Perspective: Update on Idiopathic Intracranial Hypertension

Beau B. Bruce, MD, MS1,2, Valérie Biousse, MD1,2, and Nancy J. Newman, MD1,2,3
1 Department of Ophthalmology, Emory University, Atlanta, GA 30322
2 Department of Neurology, Emory University, Atlanta, GA 30322
3 Department of Neurological Surgery, Emory University, Atlanta, GA 30322

Abstract

Purpose—Provide an update on various features of idiopathic intracranial hypertension.

Design—Perspective.

Methods—Selected articles on the epidemiology, clinical and imaging features, natural history, pathophysiology, and treatment of idiopathic intracranial hypertension were reviewed and interpreted in the context of the authors’ clinical and research experience.

Results—Idiopathic intracranial hypertension is primarily a disease of obese women of childbearing age, but it can affect patients of any weight, sex, and age. Although a relatively rare disorder, idiopathic intracranial hypertension’s associated costs in the U.S. entail hundreds of millions of dollars. Even following treatment, headaches are frequently persistent and may require the continued involvement of a neurologist. Quality of life reductions and depression are common among idiopathic intracranial hypertension patients. However, visual dysfunction, especially visual field abnormalities, represents the major morbidity of this disorder, and serial automated perimetry remains the primary mode of patient monitoring. Patients who are men, black, very obese, or anemic are at higher risk of visual loss. Vitamin A metabolism, adipose tissue as an actively secreting endocrine tissue, and cerebral venous abnormalities are areas of active study regarding idiopathic intracranial hypertension’s pathophysiology. Treatment studies show that lumbar puncture is a valuable treatment (in addition to its crucial diagnostic role) and that weight management is critical. However, open questions remain regarding the efficacy of acetazolamide, CSF diversion procedures, and cerebral venous stenting.

Conclusions—Many questions remain unanswered about idiopathic intracranial hypertension. Ongoing studies, especially an ongoing NIH-funded clinical trial of acetazolamide, should provide more insight into this important, yet poorly understood syndrome of isolated intracranial hypertension.
Keywords
Idiopathic Intracranial Hypertension; Venous Sinus Stenosis; Ventriculoperitoneal Shunting; Lumboperitoneal Shunting; Optic Nerve Sheath Fenestration; Venous Sinus Stenting

Introduction
Idiopathic intracranial hypertension is a syndrome characterized by increased intracranial pressure of unknown cause (Table 1). By definition, idiopathic intracranial hypertension encompasses patients with isolated raised intracranial pressure that is not related to an intracranial process, cerebral venous thrombosis, or a meningeal process. Additionally, patients who develop a syndrome of raised intracranial pressure secondary to certain medications or who are found to have cerebral venous sinus stenoses (not thrombosis) are still conventionally classified as having idiopathic intracranial hypertension. Therefore, although not always literal, the term “idiopathic intracranial hypertension” is currently the preferred designation for this disorder in the English literature, rather than “pseudotumor cerebri” (often including patients with other causes of raised intracranial pressure) and “benign intracranial hypertension” (erroneously reassuring, considering that a substantial proportion of idiopathic intracranial hypertension patients irreversibly lose vision). Many questions remain open in the field of idiopathic intracranial hypertension, and this perspective emphasizes recent studies regarding the epidemiology, clinical and imaging features, pathophysiology, and treatment of idiopathic intracranial hypertension.

Epidemiology
Idiopathic intracranial hypertension occurs most frequently among obese women of childbearing age. A recent multicenter case-control study of newly-diagnosed women with idiopathic intracranial hypertension compared to women with other neuro-ophthalmologic disorders, showed a dose relationship of higher body mass index (BMI) associated with a greater risk of idiopathic intracranial hypertension. Interestingly, this study also showed that even non-obese patients were at greater risk for idiopathic intracranial hypertension if they had a recent moderate weight gain (5–15%).

Despite a high predilection for obese young women, idiopathic intracranial hypertension can occur in children, older adults, and in non-obese persons of either sex. This disorder is rare in pre-pubertal children, with characteristics distinct from the adult form, including no apparent predilection for obese girls. After puberty, however, the rate of obesity and the gender predilection is similar to that in the adult idiopathic intracranial hypertension population. A recent large series confirmed that only about 10% of idiopathic intracranial hypertension patients are men. While affected men have a similar BMI when compared to affected women, they are, on average, about a decade older than women at the time of presentation. Although race does not seem to influence the incidence of idiopathic intracranial hypertension, a recent study questioned whether the association between obesity and development of idiopathic intracranial hypertension among Asians is as robust as in other populations.

Idiopathic intracranial hypertension has also been associated with other factors, such as a certain medications, anemia, and untreated obstructive sleep apnea. However, most of the evidence is largely anecdotal, and studies evaluating the relationship between obstructive sleep apnea and idiopathic intracranial hypertension are still ongoing.
It was recently suggested that the economic costs of idiopathic intracranial hypertension in the United States exceed $444 million dollars per year, mostly because of frequent hospital admissions, unsatisfactory treatment options, and lost productivity of young patients.\textsuperscript{9} The rising incidence of obesity in the world will likely increase the prevalence of idiopathic intracranial hypertension, resulting in further idiopathic intracranial hypertension-related expenses.

**Clinical features**

Idiopathic intracranial hypertension typically presents with symptoms and signs of raised intracranial pressure. Headache, the most common symptom at presentation, is less likely to be reported by men than by women.\textsuperscript{5} Many idiopathic intracranial hypertension patients suffer from persistent headaches,\textsuperscript{10} even after normalization of the intracranial pressure, and frequently require the continued involvement of a neurologist for adequate treatment. Patients with idiopathic intracranial hypertension also experience depression, anxiety, and reduced quality of life. These reductions of quality of life are more than would be expected based on the patients’ persistent headaches and co-morbid obesity.\textsuperscript{2, 10} Ophthalmologists should be attuned to these issues and seek appropriate consultations in idiopathic intracranial hypertension patients who have chronic complaints.

Papilledema is the most common sign of idiopathic intracranial hypertension. It is indeed not uncommon to diagnose idiopathic intracranial hypertension after papilledema is detected on a routine eye examination on asymptomatic patients, explaining why ophthalmologists often first diagnose this disease. This is particularly common in men who often do not complain of headaches.\textsuperscript{5} Papilledema can result in insidious and slowly progressive visual loss, which is usually reversible with appropriate treatment. However, up to 25\% of idiopathic intracranial hypertension patients develop secondary optic atrophy and associated permanent visual loss.\textsuperscript{11}

Visual loss is usually relatively mild at presentation but progresses insidiously. In fact, most patients have visual field defects on automated perimetry at presentation, but are unaware of their visual dysfunction. Visual field abnormalities typically progress from enlargement of the physiologic blind spot, to nasal and arcuate defects, and ultimately to severe visual field constriction. All idiopathic intracranial hypertension patients must be monitored carefully with formal automated perimetry, with more aggressive intervention taken whenever deterioration of visual fields is documented.

Several demographic risk factors for visual loss in idiopathic intracranial hypertension have been identified. In one recent study, black patients with idiopathic intracranial hypertension were 3 times more likely than non-black patients to have severe visual loss in at least one eye and were nearly 5 times more likely to be blind in both eyes.\textsuperscript{12} This difference in visual prognosis was likely unrelated to racial differences in diagnosis, treatment, or access to care. Black patients with idiopathic intracranial hypertension appear to have a more aggressive disease and, therefore, need closer follow-up and a lower threshold for early aggressive intervention. A second study from the same patient database showed that men were more likely to have worse visual acuity and visual fields at presentation and follow-up, and were less likely to report headaches than women,\textsuperscript{5} with the odds of severe visual loss for men at least double those of women. Thus, men also likely need more aggressive intervention when visual loss ensues, and closer follow-up given their lower propensity for headache.\textsuperscript{5} The same investigators also found that increasing degrees of obesity are associated with an increasing risk of severe visual loss (Szewka AJ, personal communication, 2011), but that while idiopathic intracranial hypertension patients with a normal body mass index or who were over the age of 50 were only a small proportion of patients with idiopathic intracranial...
hypertension (<5% each of all idiopathic intracranial hypertension patients at the study’s tertiary referral centers), these patients tended to have better visual outcomes than the more typical idiopathic intracranial hypertension patient.3

Rarely, patients with idiopathic intracranial hypertension may have an acute onset of symptoms and signs of raised intracranial pressure (so-called “fulminant” or “malignant” idiopathic intracranial hypertension), with rapid worsening of visual loss over a few days, but meet the criteria for idiopathic intracranial hypertension with normal brain MRI and venography.13 In a study of 16 such “fulminant idiopathic intracranial hypertension” cases, immediate surgical treatment was required because of ongoing severe visual loss in all patients; 50% remained legally blind and the visual fields remained severely impaired in all cases. Prompt recognition and early aggressive treatment of patients with fulminant idiopathic intracranial hypertension is therefore essential.13

Occasionally, non-physiologic visual field constriction occurs in patients who have coexisting organic visual loss from papilledema,14 making management decisions difficult. Additionally, it is common to observe non-specific visual field depression and constriction related to poor test reliability on automated perimetry obtained in idiopathic intracranial hypertension patients who have headaches and feel poorly. Patients with visual loss from raised intracranial pressure should have obvious papilledema, unless they have already developed severe secondary optic atrophy. In patients with raised intracranial pressure without papilledema, another cause of visual loss or non-organic visual loss should be considered. Visual loss secondary to raised intracranial pressure in the setting of no visible papilledema has been reported, but remains exceedingly rare and its existence hotly debated.15

The role of optical coherence tomography (OCT) in the evaluation of papilledema remains unclear. A few studies have proposed an adjunctive utility of optic nerve imaging by OCT in differentiating pseudopapilledema from papilledema and in monitoring the thickness of the peripapillary retinal nerve fiber layer during the course of idiopathic intracranial hypertension.16 However, the reductions in the retinal nerve fiber layer observed as disc edema resolves may not be easily differentiated from axonal loss reflecting disease progression rather than improvement. At this time, quantification of visual function by ophthalmic examination and automated perimetry remains much more helpful than anatomical characterization of the optic nerve with OCT in the monitoring of patients with idiopathic intracranial hypertension.

Although brain imaging must be “normal” in order to diagnose idiopathic intracranial hypertension,1 imaging changes associated with raised intracranial pressure are commonly observed in idiopathic intracranial hypertension patients. These include an empty sella or flattening of the pituitary gland, tight subarachnoid spaces, flattening of the posterior globes, protrusion of the optic nerve heads, enhancement of the prelaminar portion of the optic nerve heads, distension of the optic nerve sheaths, and vertical tortuosity of the optic nerves.17 Although cerebral venous thrombosis must be ruled-out in patients with suspected idiopathic intracranial hypertension,18 numerous studies from the last decade have shown that unilateral stenosis of the dominant transverse sinus or bilateral stenoses of the transverse sinuses, often with measurable hemodynamic gradients, are common in typical idiopathic intracranial hypertension patients (see below).19

Pathophysiology

The pathophysiologic mechanisms underlying the raised intracranial pressure in idiopathic intracranial hypertension remain unclear, but those proposed classically include increased brain water content, excess CSF production, reduced CSF absorption, and increased cerebral
venous pressure. More recently, connections between the CSF space and nasal lymphatics have been demonstrated, and it has been suggested that these pathways may play a role in the development of idiopathic intracranial hypertension.\textsuperscript{20} Regardless of the final mechanism or combination of mechanisms resulting in increased intracranial pressure in these patients, any pathophysiologic theory must ultimately account for the remarkable predilection idiopathic intracranial hypertension has for obese, young women. Indeed, a role for sex hormones in the pathogenesis of idiopathic intracranial hypertension is suspected given the disorder’s preferential occurrence among post-pubertal, pre-menopausal women,\textsuperscript{5} and the absence of a gender preference before puberty.\textsuperscript{4}

One long-standing hypothesis for the pathogenesis of idiopathic intracranial hypertension involves abnormal vitamin A metabolism. While early studies had found conflicting evidence for the role of vitamin A based on serum levels,\textsuperscript{21} two recent studies have shown that the retinol level is elevated in the CSF of patients with idiopathic intracranial hypertension.\textsuperscript{22, 23} One of these studies also demonstrated that patients with idiopathic intracranial hypertension have higher levels of serum, but lower levels of CSF, retinol binding protein.\textsuperscript{23}

These observations regarding vitamin A may be linked to another area of emerging interest in endocrinology and idiopathic intracranial hypertension,\textsuperscript{24} the nature of adipose tissue as an actively secreting endocrine tissue.\textsuperscript{25} In particular, adipose tissue-derived retinol binding protein is released from adipose tissue and acts as a modulator of insulin sensitivity.\textsuperscript{21} Other adipose-produced cytokines, such as leptin, have been implicated in the pathophysiology of idiopathic intracranial hypertension but their role remains unclear.\textsuperscript{24} Because the hormonal secretions and biological functions of adipose tissue are highly dependent on its regional distribution in the body,\textsuperscript{25} fat distribution may ultimately be as important as total adiposity in the pathogenesis of idiopathic intracranial hypertension.\textsuperscript{26} For example, one study suggested that obese women with idiopathic intracranial hypertension may have a preferential accumulation of fat in the lower body relative to obese women in the same age range without idiopathic intracranial hypertension.\textsuperscript{27} However, this finding is somewhat surprising given that idiopathic intracranial hypertension has been potentially associated with conditions related to increased intra-abdominal, visceral fat, such as elevated levels of adipose tissue-derived retinol binding protein,\textsuperscript{21} polycystic ovarian disease in women,\textsuperscript{28} and androgen deficiency in men.\textsuperscript{26}

Increased intracranial venous pressure related to stenosis of the cerebral venous sinuses is another proposed causal mechanism of idiopathic intracranial hypertension that has received substantial recent interest.\textsuperscript{19} Since CSF exits the cranium passively via the arachnoid granulations into the intracranial venous sinuses, a downstream stenosis of a dominant transverse sinus or stenoses of both transverse sinuses can impair venous outflow, resulting in cerebral venous hypertension and impaired CSF absorption. While there is little doubt that these venous stenoses exist, what is less clear is whether they are incidental, secondary to increased intracranial pressure, or causal. Some anatomic studies have suggested that these stenoses might be incidentally related to the presence of trabeculae, septae, or large arachnoid granulations in the transverse sinuses.\textsuperscript{29} In addition, transverse venous sinus stenoses are also incidentally found in patients without intracranial hypertension, suggesting that they may have no functional significance in some patients. Others have proposed that the distal portion of the transverse venous sinuses can become narrowed by external compression from increased intracranial pressure, a hypothesis supported by resolution of some of these stenoses following lumbar or cervical puncture or CSF shunt placement.\textsuperscript{30} Such external compression of the sinuses likely leads to a positive feedback loop of increased venous pressure leading to impaired CSF absorption, leading to further increases
in intracranial pressure, which further compresses the venous sinuses until an equilibrium is established.

Beyond frank thrombosis and sinus stenosis, there is yet another venous mechanism proposed in the development of increased intracranial pressure, namely microthrombosis within the cerebral vasculature from thrombophilia, resulting in increased cerebral venous pressure and impaired CSF absorption.31 While many would argue that the presence of any thrombophilia would make these cases ineligible for the diagnosis of idiopathic intracranial hypertension, the strength of the associations between underlying systemic hypercoagulable disorders and so-called idiopathic intracranial hypertension in these studies is disturbing. Currently, we do not obtain routine systemic hypercoagulation studies in presumed idiopathic intracranial hypertension patients unless there is a personal or family history of systemic thrombosis.

Various medications have been proposed to cause or precipitate idiopathic intracranial hypertension (such as tetracycline and its derivatives, cyclosporine, lithium, nalidixic acid, nitrofurantoin, oral contraceptives, levonorgestrel, danaxol, and tamoxifen), there is compelling data only in a few cases. It is appropriate to discontinue potentially associated medications, particularly those in which an association is very likely, such as tetracyclines.11 However, it is likely that others, such as oral contraceptives, have been implicated only by their association with the young women most at risk for idiopathic intracranial hypertension.

Studies evaluating the relationship between obstructive sleep apnea and idiopathic intracranial hypertension are ongoing; ultimately these studies may show that obesity is the only pathophysiological link between the two disorders, or that coexisting obstructive sleep apnea may worsen the prognosis for idiopathic intracranial hypertension patients.5, 12, 26 We routinely screen our idiopathic intracranial hypertension patients with the Berlin questionnaire for sleep apnea and refer our patients for overnight polysomnography when the clinical suspicion for obstructive sleep apnea is high.32

**Management**

The management of idiopathic intracranial hypertension patients depends on the course of idiopathic intracranial hypertension, which is highly variable. Most idiopathic intracranial hypertension patients do well with only one lumbar puncture (performed as part of the diagnostic evaluation) and medical management, including weight loss. When idiopathic intracranial hypertension is associated with an identified possible triggering factor, such as a specific medication, anemia, or untreated obstructive sleep apnea, discontinuation of the offending medication or treatment of the triggering factor often results in rapid improvement.

The two goals of treatment in idiopathic intracranial hypertension are to preserve vision and to alleviate bothersome symptoms of increased intracranial pressure, particularly headaches. The treatment of raised intracranial pressure itself begins with the diagnostic lumbar puncture. The opening pressure should be measured in the relaxed, lateral decubitus position without sedation to avoid spurious elevations in intracranial pressure. The lumbar puncture is often effective in transiently improving symptoms and signs. Interestingly, it is not uncommon to observe a lasting clinical remission following a single lumbar puncture in some idiopathic intracranial hypertension patients,33 obviating the need for further medical or surgical treatment. Mathematical models explain this phenomenon by the interaction of various factors, such as CSF formation, compliance, cerebral blood flow, and outflow resistance, which can lead to multiple stable and unstable equilibrium levels of intracranial pressure in idiopathic intracranial hypertension.19 If a single lumbar puncture lowers the CSF pressure beyond the threshold level of an unstable equilibrium, the intracranial pressure
may settle into a lower stable pressure state until other factors cause the pressure to exceed that threshold. These recent observations emphasize the importance of the lumbar puncture as a therapeutic procedure in idiopathic intracranial hypertension in addition to its diagnostic importance.

Patients with persistent symptoms and signs can be treated using medical and surgical approaches, although there are no results from full-scale randomized controlled trials prospectively assessing and comparing these treatments. Weight loss is a critical part of the treatment of overweight and obese idiopathic intracranial hypertension patients. Only a modest degree of weight loss (about 5–10% of total body weight) is usually required for improvement in symptoms and signs. A recent study of 25 obese women with idiopathic intracranial hypertension showed that weight loss effectively reduces not only headaches and papilledema, but also intracranial pressure. However, weight loss is often not an effective short-term treatment and, thus, other treatments must be initiated in parallel for most patients. Bariatric surgery can be considered in morbidly obese idiopathic intracranial hypertension patients in whom attempts at weight loss have been unsuccessful or in whom other medical morbidities of obesity already coexist.

Carbonic anhydrase inhibitors, such as acetazolamide (1–2 g daily, divided two to three times daily), are the main medical treatment prescribed for idiopathic intracranial hypertension, although no trial data are currently available to confirm their effectiveness. The preliminary results of the idiopathic intracranial hypertension Pilot Trial from Birmingham, UK, in which 50 patients were randomized to receive acetazolamide or no acetazolamide, emphasized the practical difficulties of performing such a study because of poor recruitment and medication side-effects (paresthesias, altered taste sensation, and lethargy). However, beginning in 2009, the National Eye Institute of the National Institute of Health has sponsored the Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) to proceed with a multicenter, double-blind, placebo-controlled clinical trial, called the IIHTT (the Idiopathic Intracranial Hypertension Treatment Trial), comparing the efficacy of acetazolamide and placebo in the treatment of idiopathic intracranial hypertension patients with moderate visual field defects. All patients are also treated with a low-sodium diet and participate in a standardized weight loss program (http://www.nordicclinicaltrials.com/).

Steroids have been used as a treatment for idiopathic intracranial hypertension in the past, but are associated with significant long-term side effects, such as weight gain (obviously undesirable in this patient population), and therefore should not be prescribed. High-dose intravenous steroids are still occasionally used in patients with rapidly progressive visual loss from fulminant idiopathic intracranial hypertension while a more definitive treatment is organized.

Surgery is required in patients with a fulminant onset of disease or when other treatments have failed to prevent progressive visual loss. The choice of procedure depends on local resources, as well as the patient’s symptoms and signs. In patients with papilledema who have severe visual loss, but minimal or no headache, optic nerve sheath fenestration (ONSF) is often advised, while in those with visual loss, papilledema, and headache, a CSF diversion procedure, such as ventriculo- or lumbo-peritoneal shunting, is preferred. Aggressive management with CSF shunting is usually required to prevent catastrophic visual loss in those with acute and rapidly progressive visual loss. These patients might benefit from a transient lumbar drain while awaiting a more definite surgical procedure.

Studies have shown that stenting of transverse venous sinus stenoses reduces cerebral venous pressure, reduces intracranial pressure, and improves symptoms and signs in selected
idiopathic intracranial hypertension patients. However, as discussed above, it remains unclear whether treating these stenoses is aimed at a primary pathophysiologic process or merely a secondary phenomenon. Regardless, endovascular venous sinus stenting can result in serious complications, such as stent migration, venous sinus perforation, in-stent thrombosis, subdural hemorrhage, and the development of recurrent stenoses immediately proximal to the stent. Because prospective controlled studies are lacking and the indications for this treatment remain poorly defined, we do not recommend this procedure in routine clinical practice.

Conclusion

Many questions remain unanswered about idiopathic intracranial hypertension. Its association with female gender and obesity is striking. However, recent large studies indicate that idiopathic intracranial hypertension can also occur in men, non-obese adults, older adults, and in pre-pubertal children. Identification of subgroups at high risk for irreversible visual loss, such as black patients, men, and patients with fulminant idiopathic intracranial hypertension, helps determine management approaches and refine follow-up strategies. Ongoing studies, as well as a recently begun NIH-funded clinical trial, are promising and should provide more insight into this important, yet poorly understood syndrome of isolated intracranial hypertension.

Acknowledgments

Funding/Support: This study was supported in part by a departmental grant (Department of Ophthalmology) from Research to Prevent Blindness, Inc., New York, by core grant P30-EY06360 (Department of Ophthalmology). Dr. Bruce receives research support from the NIH/PHS (KL2-RR025009, UL1-RR025008), NIH/NEI (K23-EY019341), and the Knights Templar Eye Foundation; and received the American Academy of Neurology Practice Research Fellowship. Dr. Biousse receives research support from NIH/PHS (UL1-RR025008). Dr. Newman is a recipient of the Research to Prevent Blindness Lew R. Wasserman Merit Award.

Other Acknowledgements: None.

References


Figure 1. Magnetic resonance imaging findings in IIH
(Top left) Empty sella (star) on sagittal T1-weighted imaging. (Top right) Dilated optic nerve sheaths (arrowheads) and posterior globe flattening (arrowheads) on axial T2-weighted imaging. (Bottom) Bilateral transverse cerebral venous stenosis, right greater than left (arrowheads), as seen on coronal (Bottom left) and sagittal (Bottom right) contrast-enhanced magnetic resonance venography.
Table 1
Modified Dandy Criteria for Idiopathic Intracranial Hypertension

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Signs and symptoms of increased intracranial pressure (headaches, nausea, vomiting, transient obscurations of vision, papilledema).</td>
</tr>
<tr>
<td>2</td>
<td>No localizing, focal neurologic signs, except unilateral or bilateral VI nerve paresis.</td>
</tr>
<tr>
<td>3</td>
<td>CSF opening pressure $\geq$ 25 cm, but without cytologic or chemical abnormalities.</td>
</tr>
<tr>
<td>4</td>
<td>Normal neuro-imaging adequate to exclude cerebral venous thrombosis, i.e., magnetic resonance imaging of the brain, often with</td>
</tr>
<tr>
<td></td>
<td>additional sequences (computed tomography or magnetic resonance venography).</td>
</tr>
</tbody>
</table>