus, this procedure should not be recommended routinely.

Standard procedure—With the patient under general anesthesia, a percutaneous venoplasty is performed. A stent is then deployed at the site of the previous stenosis. Manometry is often performed following deployment of the stent, to confirm that any

pressure gradient across the stenosis has been alleviated. Note that long-term antiplatelet treatment is required to prevent in-stent thrombosis.

Contraindications—Contraindications to this procedure have not been clearly defined, but might include active infection and use of anticoagulants.

Complications—Common complications include transient frontal or temporal headache due to stretching of the meninges covering the transverse sinus. Transient hearing loss has also been reported. There are reports of more serious complications, including in-stent thrombosis, subdural hemorrhage, and death in one patient [51, 52, 55•, Class IV]. Some patients develop recurrent stenoses proximal to the stent, with recurrent symptoms and signs of increased ICP [50, 52, 55•, Class IV].

Special points—Since these patients require ongoing treatment with antiplatelet agents, other surgical treatment options should be considered in preference to this procedure.

Pediatric considerations

- IIH can occur in children and adolescents. In pre-pubertal children, IIH is not typically associated with obesity and, thus, weight loss is not an effective or appropriate treatment option. Treatment is otherwise similar to that for adult cases, although medication doses need to be adjusted according to patient weight.
- An important point that should be considered in pediatric patients is that the normal range for CSF opening pressure is higher than in adults, with opening pressures of up to 28 cm of H₂O being within normal limits [56, 57•].

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Table 1

Modified Dandy diagnostic criteria for IIH

1	Symptoms and signs of increased ICP
2	No localizing neurologic signs, except for unilateral or bilateral sixth nerve palsies
3	Increased CSF opening pressure, but normal CSF composition
4	No evidence of hydrocephalus, mass, structural, or vascular lesion on imaging
5	No other cause of increased ICP identified