

## REVIEW ARTICLE

## Idiopathic Intracranial Hypertension

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IN THE EARLY 20TH CENTURY, SOON AFTER THE TECHNIQUE OF LUMBAR puncture was devised, Max Nonne, a German neurologist, described a syndrome of headache accompanied by swollen optic disks in patients with raised cerebrospinal fluid (CSF) pressure.<sup>1</sup> He called the condition pseudotumor cerebri, because none of the patients proved to have a brain tumor. This name is still used,<sup>2</sup> although it has largely been supplanted by the term idiopathic intracranial hypertension.<sup>3</sup> This review explores current ideas about the disease, with emphasis on the importance of dural venous sinus stenosis and new treatment options.

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CME



## CLINICAL DIAGNOSIS

More than 95% of patients with idiopathic intracranial hypertension are women of childbearing age with obesity.<sup>4</sup> Men are seldom affected, for unknown reasons. Even among women with obesity the disease is rare; it occurs in about 1 in 500 female persons with a body-mass index (the weight in kilograms divided by the square of the height in meters) higher than 30.<sup>5,6</sup> The prevalence of the disease is rising, driven by surging obesity rates.<sup>7</sup> A history of recent weight gain often precedes the onset of symptoms.<sup>8,9</sup> Idiopathic intracranial hypertension can occur in children, but before puberty the association with obesity and female sex is less marked.<sup>10</sup>

Before a diagnosis is made, other potential causes of raised intracranial pressure (ICP) should be considered. An alternative cause should be sought, especially in patients who do not fit the typical clinical profile. Tetracycline-class antibiotics and retinoids (vitamin A and associated compounds) induce rare secondary forms of intracranial hypertension.<sup>11,12</sup> Vascular disorders such as cerebral venous sinus thrombosis and dural arteriovenous fistula can mimic idiopathic intracranial hypertension.<sup>13,14</sup>

Headache is the most common initial symptom, reported in 84% of patients.<sup>15</sup> The headache pain is described as constant or daily in approximately half of affected patients. A history of migraine is common. Other prominent symptoms are transient visual obscurations (in 68% of affected patients), neck or back pain (in 53%), pulse synchronous tinnitus (in 52%), visual loss (in 32%), and diplopia (in 18%).<sup>4</sup> Idiopathic intracranial hypertension is an occasional cause of rhinorrhea or serous otitis media resulting from a CSF leak at the skull base.<sup>16</sup>

Papilledema is the most important sign and usually the only one. Apart from occasional palsy involving the sixth nerve, the neurologic examination is usually otherwise normal, although atypical findings, including other cranial neuropathies, have been described.<sup>17</sup> The diagnosis is sometimes missed because patients with idiopathic intracranial hypertension have symptoms that are easily confused with those of more common disorders, the clinical picture is incompletely developed when there is only borderline elevation of ICP, or the ocular fundi are not examined.

## KEY POINTS

**IDIOPATHIC INTRACRANIAL HYPERTENSION**

Idiopathic intracranial hypertension, also called pseudotumor cerebri, refers to elevated cerebrospinal fluid (CSF) pressure that develops most often in women of reproductive age with obesity, causing headache, neck pain, pulsatile tinnitus, and visual symptoms.

Funduscopy examination is critical to identifying papilledema, which is present in 95% of affected patients.

Magnetic resonance imaging rules out hydrocephalus or tumor and reveals characteristic findings that include a partially empty sella, distended optic-nerve sheaths, protrusion of the optic disks into the vitreous cavity, and stenosis of the distal transverse dural sinuses.

Lumbar puncture shows a high opening pressure and normal CSF, but ambiguous readings can occur because of overlap in the range of pressures recorded in patients with idiopathic intracranial hypertension and in unaffected persons.

Nearly all patients can be treated medically with acetazolamide to reduce CSF production and with agonists to glucagon-like peptide-1 or gastric inhibitory polypeptide to induce weight loss.

Prompt surgical intervention is necessary if papilledema threatens vision.

CSF shunting has been the standard surgical treatment; however, dural venous sinus stenting, which breaks the positive feedback cycle driving high intracranial pressure, is gaining wider acceptance.

**OCULAR FINDINGS**

Papilledema is edema of the optic disks caused by elevated ICP (Fig. 1). Many physicians find viewing the optic disks with an ophthalmoscope difficult, especially if the pupils are not dilated pharmacologically. A potential solution to the challenge of screening for papilledema in emergency departments is offered by autofocus fundus cameras that do not require pupil dilation.<sup>18</sup> Patients with suspected papilledema should be referred as rapidly as possible to an optometrist or ophthalmologist to confirm the finding and to exclude other causes of optic-disk edema, such as pseudopapilledema from optic-disk drusen.

Vision loss caused by papilledema progresses gradually from the periphery of the visual field, sometimes going unnoticed at first. Central acuity is affected last, unless fluid from the optic disk leaks into the macula.<sup>19</sup> Any reduction in acuity suggests substantial damage to the optic nerve. Prompt intervention is crucial, because the greatest threat posed by idiopathic intracranial hypertension is irreversible blindness. Computerized perimetry testing, which is more sensitive and reproducible than confrontation visual field testing, is invaluable for assessing optic-nerve function and guiding treatment (Fig. 2).<sup>20</sup>

The absence of papilledema suggests that the ICP is normal, but it does not rule out idiopathic intracranial hypertension. At least 5% of patients, especially those with only slight elevation

of ICP, have little or no papilledema.<sup>21</sup> Fundus examination is sometimes inconclusive, because it can be difficult to distinguish between an unaffected patient with physiologic blurring of the optic disk margins but no papilledema and a patient with incipient or trace papilledema.<sup>22</sup> Optical coherence tomography can be used to assess the thickness of the retinal nerve fiber layer surrounding the optic disk, but this measurement does not eliminate the potential for diagnostic uncertainty about disk swelling. Fortunately, a slight degree of papilledema can be tolerated by optic disks with little risk to vision. For most patients with a new diagnosis of idiopathic intracranial hypertension, the main challenge is management of headache.

The severity of papilledema must be judged relative to the degree of optic atrophy. Swollen optic disks eventually subside and become atrophic flat optic disks if the ICP remains uncontrolled. Patients occasionally present with advanced vision loss and pale optic disks that show little swelling owing to damage from chronic, undiagnosed idiopathic intracranial hypertension.

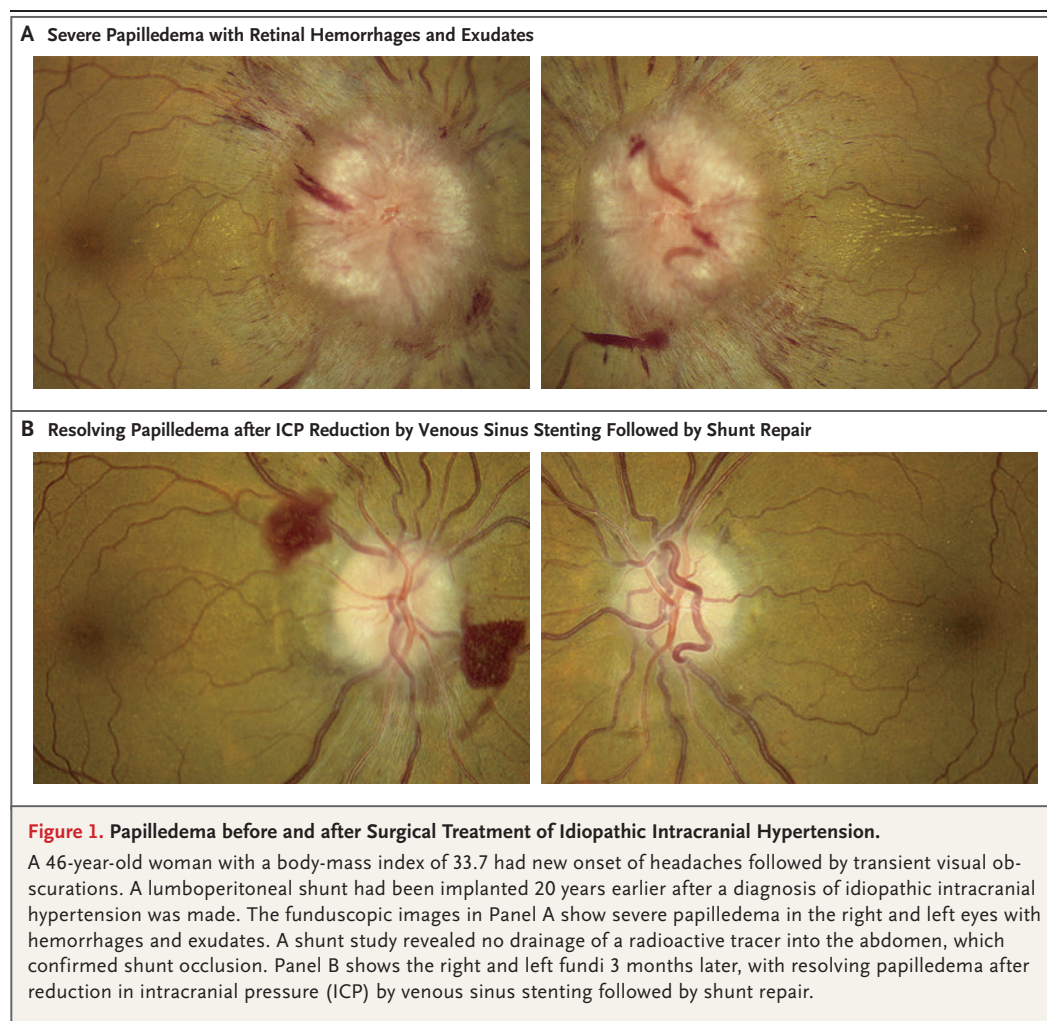
**NEUROIMAGING AND IMPLICATIONS FOR PATHOPHYSIOLOGY**

The term pseudotumor is apt, because the presence of an intracranial mass lesion must be ruled out for a diagnosis of idiopathic intracranial hypertension. Although computed tomography (CT)

may be adequate to accomplish this goal, magnetic resonance imaging (MRI) is superior to CT for the evaluation of patients with papilledema from suspected idiopathic intracranial hypertension. Sequences are obtained before and after administration of gadolinium, and magnetic resonance venography is performed. Imaging findings resulting from raised ICP include protrusion of the optic disks into the vitreous cavity, flattening of the posterior globes, CSF distention of the optic-nerve sheaths, descent of the cerebellar tonsils, and a partially empty sella.<sup>23,24</sup> The most notable finding, because of its implications for the pathophysiology of idiopathic intracranial hypertension, is transverse dural sinus stenosis (Fig. 3), which was present in 94% of patients in one series.<sup>25</sup> It is usually present on both sides or

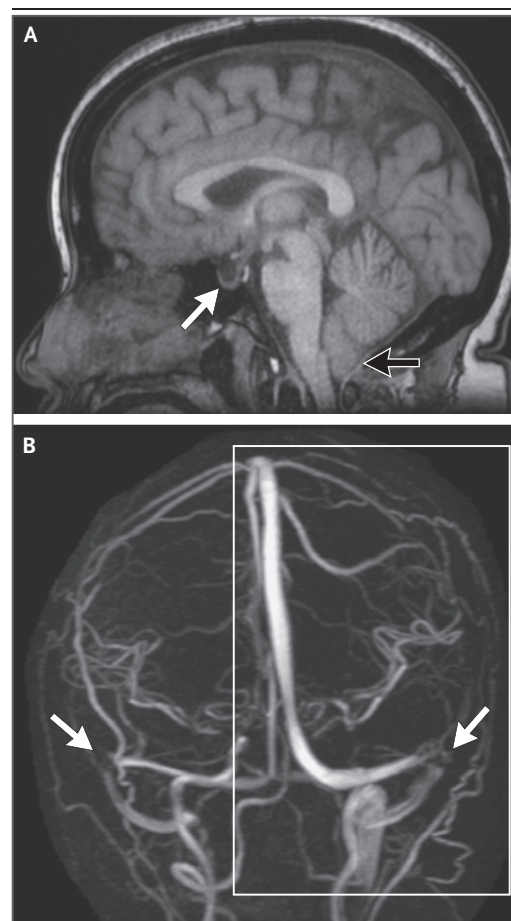
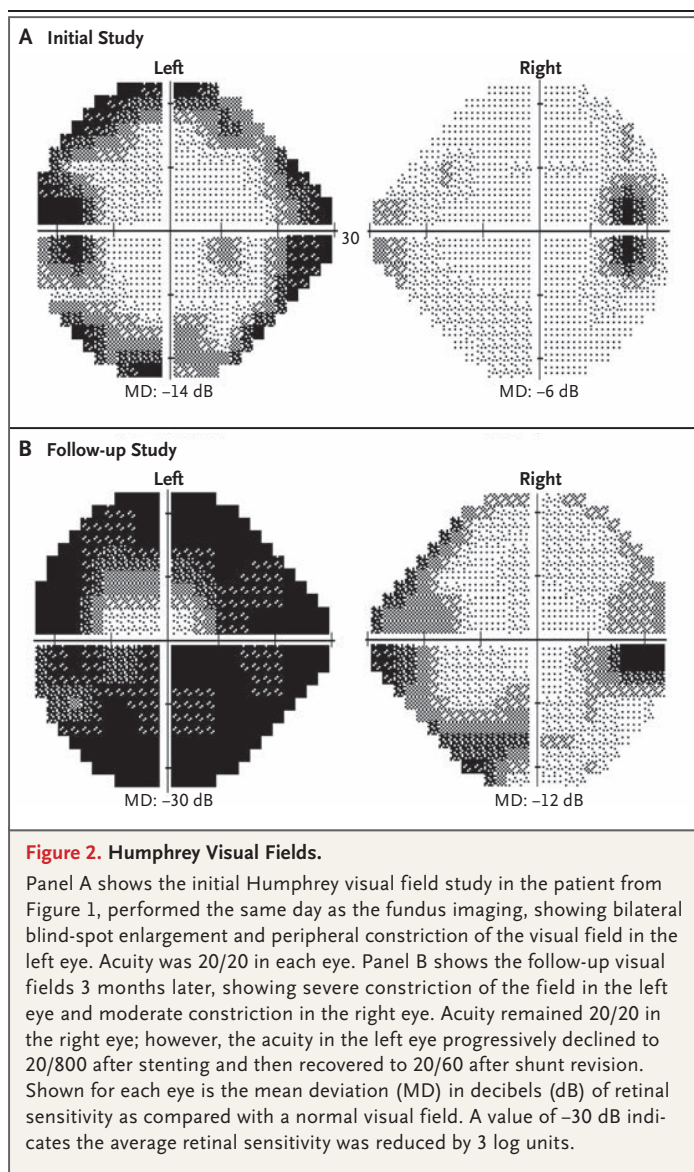
is present on one side with a hypoplastic transverse sinus on the other side. Although not specific for idiopathic intracranial hypertension, transverse dural sinus stenosis is seen in less than 5% of persons without the disease.<sup>26,27</sup>

The observation of dural sinus stenosis in patients with idiopathic intracranial hypertension has given rise to a theory that the condition is driven by a positive feedback cycle that produces clinical manifestations (Fig. 4).<sup>28</sup> The process begins with the elevation of jugular venous pressure caused by truncal obesity.<sup>29</sup> This increase in venous pressure, transmitted to the intracranial dural venous sinuses, reduces the gradient for the normal course of CSF absorption across the cerebral dural sinuses. To maintain the rate of CSF removal, the ICP becomes elevated. The rise in ICP



compresses the dural sinuses, especially at the junction of the transverse and sigmoid sinuses, creating a functional stenosis. Focal stenosis at this site exacerbates cerebral venous hypertension, further increasing ICP. Direct support for this proposed mechanism comes from the observation that venous manometry reveals a pressure gradient across the narrowed distal transverse sinuses in idiopathic intracranial hypertension, which is relieved by the rapid removal of a large volume of CSF by means of lumbar puncture.<sup>30-32</sup> In addition, successful medical treatment of papilledema can reverse transverse sinus stenosis.<sup>33</sup>

This theory implies that many, if not most, patients with idiopathic intracranial hypertension harbor subclinical disease, manifested by intermittent headache and other pressure-related symptoms as ICP fluctuates across the threshold between normal and elevated levels. This concept is supported by the observation that the median ICP is 10 to 15% higher in persons with obesity



than in persons who are not obese.<sup>34</sup> The mechanism that triggers a minority of patients, among a large population at risk, to convert from a compensated state to overt idiopathic intracranial hypertension remains unknown. Recent weight gain may be responsible in some cases.

Findings on MRI that are suggestive of increased ICP, as described above, are observed oc-

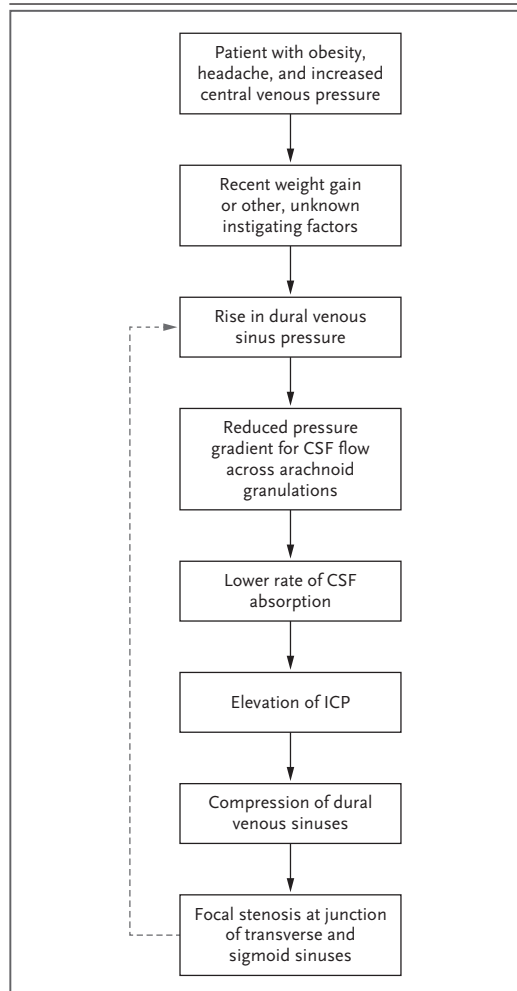
asionally in patients referred for neuroimaging, sometimes without the clinician having suspected idiopathic intracranial hypertension. Consequently, neuroradiologists have become a source of referrals to ophthalmologists and neurologists to rule out papilledema. If the fundus examination is normal, the diagnosis of idiopathic intracranial hypertension without papilledema must be considered if the patient fits the clinical profile and the evidence from neuroimaging that supports the features of increased ICP is compelling.<sup>35</sup>

DIAGNOSTIC AND THERAPEUTIC ASPECTS OF MEASURING CSF PRESSURE

If neuroimaging has eliminated a mass lesion or venous thrombosis from consideration, a lumbar puncture is usually performed to measure the lumbar subarachnoid opening pressure and to sample the CSF. A manometer reading that is higher than 25 cm of water (18.4 mm Hg) when measured with the patient in the lateral decubitus position is considered to be diagnostic for idiopathic intracranial hypertension if the CSF composition is normal and the clinical circumstances are appropriate.<sup>36</sup> Uncertainty can arise for several reasons. Occasionally, patients with idiopathic intracranial hypertension have had an opening pressure of less than 25 cm of water, and in some series, 2.5% of patients without the disease have had opening pressure higher than this level.<sup>34,37</sup>

Lumbar puncture captures a pressure reading at a single moment, but as with blood pressure, ICP varies widely with changes in activity and posture.<sup>38</sup> Owing to obesity, lumbar puncture may be difficult to perform in persons with idiopathic intracranial hypertension, leading to inaccurate readings from incorrect positioning, abdominal pressure, straining, and needle misplacement. Many such patients are referred to radiologists, who often perform the procedure with the patient in a prone position. When a lumbar puncture is performed in a patient in that position, the needle length (9 cm) should be added to the height of the fluid column in the manometer. If this step is not taken, the reported ICP value may be inaccurate.<sup>39,40</sup>

Although lumbar puncture has been considered essential for the diagnosis of idiopathic intra-



**Figure 4. Postulated Mechanism of Idiopathic Intracranial Hypertension.**

Weight gain increases central venous pressure, which increases dural venous sinus pressure and ICP. The increased ICP compresses the dural venous sinuses, worsening venous hypertension. The cause of stenosis becoming focal at the junction of the transverse and sigmoid sinuses remains unexplained. Weight loss and acetazolamide induce remission, presumably by reversing the positive feedback cycle that drives intracranial hypertension. CSF denotes cerebrospinal fluid.

cranial hypertension, a reasonable argument can be made for omitting the procedure in selected patients. When papilledema is mild or absent, lumbar puncture is likely to yield an opening pressure of between 20 and 30 cm of water. A reading in this range provides little diagnostic information, because it overlaps with pressures recorded in healthy persons. The opinion has been offered that forgoing lumbar puncture and simply initiating treatment is a reasonable approach if the patient's clinical findings are typical; MRI shows transverse sinus stenosis, a partially empty sella, and no meningeal enhancement; and there are no red flags suggestive of an alternative diagnosis.<sup>41,42</sup> The risk of missing a case of aseptic meningitis that mimicked idiopathic intracranial hypertension because CSF analysis was not performed was shown to be less than 1% in one retrospective series.<sup>37</sup>

When papilledema is moderate to severe, lumbar puncture is diagnostically useful because the pressure reading is likely to be unequivocally high. It is usual to remove a generous volume of CSF (e.g., 30 to 40 ml) to lower the ICP immediately and protect the optic disks from damage.<sup>43</sup> It is not typically necessary to measure the closing pressure. The hole created by puncturing the dura often allows fluid egress for up to a week. When the ICP is high, this drainage is therapeutic, and accordingly, application of a blood patch should be avoided unless an orthostatic headache is intractable and clearly due to low ICP. The CSF is examined for glucose and protein levels and for cell count. If this analysis is normal, no further CSF testing is necessary.

Serial lumbar punctures are an impractical strategy for managing high ICP, except as a temporizing measure in the setting of severe vision loss.<sup>44</sup> Once a lumbar puncture has confirmed the diagnosis of idiopathic intracranial hypertension, repeated measurements have limited value. An exception arises in patients with optic atrophy who are unable to cooperate with visual field testing. In this setting, fundus examination may reveal little or no papilledema, but insidious loss of vision can progress undetected. The only way to be certain that ICP is under adequate control may be to measure it by means of lumbar puncture, sometimes repeatedly. Rarely, continuous invasive intracranial monitoring is necessary for diagnostic purposes.<sup>45-48</sup>

## TREATMENT

Most patients with suspected idiopathic intracranial hypertension can be treated in an outpatient setting, provided the evaluation is performed expeditiously. Referral to an emergency department is appropriate if there is vision loss. Many patients with the disease have limited insurance coverage and come to emergency departments to access health care.<sup>49</sup> They are more likely to be Black or Hispanic, have low income, and have a history of depression, anxiety, or diminished self-esteem related to their obesity.<sup>50-52</sup> A respectful approach to such patients is essential to build rapport, especially when addressing sensitive issues such as weight reduction and overuse of headache medication.

Once treatment has begun, the visual acuity, visual fields, and ocular fundi are evaluated regularly to monitor optic-nerve function. The examinations can be performed by an optometrist and the information shared with a physician. The frequency of examinations should be tailored to the severity of the patient's condition.

### MEDICAL TREATMENT

Weight reduction combined with oral acetazolamide have been the mainstays of treatment for idiopathic intracranial hypertension.<sup>53,54</sup> Acetazolamide inhibits carbonic anhydrase, an enzyme that mediates CSF secretion. The usual dose is a 500-mg extended-release capsule taken two to four times per day. Escalating the dose over several days may reduce side effects such as nausea and paresthesias of the hands and feet. Acetazolamide is safe for use during pregnancy.<sup>55</sup> In otherwise healthy patients, it has been my practice to omit monitoring of electrolyte levels. Topiramate, another carbonic anhydrase blocker, was effective in reducing ICP in a small, nonrandomized trial, possibly by inhibition of carbonic anhydrase and induction of weight loss.<sup>56</sup> Glucocorticoids have no role in treatment, even in the context of catastrophic vision loss. Patients with idiopathic intracranial hypertension need not be instructed to stop taking oral contraceptives.

Weight loss results in improvement in patients with idiopathic intracranial hypertension but is difficult to achieve and sustain with the use of diet and exercise.<sup>57</sup> A randomized trial has shown that bariatric surgery was superior to

weight-loss programs, leading to an average 21.4-kg weight loss and an average reduction in ICP at 12 months of 7.2 cm of water.<sup>58</sup> Gastric bypass was more effective than sleeve or banding operations, resulting in a mean weight loss of 36.0 kg and a mean decrease in ICP of 15.5 cm of water.<sup>59</sup>

Glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide agonists offer an alternative to bariatric surgery. In addition to inducing weight loss, GLP-1 agents appear to reduce ICP by inhibiting CSF secretion in an animal model.<sup>60</sup> There are limited data from prospective, randomized trials showing efficacy of GLP-1 agonists in the treatment of idiopathic intracranial hypertension.<sup>61</sup> Nevertheless, the benefits reported from bariatric surgery strongly suggest that these agents could fundamentally change the management of the disease. I have treated patients with oral semaglutide and have observed a 10 to 15% reduction in weight accompanied by resolution of papilledema in approximately 4 months. GLP-1 and gastric inhibitory polypeptide agonists should be made available to all patients with obesity and idiopathic intracranial hypertension at the time of diagnosis. Weighing patients at each office visit is helpful to track decreasing body-mass index. In the future, it is likely that fewer surgical procedures (discussed below) will be necessary to treat idiopathic intracranial hypertension because treatment with incretin receptor agonists will result in remission by means of weight loss.

#### **SURGICAL TREATMENT**

Occasionally, drastic vision loss, fulminant papilledema, and elevated ICP develop in patients who have had symptoms for only a few days or weeks.<sup>62</sup> Such cases support the theory that idiopathic intracranial hypertension can smolder undetected and then erupt when dural sinus stenosis causes a sudden rise in ICP (Fig. 4). If surgery cannot be performed within hours, placement of a temporary lumbar drain can buy time. Surgical intervention is necessary when visual acuity has become reduced and the pace of vision loss is too rapid to wait for papilledema to improve gradually through weight loss and treatment with acetazolamide. Excessive delay before resorting to surgery risks permanent visual loss. There are three surgical options: fenestration of the optic-

nerve sheath, placement of a dural venous sinus stent, and CSF shunting. The only reason to perform surgery is to prevent vision loss. Surgery is not advised to treat headache or pulsatile tinnitus, because these symptoms can be mitigated by medical treatment and weight loss according to consensus guidelines.<sup>63</sup>

Randomized clinical trials to determine the best surgical procedure for patients with idiopathic intracranial hypertension have floundered because of low patient recruitment. Each surgical alternative offers advantages and is associated with different complications.<sup>64</sup> In the absence of agreement regarding the best procedure, all three options should be discussed with patients.

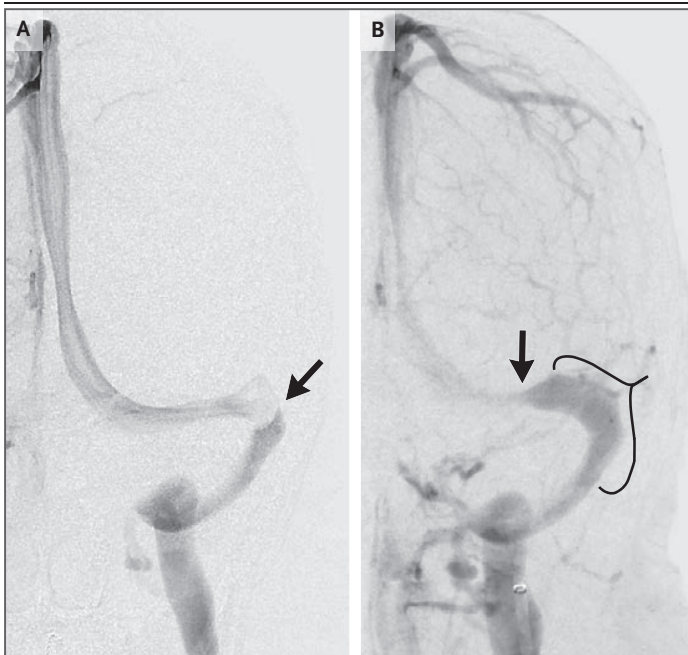
#### *Fenestration of the Optic-Nerve Sheath*

In fenestration of the optic-nerve sheath, an ophthalmologist creates an aperture in the optic-nerve sheath just behind the globe, relieving papilledema by allowing CSF to drain into the orbit. Sometimes, papilledema improves in the contralateral eye as well, but usually the operation must be done bilaterally. One study showed a 2% risk of vision loss from injury to the optic nerve from the procedure when it was performed for another condition, anterior ischemic optic neuropathy.<sup>65</sup> The fenestration usually closes within months, but adhesions form between the cut edges of the nerve sheath and the pia arachnoid, protecting the optic disk from high pressure by isolating it from the retrobulbar subarachnoid space.<sup>66</sup>

The major drawback of this procedure, besides the risk of surgically induced optic-nerve damage and blindness, is that it does not lower the ICP.<sup>67</sup> Therefore, headache, diplopia, and tinnitus often persist. Vision loss can progress if postoperative scarring fails to seal off the periorbital subarachnoid space. In one series, 17 of 35 patients who underwent fenestration of the optic-nerve sheath ultimately received a CSF shunt or venous sinus stent to protect their vision.<sup>68</sup>

#### *Dural Venous Sinus Stent*

To place a dural venous sinus stent, with the patient under general anesthesia, an interventional radiologist threads a stent across the stenosis affecting the dominant transverse sinus after first verifying that a sizable venous pressure gradient



**Figure 5. Stenting of the Dominant Transverse Sinus.**

Panel A shows a catheter angiography image of the venous phase after contrast injection into the carotid artery in the patient from Figure 1, confirming stenosis of the distal left transverse sinus before treatment (arrow). A stent was placed because the patient's lumboperitoneal shunt was occluded, but her vision continued to worsen. Panel B shows a follow-up study 6 weeks later with a new stenosis (arrow) upstream from the stent (bracket). A second stent (not shown) was placed across the new stenosis, but the patient's visual acuity continued to decline. A month later, the lumboperitoneal shunt was revised, leading to partial recovery of acuity to 20/60 in the left eye, but the visual field remained severely constricted (Fig. 2B).

exists across the region.<sup>28,69</sup> The appealing feature of this procedure is that it corrects the anatomical obstruction that is considered central to the self-reinforcing rise in ICP (Fig. 4). In a summary of 19 reported series, the risk of subdural or intracerebral hematoma was shown to have been small (0.49%), but two deaths were reported.<sup>70</sup> The same review reported a mean drop in CSF pressure of 13.3 cm of water.<sup>70</sup> Patients receive aspirin and clopidogrel for up to 6 months after the procedure to prevent stent thrombosis.

The most serious limitation of venous sinus stenting is that the ICP is lowered, but not to a level in the normal range in some patients.<sup>70</sup> If the ICP remains elevated, visual function may continue to deteriorate. Opening pressure cannot be checked immediately after stent placement, because lumbar puncture is contraindicated in patients receiving dual antiplatelet drugs.

Many patients continue to receive acetazolamide owing to concern that stenting has been only partially effective. In various series, 15% of patients showed development of a new stenosis adjacent to the stent (Fig. 5).<sup>70-72</sup> Recurrent stenosis is evidence that ICP is still high, exposing the optic disks to ongoing damage precisely at the time decisive relief is paramount. A second stent can usually be inserted to lower ICP further, but sometimes a CSF shunt is needed to arrest vision loss.

#### CSF Shunt

Although venous sinus stenting has been gaining popularity, placement of a CSF shunt remains the standard treatment for medically refractory idiopathic intracranial hypertension. A shunt immediately reduces ICP to the normal range, protects the optic disks, and allows acetazolamide treatment to be stopped. Drainage of CSF is regulated by an externally programmable shunt valve, whereas with a venous sinus stent, the physician has no direct control over ICP. The two shunt systems, lumboperitoneal and ventriculoperitoneal, have similar failure and complication profiles.<sup>73</sup> The use of a lumboperitoneal shunt avoids the slight risk associated with threading a catheter through brain tissue and the need to implant connecting hardware on the skull. Most neurosurgeons have more experience with ventriculoperitoneal than lumboperitoneal shunting, and the advent of intraoperative navigational imaging has made it easier to place the proximal catheter into the typically small ventricles associated with idiopathic intracranial hypertension.

The major drawback of CSF shunts is the associated high incidence of failure, usually owing to catheter blockage. Reports vary, depending on method and follow-up, but revision in 20 to 40% of cases is typical.<sup>74</sup> When a shunt fails, it usually does so soon after implantation and is apt to fail repeatedly.<sup>75,76</sup> Shunt failure, whether real or potential, is responsible for many emergency department visits. After an acute shunt obstruction occurs, papilledema takes at least a week to appear and may never develop if the optic disks have become atrophic, so a fundus examination may be unrevealing.

Evaluation requires neuroimaging, shunt function studies, and sometimes, lumbar puncture. One opinion, formed on the basis of a series from an experienced center, is that shunt success improves when a neurosurgeon who specializes in

idiopathic intracranial hypertension performs the operation and the peritoneal catheter is inserted by means of laparoscopy.<sup>75</sup> A CSF shunt, when trouble-free and working properly, most dependably halts vision loss from idiopathic intracranial hypertension. However, given the propensity of CSF shunts to malfunction, it is not surprising that some neurosurgeons have come to embrace venous sinus stenting.<sup>76</sup>

#### CONCLUSIONS AND FUTURE DIRECTIONS

The rising prevalence of obesity has increased the population at risk for idiopathic intracranial hypertension. Diagnosis is challenging when papilledema is subtle or absent and ICP barely exceeds the normal range. Discovery of a noninvasive technique for accurate measurement of ICP would facilitate the evaluation of patients with headache from suspected idiopathic intracranial hypertension. Neuroimaging has furnished an

important clue to the mechanism of this disease by revealing focal stenosis of the distal transverse sinuses, which activates a positive feedback cycle that drives ICP elevation. This cycle can be broken by treatment with GLP-1 or gastric inhibitory polypeptide agonists to induce weight loss and acetazolamide to reduce CSF production. When papilledema is severe enough to threaten irreversible vision loss, a surgical procedure is performed urgently to prevent blindness. Randomized trials are needed to determine which of the two most common operations—CSF shunting or venous sinus stenting—is superior. The optimal care of patients with severe idiopathic intracranial hypertension is complex, with the potential for permanent impairment of vision despite appropriate treatment.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

#### AUTHOR INFORMATION

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