

Idiopathic Intracranial Hypertension

Important Questions Answered With More to Come

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There have been nearly 100 articles written per year over the last 30 years about idiopathic intracranial hypertension (IIH).¹ Despite these reports, many questions remain concerning IIH



Related article

including a need for better understanding of the etiology and risk factors for disease development, the concern that a single measurement may not reflect the dynamic and variable nature of intracranial pressure, a lack of uniform agreement concerning medical management with diuretics, and finally a continued lack of uniform guidelines concerning the necessity and timing of surgical intervention (shunt vs optic nerve sheath decompression). Unfortunately, despite all of our best efforts, many patients ultimately lose significant amounts of vision. Additionally, in some patients, there continues to be difficulty distinguishing papilledema from pseudopapilledema.

The current issue of *JAMA Neurology* contains preliminary results of the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT).² The IIHTT is a multicenter, randomized, double-blinded, placebo-controlled study of weight reduction and low-sodium diet coupled with acetazolamide vs placebo in patients with IIH and mild vision loss. The current article reports on patient characteristics and examination findings in patients with IIH and mild vision loss. Through their systematic collection of data, the IIHTT investigators will study the role of obesity and vitamin A in the etiology of IIH, characterize the myriad of signs and symptoms that occur in these patients, and determine the effects of this disorder on quality of life. They will evaluate the results of visual field testing at presentation and over time. Ultimately, they will determine the true effects of optimal noninvasive treatments (diet and diuretics) and carefully determine the role of ocular coherence tomography (OCT) in the identification and follow-up of patients with papillema. The article highlights patient characteristics and symptoms and the reader is encouraged to carefully consider this informative report; the importance of the anticipated, as well as unanticipated, findings; and what might be expected to come from this trial over time. The trial is the work of NORDIC (Neuro-Ophthalmology Research Disease Investigator Consortium),³ a group of investigators who have come together as a powerful research consortium for this and other clinical trials—now and in the future.

The typical patient with IIH, a condition that affects 20 in 100 000 obese young adult women,⁴ is generally easily recognized and accurately diagnosed. In addition, general guidelines exist to inform management with weight loss and diuret-

ics and the critical role of serial visual field testing in following up these patients. Despite these guidelines, 10% of patients end up effectively blind in 1 eye.^{5,6} A recent Cochrane Database review reminds us that there had been no prospective, large, multicenter, double-blind, placebo-controlled trials studying this disorder.⁷ Our knowledge concerning the etiology, signs and symptoms, and management of this condition is largely based on retrospective series and anecdotal reports. To my knowledge, 4 studies to date have looked at patients prospectively,^{5,8-10} with only 1 attempting a prospective treatment trial.⁸ In this feasibility study, 50 patients were enrolled and acetazolamide was compared with no treatment, although no strict randomization was done based on vision loss criteria. The study reported challenges with patient enrollment and recommended that, in future trials, a composite score based on both visual fields and optic disc photographs be used to compare treatment groups.⁸ The IIHTT is long overdue.

This initial publication from the IIHTT Study Group² reports on a large prospective cohort of untreated patients with IIH in an effort to characterize the disease and associated symptoms and examination findings. With participants strictly meeting the modified Dandy criteria for the diagnosis of IIH and being recruited from 38 different sites across the country, this study certainly represents the largest group of patients with this condition that has ever been studied with such strict screening and enrollment criteria. Because the cohort of patients being studied has been enrolled in a treatment trial for patients with mild vision loss, the patients described in this report are necessarily skewed toward those who have less severe disease. In fact, somewhat surprising was the rate of non-enrollment in the study, which included a significant number of patients whose visual field loss was outside of the range of eligibility, clearly indicating that future studies must be directed at patients with more severe disease. The authors pointed out the striking female preponderance of their study group. Only 4 of the 165 patients were men, causing the authors to question whether this condition really exists in men and continue their search for a risk factor or disease etiology that is unique to women. Typical findings that were expected, of course, were the patients being young adults and the vast majority being obese, with an average body mass index (calculated as weight in kilograms divided by height in meters squared) of approximately 40. As expected, the most common symptoms were headache, transient visual obscurations, and pulsatile tinnitus. A somewhat unexpected finding was the high prevalence of back pain (53%), a symptom that may have been previously underreported or dismissed.

As expected, patients (68%) commonly reported transient visual obscurations, with the median number of episodes being 1 per day. Despite the strict criteria for only mild visual field loss present on perimetry, one-third of patients in this study reported vision loss as part of their symptom complex. The most common visual field defect characterized was enlargement of the blind spot along with a partial arcuate defect. The authors emphasized that these defects could only be detected with formal perimetry. Somewhat surprising, and not fully explained in this article, was the fairly high prevalence of mild reduction in visual acuity. More than 20% of the patients did not reach the 20/20 level of acuity in their better eye. This is a finding that generally would be unexpected because this condition is only thought to affect visual acuity later in its course. We will have to await further reports concerning OCT findings to gain better insight into whether this was on the basis of macula or optic nerve dysfunction. This finding of slightly reduced acuity in more than 20% of patients did not correlate with either the degree of visual field loss or the degree of papilledema. Similarly, the degree of papilledema did not correlate with the automated visual field mean deviation (a weighted average of depth of visual field defect across the visual field). Papilledema was also found to be asymmetric (>2-grade difference) in 12 patients (7%). Given the mild vision loss entry criteria, afferent pupillary defects were only found in 5% of patients. There was a relatively low prevalence of esotropia on examination; however, there was a fairly high rate of reported double vision (18%) as part of the symptom complex, suggesting that many patients may have only transient sixth nerve dysfunction as a manifestation of their elevated intracranial pressure.

Given the prevalence of headache (the most common symptom in this cohort, present in 84% of patients) and visual symptoms, not surprisingly, this study has demonstrated a significant impact of the condition on quality of life as reported by patients. Somewhat surprising was the prevalence of fairly severe headaches. The average headache severity was rated at 6.3 on a scale of 10 and about 5% of patients reported a severity of 10 of 10, indicating a more severe headache than might have been expected. In half the patients, these headaches were either constant or daily. Patients reported both pulse synchronous and nonpulsatile tinnitus. On standardized lumbar puncture, the range of opening pressures was between 210 and 670 mm H₂O and the pressure did not correlate with either the body mass index or with the degree of visual field loss on perimetric testing. There was a high prevalence of symptoms suggestive of sleep apnea.

The reader is also directed to some other findings that have already been informally reported by the IIHTT including (1) great success with weight loss, noting that more than half of the patients lost 6% or more of their body weight; (2) acetazolamide was very well tolerated in large doses, with rare episodes of kidney stones; (3) only 7 of 165 patients were judged to be treatment failures; (4) a fair amount of variability in the visual fields were noted including a false-positive, or bad day, visual field, which, when simply repeated, returned to baseline; and (5) a unique OCT finding that may

be more commonly seen in papilledema as opposed to other causes of disc edema/elevation.¹ These preliminary results suggest that this type of treatment strategy is possible and that weight loss can be significant and have a profound impact on the patient's clinical course. Of course, the importance of visual fields in the decision making concerning this disorder is well established and reports that detail the variability of these visual field changes will also inform decisions concerning interexamination variability and how to use this information when considering advancing treatment. We will eagerly await the formal reports concerning all of these preliminary findings.

The NORDIC research group and the IHTT have set the stage with this clinical trial to answer many important questions about this disorder. It is very likely that this study will definitively answer the question about early treatment and the role of weight loss, with and without diuretics, in the management of this condition. We now have an incredible resource of data that carefully defines the signs and symptoms associated with this disease and soon may know more concerning the etiology of this condition, why it is almost exclusively a disease in women, and what roles vitamin A levels and weight gain or obesity play in its pathogenesis. This is a wonderful example of how a research study group can come together to study a disease at multiple centers across the country with a large number of patients who are strictly screened and enrolled into trials that are much more meaningful than the anecdotal reports and the retrospective series that can come from single institutions. Hopefully, this model will be applied to this condition and others in neuro-ophthalmology going forward. The stage will be set for better understanding concerning the management of patients with the more concerning moderate or severe vision loss at presentation. Because the major morbidity of this condition is significant vision loss, this group must plan to study patients with moderate to severe vision loss and inform us as to how these patients should best be managed, the limitations of medical therapy, and the role of surgical therapy when vision loss develops. Further information concerning the appearance of papilledema as graded by examiners vs a reading center and the potential input that we will get from OCT should also prove very useful. Finally, in appreciation of how disruptive this condition is with its profound effect on patients' quality of life, this study is certainly very informative.

We have finally reached a point where this large cohort of patients with IIH is being studied and reported in a detailed fashion. The clinical profile of this condition, at least in patients with mild vision loss, is now well established. This article also raises the distinct possibility that the condition does not occur in men or, at the very least, that men should be thoroughly investigated for secondary causes of intracranial pressure elevation such as sleep apnea or dural arteriovenous malformations. This and subsequent studies from the group will give us the best chance of understanding this vexing condition and its devastating consequences in so many patients. They have established a model for studying this disorder going forward, and NORDIC and the authors are to be congratulated for this critical contribution.

ARTICLE INFORMATION

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