Neuro-ophthalmology Update

Cerebral venous sinus stenting for pseudotumor cerebri
A review

Sivashakthi Kanagalingam a, Prem S. Subramanian a,b,⇑

Abstract

Pseudotumor cerebri is characterized by headaches, visual field changes, papilledema and an elevated cerebrospinal fluid opening pressure without evidence of an intracranial mass. In the setting of failed medical therapy, surgical options such as ventriculoperitoneal shunts and optic nerve sheath fenestrations are considered. Recently, venous sinus stenting has emerged as a new treatment option for patients with pseudotumor cerebri. We review the role of cerebral venous sinus stenting in the management of patients with medically refractory pseudotumor cerebri. Although long-term studies are needed in this field, the current reports indicate a favorable outcome for preventing vision loss and symptom control.

Keywords: Pseudotumor cerebri, Idiopathic intracranial hypertension, Venous sinus stenting, Vision loss, Papilledema

Introduction

Pseudotumor cerebri (PTC) is a syndrome characterized by raised intracranial pressure (ICP) in the absence of space-occupying intracranial lesions on imaging, elevated CSF opening pressure of >25 cm of water, and normal CSF composition.1,2 The annual incidence in the general population is approximately 1–2 per 100,000 in North America.3,4 However, in obese women of ages 22–44 years the incidence surges to 14.9–19.3 per 100,000.3 Clinically, as many as 90% of patients experience headaches,5 while 70% experience transient visual obscurations and pulsatile tinnitus.5,6 Binocular horizontal diplopia can also occur in the setting of unilateral or bilateral sixth nerve palsy, a non-localizing sign secondary to raised intracranial pressure. Papilledema seen in these patients is usually bilateral but may be asymmetric.7 Associated vision loss can be severe in up to 25% of patients, with blindness reported in 10% of cases.8–10

Conventional treatments have been aimed at controlling the headaches and preventing permanent vision loss from ensuing. Given the integral relationship between obesity and PTC, weight loss remains the most important aspect of PTC management, with as little as 5–10% of total body weight loss having been found to be effective in symptom control and papilledema improvement.11 However, weight loss is a long-term lifestyle modification and an ineffective immediate therapy. Medical treatments that include carbonic anhydrase inhibitors such as acetazolamide and to piramate are frequently used. A recent multi-center, randomized double-masked trial established that acetazolamide in conjunction with weight loss led to better and more rapid improvement in visual fields and papilledema grade than did diet alone. Nonetheless, with acetazolamide and to piramate, patients often report paraesthesias, altered taste sensation, and lethargy.12
Occasionally, oral steroids are adopted in the treatment of the fulminant variant of PTC. However, its side effect profile includes weight gain, making this a poor treatment choice in obese patients.

Surgical intervention is required for the subset of patients who continue to experience intractable headaches and progressive vision loss despite medical therapy. Customarily, optic nerve sheath fenestration (ONSF) is preferred in patients with vision loss due to severe papilledema with relatively mild or no other symptoms of increased ICP, whereas CSF diversion procedures (e.g., ventriculoperitoneal and lumbo-peritoneal shunting) are preferred in patients with visual loss, papilledema, and significant systemic symptoms of increased ICP such as headache. However, these modalities are not without their pitfalls. ONSF carries a risk of vision loss, pupillary and motility dysfunction, and up to a 32% failure rate with recurrence of visual symptoms in PTC patients. Shunting procedures have been associated with shunt migration, infection, intra-cerebral hemorrhage, and acquired Chiari malformation. Shunt failure and revision rates have been reported as being as high as 60% for lumbo-peritoneal shunts, and 30% for ventriculo-peritoneal shunts.

Anatomic abnormalities of the cerebral venous sinuses have been identified in a number of patients with PTC, and venous sinus stenting has emerged in recent years as an alternative treatment modality for these patients. We review the current literature to assess the role of cerebral venous sinus abnormalities in the pathogenesis of PTC and the potential benefit of interventional treatment.

**Pathophysiology**

The mechanisms that underlie PTC are poorly understood and have been subject to long standing debate and speculation. Prior theories have proposed increased CSF production or decreased CSF absorption as an underlying etiology. Recently, intracranial venous hypertension associated with venous sinus stenosis has been implicated as a possible mechanism for PTC. Cerebral venous sinus thrombosis represents the extreme variant of such a phenomenon and will not be discussed in this article, as its treatment is quite dissimilar (anticoagulation rather than physical relief of the obstruction). Rather, severe narrowing of one or more venous outflow channels would increase the pressure gradient across which CSF is resorbed at the arachnoid granulations and cause increased ICP. Narrowing occurs most commonly at the distal transverse sinus or transverse/sigmoid sinus junction, either unilaterally or bilaterally. Anatomic variability of the cerebral venous sinuses is well described, and venous sinus stenosis is distinct from these normal findings. The consequences of the sinuses at the torcular herophili drain into each transverse sinus asymmetrically. The right transverse sinus is usually larger and drains the superior sagittal sinus, whereas the smaller left transverse sinus usually drains the straight sinus. Anatomical studies with cadaver dissections have observed the presence of septa, especially larger septa, which could be an etiologic factor in the development of an intrinsic pattern of venous stenosis resulting in PTC. The venous sinuses are also a site for arachnoid granulations, which are extensions of arachnoid mater and subarachnoid space through the wall of the dural venous sinuses. They increase in number with advancing age and are thought to play a role in the resorption of CSF and can cause focal intraluminal filling defects in 24% of CT examinations and 13% of contrast-enhanced MR studies in normal populations. When arachnoid granulations are enlarged, they can obstruct either one or both transverse sinuses. It is thought that this obstruction creates a resistance to flow, with ensuing decreased absorption of the CSF and a concomitant increase in intracranial pressure. As discussed below, relief of obstruction by a hypertrophic arachnoid granulation has been shown to relieve PTC symptoms and signs.

There is also evidence to suggest that transverse sinus stenosis may occur as a secondary phenomenon in response to elevated intracranial pressure. King et al. described the reduction of the venous pressure in the superior sagittal and transverse sinus, disappearance of the pressure gradient across the transverse sinus, and resolved stenosis with CSF drainage. De Simone et al. presented a case of bilateral transverse sinus stenosis without any evidence of flow gaps. Reversal of the stenosis was noted just 24 h after the removal of 20 mL of CSF. Another reported patient with an opening pressure of 50 cm H2O had magnetic resonance venography (MRV) immediately before and 15 min after a lumbar puncture (LP). Partial resolution of the transverse sinus narrowing was detected with CSF drainage. A subsequent third LP reduced the pressure to 8 cm H2O and showed complete resolution of the stenosis. These findings have been reproduced by others who have reported a similar pattern of reversal of the venous sinus stenoses either by means of lumbar puncture or by CSF shunting.

Some authors have suggested the presence of a positive feedback mechanism in linking these physiological processes. Remodeling of the transverse sinus wall in response to sustained external compression from elevated ICP may lead to fibrosis and formation of a fixed narrowing that cannot reverse even with normal ICP. Changes in the bony groove occupied by the transverse sinus have been reported in patients with chronic ICP elevation and venous sinus stenosis. Regardless of the initial precipitating cause of the focal stenosis, it is suggested that a cyclical mechanism of sinus stenosis and venous hypertension further reduces CSF absorption, raises ICP and causes worsening venous stenosis.

Irrespective of these conflicting reports, it is apparent that a venous stenosis is somehow an important element in the PTC progression, be it causative or resultant. Developments and refinements in MRV imaging have now revealed that a majority of PTC patients have transverse sinus narrowing. Farb et al. utilized a high resolution, auto triggered elliptic-centric-ordered (ATECO) 3-dimensional, gadolinium enhanced MRV to detect venous stenosis. The conventional use time-of-flight MR venography (TOF MRV), a 2-dimensional system, frequently suffers from artifacts in the region of the distal transverse sinus because of in-plane, turbulent, and tortuous flow. These artifactual signal losses may be a reason as to why the role of venous stenosis in PTC was not identified or recognized in earlier literature. Higgins et al. reanalyzed the MRVs of twenty PTC patients that were initially interpreted as normal. Bilateral lateral sinus flow gaps were identified in 13 of 20 patients with PTC, and in none of 40 controls. Kumpe et al. reported that although...
fifteen patients in their series had evidence of filing defects on either CT venography or MR venography, seven were initially interpreted as normal. With the ATECO MRV technique, Farb et al.42,44 have identified the presence of venous sinus stenoses in more than 90% of patients with PTC, compared to a mere 6.8% in the control asymptomatic group. They concluded that ATECO MRV can detect sinusvenous stenosis in PTC patients with a sensitivity and specificity of 93%. In another recent study43, 90% of 51 PTC patients displayed evidence of bilateral transverse sinus stenosis on MR venography.

Zheng et al.44, reported a patient with PTC symptoms who was found to have a large arachnoid granulation in the left dominant transverse sinus with a hypoplastic contralateral transverse sinus. Venous stenting across the arachnoid granulation successfully reduced the pressure gradient across the previously stenotic region. Lumbar puncture a month later showed normal opening pressures, and at 3 months the patient was noted to be asymptomatic. Donnet et al.45 stented the transverse sinus often in PTC patients and documented a normalization of the CSF opening pressure 3 months post procedure. This does appear to support venous stenosis as a principal cause of raised intracranial pressure.

Endovascular procedures and characteristics

Higgins et al.21 were the first to report transverse sinus stenting in 2002 in a PTC patient with bilateral distal transverse sinus stenoses who had failed medical therapy. They noted improved symptoms and clinical signs, including reduction of the pressure gradient and normalization of her CSF pressures. Since then, there has been tremendous interest in this approach, and numerous other authors have published their venous sinus stenting data with outcomes reflecting both anatomic and symptomatic resolution of abnormal findings.

As noted above, venous sinus stenosis may occur secondarily in some PTC patients, and clinical and research team members have taken a variety of approaches to investigate the cerebral venous system before attempting any intervention. In all instances, pre-procedural testing is selected to identify the structural changes first, and if they are seen, then further studies to establish the presence of a pressure gradient across the abnormal area are performed. Some authors42,46 opted for patients to undergo cerebral venography and manometry under light sedation after they showed evidence of transverse sinus stenosis with contrast-enhanced MRV. If a significant pressure gradient was found across the stenotic area, then placement of the venous sinus stent was undertaken at the next available opportunity under general anesthesia. Other authors47 opted to carry out the venography under general anesthesia followed by stent placement in the same sitting if a significant pressure gradient existed. It has been suggested that the induction of general anesthesia causes artificially elevated venous sinus pressure measurements due to positive pressure ventilations, vasoactive anesthetic agents and variations in PaCO2.48,49 However, Kumpe50 noted that pressure gradients decreased in 11 patients and increased only in 2 under general anesthesia as compared with their corresponding readings that were taken while awake.

Antiplatelet therapy was used routinely in the peri- and post-procedural periods. Aspirin and clopidogrel together were usually started 4–5 days prior to angiography46,49 with intravenous heparin administered throughout the procedure to maintain an activated clotting time of more than twice the normal level. Dual therapy with clopidogrel and aspirin was continued for a period of 3–6 months to allow epithelialization of the stent to occur.42,50,51 This was followed by aspirin therapy for a year. Other studies48,52 employed warfarin in addition to aspirin for 2 months followed by prolonged aspirin therapy.

While most authors did measure pressure gradients across the stenotic regions, the gradient level at which stenting was considered is variable across institutions.42,44,46,48 In most studies, stenting of the dural sinus was undertaken when the pressure gradient exceeded or equaled 10 mmHg.42,45,48,50,52 Ahmed et al.46 opted to stent patients when a gradient difference of 8 mm hg was noted and, Radvany et al.49 used a gradient of greater than 4 mmHg. There was one study51 that did not report their measured gradients.

In most studies, unilateral venous sinus stenting was done despite the presence of bilateral stenosis, with the apparent dominant side or the side with the higher pressure gradient selected. A large retrospective group analysis of 143 cases53 comprising of 15 studies showed that stents were placed in the right transverse sinus or sigmoid sinus in 69%, the left transverse sinus or sigmoid in 27%, or both sinuses in 4%. Fields54 stented a patient whose dominant sinus had stenosis. In the presence of bilateral stenosis, Radvany et al.55 opted to stent the side with the larger pressure gradient.

Clinical outcomes

In the largest cohort of 52 PTC patients46 who underwent venous sinus stenting, all 46 with papilledema on presentation had resolution of papilledema post venous sinus stenting. On presentation, 30 of the 46 patients with papilledema had varying degrees of visual field defects ranging from enlarged blind spots to severe visual field defects. Post stenting, only 7 patients had persisting visual field loss, of whom 4 had optic atrophy. Headache resolved in 40 and did not change in 3 patients post procedure. Interestingly, the headaches recurred in 6 patients and papilledema in 4 patients due to re-stenosis of the venous sinus. After re-stent placement, the headaches and papilledema resolved in 5 and 4 of the patients respectively.

A Chinese study54 of 24 patients stented reported resolution or improvement in headaches of 16 patients, vision in 13 patients, and papilledema in 10 patients. In his initial case series from 2002, Higgins51 reported 12 cases of venous sinus stenting, after which 5 became asymptomatic, 2 improved and 5 remained unchanged. Bussiere et al.47 reported 10 patients of whom 8 reported improved headache symptoms, and 2 noted complete resolution of their headaches. Papilledema was resolved completely or improved in 9 patients, with the remaining patient experiencing visual impairment associated with optic atrophy. Donnet et al.45 reported 10 patients of which after stenting, 6 reported no headache, 2 were improved, and 2 were unchanged. All 10 patients had documented papilledema on presentation which resolved post stenting. However, in 2 patients, optic atrophy was noted. Pulsatile tinnitus resolved for all 10 patients. There was also a normalization of CSF and venous sinus pressures. At 3 months post procedure, lumbar punctures revealed CSF
pressures varied from 9 to 19 cm H2O in this group of patients. All stents were noted to be patent on follow up. Radvany et al.49 noted that all 12 patients were found to have headache and papilledema upon presentation. Post stenting, the headaches resolved in 2 patients, improved in 5 patients and persisted in the remaining 5. Tinnitus improved in 11 patients. They reported resolution of papilledema in 11 patients.

Kumpe et al.42 stented 18 patients, 16 of whom were available for fundoscopic follow up. Fifteen of these patients showed resolution of papilledema. Visual acuity remained stable or improved in 15 patients. Two patients reported no change in their headaches. Ten patients reported improvement but persisting headache of some nature, and 2 patients reported no change. Albuquerque et al.51, stented 18 patients, of whom 12 patients reported improved headaches, 2 noted unchanged symptoms and 1 noted worsening headache.

Owler et al.48 had a smaller series of 4 patients whose stenotic sinuses were stented. Of these 4 patients, 3 reported resolution of their headaches, and 1 experienced occasional headaches despite normal CSF measurements. Three patients had resolved papilledema and 1 had no change on fundus examination. All 3 stented patients reported by Lazzaro et al.35 showed resolution of papilledema, with 2 patients reporting improved headaches. The remaining patient noted no change in symptoms post procedure. Arac56, Ogungbo, Paquet57, Rajpal58 and Teleb59, each published case reports of individual patients who underwent venous sinus stenting. These 5 patients all were noted to have resolution of headaches. All but one had resolution of papilledema.

A meta-analysis60 of 19 studies with a total of 207 patients looked at the overall clinical outcomes, although visual outcome data were not uniformly reported in the included studies. The authors reported an improvement rate of 81% with regard to headaches, 87% for papilledema, and 95% for pulsatile tinnitus.

The persistence of headaches in some form, especially amongst female patients correlates with prior reports where as many as 48–68% of PTC patients with PTC still experience headaches despite successful treatment.61,62 McGirt et al.61 reported as many as 48% of patients in their series experiencing severe headaches despite an adequately functioning shunt. Patients with PTC often have other causes of headaches, particularly those of migraine etiologies.63 Data analysis of these headache symptoms and their response to therapy in the IIHTT is currently under investigation. Overall, we recommend headache resolution in itself should not be used as a primary marker for successful PTC treatment.

Follow up periods varied amongst studies, with the shortest being 2 months64, and the longest at 136 months.42 In the largest series46 the mean pressure gradient across the stenosis dropped from 19.1 mmHg to 0.6 mmHg post-stenting. Comparable decreases have been observed in the other studies as well.42,47,50,52 Since long-term or later measurement of the pressure gradient is unlikely to be done routinely given its invasive nature, we can only postulate but not confirm that the gradient does not recur in asymptomatic patients.

Complications

Two patients developed in-stent thrombosis52 that resolved with anti-thrombotic therapy. Re-stenting was necessary in 6 of 52 patients (12%) in the largest series.46 Five of these 6 patients required an additional stent placement, whereas the remaining 1 patient required 4 stents sequentially. Fields et al.50 reported 2 patients requiring further management with VP shunting and 2 other patients who underwent bilateral stenting. Higgins et al.57 re-stented two of patients in their series. Kumpe et al.42 had two patients that required retreatment. One patient needed re-stenting, while the other required intracranial thrombolysis for thrombus formation that occurred downstream from the stent. Radvany et al.49 had two patients who developed headaches and recurrent papilledema post treatment. They were both found to have transverse sinus stenosis proximal to the stent. Both patients were re-stented; 1 experienced resolution of symptoms whereas the other patient required a VP shunt with eventual improvement in her clinical findings. There is some evidence that oversizing the stent, a standard technique in arterial procedures, may contribute to restenosis by causing collapse of the more distensible venous sinus wall just proximal to the stent terminus. After reducing stent diameter to more closely match the vessel size, we have not had any restenosis in our stented patients.

Kumpe et al.42 reported 1 patient with a subdural hemorrhage, and 2 other patients with minor complications of a urinary tract infection and syncope. Ahmed et al.46 reported 1 patient with a subdural hemorrhage from a perforated intracranial vein, and another patient who developed subdural, subarachnoid and intra-cerebral bleeding. They also had 2 other patients with transient hearing loss. The three patients in these studies who suffered intracranial hemorrhages underwent surgical decompression. Albuquerque et al.51 reported a patient who had a retroperitoneal hematoma post procedure, and Fields et al.50 described 1 patient with a femoral pseudoaneurysm.

Discussion

Venous sinus stenosis has proved to be a significant finding in PTC patients, and venous stenting has emerged as an effective treatment modality. However, it is not without significant attendant risks. The most common complication appears to be recurrent stenosis immediately proximal to the stent. Other complications include stent migration, in-stent thrombosis and, most concerning, intracranial hemorrhage. As Friedman53 noted in a point counter-point article, PTC is not a life threatening disease, yet the surgical options offered do carry fatal complications. These should be taken into consideration when offering surgery to candidates with milder disease processes. Weight loss and acetazolamide should continue to be the first line therapy for PTC patients. However, it should be noted that as many as 18–22% of PTC patients do not respond to maximal medical therapy and weight loss regimens.64

Failure or intolerance to medical therapy should then prompt secondary surgical measures; optic nerve sheath fenestration, CSF diversion procedures and venous sinus stenting are all acceptable options. All patients should have an MRV with gadolinium contrast at initial presentation. If venous sinus stenosis is detected on MRV, and if patients subsequently fail medical therapy, then they should undergo diagnostic angiography and manometry. We propose that the manometry should be performed while the patient is
mildly sedated to avoid the effects of general anesthesia on the pressure gradient measurements. If significant venous stenosis is noted and a pressure gradient is present, then venous sinus stenting should be undertaken.

It has been observed that unilateral stenting of the transverse sinus is sufficient to reduce pressure gradients despite the presence of bilateral transverse sinus stenoses. After venous sinus stenting, physicians must also be alert to the recurrence of PTC symptoms and papilledema, which would suggest re-stenosis. There are some data to suggest that patients who had higher sagittal sinus pressures on initial venography and higher gradient values across the stenosis were more likely to require re-stenting. In this study, the mean time to re-stenting was 20 months, with a range of 1–58 months. This finding further highlights the fact that long-term data are needed to assess for stent patency, its efficacy in preventing vision loss, and symptom control in this patient population. Stent patency may be evaluated by noninvasive techniques such as CT venography.

Other factors to consider in deciding upon a surgical treatment method include the six-month period of anticoagulation that is required post stenting. If venous sinus stenting fails to halt vision loss, other surgical measures like CSF diversion and ONSF may not be an immediate option during this period of anti-coagulation, as an increased risk of intracranial and retrobulbar hemorrhages respectively will exist.

The prevalence of PTC is on the rise given the increase of obesity rates in the general population. It has been estimated that the yearly costs of PTC patients have exceeded $444 million in the United States alone. A recent study looked at the economic burden of CSF shunting procedures versus venous sinus stenting. The authors compared 86 adults who had undergone stenting procedures for PTC to 110 children who were shunted for hydrocephalus. There was no cost difference for the initial procedure for both shunts and stents. However, 87% of the stents placed had required just 1 stent procedure over the 12-year period compared with 45% of shunts that required just one procedure. The costs of stent revisions and treatment related to shunt infections made the shunting procedure approximately five times more costly overall. This is likely an important consideration in the current economic environment of medical practice.

**Conclusion**

Since the recognition of venous sinus stenosis in PTC patients, it has become evident that there is a role for venous sinus stenting in the management of these patients. Results of multiple series have shown good resolution of papilledema and symptomatic control that is comparable to other treatment modalities. All patients that have failed medical therapy PTC should undergo contrast-enhanced MRV or CTV to confirm the presence or persistence of any venous sinus stenosis that may be contributory to the high ICP. Venous sinus stenting then should be considered if the measured pressure gradient across the stenosis is significant.

**Conflict of interest**

The authors declared that there is no conflict of interest.

**References**

31. De Simone R, Marano E, Fiorillo C, et al. Sudden re-opening of
collapsed transverse sinuses and long-standing clinical remission after a
immediate resolution of venous sinus “obstruction” after reducing
35. Baryshnik DB, Farb RI. Changes in the appearance of venous sinuses after
36. Biousse V, Bruce BB, Newman NJ. Update on the pathophysiology
37. De Simone R, Ranieri A, Bonavita V. Advancement in idiopathic
38. Conner SE, Siddiqui MA, Stewart VR. The relationship of transverse
sinus stenosis to bony groove dimensions provides an insight into the
43. Riggeal BD, Bruce BB, Saindane AM, et al. Clinical course of
44. Zheng HB, Zhou M, Zhao B, et al. Pseudotumor cerebri syndrome and
idiopathic intracranial hypertension: clinical and radiological outcome
for idiopathic intracranial hypertension: a review of 52 patients and of
47. Bussiere M, Falero Rm Nicolle D, et al. Unilateral transverse sinus
outcomes following endovascular stenting for pseudotumour cerebri
50. Fields JD, Javedani PP, Falardeau J, et al. Dural venous sinus
for benign intracranial hypertension: clinical indications, technique, and
53. Puffer RC, Mustafa W, Lanzino G. Venous sinus stenting for idiopathic
57. Rajpal S, Niemann DB, Turk AS. Transverse venous sinus stent placement as treatment for benign intracranial hypertension in a
stenting in idiopathic intracranial hypertension with bilateral stenosis: a
presenting with ataxia and hyper-reflexia in a non-obese woman
60. Teleb MS, Czpie ME, Lazzaro MA, et al. Idiopathic intracranial
62. Friedman DI, Rausch EA. Headache diagnosis in patients with treated
63. Ahmed R, Friedman DI, Halmagyi GM. Stenting of the transverse
pseudotumour cerebri: a cost comparison with CSF shunting. AM J