

# THE PSEUDOTUMOR CEREBRI SYNDROME IN PREGNANCY

**Steven L. Galetta, MD**  
**Laura J. Balcer MD, MSCE**  
NYU School of Medicine  
New York, NY

The diagnosis of pseudotumor cerebri, or idiopathic intracranial hypertension (IIH), is established in the characteristic patient with evidence of papilledema, imaging that does not suggest a structural lesion, and a CSF examination that shows both normal composition and elevated intracranial pressure. The patient with IIH is typically a young woman who is above ideal body weight or obese, but the condition may also occur in obese men and in children, who are less likely to be obese than their adult counterparts. Recent studies have further refined the definition of IIH. First, a large study of children has redefined normal CSF opening pressure for children. In the obese or sedated child, an opening pressure of 280mm H<sub>2</sub>O has been suggested as the requirement to confidently claim that the intracranial pressure is increased. Otherwise, the diagnostic criteria for children and adults continue to rely on a CSF lumbar opening pressure of 250mm H<sub>2</sub>O or greater [1,2]. The diagnosis of IIH in pregnancy is the same as in the non-pregnant patient requiring MRI scanning and lumbar puncture.

The brain MRI scan may demonstrate changes suggesting the presence of increased intracranial pressure and can be used to support the diagnosis of IIH. These findings include an empty sella, flattening of the posterior globes, distention of the perioptic subarachnoid spaces and narrowing of the transverse venous sinuses [1]. The finding of venous sinus narrowing has generated a great debate as to whether this could be the etiology of IIH, and whether venous stenting might be part of the IIH treatment paradigm. Furthermore, it is unclear whether the venous stenosis is produced by increased intracranial pressure, is a primary factor in the genesis of the intracranial pressure, or could just be part of a vicious cycle. Nonetheless, the presence of these MRI findings alone can only suggest the diagnosis of intracranial hypertension even in the absence of a measured elevated CSF opening pressure.

Over the last several decades, it has become increasingly evident that some patients with idiopathic increased intracranial pressure may not manifest papilledema. This variability is likely due to anatomical differences and other factors affecting the optic nerve. The diagnosis of IIH can now be met even in the absence of papilledema if the patient has documented elevated CSF pressure, fits all of the typical clinical criteria, and has bilateral or unilateral sixth nerve palsy [1]. In patients without a sixth nerve palsy, the MRI criteria above may only provide supportive evidence for the diagnosis. Of course, it can be argued that a sixth nerve palsy may not be necessary as a diagnostic requirement in those patients with a typical headache syndrome and a documented elevated opening CSF pressure (with normal constituents). Not every patient with increased intracranial pressure has papilledema or a sixth nerve palsy, so like most criteria they may not apply to every patient encountered in practice. Patients may have elevated intracranial pressure before papilledema develops, while others will never develop papilledema despite such elevation.

Headache is the most frequent symptom of IIH and it is found in over 90% of patients [3]. Other common complaints include pulsatile tinnitus, transient visual obscurations (TVOs) and diplopia. Up to 86% develop vision loss; this is severe and blinding in 10% [4, 5]. The Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) is the first prospective study [6] providing an evidence-based medical strategy in IIH patients with mild visual loss [7]. The IIHTT also outlines baseline characteristics of newly diagnosed patients, and delineates the significant impact even mild visual loss has on QOL [7-9]. However, the data on managing those with more severe visual loss remains lacking, and there are no controlled trials guiding use of surgical and endovascular options for progressive vision loss [10]. The management of IIH as described below is adapted from the recent paper of Hainline et al [28].

Acetazolamide, a carbonic anhydrase inhibitor that reduces CSF production and lowers ICP was shown to improve mild visual function in IIH [11]. In the IIHTT, patients with mild visual loss were randomized to acetazolamide or placebo. Both groups received a supervised low sodium weight-loss diet and exercise program. Of 165 participants who met criteria, only 4 were men supporting the notion that endocrine factors are involved in the pathogenesis of IIH [11].

In the IIHTT, the difference in visual function by visual field PMD (the primary outcome) between groups was less than anticipated. A pilot study conducted prior to the IIHTT anticipated a PMD treatment difference of 1.3 dB [7]. However, the PMD difference between the acetazolamide and placebo groups was 0.71 dB favoring the acetazolamide arm. [6]. Acetazolamide treatment had a pronounced effect in decreasing papilledema grade in patients with advanced papilledema (grade 3-5) and was associated with improved QOL scores.

Most neuro-ophthalmologists prescribe acetazolamide at 1 to 2 grams (g) daily for IIH [7], yet the IIHTT used doses up to 4g daily. This dose may be required to achieve the desired inhibitory effect on CSF production [7] with relatively few adverse events [6]. Indeed, in the IIHTT the withdrawal rate was the same in both groups. Symptoms of paresthesias, fatigue and dysgeusia were significantly higher in the acetazolamide group. Weight loss was doubled (3.45 kg vs. 7.5 kg) in patients who received acetazolamide, which itself may lead to reduced papilledema. However, further analysis found this weight reduction was independent of the effect of acetazolamide on visual function [6]. In summary, the IIHTT found benefit to use of high dose acetazolamide for treatment of IIH with mild visual loss, but did study patients with more severe visual loss associated with IIH.

There are no controlled trials comparing surgical procedures for treatment of IIH-related severe, progressive visual loss [10]. Some patients with IIH may fail maximal medical therapy and surgical intervention may be the only option to save vision [10]. The most widely used surgical procedures are optic nerve sheath fenestration (ONSF) for significant visual loss, and ventriculoperitoneal or lumboperitoneal shunting for intractable headache with or without visual loss [12]. However, each procedure has its limitations. ONSF carries a risk of optic nerve injury and has limited role as a primary treatment for headache in IIH [3]. Shunts frequently require revision and the revision rates may be as high as 75% at 2 years [13,14]. Shunt failure may result in rapid vision loss associated with an acute rise in ICP [15]. Although shunting is often used to treat headache in IIH, its long-term efficacy remains unproven [3].

MR venography demonstrates that the majority of IIH patients have venous sinus stenosis [16]. It is unclear if such stenosis is the cause or consequence of IIH, although demonstrated resolution of collapsible venous sinus segments after CSF drainage and pressure normalization have suggested that the latter is true (Figure 1) [17,18]. Cerebral venous sinus narrowing usually develops at the transverse sinuses or transverse/sigmoid junction, and may be bilateral or unilateral [19]. If consequential, sinus stenosis might worsen IIH by further hindering the removal of CSF [3]. Modeling studies have hypothesized that when a significant pressure gradient is present, stenting should relieve ICP elevation and improve venous resorption [19].

Higgins et al. [20] first reported a case of venous sinus stenting with successful reversal of symptoms, elevated ICP and bilateral papilledema. In the largest cohort of 52 patients who underwent unilateral cerebral venous sinus stenting, all had resolution of papilledema, 23 of 30 had resolution of visual field loss, and headache persisted in only three [21]. Some authors have suggested routine pressure gradient measurements with catheter venography in all IIH patients, with stent treatment if stenosis is hemodynamically significant [22]. However, investigators have found no correlation between the degree of cerebral venous sinus stenosis and prognosis, visual loss or opening pressure; this casts doubt on routine, invasive testing and surgical intervention [23]. Stenting has potentially serious complications, including subdural or intracerebral hemorrhage, venous sinus perforation, stent migration, and in-stent thrombosis [24]. Re-stenting rates are relatively low [21]. Stenting is followed by anti-coagulation, which can complicate secondary management if unsuccessful [25]. Both dual anti-platelet therapy and warfarin have been used, which can increase the risk of intracranial and retrobulbar hemorrhage with shunting and ONSF, respectively [25]. While promising, cerebral venous stenting has unclear long-term implications.

Overall, the management of IIH in the pregnancy is similar to those patients who are not pregnant [26,27]. One reported case of a teratoma in pregnancy associated with acetazolamide has limited its use particularly in the first trimester. However, recent large studies of pregnancy and acetazolamide have not found any association with teratoma [26,27]. Many neuro-ophthalmologists now use this medication to limit visual loss in pregnancy but it is always wise to clear it with patient's obstetrician doctor. LP shunting and optic nerve fenestration have also been employed in patients who are pregnant with severe visual loss.

## References

1. Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. *Neurology* 2013, in press.
2. Avery RA, Shah SS, Licht DJ, et al. Reference range for cerebrospinal fluid opening pressure in children. *N Engl J Med* 2010;363:891-893.
3. Mallery RM, Friedman DI, Liu GT. Headache and the pseudotumor cerebri syndrome. *Curr Pain Headache Rep* 2014;18:446.

4. OCT Sub-Study Committee for NORDIC Idiopathic Intracranial Hypertension Study Group, Auginer P, Durbin, Feldon S, et al. Baseline OCT measurements in the idiopathic Hypertension treatment trial, part 1: quality control, comparisons, and variability. *Invest Ophthalmol Vis Sci* 2014;55:8180-8188.
5. Wall M, George D. Idiopathic intracranial hypertension. A prospective study of 50 patients. *Brain* 1991;114:155-180.
6. The NORDIC Idiopathic Intracranial Hypertension Study Group Writing Committee. Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss: the Idiopathic Intracranial Hypertension Treatment Trial. *JAMA* 2014; 311:1641-1651.
7. Friedman DI, McDermott M, Kiebertz K, et al. The Idiopathic Intracranial Hypertension Treatment Trial: Design Considerations and Methods. *J Neuro-Ophthalmol* 2014;34:107-117.
8. Wall M, Kupersmith MJ, Kiebertz KD, et al. The idiopathic intracranial hypertension treatment trial: clinical profile at baseline. *JAMA Neurol* 2014;71:693-701.
9. Quality of life in idiopathic intracranial hypertension at diagnosis: IIH Treatment Trial results. *Neurology* 2015;84:2449-2456.
10. Spitze A, Malik A, Lee AG. Surgical and endovascular interventions in idiopathic intracranial hypertension. *Curr Opin Neurol* 2014;27:69-74.
11. Horton JC. Acetazolamide for pseudotumor cerebri: evidence from the NORDIC trial. *JAMA* 2014;311:1618-1619.
12. Galetta SL, Balcer, LJ. All choked up about the pseudotumor cerebri syndrome. *Neurology* 2013;81:1112-1113.
13. McGirt MJ, Wodworth G, Thomas G, et al. Cerebrospinal fluid shunt placement for pseudotumor cerebri-associated intractable headache: predictors of treatment response and an analysis of long-term outcomes. *J Neurosurg* 2004;101:627-632.
14. Elder DE, Goodwin CR, Kosztowski TA, et al. Venous sinus stenting is a valuable treatment for fulminant intracranial hypertension. *J Clin Neurosci* 2014;22:685-689.
15. Rizzo JL, Lam KV, Wall M, et al. Perimetry, retinal nerve fiber layer thickness and papilledema after cerebrospinal fluid shunting in patients with idiopathic intracranial hypertension. *J Neuro-Ophthalmol* 2015;35:22-25.
16. Farb RI, Vanek I, Scott JN, et al. Idiopathic intracranial hypertension: the prevalence and morphology of sinovenous stenosis. *Neurology* 2003;60:1418-1424.
17. Rohr A, Dörner L, Stingele R et al. Reversibility of venous sinus obstruction in idiopathic intracranial hypertension. *Am J Neuroradiol* 2007;28: 656-659.
18. King JO, Mitchell PJ, Thomson KR, et al. Manometry combined with cervical puncture in idiopathic intracranial hypertension. *Neurology* 2002;58:26-30.
19. Kanagalingam S, Subramanian PS. Cerebral venous sinus stenting for pseudotumor cerebri: a review. *Saudi J Ophthalmol* 2015;29:3-8.
20. Higgins JN, Owler BK, Cousins C, et al. Venous sinus stenting for refractory benign intracranial hypertension. *Lancet* 2002;359:228-320.
21. Ahmed RM, Wilkinson M, Parker GD, et al. Transverse sinus stenting for idiopathic intracranial hypertension: a review of 52 patients and of model predictions. *AJNR Am J Neuroradiol* 2011;32:1408-1414.
22. Kumpe DA, Bennett JL, Seinfeld J, et al. Dural sinus stent placement for idiopathic intracranial hypertension. *J Neurosurg* 2012;116:538-548.
23. Riggeal BD, Bruce BB, Saindane AM, et al. Clinical course of idiopathic intracranial hypertension with transverse sinus stenosis. *Neurology* 2013;80:289-295.
24. Dave SB, Subramanian PS. Pseudotumor cerebri: an update on treatment options. *Indian J Ophthalmol* 2014;62:996-998.
25. Goodwin CR, Elder BD, Ward A, et al. Risk factors for failed transverse sinus stenting in pseudotumor cerebri patients. *Clin Neurol Neurosurg* 2014;127:75-78.
26. Kesler A, Kupfermanc M. Idiopathic intracranial hypertension and pregnancy. *Clin Obstet Gynecol* 2013;56:389-395.
27. Falardeau J, Lobb BM, Golden S, Maxfield SD, Tanne E. The use of acetazolamide during pregnancy in intracranial hypertension patients. *J Neuro-Ophthalmol* 2013;33:9-12.
28. Hainline C, Rucker JC, Balcer LJ. Current concepts in pseudotumor cerebri. *Curr Opin Neurol* 2016;29:84-93.