Venous Sinus Stenting for Idiopathic Intracranial Hypertension

A review of risk factors, pathophysiology, medical treatment options, the role of venous sinus stenting, and future directions, including ongoing clinical trials.

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We may well be dealing with a condition that has more than one underlying anatomic or etiologic basis. ... They behave much in the same way, except in degree and duration.

—Walter Dandy[1]

Idiopathic intracranial hypertension (IIH) is a condition characterized by elevated intracranial pressure (ICP) without a distinct etiology.[2,3] Although IIH has also been referred to as pseudotumor cerebri or benign intracranial hypertension, this article refers to the disease process as IIH.

IIH generally presents with headaches but can also include pulsatile tinnitus or auditory complaints, visual abnormalities such as diplopia or obscurations, vision loss, cerebrospinal fluid (CSF) leak, and even cognitive impairment.[4,5] Patients with IIH describe varying characteristics of their headaches, from a pressure headache to migraine-like symptoms,[6] and may often experience headaches for years before diagnosis. In patients not experiencing significant headaches, constant auditory complaints such as ringing in the ears or hearing their heartbeat may be the primary issue. Some patients only present with papilledema discovered on routine examination.[7] IIH patients often report a significant decrease in quality of life, with difficulty obtaining the appropriate diagnosis and subsequent care.[7]

To confirm an IIH diagnosis, physicians usually require the presence of papilledema with direct evidence of elevated ICP, customarily via opening pressure obtained during lumbar puncture.[2] CT or MRI often reveals radiographic features notable for elevated ICP, such as empty sella turcica, small ventricles, distention of the optic nerve sheath, posterior globe flattening, optic nerve protrusion, or transverse venous sinus stenosis.[8] Neuroimaging rules out an alternative cause of elevated ICP, and the absence of these listed findings does not eliminate the diagnosis of IIH. Angiographic evidence of IIH can include unilateral or bilateral venous sinus stenosis and a pressure gradient across the site of stenosis, determined by venous manometry.

RISK FACTORS AND INCIDENCE

The disease process predominantly affects overweight females of reproductive age, but men can also be affected. Risk factors include but are not limited to female sex, obesity, hormonal disruption, steroid withdrawal, vitamin A intoxication, systemic lupus erythematous, amiodarone use, sarcoidosis, and iron deficiency anemia.[9] The incidence of IIH is estimated at 0.03 to 7.8 per 100,000.[10] Interestingly, the incidence of the disease has more than doubled within the last 2 decades. This could partially be attributed to increasing rates of obesity.[10-12] IIH imposes a significant economic burden, with morbidity resulting in lost income and increased health care costs—values that have multiplied fivefold over the last 10 years.[13]

PATHOPHYSIOLOGY

The diagnostic criteria for IIH are well recognized, but the pathophysiology of the disease is not understood.

One theory centers on the disruption of CSF dynamics resulting in increased ICP. Investigations have studied abnormalities of the choroid plexus leading to possible CSF hypersecretion, or modifications in the arachnoid granulations leading to diminished CSF resorption. Others suggest that elevated venous outflow pressure or even lymphatic obstruction could bring about the elevated ICP in IIH.[14]

Obesity and IIH are related. This is likely due to one or many of the associated physiologic changes in obesity, such as metabolic syndrome or increased intra-abdominal and thoracic pressure, leading to elevated central venous pressure and a higher threshold for CSF outflow.[15] The risk of developing IIH drastically rises with increased body mass index (BMI),[11] and weight gain correlates with disease progression; BMI > 40 kg/m^2 is associated with a worse prognosis and higher rates of disease recurrence.[2,16,17] In one study, patients who lost weight experienced lower ICP, reduced headache frequency, improved papilledema, and visual acuity.[18] Investigating the role of metabolic dysfunction that commonly exists in obesity is warranted, such as diabetes or polycystic ovarian syndrome.[11,19]

The disproportionately female predominance of IIH suggests that a hormonal imbalance may also be a contributor to development. Additionally, overweight females frequently have elevated levels of circulating androgens, a finding also present in IIH patients.[20] We know weight loss leads to a reduction in disease severity, but it can also lead to a reduction in circulating androgens.[21] Compared to metabolically matched controls, women diagnosed with IIH have significantly higher levels of CSF testosterone, androstenedione, and serum testosterone.[22] Additional studies are needed to investigate the relationship between obesity, patient sex, and hormonal dysregulation in IIH.[3,23]

TREATMENT

Treatment for IIH focuses on symptom relief and reduction of elevated ICP. Carbonic anhydrase inhibitors (CAI) such as acetazolamide are the standard medical treatment for IIH. CAIs work by blocking the enzyme responsible for CSF production and thereby reducing ICP.[24] Topiramate is also frequently prescribed because it works as a CAI but also assists with headache prophylaxis and weight loss as an appetite suppressant.[25] Those in need of additional headache management may begin with over-the-counter pain medications such as acetaminophen or nonsteroidal anti-inflammatory drugs. Opiates can be used for more severe headaches, but patients are often placed on migraine prophylaxis.[25]

Weight loss and lifestyle modifications are also encouraged for management of IIH.[26] Some patients improve after undergoing bariatric surgery, although these benefits will often take months to realize.[17] However, urgent and usually invasive intervention is indicated if patients are rapidly losing vision. Prior to venous sinus stenting (VSS), CSF diversion with ventriculoperitoneal shunting (VPS) or lumboperitoneal shunting was the primary surgical intervention for the management of rapid vision loss in IIH.[27] Some specialized centers may also perform optic nerve sheath fenestration in the setting of acute vision loss. Although VSS is also invasive, it is not nearly as invasive as VPS placement. Studies have recently demonstrated that VSS procedures are significantly on the rise, increasing by approximately 80% per year with a parallel yearly decrease in VPS procedures of 54%.[27]

VSS

With more knowledge and diagnoses of venous stenosis and pressure gradient in the setting of IIH, VSS has become an effective therapeutic option. In 1994, Marks et al were the first to describe stenting a pressure gradient across a focal segment of venous sinus stenosis.[28] Today, VSS is offered to patients who have undergone diagnosis of IIH and experienced failure of medical management in the setting of a significant pressure gradient across a stenotic dural sinus (> 8 mm Hg is usually deemed significant).[29] The safety profile of VSS is good, with serious complications ranging from 0.9% to 2.2%.[30,31] IIH patients treated with VSS have reported improvements in headache, tinnitus, vision, and papilledema.[32] A reduction in ICP and resolution of the trans-stenotic pressure gradient have both been shown immediately after VSS placement.[31]

Patients with a lower pressure gradient across a segment of venous sinus stenosis have also demonstrated significant improvement of IIH symptoms.[33] A 2022 study by Inam et al demonstrated that at 6-month follow-up, patients with a pressure gradient ≤ 4 mm Hg or from 5 to 8 mm Hg across a segment of venous sinus stenosis had equal improvements in papilledema, clinical symptoms, and low opening pressure on lumbar puncture compared with those with a pressure gradient > 8 mm Hg.[33] These results call for reevaluation of our criteria for this potentially vision-sparing procedure. In fact, VSS is now frequently offered acutely if a patient presents with IIH and rapidly deteriorating vision.

Although VSS has shown promise in the acute and subacute treatment of IIH, a selection of patients has eventual recurrence of symptom return.[7] This is likely because VSS improves venous outflow but may not

affect the underlying pathophysiology of IIH. Some patients may return with venous stenosis adjacent to their stent or in a new location entirely.[7,30] Meta-analyses have reported restenosis rates of approximately 14% to 20% after VSS.[31,32,34] As the primary pathophysiology of IIH remains to be understood, so too does the reason behind new sites of stenosis presenting after VSS.

A 2024 meta-analysis by Lim et al showed that 22% of patients experience symptom persistence or recurrence after VSS.[31] One of the largest VSS studies to date included 178 patients followed clinically for an average of 319 days and found that symptoms recurred in 60% of patients at a mean of 274 days postprocedure.[35] Although this is important for patient and physician expectations regarding symptom resolution, the same study confirmed lasting improvements in papilledema and ICP in approximately 75% of patients.[35]

FUTURE DIRECTIONS

Venous stenting has brought new attention to the management, treatment, and concept of IIH. Currently, the procedure is performed using off-label devices such as the Zilver self-expanding stent (Cook Medical), Wallstent (Boston Scientific Corporation), or Precise Pro stent (Cordis). Intracranial venous stents are also in development. The BosStent (Sonorous NV) and River stent (Serenity Medical) are being developed for this purpose and at the time of this publication are undergoing in-human clinical trials. Yet, major questions remain. What causes IIH, and why does VSS help some patients and not others, or maybe some for only a short period of time? Randomized controlled trials (RCTs) are needed to evaluate the current treatment options for IIH and help answer these questions.

An ideal study would be randomized, prospective, and as objective as possible when quantifying outcomes. It must of course compare CSF diversion, the current surgical gold standard, with the newer modality, VSS. Medical management certainly has a role to play as well, and this must be incorporated into decision-making. Finally, as with any unknown but promising therapy, we will need long-term follow-up.

The following is a brief review of current relevant clinical trials:

- OPEN-UP (NCT02513914), which is studying operative procedures compared to endovascular neurosurgery for untreated pseudotumor trial
- VSSIIH (NCT01407809), which is studying VSS for IIH refractory to medical therapy
- A study of VSS with the River stent for IIH (NCT03556085)
- A multinational RCT based in the United Kingdom that plans to assess CSF diversion against VSS in those with IIH and grade 3 or worse papilledema (NIHR131211)

These trials could potentially provide valuable insights into the disease process and treatment of IIH, no matter the outcome.

CONCLUSION

IIH continues to be a challenging, increasingly common disease to treat, and we still lack proper understanding of its pathophysiology. Medical management will continue to be the primary treatment option, but intervention becomes critical when patients have a poor quality of life, cognitive or visual changes, and, most urgently, vision loss. VSS is a relatively new, safe minimally invasive treatment option with growing popularity.

The fact that VSS changes the natural history for many patients is promising but also raises more questions than answers. Recent data from patients with longer follow-up suggest that symptoms return at rates higher than initially anticipated, and this should be explained to patients and their families to manage expectations accordingly.[35] RCTs with larger patient cohorts followed for longer durations will help guide management in a future that will most certainly include VSS. ■

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