

CAN WE PREDICT THE PROGNOSIS/OUTCOME OF IIH PATIENTS?

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LEARNING OBJECTIVES

1. The attendee will be able to recognize IIH patients at high risk for visual loss
2. The attendee will be able to initiate appropriate therapy based on the patient's characteristics and clinical presentation
3. The attendee will be able to plan appropriate follow-up based on the expected clinical course of the patient with IIH

CME QUESTIONS

1. Which of the following statements about fulminant IIH is FALSE:
 - a. Fulminant IIH is characterized by acute very severe headaches.
 - b. Fulminant IIH is associated with a high risk of visual loss.
 - c. Most patients with visual loss in the setting of fulminant IIH recover normal visual function with appropriate management.
 - d. Most patients with fulminant IIH need aggressive treatment, which often include surgery.
 - e. Most patients with fulminant IIH have very elevated CSF opening pressures.
2. Which of the following statement about the visual outcome of IIH patients is FALSE:
 - a. Men with IIH have a worse visual prognosis than women with IIH.
 - b. Black IIH patients have a worse visual prognosis than Caucasian IIH patients.
 - c. Morbidly obese patients have a worse visual prognosis than moderately and non-obese IIH patients.
 - d. Pregnant women with IIH have a worse prognosis than non-pregnant women with IIH.
 - e. Anemia and obstructive sleep apnea are systemic conditions associated with an overall worse outcome of IIH.

3. Which of the following statement about the evaluation of visual function IIH patients is FALSE:
 - a. Automated perimetry detects early changes in papilledema.
 - b. Measurement of visual acuity and repeat funduscopic examination are not a reliable way to follow patients with papilledema and IIH.
 - c. Repeat measurements of the retinal nerve fiber layer thickness by OCT is better than perimetry to follow-patients with papilledema and IIH.
 - d. Progressive normalization of the retinal nerve fiber layer thickness on OCT is not necessarily indicative of a good visual prognosis in IIH patients with papilledema.

KEYWORDS

1. Idiopathic Intracranial Hypertension
2. Fulminant Idiopathic Intracranial Hypertension
3. Visual Outcome
4. Prognostic Factors

INTRODUCTION

Idiopathic intracranial hypertension (IIH) has a highly variable clinical presentation and outcome, making the management and follow-up of an individual patient a challenge for both neurologists and ophthalmologists. Because a number of patients irreversibly lose vision or have a chronic disease with reduced quality of life, the term "benign intracranial hypertension" is not used anymore (1–7).

In most patients, IIH has a self-limited course, and symptoms and signs resolve with the diagnostic lumbar puncture, weight loss and medical treatment (6). In others, chronic symptoms (mostly headaches) result in altered quality of life (8). Indeed, many IIH patients suffer from persistent headaches, even after normalization of the intracranial pressure (ICP), and frequently require the continued involvement of a neurologist for adequate treatment (8,9). Patients with IIH also experience depression, anxiety, and reduced quality of life (8), which are found more often than would be expected based on the patients' persistent headaches and co-morbid obesity (8,10).

Papilledema from IIH can result in insidious and slowly progressive visual loss, which is usually reversible with appropriate treatment. Wall and George (11) noted visual field defects in up to 96% of eyes depending on the perimetry used; most defects were mild and most patients were not aware of the visual field changes (11). Other studies (7,12,13) reported a similar percentage of mild visual field defects. Although visual loss is usually relatively mild at presentation, it may progress insidiously. Indeed, up to 25% of IIH patients develop secondary optic atrophy and associated permanent visual loss (4,5,11,13,14). Blindness occurs in at least one eye in 8–10% of patients (3,11).

Although IIH is self-limited in many patients, it can also be a chronic disease, with delayed worsening and recurrence (7,14–16). The long-term relapse rate (over 10 years) was only 15% in a recent study (15), whereas two earlier studies had a relapse rate of 38.4% (over 6.2 years) (17) and 28% (over 2 years) (7). Older studies (14,18) suggested a low relapse rate of 10%. The variation in recurrence rates among studies is likely explained by differences in the definition of IIH relapse.

DO SPECIFIC FEATURES ALLOW PREDICTION OF WHICH EYES MAY LOSE VISUAL FUNCTION, AND WHICH PATIENTS MAY HAVE A CHRONIC COURSE OR RECURRENCES?

Predicting which patient might be at risk for severe visual loss when evaluating new patients with presumed IIH is challenging, but essential, as it determines the strategies chosen for monitoring and management (6,19).

Several demographic risk factors for visual loss in IIH have been identified (Table).

Table: Factors [independently*] associated with a worse visual outcome in idiopathic intracranial hypertension

Male gender*
Race (black patients)*
Morbid obesity*
Marked recent weight gain*
Anemia
Obstructive sleep apnea
Acute onset of symptoms and signs of raised intracranial pressure (fulminant IIH)*
High grade papilledema
Lack of headaches*
Lack of ophthalmological oversight*

GENDER

Only about 10% of IIH patients are men (20,21). While affected men have a similar body mass index (BMI) when compared to affected women, they are, on average, about a decade older than women at the time of presentation. Although men develop IIH less frequently than women, their visual prognosis is worse, perhaps because they have less headaches to alert them to the problem (21). In one study by Bruce et al. (21), men were more likely to have worse

visual acuity and visual fields at presentation and follow-up, 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 (20,21).

RACE

Although race does not seem to influence the incidence of IIH, race appears to be an important determining factor of a patient's visual prognosis, worse in black patients compared with whites living in the US (22), and worse in white US IIH patients compared with white French IIH patients (23). Bruce et al. (22) showed that black patients with IIH 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. In that study, this difference in visual prognosis was likely unrelated to racial differences in diagnosis, treatment, or access to care, suggesting that black patients with IIH appear to have a more aggressive disease and, therefore, need closer follow-up and a lower threshold for early aggressive intervention. Interestingly, a difference in visual outcome in two populations of white IIH patients was suggested by Mrejen et al. (23), who showed that white US IIH patients had a worse visual outcome than white French IIH patients, independent of BMI and other associated factors.

OBESITY

IIH occurs most frequently among obese women of childbearing age. Daniels et al. (10) showed a dose relationship of higher body mass index (BMI) associated with a greater risk of IIH. Interestingly, this study also showed that even non-obese patients (BMI<30) were at greater risk for IIH if they had a recent moderate weight gain as low as 5 to 15% of their weight. Wall and George (11) had previously shown that marked recent weight gain was highly correlated with poor visual outcome. Another recent study (16) showed that a group of 26 women with recurrent IIH had a greater BMI at the time of recurrence compared to their BMI at the time of initial diagnosis. This study also suggested that even moderate weight gain might be a risk factor for recurrence. Additionally, Szwedka et al. (24) demonstrated that increasing degrees of obesity were associated with an increased risk of severe visual loss. Patients with BMI ≥40 (World Health Organization Obese Class III) were more likely to have severe papilledema at first visit than those with a lower BMI (p = 0.02). There was a trend toward more severe visual loss at last follow-up among patients with BMI ≥40 (18% vs 11%, p = 0.067). Logistic regression modeling found that 10-unit (kilogram per square meter) increases in BMI increased the odds of severe visual loss by 1.4 times (95% confidence interval, 1.03–1.91, P = 0.03) after controlling for sex, race, diagnosed hypertension, and diagnosed sleep apnea. The exact relationship between obesity and IIH remains poorly understood, with several etiologic hypotheses proposed, including increased central venous pressure and various hormonal and metabolic changes commonly found in obese patients (25). This trend for severe papilledema and visual loss associated with increasing BMI suggests that very obese IIH patients should be closely monitored for progression of visual field loss.

AGE

Similar to adults with IIH, visual loss in pediatric IIH is usually mild and reversible, but it can rarely be devastating and permanent (26). Visual field deficits are often difficult to identify in young children who might not perform perimetry reliably. A study from Israel (27) suggested that pubertal children might have a worse visual outcome than prepubertal, teenage and adult patients. The recurrence rate in children seems to be similar to that of adults with IIH, ranging from 6 to 22% (28), and may be more common in obese teenagers who initially lose weight and subsequently regain it (28).

MEDICATIONS

While various medications have been proposed to cause or, more likely, to precipitate IIH (such as tetracycline and its derivatives, cyclosporine, lithium, nalidixic acid, nitrofurantoin, oral contraceptives, levonorgestrel, danaxol, and tamoxifen) (4), there are compelling test-retest data only in a few individual patients (such as in patients treated with tetracyclines, particularly minocycline) (29). The prognosis of IIH precipitated by medications tends to be good, with a self-limited course once the drug is discontinued (30). However, fulminant IIH has been described in patients with severe increased ICP precipitated by minocycline (30,31) and visual loss should not be overlooked in these patients.

ANEMIA

Anemia at the time of diagnosis has been associated with worse visual outcome in IIH patients (22,32). In a few patients, prompt treatment of the anemia resulted in dramatic improvement of visual function (32).

HYPERTENSION

Although no study has definitely linked high blood pressure with a worse outcome in IIH, a few authors have suggested a trend towards worse visual outcome in IIH patients with poorly controlled hypertension (11,14,22). This might be explained by an increased vulnerability of the optic disc in patients with pre-existing severe hypertensive retinopathy (33).

OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea (OSA) is associated with IIH (4). It is unclear, however, whether obesity is the common pathophysiological link, or whether OSA is another factor capable of triggering IIH in predisposed patients. It has also been suggested that OSA might portend a worse prognosis for IIH patients (21,34).

CLINICAL CHARACTERISTICS OF IIH PATIENTS AS PREDICTORS OF OUTCOME

Lack of headaches.

Almost all patients with IIH first seek medical attention because of headaches. Patients without headaches at presentation are likely to be diagnosed at a much later stage, when asymptomatic papilledema is already responsible for irreversible visual field changes. This might explain why the absence of headache is associated with a worse visual

outcome in IIH (19), and might contribute to the worse outcome of men with IIH, who are less likely to report headaches than women with IIH (21). This has also been observed in children (35).

Transient visual obscurations

Transient visual obscurations (very brief episodes of blurred vision, which may be uni- or bilateral and are classically precipitated by postural changes) occur in about two-thirds of patients with papilledema from IIH. Although they are often perceived as worrisome by patients, they are not associated with a poor visual outcome (4,11,13,14).

Severity of papilledema

Most authors agree that the severity of papilledema does not correlate with the visual outcome (4,11,13,14). However, only patients with obvious papilledema develop visual loss, and the amount of visual loss correlates grossly with the grade of papilledema (eyes with more disc edema have more visual loss) (4,33,36). It is therefore unlikely for patients with mild papilledema and no visual loss at presentation to eventually develop severe visual field defects, whereas patients with severe papilledema at presentation should be followed very closely with serial visual field testing in order to prevent devastating visual loss.

Visual field deficits at presentation

Visual loss at the onset of the disease is predictive of poor visual outcome (14,19). Indeed, most patients with severe visual field defects at presentation have either a fulminant course (see below) or a delayed diagnosis with already secondary optic atrophy at the time of diagnosis.

Fulminant course

Rarely, patients with IIH may have an acute onset of symptoms and signs of raised ICP (so-called "fulminant" or "malignant" IIH), with rapid worsening of visual loss over a few days, but meet the criteria for IIH with normal brain MRI and venography (1). In a study of 16 such "fulminant IIH" cases (37), 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 IIH is therefore essential.

PREGNANCY

Because IIH is a disease which predominantly affects young women of childbearing age, IIH is often seen in pregnant women; however, it is important to emphasize that IIH is not more common in pregnant compared to non-pregnant women (38,39). IIH can be diagnosed at any time during pregnancy, but most new cases occur in the first or second trimester. However, any symptom of presumed "IIH" at the end of pregnancy or in the post-partum period should be concerning for cerebral venous thrombosis which can mimic IIH (40). Although the management of IIH can be challenging during pregnancy, the prognosis does not seem different from non-pregnant women. Idiopathic intracranial

hypertension does not interfere with pregnancy and these patients have the same rate of spontaneous abortion as the general population. Method of delivery, anesthesia and analgesia should be based only on obstetrical considerations (38). Indeed, although vaginal delivery is associated with a severe increase in ICP, even in normal patients, it is transient and does not alter the prognosis of IIH.

OPTICAL COHERENCE TOMOGRAPHY

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 monitoring the thickness of the peripapillary retinal nerve fiber layer (RNFL) during the course of IIH (41–46). However, in most cases, the reductions in the RNFL thickness observed as disc edema resolves cannot be easily differentiated from axonal loss reflecting disease worsening rather than improvement, suggesting that 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 IIH and the prediction of visual outcome.

Ongoing studies are investigating whether OCT can help predict the visual outcome of patients with papilledema. A recent study (46) suggested that scanner laser polarimetry combined with RNFL measurement with OCT might be helpful in identifying axonal injury associated with permanent visual loss in patients with RNFL thickening from disc edema. An ongoing OCT study in IIH patients with papilledema (Kardon R, personal communication) suggests that 3D ganglion cell layer segmentation might be possible with OCT and might allow early detection of axonal loss in the presence of disc edema. Such findings would help predict which patients need more aggressive treatment and careful follow-up.

CSF OPENING PRESSURE

The grade of papilledema does not correlate with CSF opening pressure. In addition, the CSF opening pressure varies greatly from one IIH patient to another. However, a few studies have suggested that some patients with severe visual field defects at presentation (such as black patients with a worse visual outcome (22), or those with fulminant IIH), have very high CSF opening pressures (37).

BRAIN IMAGING

Although brain imaging must be “normal” in order to diagnose IIH (1), imaging changes associated with raised ICP are commonly observed in IIH patients (47). These include an empty sella or flattening of the pituitary gland, 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. Although cerebral venous *thrombosis* must be ruled-out in patients with suspected IIH (40), 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 IIH patients (48,49). Three recent studies have assessed the relationship between the visual outcomes of IIH patients and radiologic findings (VanStavern et al., Riggeal et al., personal communications—presented at NANOS 2012; Saindane et al., personal communication). In all 3 studies, none of the MRI abnormalities described above (including transverse sinus stenoses) were indicative of a worse outcome. Similar results had already been suggested in 1982 by Corbett et al. (14) and in 1984 by Orcutt et al. (33), who reported no correlation between visual outcomes and the findings of empty sella or dilation of the optic nerve sheath on brain imaging.

CONCLUSION

Although the pathophysiology of IIH remains unknown, identification of subgroups of patients at high risk for irreversible visual loss, such as men, black patients, morbidly obese patients, and patients with fulminant IIH, helps determine management approaches and follow-up strategies.

CME ANSWERS

1. c
2. d
3. c

REFERENCES

1. Friedman DI, Jacobson DM: Diagnostic criteria for idiopathic intracranial hypertension, *Neurology*, 2002;59:1492–1495.
2. Friedman DI, Jacobson DM.: Idiopathic intracranial hypertension, *J Neuroophthalmol*, 2004; 24: 138–145.
3. Ball AK, Clarke CR.: Idiopathic intracranial hypertension, *Lancet Neurology*, 2006; 5: 433–442.
4. Wall M.: Idiopathic intracranial hypertension, *Neurol Clin*, 2010; 28: 593–617.
5. Digre KB: Idiopathic intracranial hypertension, *BMJ*, 2010; 341:c2836.
6. Biousse V, Bruce BB, Newman NJ.: Update on the pathophysiology and management of idiopathic intracranial hypertension, *J Neurosurg Psychiatry*, 2012; 83: 488–494.
7. Yri HM, Wegener M, Sander B, et al.: Idiopathic intracranial hypertension is not benign: a long-term outcome study, *J Neurol*, 2012; 259: 886–894.
8. Kleinschmidt JJ, Digre KB, Hanover R: Idiopathic intracranial hypertension: relationship to depression, anxiety, and quality of life, *Neurology*, 2000; 54: 319–324.
9. Friedman DI, Rausch EA: Headache diagnoses in patients with treated idiopathic intracranial hypertension. *Neurology* 2002; 58: 1551–1553.
10. Daniels AB, Liu GT, Volpe NJ, et al.: Profiles of obesity, weight gain, and quality of life in idiopathic intracranial hypertension (pseudotumor cerebri), *Am J Ophthalmol*, 2007; 143: 635–641.
11. Wall M, George D: Idiopathic intracranial hypertension. A prospective study of 50 patients, *Brain* 1991; 114: 155–180.
12. Rowe FJ, Sarkies NJ: Visual outcome in a prospective study of idiopathic intracranial hypertension, *Arch Ophthalmol*; 1999; 117: 1571.
13. Rush JA: Pseudotumor cerebri. Clinical Profile and visual outcome in 63 patients, *Mayo Clin Proc*, 1980; 55: 541–546.

14. Corbett JJ, Savino PJ, Thompson HS, et al.: Visual loss in pseudotumor cerebri. Follow-up of 57 patients from five to 41 years and a profile of 14 patients with permanent severe visual loss, *Arch Neurol*, 1982; 39: 461–474.
15. Shah VA, Kardon RH, Lee AG et al.: Long-term follow-up of idiopathic intracranial hypertension: the Iowa experience, *Neurology*, 2008; 70: 634–640.
16. Ko MW, Chang SC, Ridha MA, et al: Weight gain and recurrence in idiopathic intracranial hypertension: a case-control study, *Neurology*. 2011; 76: 1564–1567.
17. Kesler A, Hadayer A, Goldhammer Y, et al.: Idiopathic intracranial hypertension: risk of recurrences, *Neurology*, 2004; 63: 1737–1739.
18. Johnston I, Paterson A: Benign intracranial hypertension. I. Diagnosis and prognosis, *Brain* 1974; 97: 289–300.
19. Corbett JJ, Thompson HS. The rational management of idiopathic intracranial hypertension. *Arch Neurol* 1989; 46: 1049–1051.
20. Digre KB, Corbett JJ.: Pseudotumor cerebri in men, *Arch Neurol*, 1988; 45: 866–872. Erratum in: *Arch Neurol* 1989; 46: 172.
21. Bruce BB, Kedar S, Van Stavern GP, et al.: Idiopathic intracranial hypertension in men, *Neurology*, 2009; 72: 304–309.
22. Bruce BB, Preechawat P, Newman NJ, et al.: Racial differences in idiopathic intracranial hypertension, *Neurology*, 2008; 70: 861–867.
23. Mrejen S, Vignal C, Bruce BB, et al.: Idiopathic intracranial hypertension: a comparison between French and North-American white patients, *Rev Neurol (Paris)*, 2009; 165: 542–548.
24. Szewka AJ, Bruce BB, Newman NJ, Biousse V. Idiopathic intracranial hypertension: Relation Between Obesity and Visual Outcomes. *J Neuroophthalmol* 2012 Jan 3. [Epub ahead of print]
25. Ooi LY, Walker BR, Bodkin PA, et al.: Idiopathic intracranial hypertension: can studies of obesity provide the key to understanding pathogenesis?, *Br J Neurosurg*, 2008; 22: 187–194.
26. Babikian P, Corbett J, Bell: Idiopathic intracranial hypertension in children: the Iowa experience, *J Child Neurol*, 1994; 9: 144–149.
27. Stiebel-Kalish H, Kalish Y, Lusky M, et al: Puberty as a risk factor for less favourable visual outcome in idiopathic intracranial hypertension, *Am J Ophthalmol*, 2006; 142: 279–283.
28. Ko MW, Liu GT: Pediatric idiopathic intracranial hypertension (pseudotumor cerebri), *Horm Res Paediatr*, 2010; 74: 381–389.
29. Friedman DI.: Medication-induced intracranial hypertension in dermatology, *Am J Clin Dermatol*, 2005; 6: 29–37.
30. Kesler A, Goldhammer Y, Hadayer A, et al.: The outcome of pseudotumor cerebri induced by tetracycline therapy, *Acta Neurol Scand*, 2004; 110: 408–411.
31. Fraser CL, Biousse V, Newman NJ.: Minocycline-induced fulminant intracranial hypertension, *Arch Neurol*, 2012 Apr 9. [Epub ahead of print] PubMed PMID: 22490325.
32. Biousse V, Rucker JC, Vignal C, et al.: Anemia and papilledema, *Am J Ophthalmol*, 2003; 135: 437–446.
33. Orcutt JC, Page NGR, Sanders MD: Factors affecting visual loss in benign intracranial hypertension, *Ophthalmology*, 1984; 91: 1303–1312.
34. Wall M, Purvin V: Idiopathic intracranial hypertension in men and the relationship to sleep apnea, *Neurology*, 2009; 72: 300–301.
35. Lim M, Kurian M, Penn A, et al.: Visual failure without headache in idiopathic intracranial hypertension, *Arch Dis Child*, 2005; 90: 206–210.
36. Wall M, White WN: Asymmetric papilledema in idiopathic intracranial hypertension: prospective interocular comparison of sensory visual function: *Invest Ophthalmol, Vis Sci*, 1998; 39: 134–142.
37. Thambisetty M, Lavin PJ, Newman NJ, et al.: Fulminant idiopathic intracranial hypertension, *Neurology*, 2007; 68: 229–232.
38. Digre KB, Varner MW, Corbett JJ.: Pseudotumor cerebri and pregnancy, *Neurology*, 1984; 34: 721–729.
39. Huna-Baron R, Kupersmith MJ.: Idiopathic intracranial hypertension in pregnancy, *J Neurol*, 2002; 249: 1078–1081.
40. Biousse V, Ameri A, Bousser MG.: Isolated intracranial hypertension as the only sign of cerebral venous thrombosis, *Neurology*, 1999; 53: 1537–1542.
41. Heidari G, Rizzo JF 3rd.: Use of optical coherence tomography to evaluate papilledema and pseudopapilledema, *Semin Ophthalmol*, 2010; 25: 198–205.
42. Waisbourd M, Leibovitch I, Goldenberg D, et al.: OCT assessment of morphological changes of the optic nerve head and macula in idiopathic intracranial hypertension, *Clin Neurol Neurosurg*, 2011; 113: 839–843.
43. Skau M, Yri H, Sander B, et al.: Diagnostic value of optical coherence tomography for intracranial pressure in idiopathic intracranial hypertension, *Graefes Arch Clin Exp Ophthalmol*, 2012 May 18. [Epub ahead of print] PubMed PMID: 22592348.
44. Wang JK, Kardon RH, Kupersmith MJ, et al.: Automated quantification of volumetric optic disc swelling in papilledema using spectral-domain optical coherence tomography, *Invest Ophthalmol Vis Sci*, 2012; 53: 4069–4075.
45. Kupersmith MJ, Sibony P, Mandel G, et al.: Optical coherence tomography of the swollen optic nerve head: deformation of the peripapillary retinal pigment epithelium layer in papilledema, *Invest Ophthalmol Vis Sci*, 2011; 52: 6558–6564.
46. Kupersmith MJ, Kardon R, Durbin M, Horne M, Shulman J. Scanning laser polarimetry reveals status of RNFL integrity in eyes with optic nerve head swelling by OCT, *Invest Ophthalmol Vis Sci*, 2012; 53: 1962–1970.
47. Degnan AJ, Levy LM.: Pseudotumor cerebri: brief review of clinical syndrome and imaging findings, *AJNR Am J Neuroradiol*, 2011 Jun 16. [Epub ahead of print] PubMed PMID: 21680652.
48. Farb RI, Vanek I, Scott JN, et al.: Idiopathic intracranial hypertension: the prevalence and morphology of sinovenous stenosis, *Neurology*, 2003; 60: 1418–1424.
49. Ahmed R, Friedman DI, Halmagyi GM: Stenting of the transverse sinuses in idiopathic intracranial hypertension, *J Neuroophthalmol*, 2011; 31: 374–380.

WEIGHT LOSS IN IIH

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LEARNING OBJECTIVES

1. Understand the relationship between obesity and idiopathic intracranial hypertension
2. Know what is involved in lifestyle (weight) management programs
3. Appreciate the relationship between onset and recurrence of IIH and weight gain

CME QUESTIONS

1. Which of the following strategies are successful approaches of lifestyle (weight) management programs.
 - a. Low energy diets (high volume, low calorie)
 - b. Use of liquid dietary supplements
 - c. Stressing a combination of behavior, nutrition and exercise programs
 - d. Institution of a diet very low in fat
2. You are counseling an IIH patient in weight loss. Which of the following statements are true.
 - a. You will need to lose as much weight as you can.
 - b. Large volume low calorie foods are a proven strategy for weight loss in IIH
 - c. Motivational intervention improves weight loss results
 - d. The most important issue with weight loss is being sure the patient starts an exercise program of at least ½ hour 4 times a week.
3. What percentage of weight loss has been shown to correlate with reduction of papilledema?
 - a. 0–5%
 - b. 5–10%
 - c. 10–15%
 - d. 15–20%.

KEYWORDS

1. Idiopathic Intracranial Hypertension
2. Pseudotumor Cerebri
3. Weight Loss
4. Treatment
5. Idiopathic Intracranial Hypertension Treatment Trial

INTRODUCTION

It has been well known that IIH is associated with obesity. Weight gain is considered a risk factor for disease onset and recurrences. Weight loss has been well documented in several case series to be associated with improvement in symptoms and signs and to be associated with lowering of intracranial pressure. While the mechanism of how weight loss achieves these beneficial effects is unclear, it remains a cornerstone of treatment. Patients benefit from a program of nutritional and IIH education, motivation, behavioural modification and an exercise/mobility program. Using these techniques, the Idiopathic Intracranial Hypertension Treatment Trial has been successful in achieving weight loss in most enrolled subjects.

CASE

A 24 year old obese woman was found to have bilateral optic disc edema on routine ophthalmologic examination. When questioned, she reported mild headache and pulse synchronous tinnitus but had no other symptoms. She had gained 25# over the preceding year. Her evaluation showed a partially empty sella and lumbar puncture showed an opening pressure of 280 mm water with normal CSF constituents. Perimetry showed a mean deviation (MD) of -3.18 dB in the worst eye (OS). She was counseled in weight loss as treatment.

She returned one month later. Her weight was unchanged and automated perimetry now showed a MD of -5.82 dB. She was again counseled in weight management and was started on acetazolamide 500 mg p.o. bid.

She returned one month later with more frequent headaches. She had gained 5 pounds. Her MD had worsened to -6.62 dB. An optic nerve sheath fenestration was discussed. She stated she was afraid of surgery and would now get serious about weight loss. Acetazolamide was increased to 1000 mg bid. One month later, she had not lost weight and MD had worsened to -7.76 dB. An optic nerve sheath fenestration was recommended but she declined.

She returned one month later with fewer headaches having lost 16 pounds still on acetazolamide 1000 mg bid. MD was -3.58 dB. Over the following six months she maintained her weight loss, acetazolamide was tapered and her MD fell to -2.08 dB.

THE OBESITY EPIDEMIC

Obesity in the U. S. has been on the rise for decades. According to the CDC, www.cdc.gov/obesity/data/adult.html more than one-third of U.S. adults (35.7%) are obese (BMI > 30 which is about 30 lbs. overweight for 5' 4" person). In 2008, medical costs associated with obesity were estimated at \$147 billion. Blacks have the highest age-adjusted rates of obesity (49.5%) compared with Mexican Americans (40.4%), all Hispanics (39.1%) and non-Hispanic whites (34.3%). The South has the highest prevalence of obesity (29.5%), followed by the Midwest (29.0%), the Northeast (25.3%) and the West (24.3%).

OBESITY AND IIH

The relationship between IIH and obesity was first reported about 50 years ago.¹ Of all risk factors and related conditions, it is the most common.² Over 90% of IIH patients are obese.¹ ³ Along with the increase in obesity in the US, the incidence of IIH has increased. In 1988 the incidence of IIH in Iowa and Louisiana was reported at 1.0/100,000.⁴ When looked at by gender (90% women) and obesity (90% obese), the incidence was 19/100,000 in obese women of ages 15–44.⁴ In a study done 25 years later in Mississippi (the obesity capital of the country), a doubling of the incidence to 2.0/100,000 was found (22.5/100,000 in obese women of childbearing years).⁵ The incidence of IIH in Sapporo, Japan⁶ and Parma, Italy⁷ is low as is obesity these regions. Not only is recent weight gain correlated to disease onset³ but also to disease recurrences.^{3,8}

The first study to use diet to treat IIH was by Newborg in 1974.⁹ She treated 9 IIH patients with Kempner's rice/reduction diet. The diet consisted of 400–1000 calories per day provided by fruits, rice, vegetables and in some cases 1–2 oz. of meat. No salt was used in meal preparation. Fluids were restricted to 750–1250 ml per day and sodium to less than 100 mg per day. The patients lost from 13%–38% total body weight and all had improvement in IIH symptoms and "remission" of papilledema. Unfortunately, visual function was not assessed.

Kupersmith and colleagues retrospectively reviewed the charts of 58 IIH patients treated with diuretics.¹⁰ The mean time to improve one papilledema grade was about 4 months in patients with weight loss compared to about 1 year in patients without weight loss. Papilledema resolved in 28 of 38 patients (74%) who lost weight compared to 8 of 20 (40%) without weight loss.

Johnson and coworkers in a retrospective analysis studied 15 consecutive obese IIH patients treated with acetazolamide and a weight reduction diet for 24 weeks.¹¹ Nine of 11 patients whose papilledema grade improved had weight loss. Interestingly, 6% weight loss was associated with resolution of marked papilledema. This is similar to the results of a treatment trial pilot study (Wall, Corbett and Goodwin, unpublished results).

Sinclair et al.¹² measured intracranial pressure in 25 female idiopathic intracranial hypertension patients who followed a high volume, low caloric diet. The diet resulted in a

average weight loss of 15.7 kg—34.6 lbs. and intracranial pressure fell an average of 80 mm of water. Symptoms and papilledema also improved.

Sugerman performed gastric weight reduction surgery in 24 morbidly obese women with IIH.¹³ Symptoms resolved within 4 months with the procedure in 18 of 19 patients who had at least one year of follow-up. There were many significant but treatable surgery-related complications. Since very obese patients commonly fail weight management programs, this is a viable treatment for the morbidly obese.

LEPTIN

A variety of hormones have been investigated in the pathogenesis of IIH. Leptin, secreted by fat cells, acts as a signaling factor regulating body weight and energy balance. With forced weight gain, leptin levels increase; in an attempt to return weight to baseline; with weight loss, leptin levels decrease. The mean concentration of leptin in plasma of lean subjects is much lower than that of obese ones. In addition, leptin levels are three times greater in women than men. Leptin binding sites are found in leptomeninges and choroid plexus, the site of CSF production. It is possible that high leptin levels could stimulate CSF production. Weight loss, by lowering leptin levels might therefore decrease production and lower intracranial pressure. A variety of studies have been published on this topic with conflicting results.^{14–17}

SODIUM

As Friedman and colleagues have shown, there is a subset of IIH patients with orthostatic edema.¹⁸ They reported that IIH patients had impairment of excretion of both a standard saline load and a water load. This work suggested low salt diets and fluid restriction may be beneficial for IIH patients.

Although there is a strong relationship between female gender, obesity, and IIH, the mechanisms underlying these relationships are unknown. Is it weight loss *per se*? Could it be that weight gain with fat deposition increases the fat content of the arachnoid granulations contributing to absorption block? Is it the fluid accumulation that accompanies weight gain so that dieting and the associated loss of fluid is contributory? Is there a sodium mechanism? Do IIH patients have a defect in sodium metabolism and retain fluid in their CSF? Or is it that with dieting one eats less of a dietary constituent such as vitamin A? Is it due to an obesity hormone like leptin? Clearly weight loss is beneficial for treatment of IIH; hopefully the mechanism of this improvement will become apparent.

LIFESTYLE MANAGEMENT PROGRAMS

Since a weight management program appears effective and is a healthful intervention we believe all overweight patients with IIH should be treated with this modality. It has been suggested that one's weight is the interaction between what one eats and one's lifestyle and much research confirms most obese patients need to change both eating habits and

lifestyle. It is thought that the progressive sedentary lifestyle of Americans coupled with cheap and accessible corn-based products has helped to fuel the obesity epidemic.

Simply telling a patient that they have to lose weight is often not an effective approach. Successful programs address *behaviors* (stress reduction, behavior modification, dealing with cravings), *nutrition* (caloric content of foods, focus on high volume, low calorie foods, avoiding foods with “hidden” calories, and *lifestyle*—a more active, less sedentary lifestyle including regular exercise. Maybe most important is helping the patient to find motivation to change their lifestyle.

MOTIVATIONAL INTERVIEWING

MI is a counseling approach used to elicit behavior change that uses a collaborative, patient-centered form of guiding to elicit and strengthen motivation for change. It relies on the presence of ambivalence toward the goal (pros and cons of losing weight) and assists the patient to actively develop a plan to improve their health. So instead of a physician simply recommending weight loss, MI would direct the patient to clarify the pros and cons of weight loss. It would then identify and assist in overcoming obstacles and encourage small steps. For example, the physician can ask “Have you ever attempted weight loss before? What was helpful? What kinds of problems do you expect to encounter? How do you think you could deal with them?”

AN APPROACH IN THE NEURO-OPHTHALMOLOGY CLINIC TO LIFESTYLE MANAGEMENT

1. *Educate the patient about IIH and the potential for blindness.* Be sure the patient understands the risks of future visual loss including blindness and that weight loss often lowers intracranial pressure and reduces symptoms and signs. Let the patient know that it is not necessary to become thin as in many cases a 5–10% total weight loss allows a reduction in medication and sometimes, remission of IIH. Hopefully, this will give the patient added motivation. I like to tell patients what has worked for other IIH patients. A successful strategy has been let the patient know studies have shown that we tend to eat the same volume of food every day. This has led to the approach of eating predominantly high volume low calorie foods (such as fresh fruits and vegetables) and guard against calories in drinks such as sugary beverages. We also recommend a low salt diet and may give patient a handout that details the sodium content of foods and drinks as like sugar, sodium is often hidden.
2. *Explore the patient’s history of weight loss and lifestyle change* Ask how the patient has tried in the past. Inquire as to whether they have learned the caloric content of food and drink. Ask “Are you considering weight loss now?” “What are the pros and cons of losing weight?” and “Do the pros of changing outweigh the cons?”
3. *Consider further dietary/lifestyle education* If the patient is motivated to lose weight, more education

may be needed such as learning about nutrition, stress management or relapse prevention. It is useful to consult the appropriate health care professional for this intervention. There are many excellent weight management clinics available to address these issues.

4. *Assess the Patient’s Understanding and Concerns and Set a Goal* Toward the end of the counseling ask something like “On a scale of 1–10, with 10 being 100% ready to take action, how ready are you to lose weight?” If they are ready, establish a reasonable goal for weight loss such as “a 5–10% weight loss over 6 months for a total loss of between XX and YY pounds.”

A plan developed and endorsed by the patient is more likely to be followed than one that you promote. A video example of MI for weight loss can be found at <http://www.youtube.com/watch?v=dm-rJJPCuTE>. Figure 1 shows a meta-analysis of studies of weight loss using MI.¹⁹

Figure 1. Meta-analysis of motivational interviewing studies and weight loss.¹⁹

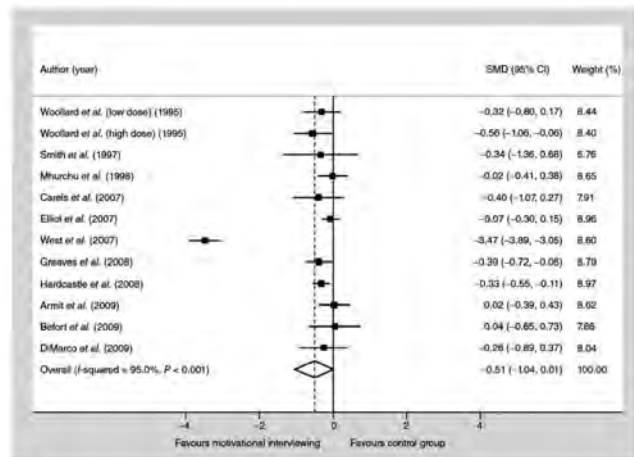


Figure 2 Meta-analysis of standardized change scores in body mass index (BMI) in motivational interviewing intervention group compared with control. Degrees of shading corresponds with study weighting in random-effects model. SMD, standardized mean difference.

WEIGHT LOSS IN THE IIHTT

NORDIC has involved the New York Obesity Research Center (NYORC) to administer the IIHTT lifestyle management program. Two program directors with more than 30 years of combined experience with obesity and weight loss share the responsibility of supervising weight-loss coaches who implement the treatment to subjects via telephone.

The intervention covers all three disciplines of weight loss and lifestyle modification 1) *behavior*: problem solving, assertiveness training, social support, managing high risk situations, automatic thoughts, and relapse prevention; 2) *physical activity*: obstacles, flexibility, aerobic and resistance exercise, and goal setting. Subjects are provided with pedometers for measuring steps, and rubberized exercise tubing for resistance exercise; 3) *nutrition*: meal planning, calorie burning, portion control, fat counting, and energy density.

The diet intervention is implemented in two phases:
Phase 1: Subjects are given a 500 to 1000 calorie deficit goal to determine their calorie needs and are instructed to follow a partial meal replacement (PMR) diet.²⁰ Studies show that weight loss is greater for patients utilizing PMR diets compared to reduced-calorie diets. A weight decrease from baseline of 10% on average is the goal. Sample menus from the DASH eating plan are provided and modifications are made to account for individual preferences. Ten out of the twenty-four weekly calls are devoted to nutrition topics. Subjects follow a manual each week that includes an overview of the information along with a homework assignment to implement the information into their diet. All subjects are instructed to keep daily food records of their food and beverage intake.

Phase 2: After the initial 24 weeks the telephone sessions move to once every other week. Subjects have the option to transition to a balanced-deficit diet (BDD) or continue with the PMR diet. The BDD is modeled after the DASH eating plan²¹ and Therapeutic Lifestyle Diet of NCEP²² and does not include the use of meal replacements. This diet contains approximately 20% of calories from protein, 25–30% from fat and the remainder from carbohydrate. Additional information and instructions are provided on a low-energy-dense diet,²³ portion control,²⁴ and environmental influences on diet.²⁵ An emphasis on maintaining weight loss is the theme throughout this phase.

CONCLUSION

Weight loss and lifestyle management is a cornerstone of IHH treatment. With weight loss of 5–10% total body weight, many patients have a reduction in symptoms and signs and can reduce medication. The technique of motivational interviewing leads to better results than control programs. The neuro-ophthalmologist can play a major role in assisting the IHH patient with weight loss and lifestyle management.

CME ANSWERS

1. a, b, c
2. b, c
3. b

REFERENCES

1. Greer M. Benign intracranial hypertension. VI. Obesity. *Neurology*. 1965;15:382–388.
2. Giuseffi V, Wall M, Siegel PZ, Rojas PB. Symptoms and disease associations in idiopathic intracranial hypertension (pseudotumor cerebri): a case-control study. *Neurology*. 1991;41:239–244.
3. Wall M, George D. Idiopathic intracranial hypertension. A prospective study of 50 patients. *Brain*. 1991;114:155–180.
4. Durcan FJ, Corbett JJ, Wall M. The incidence of pseudotumor cerebri. Population studies in Iowa and Louisiana. *Arch Neurol*. 1988;45:875–877.
5. Garrett J, Corbett JJ, Braswell R.A., Santiago M. The increasing incidence of IHH. The effect of obesity on frequency of occurrence in Mississippi. *Ann Neurol*. 2004;56:S69.
6. Yabe I, Moriwaka F, Notoya A, Ohtaki M, Tashiro K. Incidence of idiopathic intracranial hypertension in Hokkaido, the northernmost island of Japan. *Journal of Neurology*. 2000;247:474–475.
7. Carta A, Bertuzzi F, Cologno D, Giorgi C, Montanari E, Tedesco S. Idiopathic intracranial hypertension (pseudotumor cerebri): descriptive epidemiology, clinical features, and visual outcome in Parma, Italy, 1990 to 1999. *European Journal of Ophthalmology*. 2004;14:48–54.
8. Ko MW, Chang SC, Ridha MA, et al. Weight gain and recurrence in idiopathic intracranial hypertension: a case-control study. *Neurology*. 2011;76:1564–1567.
9. Newborg B. Pseudotumor cerebri treated by rice reduction diet. *Arch Intern Med*. 1974;133:802–807.
10. Kupersmith MJ, Gamell L, Turbin R, Peck V, Spiegel P, Wall M. Effects of weight loss on the course of idiopathic intracranial hypertension in women. *Neurology*. 1998;50:1094–1098.
11. Johnson LN, Krohel GB, Madsen RW, March GA, Jr. The role of weight loss and acetazolamide in the treatment of idiopathic intracranial hypertension (pseudotumor cerebri). *Ophthalmology*. 1998;105:2313–2317.
12. Sinclair AJ, Burdon MA, Nightingale PG, et al. Low energy diet and intracranial pressure in women with idiopathic intracranial hypertension: prospective cohort study. *BMJ*. 2010;341:c2701.
13. Sugerma HJ, Felton WL, III, Sismanis A, Kellum JM, DeMaria EJ, Sugerma EL. Gastric surgery for pseudotumor cerebri associated with severe obesity. *Ann Surg*. 1999;229:634–640.
14. Ball AK, Sinclair AJ, Curnow SJ, et al. Elevated cerebrospinal fluid (CSF) leptin in idiopathic intracranial hypertension (IIH): evidence for hypothalamic leptin resistance? *Clin Endocrinol (Oxf)*. 2009;70:863–869.
15. Behbehani R, Mabrook A, Abbas JM, Al-Rammah T, Mojiminiyi O, Doi SA. Is cerebrospinal fluid leptin altered in idiopathic intracranial hypertension? *Clin Endocrinol (Oxf)*. 2010;72:851–852.
16. Lampi Y, Eshel Y, Kessler A, et al. Serum leptin level in women with idiopathic intracranial hypertension. *J Neurol Neurosurg Psychiatr*. 2002;72:642–643.
17. Subramanian PS, Goldenberg-Cohen N, Shukla S, Cheskin LJ, Miller NR. Plasma ghrelin levels are normal in obese patients with idiopathic intracranial hypertension (pseudotumor cerebri). *Am J Ophthalmol*. 2004:109–113.
18. Friedman DI, Streeten DH. Idiopathic intracranial hypertension and orthostatic edema may share a common pathogenesis. *Neurology*. 1998;50:1099–1104.
19. Jensen CD, Cushing CC, Aylward BS, Craig JT, Sorell DM, Steele RG. Effectiveness of motivational interviewing interventions for adolescent substance use behavior change: a meta-analytic review. *J Consult Clin Psychol* 2011 Aug. 1979:433–440.
20. Mifflin, et al. A new predictive equation for resting energy expenditure in healthy individuals. *Am J Clin Nut*. 2006;51.2:241–247.
21. Appel. Dietary approaches to prevent and treat hypertension: a scientific statement from the American heart association. *Hypertension*. 2006;47.2:296–308.
22. National Cholesterol Education Program Expert Panel. Detection, evaluation, and treatment of high blood cholesterol in adults (adults treatment panel III). *JAMA*. 2006;285:2486–2497.
23. Ledikwe. Low-energy-density diets are associated with high diet quality in adults in the United States. *J Am Diet Assoc*. 2006;106.8:1172–1180.
24. Wansink. Meal size, not body size, explains errors in estimating the calorie content of meals. *Ann Intern Med*. 2006;145.5:326–332.
25. Wansink. Environmental factors that increase the food intake and consumption volume of unknowing consumers. *Ann Rev Nut*. 2006;24:455–479.

HEADACHE MANAGEMENT IN IIH

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LEARNING OBJECTIVES

1. Describe features in the headache history to determine headache phenotype
2. List the criteria to diagnose medication overuse headache
3. Name symptomatic and preventive medications used to treat chronic headaches

CME QUESTIONS

1. Preventive medications with level A evidence for treating chronic migraine include:
 - a. Amitriptyline and sodium valproate
 - b. Topiramate and propranolol
 - c. Onabotulinumtoxin A and topiramate
 - d. Propranolol and onabotulinumtoxin A
2. Medication overuse headache may be caused by frequent use of which of the following?
 - a. Butalbital containing compounds
 - b. Triptans
 - c. Acetaminophen/ aspirin/caffeine
 - d. Ibuprofen
 - e. All of the above
3. The rate of recurrent headache at 3 years in patients with pseudotumor cerebri treated with shunting is approximately:
 - a. 10%
 - b. 20%
 - c. 30%
 - d. 50%
 - e. 70%

KEYWORDS

1. Idiopathic Intracranial Hypertension
2. Headache
3. Medication Overuse Headache
4. Pseudotumor Cerebri

INTRODUCTION

Headache is a common symptom when patients initially develop idiopathic intracranial hypertension (IIH) or intracranial hypertension from a secondary cause. While the headache often improves with intracranial pressure lowering therapies, it becomes a chronic problem and a long-term management challenge in some patients. Patients with refractory pain often have multifactorial headaches requiring approaches addressing the headache phenotype and other comorbidities as well as their intracranial pressure.

CASE PRESENTATION

The patient is a 40- year-old right-handed disabled curator of education (at the zoo) and former veterinary technician with a history of migraines since she was a teenager. Her migraines were severe, there was no aura or premonitory symptoms. She recalls right-sided pain, with a “circular vice” around her head. There was nausea, vomiting, photophobia, phonophobia, osmophobia. She took hydrocodone or a pain medication (or her mother had pain meds at home— acetaminophen with codeine). They would last a day usually, up to 3 days if severe. They often occurred with menses, lack of sleep. There is a strong family history of migraine so she did not seek medical attention for them.

Her headaches changed in 2000 when she felt like her head was going to explode, and the pain was global. There was diplopia and noises in her ears (whooshing and like the ocean with thumping pulse-like pain). She saw white flashes in her vision, and a sensation like TV snow in her vision that was constantly present. These symptoms evolved over a month or so. She saw her primary care doctor every day for injections for pain at the time who advised her to see an eye doctor if there was no improvement. After seeing per PCP for 5 days in a row, she saw an eye doctor who saw papilledema and sent her to the ED. She weighed about 175 lbs at the time, her weight had been stable. She was taking minocycline and oral contraceptives for a while prior to the onset of symptoms.

She had an MRI, LP and was diagnosed with pseudotumor cerebri. She began taking acetazolamide, weight loss was recommended, and she improved. She felt that she was in remission for a while and was able to go back to work and resume her usual activities. She saw an endocrinologist and was taken off minocycline. She continued to get her previous migraines from time to time and tried an elimination diet for them but she never identified any food triggers.

She continued to take medications and things were under fairly good control until about 2009, after the birth of her children. There were no problems during pregnancies. Her recurrent symptoms were headaches, diplopia, intracranial noises and possibly other symptoms (she does not recall). She believes there was more vision loss than upon her original presentation. An LP in 5/09 showed high pressure and she had optic nerve sheath fenestrations sequentially OU within two weeks of the LP. Her vision came back and there has not been any significant disc edema since then.

Her pressures remained high and she continued to have headaches, despite taking 4500 mg of acetazolamide, furosemide, and spironolactone. A VP shunt was placed in 8/2010 and was revised in June 2011 and October 2011. There was no relief from the shunt. She used to get relief from an LP, for at least a few hours, but the past few times she has had an LP, she has felt worse afterwards. She has experienced low pressure headaches in the past and these headaches were different.

Her memory has been poor over the past few months and her vocabulary has declined. She loses words and interchanges words. She has been on Topamax for 5–6 years and she is weaning off it.

Sometimes she gets tunnel vision OU lasting up to an hour. She feels detached from the environment when this occurs, her hearing changes and she can't understand what people are saying. She gets dizzy and sometimes has a fever. She is always light sensitive and wears sunglasses all the time.

Her condition affects her children and their school performance and is "ruining her life." She is angry and guilty about the effect on her children. She has not been able to work for 4.5 years, although she was planning to return to work after the birth of her first child. It has affected her marriage—her husband is supportive but this affects his job (he has to take time off and she is afraid he will lose his job).

She was hospitalized in the past for "detox" which was not successful in relieving her headaches. She does not recall what she was given. She remained off narcotics for a while. The patient was scheduled to go to Johns Hopkins next week for a lumbar drain and prolonged CSF pressure monitoring but has cancelled the appointment for now. She related that doesn't think that measuring her pressure while she is in bed would accurately reflect what she experiences in real life.

Medications: Risperdone 2 mg BID, sodium bicarbonate 650 mg QID (metabolic acidosis), hydromorphone 4 mg 1–2 times daily in 2012, Vitamin D2, pericolace, methocarbamol 750 mg TID prn muscle spasms, Miralax, levothyroxine 75 mcg daily, acetazolamide 4 gm daily, methylphenidate 30 mg daily, L-methylfolate 15 mg daily, carvedilol 12.5 mg BID (tachycardia), ducosate 100 mg BID, ondansetron 8 mg daily, spironolactone 400 mg daily, KCl 20 mEq TID,

duloxetine 60 mg daily, topiramate 300 mg daily, diazepam 2 mg, up to 5 tablets (10 mg) q HS for sleep (takes it nightly), Butorphanol two 10 mcg patches weekly.

Recently prescribed but not currently taking: hydrocodone (prior to 2012), zolpidem, tizanidine, lidocaine patch. *She has been on daily pain medications since her first VP shunt.*

Previous medications:

Symptomatic treatment: Aspirin-acetaminophen-caffeine, ibuprofen, naproxen, sumatriptan, rizatriptan, zolmitriptan (no improvement). Not taken: rizatriptan, almotriptan, naratriptan, clonazepam.

Preventive treatment: Other antidepressants and headache preventives in the past - imipramine, gabapentin, propranolol, mirtazapine, bethanacol (sativation), quetiapine, atenolol, bupropion. Onabotulinumtoxin-A helped (she had her first injections in March 2012). Topiramate helped.

Vital signs: BP 128/92 | Pulse 106 | Ht 5' 7" (1.702 m) | Wt 149 lb (67.586 kg) | BMI 23.34 kg/m²

Examination:

Acuity (best corrected with correction): 20/25–1 OU, Near vision J3 OU.

Optic nerve functions: She identified 11/11 color plates OU
Pupils: 8 mm in darkness, reactive OU, no APD. Brisker response to near than to light.

External: Lid fissures 9 mm, Levator 16 mm OD, 14 mm OS. Normal cornea.

Motility: Normal motility, pursuits and saccades, fine nystagmus in extreme horizontal gaze

Fundi: No disc edema in either eye. No definite spontaneous venous pulsations (questionably present in the right eye).

Humphrey visual fields (24–2): Reliable indices OD. In the right eye the foveal threshold was 25 dB and the mean deviation was -12.91 dB. In the left eye, there were 8% false negative errors. The foveal threshold was 29 dB and the mean deviation was -14.04 dB. There was a generalized reduction in sensitivity in both eyes with inferonasal depression and enlargement of the blind spot.

PREVALENCE AND CHARACTERISTICS OF HEADACHE IN IIH AND THE PSEUDOTUMOR CEREBRI SYNDROME (PTCS)

Over 90% of patients with PTCS have headache at the time of their medical presentation. Headache was the initial symptom in 46 of 50 patients (95%) with IIH studied prospectively between 1982–1888 (1). 39 reported pulsatile pain, and 38 indicated that the headache had gradually increased in intensity over time. In 41 patients, the pain was different from previous headaches; 44 patients indicated that it was the most severe pain they had ever experienced, 25 had associated nausea and 19 had vomiting. 28 patients had neck stiffness. 29 patients related

that the headaches awakened them from sleep. 35 patients (64%) had daily headaches; intracranial hypertension is an important cause of New Daily Persistent Headache.

Headache characteristics were further elucidated in a series of 63 consecutive patients evaluated by questionnaire at the same institution (2). Headache was reported in 92% of patients, with 75% of them indicating daily headaches. The headache was generally pulsatile and severe, lasting longer than an hour. Worsening with Valsalva was only reported by one patient, and 10 patients experienced relief with non-steroidal anti-inflammatory drugs (NSAIDs). A postural component was uncommon. Many patients experienced focal pain and the location of the pain varied considerably. Frontal and retro-ocular locations were most prevalent. Other common symptoms included nocturnal awakening, neck stiffness, nausea and vomiting. Photophobia, phonophobia and diurnal variation were not specifically assessed.

Thus, the headache characteristics of PTCS are not specific. The head pain may be intermittent or constant, focal or generalized, and have migrainous or tension-type features.

Note: Baseline data regarding headache characteristics from the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) will be presented if available.

SHUNTING FOR HEADACHE

Shunting is often considered for PTCS patients who have intractable headaches. This option may be, in part, based on improvement in the headache following a lumbar puncture, an attempted “quick fix” of the disorder, an act of desperation for a suffering patient, or influenced by patient demand. While some patients’ headaches benefit from shunting, it is far from a panacea in this regard. The largest reported experience with shunting for headache in IIH was published by the group at Johns Hopkins School of Medicine. They studied 115 shunt procedures (79 lumboperitoneal and 36 ventriculoperitoneal or ventriculoatrial) in 42 patients (3). Forty-five percent of patient had one procedure, 24% underwent two, 19% underwent 3–5, and 12% had six or more procedures. Although 95% had a significant improvement in headaches one month after the procedure, headaches recurred in 48% of patients by 36 months. Lumboperitoneal shunts were more likely to require revision (86%) than ventricular shunts (44%). Overdrainage and tonsillar herniation only occurred with lumboperitoneal shunts, which were twice as likely as ventricular shunts to become obstructed. Ventricular shunts placed with frameless stereotactic guidance were all successfully placed but 75% failed by 24 months post-insertion. In this series, lack of papilledema and symptoms lasting longer than two years were risk factors for treatment failure. Ventriculoperitoneal shunts have the additional advantage of incorporating programmable valves, although their long-term utility in IIH has not been confirmed.

NATURAL HISTORY OF HEADACHE IN PTCS

Little is known about the natural history of headache in PTCS; the IIHTT will provide important information in this regard. A retrospective study of 82 patients with IIH assessed the character of the headache at presentation and after otherwise successful treatment of their condition, using the International Classification for Headache Disorders (ICHD) classification system (4). The presenting headache resolved after the initial lumbar puncture in 15 patients. 56 patients (68%) continued to experience headaches that were different in character from their “IIH headache” following stabilization or resolution of their IIH symptoms and signs (perimetry, papilledema, headaches). The most frequently reported headache phenotypes were episodic tension type headache, migraine without aura, chronic tension type headache, medication overuse headache, idiopathic stabbing headache and benign exertional headache. Six patients had probable migraine without aura (all criteria met except for the duration of head pain). 11 patients (13%) had headaches that could not be classified and 19 patients (23%) had more than one type of headache. Most patients improved with conventional symptomatic and prophylactic headache medications.

FACTORS TO CONSIDER WHEN DETERMINING HEADACHE TREATMENT

There are no evidence-based recommendations specifically for the treatment of headaches in patients with PTCS. Nonetheless, applying the principles used in the treatment of other headache disorders is useful when developing a treatment strategy for the patient. As with other headaches, one size does not fit all. Additionally, patients may have more than one type of headache.

A. PHENOTYPE OF HEADACHE

A thorough headache history will help determine which medications and therapies may be helpful. Features such as the character of the pain (e.g., aching, pressure, throbbing, pounding), location (including involvement of the neck), intensity, presence of associated symptoms (photophobia, phonophobia, nausea, vomiting, worsening with activity), duration (intermittent vs. constant), aggravating and alleviating factors help categorize the headache type. Refer to the ICHD (available on line, see references for link) to determine if the patient’s headache are most consistent with migraine, tension-type headache, hemicrania continua, etc. (5) The headache phenotype largely guides the treatment selection.

B. PRESENCE OF MEDICATION OVERUSE

Medication overuse headache (MOH) is suspected with ergotamine, triptan (any formulation), opioid, or combination preparation (such as opioids, butalbital, caffeine and simple analgesics) intake on at least 10 days monthly. Official ICHD criteria for MOH specify that the underlying headache is chronic (present more days than not) over a three month period, with worsening of the headache during the period of overuse and improvement within 2 months

after discontinuation of the overused medication(s) for an official diagnosis. In clinical practice, patients often report worsening of their headaches within weeks of medication overuse and, on the other end of the spectrum, some patients with chronic headaches cannot recall the timing of headache worsening. Moreover, a major flaw with the ICHD criteria for MOH is that improvement after medication discontinuation is required, so one can never make a definite diagnosis of MOH on the initial evaluation.

MOH was first reported in migraine patients but it occurs in almost every type of headache disorder, including PTCS related headaches. For practical purposes, a patient using pain medications or triptans more than two or three days a week is at risk for MOH; it a common problem in PTCS in my experience. The only “safe” medications to use three or more times weekly from the standpoint of MOH are naproxen and indomethacin. In general, the longer-acting NSAIDs are least likely to cause MOH. It is critical to ask patients specifically about over-the-counter medication usage as these agents are not likely to be reported on routine questioning or intake forms.

The strategy for withdrawing medications depends on the medication being overused. Simple analgesics and over-the-counter preparations can generally be stopped abruptly. Patients will often feel worse for a few days before they feel better, particularly if the preparation used contains caffeine. Moderate use of opioids can generally be managed with a fairly rapid taper. Heavy opioid use requires gradual withdrawal; consultation with pain management or hospitalization to control the headaches and withdrawal symptoms in the initial phases of withdrawal may be necessary. Excessive daily use of butalbital-containing compounds poses a challenge because of barbiturate withdrawal—substitution with phenobarbital with a subsequent phenobarbital taper is helpful in this circumstance.

While preventive medications are less likely to be effective in the setting of medication overuse, studies of chronic migraine indicate that patients with MOH benefit from preventive therapy (specifically shown in clinical trials of topiramate and onabotulinumtoxin-A). Therefore, preventive therapies may be offered to patients as they are discontinuing overused analgesics and probably offers psychological, as well as physiological, therapeutic benefit. One must also counsel the patient not to substitute other analgesics for the ones being discontinued unless under the physician’s direction.

C. PREVIOUS TREATMENTS TRIED

The medication history includes a recounting of all previous headache treatments including the highest dose used, duration of use, effectiveness and side effects experienced. The patient’s pharmacy can provide a list of prescriptions filled if the patient does not recall the details or if previous medical records are unavailable. It is not unusual for the patient to reject a particular medication because they “already tried it and it didn’t work,” only to find out that the

dose was subtherapeutic, the medication was not dosed correctly, or it was not taken for a long enough period of time to establish effectiveness. In the absence of side effects, a two month trial of any preventive medication at a therapeutic dose is required before discarding it as a treatment option.

D. OVERALL STATUS OF IIH

Headaches occurring at the time of the initial PTCS presentation and diagnosis are usually a direct result of intracranial hypertension and therapy is directed toward lowering the intracranial pressure. As the time interval from diagnosis increases, persistent headaches may not reflect specific changes in intracranial pressure and other forms of management are often helpful. Shunt malfunction or recurrent disease is suspected in patients with previously well-controlled symptoms who have a marked worsening of headaches, particularly if the pulse-synchronous tinnitus or visual symptoms returns. In my experience, most patients can identify their “pseudotumor headache” and distinguish it from other types of headaches with great accuracy. Although frequently performed, shunt series and imaging studies are notoriously unreliable for detecting shunt failure unless the shunt is physically disconnected along its course; a shunt tap or lumbar puncture may be necessary. The patient should have a pressure well within the normal range if the shunt is working properly.

E. PRE-EXISTING HEADACHE HISTORY

Headaches are highly prevalent in the population, and migraine affects 18% of women and 6–7% of men and children. Thus, there is a reasonable chance that the population of patients at risk for developing IIH and medication-included PTCS may have a primary headache disorder as well. In fact, many patients with PTCS are diagnosed because of a change in their previous pattern of headaches rather than the new onset of headache. The pre-existing headache will likely persist or re-emerge during the patient’s disease course and should be addressed appropriately.

F. COMORBID MEDICAL AND PSYCHIATRIC CONDITIONS

Consideration of the patient’s general medical history is necessary for several reasons. The selection of medication for headache treatment is largely determined by desired and undesired effects. Common conditions co-morbid with IIH include obesity, polycystic ovarian syndrome, obstructive sleep apnea, depression, anxiety and orthostatic edema (6–8). The patient may be taking medication for other medical conditions, which requires evaluation for possible drug interactions as well as headache as a possible side effect of current treatments. It may be advantageous to use the “two birds with one bird seed” approach when selecting a treatment that targets both headache and other conditions.

TREATMENT STRATEGIES

A. LIFESTYLE MODIFICATION

Lifestyle modifications may be beneficial, especially if there is a component of a primary headache disorder. Stress the importance of maintaining a regular sleep cycle, avoiding dehydration (while balancing any tendency for fluid retention), exercising regularly and eating regularly (i.e., not missing meals). As caffeine increases intracranial pressure, is a headache trigger in some patients and is a risk factor for headache chronification with overuse, it should be limited. Weight loss is stressed as a long-term intervention for ITH. It is noteworthy that obesity is also a risk factor for progression from episodic to chronic migraine.

B. TREATMENT OF MEDICATION OVERUSE

Overused medications must be discontinued (see previous section) incorporated with patient education.

C. PREVENTIVE MEDICATIONS

Preventive therapy (Table) is considered when patients are experiencing headaches more at least once a week, and is definitely recommended if they are using symptomatic therapy 3 or more days weekly. All preventive medications are started at a low dose, and the dose is gradually increased while monitoring effectiveness, tolerability and laboratory testing if needed. Patients may require more than one preventive medication with a different mechanism of action to achieve satisfactory headache control. Medication adherence tends to be better if the patient is forewarned about expected side effects. Medication options are listed below; this is not an exhaustive list but includes medications with the best level of evidence for migraine and tension-type headache prevention that I have found useful in patients with PTCS.

Topiramate is often a good choice because it has level A evidence for migraine treatment, it has mild carbonic anhydrase activity, and it may lead to weight loss (and rarely causes weight gain). It may be used concurrently with acetazolamide, although electrolytes should be checked when using high doses of both medications. The starting dose is 25 mg at bedtime (12.5 mg for small patients, children and those patients who generally do not tolerate medications well) and it is increased by 25 mg weekly. Most patients experience effectiveness at a dose of 200 mg daily or less. A higher dose may be used if the medication is tolerated. Doses over 200 mg daily may interfere with oral contraceptives, and topiramate is contraindicated during pregnancy (cleft palate). Depression is an infrequent side effect. Cognitive dysfunction is often the limiting factor of tolerability and does not improve unless the dose is decreased. *Zonisamide* may be considered in patients who cannot tolerate topiramate.

Tricyclic antidepressants, such as amitriptyline or nortriptyline, have the advantage of efficacy for both migraine and tension-type headache prophylaxis (Level A

evidence). They are generally sedating, and thus helpful for patients who have difficulty sleeping at night. The starting dose of either medication is 10 mg at bedtime; most patients experience effectiveness with 100 mg daily or less of amitriptyline and 75 mg or less of nortriptyline. Protriptyline has less cholinergic side effects and may be alerting, rather than sedating; the starting dose is 5 mg BID. The limiting consideration for tricyclic antidepressants in this population is weight gain, which occurs frequently as a side effect. Other common side effects are dry mouth, constipation (add magnesium oxide 300–400 mg daily), tachycardia/palpitations. EKG monitoring is recommended in children.

Beta blockers, such as propranolol, nadolol, atenolol and timolol are helpful when the headaches have migrainous features (level A evidence). They are not particularly useful for the tension-type headache phenotype. They are contraindicated with concurrent asthma or COPD and may precipitate asthma or Raynaud's phenomena in patients without a history of either disorder. Common side effects are fatigue, exercise intolerance, orthostatic hypotension, and sexual dysfunction. Depression may occur. The starting dose of propranolol is 10 or 20 mg BID (much higher doses may ultimately be needed); atenolol and nadolol are started at 25 mg daily.

Calcium channel blockers, such as verapamil or amlodipine, do not have as strong level of evidence for efficacy as the preceding medication for migraine prevention but are helpful in some patients. They may cause peripheral edema and constipation (add magnesium oxide 300–400 mg daily). EKG monitoring is needed at higher doses (>300 mg daily) because of potential heart block. The starting dose of verapamil is 40–80 mg BID, amlodipine is started at 5 mg daily.

SSRI/SNRIs, particularly fluoxetine and venlafaxine, have level B evidence for efficacy in migraine prevention and are helpful in patients with co-existing depression and anxiety. Vivid dreams, loss of emotion, and weight gain are common side effects. Headache is the most commonly reported side effect in clinical trials but seldom occurs when being used for headache prevention. Bupropion, while not studied for migraine prevention, has the advantage of not producing weight gain and may be associated with modest weight loss. Bupropion may produce insomnia.

The NSAIDs *naproxen and indomethacin* may be employed for daily use with a low risk of MOH. Indomethacin appears to reduce cerebrospinal fluid (CSF) pressure in addition to its anti-inflammatory and analgesic properties (9, 10). Indomethacin is particularly helpful in patients with constant unilateral headaches, headaches associated with Valsalva maneuver and patients with brief episodes of stabbing pain. Both medications may cause significant gastrointestinal side effects (nausea, pain, ulcer, diarrhea). The starting dose of indomethacin is 25 mg BID or TID with meals; increasing to 150 mg daily if needed and tolerated.

Gabapentin has the advantage of having very few drug interactions, as it is primarily excreted by the kidneys. While it does not have a high level of efficacy for migraine in clinical trials, it is beneficial in some patients. It is quite sedating in some patients and I will often start with 100 mg at bedtime to assess tolerability. The general starting dose is 100 mg TID and the maximum dose is 3600 mg daily. Confusion and weight gain may occur.

Natural preventives: Vitamin B2 (riboflavin 300–400 mg daily), butterbur (Petadolex™ 150 mg daily), magnesium oxide (300–400 mg daily).

Valproate (sodium valproate, valproic acid) has level A evidence for migraine prevention but is not recommended for treating headaches in this population because of the side effect profile. Weight gain from valproate may be dramatic. Valproate is associated with the development of polycystic ovarian syndrome in young women and is contraindicated during pregnancy (neural tube defects). GI side effects, tremor and alopecia are common.

Onabotulinumtoxin-A is indicated for the treatment of chronic migraine (headache at least 15 days monthly for three months with a previous or current history of migraine). This option is appropriate in patients with a history of PTCS who meet criteria for the diagnosis of chronic migraine. Most insurers require that the patient has tried two Level A preventive medications to obtain coverage. The diagnosis of chronic migraine and documentation of headache disability must be documented in the medical records. Injections are given every three months.

D. SYMPTOMATIC HEADACHE TREATMENT

Symptomatic headache treatment is needed for acute exacerbations of head pain. The goal of symptomatic treatment is rapid pain relief and must be balanced with the risk of MOH if they are used too frequently. One must consider that, despite your best intentions, patients may receive symptomatic medications from other sources, including over-the counter purchases, other physicians, the emergency department, and even friends and relatives. Patients should be cautioned to avoid using symptomatic treatments (except naproxen and indomethacin) more than 3 days weekly.

Acetaminophen (paracetamol) is widely available and often used as a first line agent. It is associated with liver toxicity with doses over 3 gm daily and may lead to MOH.

Aspirin is not likely to cause MOH but may cause GI side effects, easy bruising and prolonged bleeding time, and tinnitus at high doses.

NSAIDs, such as ibuprofen, diclofenac, naproxen, indomethacin, ketorolac, celecoxib and meloxicam may be helpful. Some of these medications are available in formulations containing caffeine (for migraine), diphenhydramine or other compounds. Liver toxicity may occur with frequent use; GI side effects are

common. These drugs must be avoided in the last trimester of pregnancy. Ketorolac is limited to 15 doses monthly to avoid renal impairment.

Triptans may be used for migraine-like exacerbations, or in patients with co-existing migraine. Quantity limits by insurance companies generally preclude the development of MOH but patients sometimes get different triptan formulations from different providers and the insurance may cover them all.

Butalbital and opioids are not particularly helpful for headaches in general, have a risk of dependence and MOH, and are typically avoided unless the patient has a contraindication to triptans and other medications.

Antiemetics are a helpful adjunctive therapy when there is associated nausea and/or vomiting.

In the ED, infusion center or inpatient setting, intravenous dihydroergotamine, anti-emetics (phenothiazines, diphenhydramine, 5HT-3 blockers), ketorolac, acetaminophen, magnesium and other therapies used for migraine may be employed.

E. ADDRESS CO-MORBID ANXIETY AND DEPRESSION

As with other chronic headache disorders, anxiety and depression commonly occur in patients with IIH (7). Fear of blindness and recurrent pain, loss of employment and the associated stresses on patients and their family impact patients with PTCS. Counseling (including family therapy when appropriate), referral to a psychiatrist, stress management, cognitive behavioral therapy and biofeedback are important adjunctive treatments to a multi-disciplinary approach.

F. THE NECK AND BACK

Patients with chronic headaches frequently also have neck and upper back pain; neck pain commonly occurs as an initial symptom of IIH (1,2). C2 and C3 provide direct input into the trigeminal nucleus caudalis, one of the key brainstem structures involved in the generation of cephalgia. Thus, the neck may contribute to headache and may also be a therapeutic window for modulating head pain. A good physical therapist with expertise in cervicalgia may significantly benefit for patients who have associated neck pain.

SUMMARY

In summary, the treatment of headaches associated with IIH and PTCS often requires a multimodal approach. In the acute stage, treatment of the CSF pressure is often beneficial. However, many patients have persistent headaches which require strategies similar to those used in patients with chronic primary headache disorders. The use of shunts for headache treatment is generally not advised.

CME ANSWERS

1. c
2. e
3. d

REFERENCES

1. Wall M, George D. Idiopathic intracranial hypertension. A prospective study of 50 patients. *Brain*. 1991;114:155-80.
2. Wall M. The headache profile of idiopathic intracranial hypertension. *Cephalalgia*. 1990;10:331-5.
3. McGirt MJ, Woodworth G, Thomas G, Miller NR, Williams M, Rigamonti D. Cerebrospinal fluid shunt placement for pseudotumor cerebri-associated intractable headache: predictors of treatment response and analysis of long term outcomes. *J Neurosurg*. 2004;101:627-32.
4. Friedman DI, Rausch EA. Headache diagnoses in patients with treated idiopathic intracranial hypertension. *Neurology*. 2002;58:1551-3.
5. Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders, 2nd edition. *Cephalalgia*. 2004;24(Suppl 1):1-151.http://www.ihs-headache.org/upload/ct_clas/ihc_II_main_no_print.pdf
6. Friedman DI, Streeten DHP. Idiopathic intracranial hypertension and orthostatic edema may share a common pathogenesis. *Neurology*. 1998;50:1099-104.
7. Kleinschmidt JJ, Digre KB, Hanover R. Idiopathic intracranial hypertension. Relationship to depression, anxiety, and quality of life. *Neurology*. 2000;54:319-24.
8. Purvin VA, Kawasaki A, Yee RD. Papilledema and obstructive sleep apnea. *Arch Ophthalmol*. 2000;118:1626-30.
9. Imberti R, Fuardo M, Bellinzona G, et al. The use of indomethacin in the treatment of plateau waves: effects of cerebral perfusion and oxygenation. *J Neurosurg* 2005; 102:455-459.
10. Förderreuther S, Staube A. Indomethacin reduces CSF pressure in intracranial hypertension. *Neurology* 2000; 10:1043-1045.

TABLE: PREVENTIVE MEDICATIONS FOR HEADACHE

Medication	Starting dose	Consider with co-morbid:	Avoid with:	Common side effects	Lab testing needed
Topiramate	12.5—25 mg HS	Obesity, epilepsy, essential tremor	OCP over 200 mg daily, pregnancy	Paresthesias, fatigue, weight loss, cognitive dysfunction	
Amitriptyline, Nortriptyline	10 mg HS	insomnia	Obesity, mania	Weight gain, dry mouth, constipation, palpitations	EKG (children)
Propranolol	10–20 mg BID	Hypertension, essential tremor, anxiety	Raynauds, COPD, asthma, hypotension, concurrent calcium channel blocker	Orthostatic hypotension, fatigue, exercise intolerance, sexual dysfunction, depression	
Atenolol, Nadolol	25 mg q AM	Same as propranolol			
Verapamil	40–80 mg BID	Hypertension	Orthostatic edema, arrhythmia, concurrent beta blocker	Peripheral edema, constipation	EKG
Fluoxetine	10–20 mg daily	Depression, PMS, OCD	Mania	Vivid dreams, weight gain, loss of emotion	
Venlafaxine	37.5 mg BID	Depression, anxiety, OCD	Mania	Vivid dreams, weight gain, loss of emotion	
Bupropion	100–150 mg q AM	Depression, smoking cessation		insomnia	
Valproate	500 mg daily (ER)	Epilepsy	Pregnancy	Weight gain, PCOS, alopecia, GI side effects, tremor	LFTs in children

IIH IN KIDS

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LEARNING OBJECTIVES

1. Become familiar with common dosages of IIH medications used in children
 2. Identify the differences in clinical and demographic features between pre and post pubescent children with IIH
 3. Identify which clinical and testing variables may influence CSF opening pressure measurements in children
3. An 11 year old with intermittent headache and flat optic nerves undergoes a lumbar puncture that demonstrates an opening pressure of 26 cm of H₂O. Which of the following factors most likely influenced the opening pressure result?
 - a. Patient age (since he is pre-pubescent)
 - b. Flexed lateral recumbent position during the procedure
 - c. Body mass index
 - d. Gender
 - e. Patient required deep sedation due to anxiety

CME QUESTIONS

1. A 7 year old male with a BMI in the 50th percentile presents with bilateral papilledema, bilateral sixth nerve palsies, mild visual field loss and a CSF opening pressure of 35 cm H₂O. The contents of his CSF are normal and no other etiology is discovered. After the LP and treatment with acetazolamide, all symptoms resolve. Based on the newly proposed criteria for pre-pubescent IIH, this patient:
 - a. Did not have IIH because they have cranial nerve palsies.
 - b. Did not have IIH because he didn't complain of headache.
 - c. Did not have IIH because he isn't obese.
 - d. Had IIH since the newly proposed criteria permit cranial nerve palsies that resolve and no other etiology is discovered.
2. An 8 year old presents with IIH confirmed by a neuro-ophthalmologist. Which of the following clinical features are typical of children this age with IIH:
 - a. Less often obese compared with post-pubescent children
 - b. Larger portion of male subjects compared to teenagers with IIH
 - c. Etiology is more commonly discovered as compared to adult subjects
 - d. All of the above

KEYWORDS

1. IIH
2. Pediatric
3. Opening Pressure

INTRODUCTION

CASE:

12 yo boy presents after 2 weeks of intermittent head pain described as "pulling" or "lightning bolts" across the back of the head. He has also complained of fatigue and occasional double vision for the past two weeks. Past medical history is significant for mild pervasive developmental disorder, but he is otherwise healthy and denies use of medications.

Exam: Weight = 72 kg, height = 153 cm, BMI = 29.9 (> 95th percentile for age), VA 20/25 OU, identified 8/8 color plates OD/OS. automated visual field (Humphrey) demonstrated enlarged blind spots OU and diffusely constricted fields (MD -12 db). Ophthalmoscopy revealed bilateral papilledema.

Evaluation: MRI/V: normal. Lumbar puncture opening pressure = 51 cm H₂O. No WBC's in CSF and protein normal. Lyme studies negative. No immediate change in symptoms after the LP.

Treatment: Started on acetazolamide ER 500 BID and referred for Neuro-Ophthalmologic consultation. Two weeks after starting acetazolamide, patient continues to report intermittent head pain described as "pulling" or "lightning bolts" across the back of the head without significant change in his HVF or optic nerves.

Audience question: 1) Discontinue acetazolamide; 2) increase acetazolamide; 3) add furosemide; 4) add topiramate; 5) refer for ONSF or VPS

In this review, I will describe the similarities and differences in the diagnosis and treatment of IIH in children and adults. While IIH can occur at any age, there are important demographic and clinic features that also differ among pediatric age groups. Additionally, I will discuss previously proposed modifications to the diagnostic criteria of pediatric IIH.

EPIDEMIOLOGY

IIH is more common in adults than children, with a reported incidence in obese females as high as 20 per 100,000 adults (1). In children, the incidence is believed to be closer to 1 per 100,000 (2). However, when age of onset is considered, the incidence rate increases with age since slightly more than half of pediatric onset IIH is believed to occur after 10 years old (3). When factoring both gender and age together, males 2–11 years old have the lowest incidence (0.4 per 100,000), followed by males 12–15 years old (0.8 per 100,000), then females 2–11 years old (1.1 per 100,000) and older females 12–16 years old (2.2 per 100,000)(2). Investigators have likely chosen age cut-offs around 10 and 11 years old as the child is nearing the suspected onset of puberty. Clearly puberty is an important factor, but it can normally occur years apart within and between genders. Unfortunately, no pediatric studies have performed accurate staging of puberty in their subjects. In children who are post-pubescent, they tend to be predominantly female and overweight—similar to adults with IIH(4).

Obesity is a risk factor for IIH, but primarily in older children. Balcer and colleagues demonstrated that obesity was present in only 43% of children 11 years old and younger, whereas it was present in 81% of 12–14 year olds, and 91% of 15–18 year olds(4). This same study also found that the younger group was equally male and female, whereas the older children groups were 88% and 100% female (4). Understanding the influence of age, gender and obesity is paramount in evaluating a child with a suspicion of new onset IIH. Children without common precipitating factors or typical demographic features of IIH may warrant a more thorough evaluation to rule out secondary causes of elevated intracranial pressure.

PRECIPITATING FACTORS

A number of medical conditions and therapies have been known to precipitate IIH. Since the definition of IIH implies no known etiology, I will refer to these as precipitating factors for IIH. Approximately one-half to three-quarters of children are reported to have precipitating factor for their presumed IIH (5, 6). There is some debate about whether these associated conditions truly represent IIH or rather should be considered isolated causes of elevated ICP. Numerous medical conditions identified during childhood are believed to be associated with an increased risk of IIH including Down's syndrome, Turner's syndrome, sickle

cell anemia, iron deficiency anemia, aplastic anemia, measles, varicella, galactosemia and Hunters syndrome. Treating pediatric and adults for acute myeloid leukemia and acute promyelocytic leukemia using all trans-retinoic acid (ATRA) has also been implicated as a risk factor for IIH. In teenagers, acne vulgaris is still frequently treated with minocycline and Retina-A—both known to precipitate IIH.

Pediatric endocrinologic conditions and or treatments are the most frequently identified precipitating factors for IIH in children. Growth hormone, primarily used for congenital short stature, has a well established relationship with IIH, commonly occurring after initiating or increasing the dose. Discontinuing and or decreasing growth hormone therapy has resulted in resolution of IIH. Long term corticosteroids are frequently used to treat children with inflammatory and autoimmune conditions such as nephrotic syndrome or irritable bowel disease. All of these conditions have reported pediatric onset of IIH after or while withdrawing the corticosteroid. Levothyroxine for hypothyroidism has also been associated with pediatric IIH.

SYMPTOMS

While many of the presenting symptoms in IIH are similar to adults, there are a few key differences in children. Although children report similar headache features as adults, a number of published studies have described children with IIH who present without headache. It is unclear why these children do not have headache. Papilledema was likely discovered because either the child was being examined for another symptom or they were at age when routine eye exams are performed which incidentally revealed papilledema. Younger children may have more difficulty articulating their symptoms or have more nonspecific symptoms such as irritability or malaise. While sixth nerve palsies in adult IIH are reported to occur infrequently (i.e., 12%), some pediatric series have reported similar rates, but also rates as high as 48% (3, 7, 8). Interestingly, a series by Phillips (7) found more younger children (59%) than older children (39%) had cranial nerve palsies.

The effect of papilledema on the afferent visual system is similar in both adults in children. The challenge in caring for pediatric patients with IIH is that some may be too young to reliably complete automated or kinetic visual field testing. One must be cautious when interpreting visual field examinations in younger patients, especially those with only mild to moderate papilledema. Similar to headaches, some children will have difficulty articulating visual symptoms of diplopia (“blurry” versus “double”).

DIAGNOSIS

With the exception of pre-pubescent children, the diagnostic criteria for IIH in adults can be applied to post-pubescent children since they share similar clinical features (9). However, for pre-pubescent children, Ko and Liu(10) proposed a modified criteria that includes the addition of the following: symptoms specific to generalized increase

in ICP (e.g., blurry vision, neck pain, malaise) in the setting of a normal mental status, cranial nerve palsies without another identifiable etiology that are relieved by lowering ICP, and an opening pressure greater than 28 cm H₂O. The requirement of a higher CSF opening pressure (OP, i.e., greater than 28 cm H₂O) rather than the previously proposed 25 cm H₂O was prompted by two pediatric (11, 12) and one adult study (13) demonstrating the OP of 28 cm H₂O can be classified as normal. Since the accurate measurement and interpretation of the cerebrospinal fluid OP is paramount to the diagnosis of IIH in children, I will spend the next five minutes reviewing what factors influence these measurements in children and provide a framework for interpreting the results.

The reference range values for OP measures in children do not differ between ages. Whether examined as a continuous variable or a binary variable (i.e., above or below 10 years old), age does not impact CSF-OP measures (11, 12). While there was a trend for younger children to have lower OPs, it did not reach statistical or clinical significance. The lack of relationship between age and OP is perplexing to some investigators. However, if CSF-OP is comparable or even related to blood pressure, age-related changes in blood pressure are relatively small. For example, the 90th percentile of systolic blood pressure in a 10 year old is only 10% higher than a 1 year old. If one were to expect a 10% difference in OP between these ages, it would equate to a change of 2 centimeters of water.

Sedation appears to be the largest factor influencing CSF-OP measures in children even when controlling for age and obesity. Many children, especially those less than 14 years old require sedation to complete the LP due to anxiety, desire for pain free procedures, and clinicians concern that a non-sedated LP might be less successful. Our study found that moderate to deeply sedated children have an opening pressure nearly 5 centimeters higher than the non-sedated children independent of age and sedation medication (11). While sedation does eliminate the possibility of increasing intraabdominal pressure—known to falsely elevate OP measures(14)—deep sedation likely produces a mild hypercapnia, thereby elevating the CSF-OP measures(15). Some providers interpret relief of headache and other symptoms after the LP as evidence of elevated ICP. The frequent use of sedation complicates this interpretation as anesthetics themselves provide headache relief.

Obesity has shown to have a statistically significant impact on the CSF-OP in adults(13) and in children independent of age and depth of sedation(11). Specifically, for every increase in 10 units of BMI, the OP would increase approximately 3 centimeters of H₂O. While this is a relatively small change in OP for relatively large swings in weight, it provides further support that obesity is a common theme among those with IIH.

The influence of multiple variables on the OP measure in children requires careful interpretation. No one expects the clinician to calculate odds ratios from regression models while examining patients. How does the clinician make sense of these multivariable statistics? It is important to remember these data are derived from a large group of individuals. Most of the factors influencing OP (i.e., sedation and BMI) have modest effects on the final result and may not impact your interpretation of the entire clinical picture. For example, an OP of 42 cm H₂O is clearly abnormal regardless of their level of sedation or BMI. However, if this patient has no signs or symptoms of elevated ICP, the accuracy or meaning behind the OP measure should be questioned. On the other hand, a child with an OP of 26 cm H₂O performed under deep sedation should provide reassurance that elevated ICP is less likely, especially in the absence of objective findings such as papilledema or a sixth nerve palsy. Despite our reference range defining a cut-off value of 28 cm H₂O, the provider must equally consider the history and clinical examination when deciding whether the child likely has elevated ICP.

TREATMENT

The treatment of IIH is very similar among adults and children. Most commonly, the risk factor (e.g., obesity) or precipitating factor (e.g., minocycline) causing IIH must be removed. Medication dosing in children is determined by weight and occasionally this is altered according to age and potential side effects. The primary medical treatment of pediatric IIH is acetazolamide with a starting dose of 15–20mg/kg/day divided into two or three doses. The maximum dose of acetazolamide is approximately 50mg/kg/day. For younger children unable to take the larger, extended release tablets, most pharmacies can create a suspension (typically 250mg/5 ml). To my knowledge, the side effect profiles are similar. Furosemide is a second line treatment has a starting dose of 0.5–2.0 mg/kg/day (maximum 6mg/kg/day). Furosemide is also available in a suspension, but may not be readily available at all pharmacies. Topiramate is another second line agent with a starting dose of 1–2mg/kg/day (start at 25mg q hs, maximum 200mg per day). For children unable to swallow topiramate tablets, sprinkle caps or suspension compounded at the pharmacy is available. Many parents and providers have concerns about the cognitive side effects of topiramate in school-aged children. Adequate hydration is imperative for children taking acetazolamide, furosemide and topiramate.

Treatment of progressive or malignant IIH includes high-dose IV corticosteroids (methylprednisolone) at 15–20mg/kg/day divided every six to twelve hours with a maximum dose of 1 gram per day. Similar side effects and benefits have been reported in children with malignant IIH undergoing optic nerve sheath fenestration. CSF shunting procedures are performed in children with severe IIH, although the frequency and preferred method (i.e., ventriculoperitoneal shunt (VPS) or lumboperitoneal

shunt) is typically institution specific, with VPS being much more common in children. To my knowledge, venous sinus stenting has not been performed in children.

SUMMARY

In summary, pre-pubescent children with IIH have clinical and epidemiologic features that distinguish them from post-pubescent children and adults. These features along with a redefined value of a “normal” OP have resulted in newly proposed diagnostic criteria for IIH in pre-pubescent children.

CASE REVISITED:

Audience question: 1)Discontinue acetazolamide; 2) increase acetazolamide; 3)add furosemide; 4)add topiramate; 5)refer for ONSF or VPS

CME ANSWERS

- 1) d. Cranial Nerve Palsies That Resolve with Lowering The ICP and No Other Etiology is Discovered Are Permitted in Pre-Pubescent IIH.
- 2) d. All of the Above.
- 3) e. Patients Under Moderate-Deep Sedation Demonstrate Higher OP Values Compared to Those Not Under Sedation. Obesity May Influence OP, but This Requires Large Changes in BMI (I.E., 15 Points) to Demonstrate a Comparable Change to Deep Sedation.

REFERENCES

1. Durcan FJ, Corbett JJ, Wall M. The incidence of pseudotumor cerebri. Population studies in Iowa and Louisiana. *Arch Neurol*, 45(8):875–7. 1988.
2. Gordon K. Pediatric pseudotumor cerebri: descriptive epidemiology. *Can J Neurol Sci*, 24(3):219–21. 1997.
3. Babikian P, Corbett J, Bell W. Idiopathic intracranial hypertension in children: the Iowa experience. *J Child Neurol*, 9(2):144–9. 1994.
4. Balcer LJ, Liu GT, Forman S, et al. Idiopathic intracranial hypertension: relation of age and obesity in children. *Neurology*, 52(4):870–2.1999.
5. Scott IU, Siatkowski RM, Eneyni M, et al. Idiopathic intracranial hypertension in children and adolescents. *Am J Ophthalmol*. 124(2):253–5, 1997.
6. Youroukos S, Psychou F, Fryssiras S, et al. Idiopathic intracranial hypertension in children. *J Child Neurol*. 15(7):453–7. 2000
7. Phillips PH, Repka MX, Lambert SR. Pseudotumor cerebri in children. *JAAPOS* 2(1):33–8. 1998.
8. Kesler A, Fattal-Valevski A. Idiopathic intracranial hypertension in the pediatric population. *J Child Neurol*, 17(10):745–8. 2002.
9. Rangwala L, Liu G. Pediatric Idiopathic Intracranial Hypertension. *Survey of Ophthalmology*. 52(6):597–617. 2007.
10. Ko MW, Liu GT. Pediatric idiopathic intracranial hypertension (pseudotumor cerebri). *Horm Res Paediatr*. 74(6):381–9. 2010
11. Avery RA, Shah SS, Licht DJ, et al. Reference range for cerebrospinal fluid opening pressure in children. *N Engl J Med*. 363(9):891–3. 2010.
12. Lee MW, Vedanarayanan VV. Cerebrospinal Fluid Opening Pressure in Children: Experience in a Controlled Setting. *Pediatric Neurology*. 45(4):238–40. 2011.
13. Whiteley W, Al-Shahi R, Warlow CP, et al. CSF opening pressure: Reference interval and the effect of body mass index. *Neurology*. 67(9):1690–1. 2006.
14. Neville L, Egan RA. Frequency and amplitude of elevation of cerebrospinal fluid resting pressure by the Valsalva maneuver. *Can J Ophthalmol*. 40(6):775–7. 2005.
15. Lim MJ, Lin J-P. The effects of carbon dioxide on measuring cerebral spinal fluid pressure. *Child’s Nervous System*. 25(7):783–4. 2009.

CSF SHUNTING PROCEDURES IN IDIOPATHIC INTRACRANIAL HYPERTENSION (IIH)

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LEARNING OBJECTIVES

1. To become familiar with the different CSF shunting options for patients with IIH
2. To identify the advantages and disadvantages of using VP vs. LP shunts
3. To discuss the steps involved in diagnosing shunt malfunction

CME QUESTIONS

1. What are the potential challenges associated with LP shunt insertion and management?
 - a. Body habitus makes positioning and insertion difficult
 - b. The absence of a valve increases the risk of low-pressure signs and symptoms
 - c. High rate of obstruction and difficulty assessing an obstructed LP shunt
 - d. Difficult to evaluate infection
 - e. All of the above
2. List the different steps involved in assessing VP shunt malfunction
 - a. Bedside valve interrogation
 - b. Shunt series
 - c. Tapping the reservoir
 - d. Shuntogram
 - e. Intraoperative interrogation
 - f. All of the above
3. Identify the challenges associated with VP shunt insertion in IIH patients and ways to mitigate them.
 - a. Normal or small ventricles: use neuronavigation for insertion
 - b. Signs and symptoms of over-drainage: use anti-siphon device or programmable valve
 - c. A and B are correct
 - d. Neither A or B are correct

KEYWORDS

1. Idiopathic Intracranial Hypertension
2. Ventriculoperitoneal Shunt
3. Lumboperitoneal Shunt
4. Lumbar Drain

INTRODUCTION

A 48 year old obese female, presented with worsening of her longstanding holo-cephalic headaches, nausea and transient visual obscurations. Her physical examination on two different occasions revealed progressive worsening of her bilateral papilledema. Her MRI revealed significant narrowing of the transverse sinuses bilaterally without evidence of venous sinus thrombosis. A lumbar puncture revealed an opening pressure of 31 cm of water. A trial of acetazolamide was not successful. The patient underwent insertion of a ventriculo-peritoneal shunt. Post-operatively, her headaches and visual signs and symptoms improved significantly.

Despite medical treatment of IIH and repeated lumbar punctures, some IIH patients have persistent papilledema with visual loss, chronic headaches, increased LP opening pressure, prompting the need for more aggressive treatment (1,2). Furthermore, even after “full recovery” or prolonged interval of clinical stability, the symptoms may recur in up to 38% of patients after a time period of up to 7 years (12,13). All of these factors suggest a need for a systematic approach to CSF diversion when conservative measures fail. In this review, we will focus on the surgical strategies for CSF diversion, in hopes of providing a practical overview.

CSF DIVERSION PROCEDURES

Several procedures result in CSF diversion, thereby decreasing intracranial pressure (ICP). They are sometimes indicated in IIH patients with refractory headaches related to persistent elevated ICP or those with visual loss.

INTERMITTENT PROCEDURES

SERIAL LUMBAR PUNCTURES

Lumbar punctures can be used to decrease the ICP in patients with medically refractory IIH or in cases with contraindications to carbonic anhydrase inhibitors (such as early pregnancy). In

a minority of cases, however, a single lumbar puncture, usually the diagnostic one, may suffice to improve or even reverse the symptoms (15). It is hypothesized that in these cases, the subtraction of CSF from the intracranial compartment, is compensated for (in line with the Monro-Kellie hypothesis) by enlargement of collapsible central venous segments which in turn reduces venous hypertension, promotes CSF absorption, and causes further venous enlargement and pressure reduction in a cyclic manner until a new steady state is attained (2, 16, 1). While this hypothesis of a “causative self-limiting venous collapse” can explain the clinical improvement after single or serial lumbar punctures and during continuous CSF drainage, it still cannot predict which patient would require continuous shunting as opposed to serial punctures. Finally, the benefit of serial lumbar punctures must be weighted against its potential side effects, such as infections, and patient’s discomfort. Furthermore, lumbar puncture may be particularly difficult and hence less appealing in patients with high BMI.

LUMBAR DRAIN

Rarely, IIH patients presenting with a fulminant form and severe visual loss might benefit from a lumbar drain while awaiting a more definitive treatment. A lumbar drain can be inserted by the bedside or in the interventional radiology suite. Fluoroscopic guidance is useful especially in IIH cases where patients’ body habitus may make the identification of osseous landmarks particularly challenging. The lateral decubitus position is used; with the head flexed, chin on the chest, and legs maximally flexed toward the head. The L4–5 interspace is identified in a perpendicular line from the iliac crest or via fluoroscopy. After appropriate prepping, draping, and injecting the entry site with 1% lidocaine, the spinal needle is inserted into the interspace with the bevel up. The sylet is removed intermittently every 3 mm as the needle is advanced in order to check for CSF flow. Once flow is established and CSF samples are taken if needed, an epidural catheter is threaded and the needle is withdrawn. The catheter is then connected to a drainage system. The zero reference point is set at the level of the external auditory meatus. The amount of CSF drained per hour is regulated by the height of the drain in relation to that reference point.

SURGICAL IMPLANTS

SHUNTING

Severe intractable headaches, progressive visual loss in spite of maximal medical therapy constitute the major indications for shunting in patients with IIH (2, 17–22). The alleviation of headaches is achieved in most patients soon after shunting (3, 17–22). Long term relief is sustained in about 50% of the patients (30). Negative predictive factors for shunt failure in the treatment of IIH associated headaches include lack of papillaedema at presentation and long-standing (> than 2 years) symptoms (36). The visual outcome following shunting, however, is less uniform. Some have reported improvement and stabilization of visual symptoms in 95–100% of patients (17–20,31). Others have shown that vision continued to worsen in up to 30% of the cases (21).

LUMBAR PERITONEAL SHUNTS

Historically, lumbar peritoneal (LP) shunts were the mainstay CSF diversion therapy for IIH. The traditionally cited advantage of LP shunts over ventriculoperitoneal (VP) shunts is the ease of insertion in IIH patients who usually have small and sometimes difficult to catheterize ventricles (23, 24, 25). This is particularly true with the percutaneous method pioneered by Spetzler (26). Multiple studies have shown that when functional, LP shunts are effective in alleviating headaches and improving or stabilizing visual symptoms in patients with IIH (27–29, 33). In 1997, Burgett et al. published a series of 30 patients with IIH who underwent LP shunting. The mean follow-up period was 35 months. Seventy one percent of the examined eyes improved by at least two chart lines and only 1 eye experienced a decline in vision. Visual field improved in 64% of eyes with abnormal fields, and no eyes exhibited any worsening (27). Almost simultaneously, Eggenberger et al. (28) retrospectively reviewed 27 patients with IIH, who were observed for a median of 47 months post-shunting. Fourteen patients presented with visual loss and 13 with headaches. Vision improved or remained the same in all 14 patients, and headaches improved in all patients. In both studies and in many others, the most common complication was shunt obstruction. Eighteen of 30 patients in the Burgett et al. study (27) required shunt revision at a rate of 2.5 revisions/ patient. Four patients required exceptionally high number of revisions (38, 29, 10, 10 revision, respectively).

The revision rate due to obstruction in the Eggenberger et al study (28) was 65%. Radiological imaging is not helpful in detecting these obstructions since the ventricular size does not usually change. LP shunt obstruction can be detected by nuclear medicine studies that may reveal tracer flow into the abdomen and provides half-life time of radionuclide clearance. Other less frequent yet significant complications of LP shunts include infection, radiculopathy, shunt migration, syrxinx, low pressure headaches, tonsillar herniation, subdural hematomas.

The primary advantage of a lumbar peritoneal (LP) shunt over a ventriculoperitoneal (VP) shunt is the ability to cannulate the CSF space, in this case the thecal sac, as opposed to having to cannulate the very commonly found slit ventricles associated with IIH when considering a VP shunt. However, there are also a series of challenges associated with LP shunts that can be categorized based on insertion, perioperative immediate and delayed.

TECHNICAL INSERTION RELATED CONSIDERATIONS

Generally these patients are positioned in the lateral position to provide simultaneous access to the lumbar spine and flank. Given the often associated obesity this positioning itself creates some real challenges on a standard bed to maintain the position. The insertion site of the proximal catheter into the thecal sac can be very challenging given the body habitus. Percutaneous cannulation of the thecal

sac can be very challenging, often requiring specific long needles. Additionally, it is often difficult to get the flexion (“fetal position”) required in these patients to open the inter-laminar space and allow for the needle to access the thecal sac. This may require the use of intraoperative fluoroscopy which may be relatively less reliable. Once the proximal catheter enters the thecal sac it needs to be threaded cranially into position, which is at times challenging as the catheter often kinks within the significant tissue volume.

Following placement of the proximal catheter, the remainder then needs to be tunneled through the subcutaneous tissue into the flank region. At this point, while in the lateral position and with the significant amount of adipose tissue, the surgeon then needs to identify the peritoneum. This can prove to be quite challenging given the non-anatomic patient’s position as well as the fact that gravity is working against the surgeon. At this point the catheter is then passed into the flank within the peritoneum.

POSTOPERATIVE CONSIDERATIONS

In the immediate period postoperatively there are several key issues. The first is that in general these LP shunt systems are placed without regulatory valves or antisiphon devices. As a result, the system relies on gravity for regulation of the amount of CSF to be drained. These patients can experience unregulated over drainage “siphon effect.” This can lead to severe positional headaches similar to the phenomena associated with lumbar punctures and low-pressure headaches; and perhaps, in severe situations, can lead to tonsillar herniation. Usually the system equilibrates over a few days postoperatively once the patient starts to ambulate but there is often an adjustment period with low- pressure headaches.

Once this acute period is resolved, the absence of a valve within the system becomes increasingly relevant when questions of shunt malfunction are raised. These patients typically have complex headache patterns, and each time they experience headaches, shunt patency and function need to be addressed. Given the relatively significant rate of shunt malfunction discussed above, this is a very germane consideration. Specifically, not having the ability to interrogate the valve and system percutaneously represents a challenge. The inability to pump the shunt valve, as in the case of VP shunt, poses a disadvantage. By pumping the valve to see if it empties (representing good distal run off) and then allowing for it to refill (good proximal flow) one can get a general idea of patency of both limbs, and at times, locate the problem if there is one.

Furthermore if infection is questioned, then this requires a lumbar puncture with the associated challenges in this patient population, as opposed to, percutaneously tapping the valve under sterile technique in the case of a VP shunt.

VENTRICULOPERITONEAL SHUNT

TECHNICAL INSERTION RELATED CONSIDERATIONS

PROXIMAL CATHETER INSERTION

The positioning on these patients is supine and represents an anatomic orientation. The primary challenge has been the ability to cannulate normal or smaller than normal size ventricles in this patient population. Traditionally, predetermined landmarks were used to provide for trajectories based on historical percutaneous passages. Specifically, this involved taking measurements from the Bregma (the intersection of the coronal and sagittal sutures) and then measuring the distance between the nasion aligning with the mid-pupillary line. While these measurements often lead the surgeon to the ventricle, they can be less than reliable when the margin of error is very low, as in the case of IIH patients. In essence, in IIH patients, the surgeon used to balance the risk of a less than ideal proximal catheter placement, and hence the associated relatively high rate of proximal revision, with the benefit of having a regulated system with a valve to improve the immediate and long-term perioperative course.

The rapid evolution of frameless stereotactic navigation over the last 20 years has clearly addressed this issue. Using a thin acquisition CT scan, a 3D volume of the individual patient is recreated in an operating room using computer assisted systems. An individualized target for the catheter placement can now be created and ideal trajectories generated. This allows for the surgeon to select the optimal cannulation and dynamically place the catheter under precise stereotactic guidance; thus, making VP shunting a valid, and in our opinion, a better alternative to LP shunts in patients with IIH. This comes with the added advantage of a decreased rate of proximal obstruction by specifically selecting the target for the proximal catheter.

Moreover, this technology allows the surgeon to take advantage of the use of valves while minimizing the risk of mal-position of the proximal catheter. In addition to the primary advantage of the valve (i.e. the ability to interrogate by the bedside), the availability of programmable valves allows the surgeon to externally manipulate the opening pressure of the valve and hence increases or decreases the drainage in response to each patient’s signs and symptoms. This particular setting, helps decrease the rate of symptomatic over-drainage, subdural hematomas, and tonsillar herniation.

DISTAL CATHETER INSERTION

Once the proximal catheter is in place, it is connected to the specific valve selected. The distal catheter is tunneled subcutaneously (often using an intervening incision) to the epigastric region. Given that the patient is in a supine anatomic position, this facilitates the tunneling and

abdominal insertion. While the catheter can be placed in any quadrant of the abdomen, we prefer a direct midline approach. The midline raphe between the muscles is opened and the peritoneum visualized and catheter inserted.

Again the patients' body habitus can prove to be a significant challenge in the placement of the abdominal catheter. As a strategy to compensate for this we have used a minimally invasive laparoscopic approach to place the peritoneal catheter. In collaboration with laparoscopic surgeons, a percutaneous needle is passed into the peritoneum and the abdomen is insufflated. In this era, this is a standard and well established technique for abdominal surgery. This distal catheter is then simply inserted under direct visualization with the endoscope into the peritoneum.

This technique serves the primary role of positioning the distal catheter in a reliable fashion, and at the same time, doing so in a minimally invasive manner. (31). Both of these are valuable especially in this patient population.

SHUNT MALFUNCTION

The early signs and symptoms associated with shunt malfunction can be difficult to assess, given that they are often non-specific and commonly found in this population. Obviously more delayed clinical presentations, such as, recurrent vision loss are more specific but maybe end stage. Imaging with a conventional CT scan is not always helpful as the patient usually has normally small ventricles but still experiencing shunt malfunction. Therefore the reliance on the valve becomes an important consideration. Incremental investigations providing greater specificity and increasing invasiveness are helpful.

The first step is to percutaneously "pump" the shunt as discussed above. If it fails this test it is relatively reliable in suggesting a malfunction; however, if it passes the test it may still be obstructed, i.e., good specificity poor sensitivity. The shunt can be percutaneously tapped under sterile conditions to determine the same information of proximal

and distal flow. This improves the sensitivity significantly but still has limitations. To further enhance the sensitivity, a radioisotope can be injected into the shunt and subsequently imaged. This latter investigation-shuntogram-provides the greatest specificity and sensitivity.

Finally, once in the operating room, a similar strategy is used to locate the site of the obstruction during revision surgery. The first step is to disconnect the valve and assess the proximal catheter for flow. If there is adequate proximal flow then this suggests a distal problem. The distal catheter is similarly interrogated by disconnecting it from the valve and connecting it to a manometer and allowing for flow under gravity. This strategy allows for isolation of the malfunction and the appropriate is replaced.

OTHER SHUNT OPTIONS

In cases where the peritoneum represents a contraindication for placement of the proximal catheter, e.g., active infection or open abdominal wound, the distal catheter can be placed within the pleura or atrium of the heart. Both of these represent less than ideal choices but may be an important consideration in selected patients. The option of the ventriculo-atrial shunt (VA) involves cannulating the jugular vein and under fluoroscopy passing the catheter into the atrium. The ventriculopleural shunt requires tunneling to the thorax and through a small incision placing the distal catheter within the pleura.

SUMMARY OF SHUNTING

The higher revision rates- in both adults and pediatrics- for LP shunts in comparison to VP shunts has made it, in our opinion, less appealing to us for the treatment of IIH. For example, a large study of 42 patients (115 shunt placement) that retrospectively compared LP to VP in shunts in IIH patients over a 30 years period reported a revision rate of 86% in the former but only 44% in the later (30). The over-drainage rate was similar (14%) for both shunts. Furthermore, there was no significant difference between, the two shunting procedures with respect

Shunt Type	Primary Advantage	Primary Concern	Solution
Lumbar Peritoneal	Proximal catheter placement into the thecal sac	Higher malfunction rate Lack of a valve (Limited regulation, difficult interrogation)	
Ventriculoperitoneal	Valve (programmable if needed)	Placement into slit ventricles	Computer assisted frameless stereotactic Neuronavigation
Ventriculoatrial	Alternative to distal placement when peritoneum not available	Placement of distal catheter into vasculature/cardiac system	
Ventriculopleural	Alternative to distal placement when peritoneum not available	Placement of distal catheter into the pleura	

to distal catheter migration and infection (30). A more recent study by Tarnaris et al. where the outcomes following VP vs. LP shunting for IIH were compared concluded that patients who received LP shunts were more likely to suffer complications and require revisions than those with VP shunts. Furthermore, while not statistically significant, patients with VP shunts survived longer than their counterparts with primarily LP shunts (32). With the advent of neuronavigation for ventricular catheter insertion, the primary disadvantage of VP shunts in this patient population is mitigated. Therefore, in our experience VP shunts are well suited for IIH even in cases with normal ventricles.

CONCLUSION

The absence of randomized controlled trials addressing the different treatment options for IIH limits our ability to define a standard management plan for patients with IIH. Weight-directed therapy and medical management should be the first-line treatment in patients with mild symptoms and without visual deficits. In cases of severe headaches refractory to maximal medical management and where CSF pressures are high, we recommend consideration of lumbar punctures, if appropriate, followed by ventricular shunting if the symptoms did not improve.

CME ANSWERS

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2. f
3. c

REFERENCES

1. Lee, A., Wall M.: Idiopathic intracranial hypertension (pseudotumor cerebri): Prognosis and treatment. In: UpToDate, Brazis PW (Ed), UpToDate, Waltham, MA, 2012.
2. Biousse, V., Bruce, B.B., Newman, N.J.: Update on the pathophysiology and management of idiopathic intracranial hypertension. *J Neurol Neurosurg Psychiatry* 83:488, 2012.
3. Wall, M.: Sensory visual testing in idiopathic intracranial hypertension: measures sensitive to change. *Neurology* 40:1859, 1990.
4. Rowe, F.J., Sarkies, N.J.: Visual outcome in a prospective study of idiopathic intracranial hypertension. *Arch Ophthalmol* 117:1571, 1999.
5. Corbett, J.J., Savino, P.J., Thompson, H.S., et al.: Visual loss in pseudotumor cerebri. Follow-up of 57 patients from five to 41 years and a profile of 14 patients with permanent severe visual loss. *Arch Neurol* 39:461, 1982.
6. Bruce, B.B., Preechawat, P., Newman, N.J., et al.: Racial differences in idiopathic intracranial hypertension. *Neurology* 70:861, 2008.
7. Wall, M., George, D.: Idiopathic intracranial hypertension. A prospective study of 50 patients. *Brain* 114 (Pt 1A):155, 1991.
8. Stiebel-Kalish, H., Kalish, Y., Lusky, M., et al.: Puberty as a risk factor for less favorable visual outcome in idiopathic intracranial hypertension. *Am J Ophthalmol* 142:279, 2006.
9. Bruce, B.B., Kedar, S., Van Stavern, G.P., et al.: Idiopathic intracranial hypertension in men. *Neurology* 72:304, 2009.
10. Bruce, B.B., Kedar, S., Van Stavern, G.P., et al.: Atypical idiopathic intracranial hypertension: normal BMI and older patients. *Neurology* 74:1827, 2010.
11. Taktakishvili, O., Shah, V.A., Shahbaz, R., Lee, A.G.: Recurrent idiopathic intracranial hypertension. *Ophthalmology* 115:221, 2008.
12. Shah, V.A., Kardon, R.H., Lee, A.G., et al.: Long-term follow-up of idiopathic intracranial hypertension: the Iowa experience. *Neurology* 70:634, 2008.
13. Kesler, A., Hadayer, A., Goldhammer, Y., et al.: Idiopathic intracranial hypertension: risk of recurrences. *Neurology* 63:1737, 2004.
14. Ko, M.W., Chang, S.C., Ridha, M.A., et al.: Weight gain and recurrence in idiopathic intracranial hypertension: a case-control study. *Neurology* 76:1564, 2011.
15. De Simone, R., Marano, E., Fiorillo, C., et al.: Sudden re-opening of collapsed transverse sinuses and longstanding clinical remission after a single lumbar puncture in a case of idiopathic intracranial hypertension. *Pathogenetic implications. Neurol Sci* 25:342e4, 2005.
16. Bateman, G., Stevens, S., Stimpson, J.: A mathematical model of idiopathic intracranial hypertension incorporating increased arterial inflow and variable venous outflow collapsibility. *J Neurosurg* 110: 446, 2009.
17. Burgett, R.A., Purvin, V.A., Kawasaki, A.: Lumboperitoneal shunting for pseudotumor cerebri. *Neurology* 49:734, 1997.
18. Eggenberger, E.R., Miller, N.R., Vitale, S.: Lumboperitoneal shunt for the treatment of pseudotumor cerebri. *Neurology* 46:1524, 1996.
19. Johnston, I., Besser, M., Morgan, M.K.: Cerebrospinal fluid diversion in the treatment of benign intracranial hypertension. *J Neurosurg* 69:195, 1988.
20. Chumas, P.D., Kulkarni, A.V., Drake, J.M., et al.: Lumboperitoneal shunting: a retrospective study in the pediatric population. *Neurosurgery* 32:376, 1993.
21. Rosenberg, M.L., Corbett, J.J., Smith, C., et al.: Cerebrospinal fluid diversion procedures in pseudotumor cerebri. *Neurology* 43:1071, 1993.
22. Lundar, T., Nornes, H.: Pseudotumour cerebri-neurosurgical considerations. *Acta Neurochir Suppl (Wien)* 51:366, 1990.
23. Ingraham, F.D., Sears, R.A., Woods, R.P., Bailey, O.T.: Further studies on the treatment of experimental hydrocephalus. *J Neurosurg* 6:207, 1949.
24. Matson, D.D.: A new operation for the treatment of communicating hydrocephalus. *J Neurosurg* 6:238, 1949.
25. Vander Ark, G.D., Kempe, L.G., Smith, D.R.: Pseudotumor cerebri treated with lumbar-peritoneal shunt. *JAMA* 217:1832-1834, 1971.
26. Spetzler, R.F., Wilson, C.B., Grollmus, J.M.: Percutaneous lumboperitoneal shunt: Technical note. *J Neurosurg* 43:770, 1975.
27. Burgett, R.A., Purvin, V.A., Kawasaki, A.: Lumboperitoneal shunting for pseudotumor cerebri. *Neurology* 49:734, 1997.
28. El-Saadany, W.F., Farhoud, A., Zidan, I.: Lumboperitoneal shunt for idiopathic intracranial hypertension: patients' selection and outcome. *Neurosurg Rev.* 35(2):239, 2011
29. Binder, D.K., Horton, J.C., Lawton, M.T., McDermott, M.W.: Idiopathic intracranial hypertension. *Neurosurgery* 54(3):538; discussion 551, 2004.
30. McGirt, M.J., Woodworth, 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* 101:627, 2004.
31. Ochalski, P.G., Horowitz, M.B., Mintz, A.H., Hughes, S.J., Okonkwo, D.O., Kassam, A.B., Watson, A.R.: Minimal-access technique for distal catheter insertion during ventricular peritoneal shunt procedures: a review of 100 cases. *J Neurosurg.* 111(3):623, 2009.
32. Tarnaris, A., Toma, A.K., Watkins, L.D., Kitchen, N.D.: Is there a difference in outcomes of patients with idiopathic intracranial hypertension with the choice of cerebrospinal fluid diversion site: a single centre experience. *Clin Neurol Neurosurg.* 113(6):477,2011.
33. Abubaker, K., Ali, Z., Raza, K., Bolger, C., Rawluk, D., O'Brien, D.: Idiopathic intracranial hypertension: lumboperitoneal shunts versus ventriculoperitoneal shunts—case series and literature review. *Br J Neurosurg.* 25(1):94, 2011.

SURGICAL TREATMENT FOR IDIOPATHIC INTRACRANIAL HYPERTENSION: OPTIC NERVE SHEATH FENESTRATION

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LEARNING OBJECTIVES

1. The attendee will be able to list the indications for optic nerve sheath fenestration in IIH
2. The attendee will be able to enumerate the variety of surgical approaches utilized for ONSF
3. The attendee will be able to outline the role of ONSF as part of the global management strategy of IIH

CME QUESTIONS

1. In which scenario, in a patient with idiopathic intracranial hypertension, would an optic nerve sheath fenestration be indicated?
 - a. When the patient has headache but no vision loss.
 - b. If the patient complains of dark gray spots intermittently occurring in her vision.
 - c. In a patient with rapid severe visual loss.
 - d. In a patient who is allergic to acetazolamide.
2. What is a possible mechanism of success of an optic nerve sheath fenestration?
 - a. Solely from egress of toxic chemical milieu resulting from CSF stasis.
 - b. Reduction of elevated pressure around the optic nerve.
 - c. Reduction of CSF production.
 - d. Stimulation of astrocytes which promote axonal viability.
3. True/False: Once an Optic Nerve Sheath Fenestration is performed a patient no longer needs medical or further surgical intervention.

KEYWORDS

1. Idiopathic Intracranial Hypertension
2. Optic Nerve Sheath Fenestration
3. Nerve Fiber Layer Edema
4. Surgery
5. Compartment Syndrome

INTRODUCTION

Optic nerve sheath fenestration (ONSF) is one of the surgical treatments for visual preservation and rescue in idiopathic intracranial hypertension (IIH). A variety of ONSF surgical techniques exist but all approaches include incising and releasing the dura mater and associated arachnoid surrounding the optic nerve axons. The optic nerves are subject to the intracranial cerebral spinal fluid pressure both within the central intracranial space and within each orbit. Cerebral spinal fluid (CSF) diversion procedures or unilateral ONSF may impact the entire visual system but the benefit may be limited to the individual space drained. ONSF should be considered when axonal function is acutely compromised with the potential for recovery of dying and uninjured axonal fibers. ONSF is a complex, retrobulbar orbital surgery and should be performed by orbital surgical experts in a minimally invasive, non-traumatic fashion to lessen any further injury to the nerve. Aggressive, early surgical intervention must be considered in patients presenting with significant vision loss.

SURGICAL INDICATION AND TECHNIQUE

ONSF allows release of cerebral spinal fluid surrounding the optic nerve. In this surgical procedure, a dural window or slit is made in the tough, fibrous, retrobulbar, optic nerve dura mater. Optic nerve sheath fenestration is considered in a patient with idiopathic intracranial hypertension (IIH) with impending, progressive, or profound visual compromise or when a patient with modest visual compromise and persistent nerve fiber layer edema fails medical therapy. Patients with longstanding optic atrophy or without evidence of raised intracranial pressure are not candidates for this surgical intervention.

ONSF to halt vision loss from raised intracranial pressure has been performed for well over a century. One of the first reports of ONSF was in 1872 by DeWecker.^{1,2} Description of the first ONSF surgical technique includes palpation of the optic nerve by a finger passed behind the globe followed by blind incision of the dural sheath with a guarded knife.³ In this first report, a transconjunctival approach between the lateral and inferior rectus was used to make longitudinal incisions in the optic nerve.¹ Over the next 140 years, additional surgical approaches to the optic nerve were designed. These ONSF variations include splitting the lateral rectus, taking off the lateral wall, removing a recti muscle from the globe, torting the globe, placing drains, using mitomycin C and alternative methods of opening the dura with slits versus windows.⁴⁻²⁰ One of the most recently reported techniques involves a minimally invasive incision through the upper eyelid crease.²¹ This technique avoids any stretch on the optic nerve or torque on the globe minimizing the operative morbidity (video 1).

ONSF surgery is performed under general anesthesia with paralysis of the patient to avoid any inadvertent movement of the patient during the surgery. The time of the procedure depends on the method of accessing the optic nerve, possible medical co-morbidities which might prolong securing the airway, require additional anesthetic monitoring of the patient, additional vascular access sites, compression hose or urinary catheter placement, the physical size of the patient, and the experience of the surgeon and the surgical team. A single optic nerve sheath fenestration may be performed in as little as 15 minutes in an ideal operative environment to well over an hour. Typically the patient will remain in the hospital for at least 23 hours of post-operative observation but in the setting of profound vision loss, or complicated neurologic presentation, a more extended hospitalization might be required.

The decision to perform an ONSF is based on the tempo of visual acuity and field loss, response to medical management or cerebral spinal fluid diversion, and the level of visual compromise in one or both nerves. Some controversy exists as to whether a unilateral optic nerve sheath fenestration can be adequate to treat the entire visual system. The anatomical features and surgical outcomes involved in this medical decision making will be discussed in detail below. If both eyes are compromised, a bilateral procedure limits subjecting the patient to two independent episodes of general anesthesia. For those clinicians who opt for sequential optic nerve sheath fenestration, the worse eye is often operated on first, with the second eye considered if it either worsens post-operatively under medical management over days to weeks or if nerve fiber layer edema persists in the un-operated eye in spite of months of adequate medical management to control the other signs and symptoms. In the United States of America, the surgical coding and billing of the procedure is subject to the bilateral surgery modifier and payment by government payors and most commercial

carriers for the second eye is reduced by 50% if both eyes are operated on during a single surgical session. The correct procedural terminology code is 67570 and the -50 modifier is appended when the two optic nerves are operated on during the same operative session.²² The work relative value units assigned to this surgical procedure are 14.40 and can be compared to re-imburement of a level 5 evaluation and management consultation code of 3.77, blepharoplasty 6.81, cataract extraction with lens insertion 10.52, and vitrectomy for membrane peel 23.24.²³ If both eyes are severely compromised, the duty to preserve vision should trump any other consideration.

UNILATERAL VERSUS BILATERAL

The overriding paradigm regarding the relationship of the intraorbital optic nerve and intracranial space pressure was clearly defined by Hayreh in 1964.²⁴ Hayreh developed a primate model of raised intracranial pressure (ICP) by placing inflatable balloons in various intracranial locations.²⁴ He found that a relationship existed between degree and rate of balloon inflation and optic disc swelling and also that a critical balance existed between cerebral spinal fluid pressure and brain stem compromise. Stepwise progression of the disc findings with increasing elevation of ICP was demonstrated. Optic nerve sheath fenestration was protective on the ipsilateral side but only in part, in some scenarios, on the contralateral side. Various degrees of meshed trabeculations within the optic nerve sheath, particularly in the region of the bony canal, with attenuated flow from the intracranial space to the intraorbital optic nerve allowed for inconsistent findings between two optic nerves and the ICP. Hayreh followed his preliminary report with an exhaustive treatise in 1968 on the theories regarding optic nerve edema, further experimental evidence and a conclusion that raised intracranial pressure, successfully transmitted to the optic nerve, is responsible for papilledema. Hayreh's work laid the foundation for the findings in human clinical investigations. Histopathologic evidence of a dural fistula following ONSF in a patient who died 39 days after bilateral ONSF was demonstrated by Keltner et al in 1977.²⁵ Two additional patients with bilateral resolution following unilateral fenestration were described.²⁵ After reviewing both the literature showing limitation of effect of a unilateral ONSF and those reports of bilateral impact of a unilateral ONSF, Keltner concluded a 3 part compartment system existed made up of the subarachnoid cavities of the 2 optic nerves and the intracranial space; this 3 compartment relationship explained the variable findings.²⁶⁻²⁸

The optic nerve anatomy fulfils the criteria needed for a compartment syndrome in that the cerebral spinal fluid (CSF) pressure can rise to a point that the function of the nerve is compromised. Compartment syndrome in which increased pressure in a confined anatomical space adversely affects circulation and threatens the perfusion of the tissues therein is not unique to the optic nerve environment or anatomy. The optic nerves reside in a subarachnoid space throughout

the entire anterior visual pathway course and although decompression of one of the possibly communicating cavities may be sufficient, decompression of all 3 spaces may be required. The 3 compartment system, described by Hayreh and verbalized by Keltner, was further dissected and established by Killer et al.²⁹⁻³³ In a series of investigations, this research team detailed the complex anatomy of the optic nerve subarachnoid space, established that impairment of CSF circulation contributes to optic nerve damage, and showed a concentration gradient between spinal and optic nerve CSF.^{29,32,33}

Clinical reports demonstrating the reality of these 3 compartments are peppered throughout the literature.³⁴⁻³⁷ For instance, Mauriello et al reported 1 patient with loss of vision after ONSF which reversed following emergent CSF diversion and 3 patients whose progressive vision loss stabilized after lumboperitoneal shunts.³⁴ Failure of ONSF in severe IIH include a case report by Wilkes et al in which a 16 year old girl initially improved but then within 2 weeks, the vision again worsened, ICP was high (65 cm H₂O), CSF diversion initially halted the vision loss but then it continued to decline.³⁸ Other authors report similar findings of needing to offer CSF diversion after failed ONSF.^{37,39} The reverse situation of ONSF improving vision after CSF diversion failure has also been demonstrated.^{27,36,40,41} Failure of all the surgical treatment methods, CSF diversion or ONSF, in IIH has been reported. Shunts notoriously fail or become obstructed.⁴²⁻⁴⁵ An imaging study showing asymmetric flow of a tracer correlated with unilateral progressive vision loss after shunt failure and bilateral ONSF, the vision in the eye with the ONSF obstruction responded to optic nerve decompression.⁴⁶ In a tally of IIH case series, Wall calculated, that 11.4% of patients undergoing ONSF and 10% of patients undergoing CSF shunting procedures had worse vision post-operatively.⁴⁷ It may be that these patients had failure of the surgical procedure because of a failure to urgently address the extent of the systematic optic nerve subarachnoid space compromise.

An argument has been made for considering unilateral ONSF sufficient for the treatment of bilateral disease. Alsuhaibani et al reported 78 patients with IIH who underwent unilateral ONSF at the University of Iowa.⁴⁸ A significant reduction in the grade of papilledema was seen in both the ipsilateral and contralateral side, although all patients remained on medical management throughout the postoperative observation period. The final grade of papilledema was lower in the operative eye than in the non-operative eye. The authors contend that a unilateral optic nerve sheath fenestration may allow for sufficient contralateral improvement, in spite of their data showing that there was less improvement in the non-operative eye. In the 10 eyes undergoing bilateral ONSF, the edema score of the optic nerves was equivalent at 12 months. A spectrum of pressure situations and need for pressure reduction likely exists and the decision to fenestrate one, both, or perform concurrent or sequential CSF diversion along with medical management must be made based on the severity of the clinical findings.

MECHANISM OF ACTION

The effectiveness of ONSF in reducing and preventing ipsilateral papilledema was shown experimentally by Hayreh in 1964.²⁴ In his post-mortem specimens, Hayreh found proliferation of connective tissue at the experimental surgical site.⁴⁹ Similar histopathologic demonstration of scarring at the surgical site was reported in a human optic nerve sheath fenestration by Smith in 1969.⁹ The photomicrograph of the optic nerve presented by Smith showed the scar limited to the side with the fenestration with an open subarachnoid space on the opposite pole of the nerve.^{9,15} From the observation of the scar at the fenestration site, a theory on the mechanism of action of ONSF was postulated; this theory was that fibrosis at the site of the surgery prevents downstream flow expansion from the intracranial elevated pressure.¹⁰ The prevailing theory however, is that fenestration allows decompression of the local subarachnoid space by filtration.^{25,26} One of the first clinical experiments designed to show that ONSF works by allowing for flow through the dural fistula was trialled by Brouman et al in 1988.⁵⁰ He injected subarachnoid contrast in four patients to show leakage of dye from the surgical site. Dye was not imaged at the surgical site but this may have been a result of the imaging modality and the resolution of the dye. A physics laboratory model designed by Seiff et al attempted to demonstrate the local and consequent impact of a unilateral ONSF acting as a dural filtration window.⁵¹ This model consisted of a bottle with 2 attached tubes; when a single tube was opened the pressure was reduced ipsilaterally the most with a partial lessening of the pressure in the bottle and the contralateral tube. Neuro-imaging has demonstrated the finding of a perioptic fluid collection using T2-weighted, 3-dimensional constructive interference in steady state sequence.⁵² A corollary to the leakage of fluid allowing for decompression of the optic nerve, similar to a fasciotomy in an extremity compartment syndrome, is that the reduction in the closed compartment pressure allows for restoration of blood flow to the optic nerve. Color Doppler imaging performed before and after ONSF has shown improvement in the imaging parameters for the short posterior ciliary arteries.⁵³

OUTCOMES

A deciding factor in the outcome of ONSF is the status of the optic nerve at the time of surgery. If the optic nerve has undergone progressive loss of axonal function to the point that recovery is not possible, an ONSF or any other surgical or medical treatment is not expected to be successful at that point. Early recognition of the extent of optic nerve injury, as demonstrated by the level of visual acuity and field loss, is a key component of surgical intervention. Much like a code stroke, surgical decompression of the optic nerve needs to be performed when there is an opportunity for neuronal recovery. Success or failure of this surgery must be framed within this central nervous system limitation. In addition, surgical technique, volumes and experience have been shown to impact the outcome of any surgical procedure⁵⁴⁻⁵⁶. With ONSF, visual acuity has been shown to stabilize or improve in as much as 94% of patients.³⁷

Many small case reports detailing outcomes following ONSF for IIH exist. For instance, Goh reported 19 patients with 29 eyes in 1997. Fifteen of 29 eyes had improved visual acuity 6 months post-operatively. Visual fields at 6 months were available in 17 eyes; 9 showed improvement, 5 were unchanged and 2 eyes worsened. Of the nine patients who underwent unilateral surgery only one contra-lateral eye had improvement in visual acuity, 3 eyes had improvement in visual fields and 6 were unchanged.³⁵Very few case series have 25 or more patients with pre-operative and post-operative follow up periods of 6 months or longer and there are no prospective surgical versus medical treatment trials or unilateral versus bilateral treatment trials in the literature. Table 1 summarizes the visual acuity and visual field outcomes of the case series with more than 25 patients and extended follow up data on the majority of the patients. The cumulative data shows that approximately 74% of patients have stabilized or improved visual acuity and 87% have stabilized or improved visual fields following ONSF. Chandrasekaran et al. reported, in 2006, the outcome results of 51 eyes of 32 patients who underwent ONSF by a medial transconjunctival approach.⁴¹ Thirty-one of the patients had pre-operative and post-operative visual field data available for analysis. Thirteen eyes (42%) showed >5dB improvement in Humphrey 24–2 visual field mean deviation (MD), 17 had no change (55%), and 1 (3%) eye had worsening of the MD. Interestingly the visual field sensitivity parameters in these IIH patients ranged between 0.0 and 0.63 and showed no statistically significant difference over time, unlike the variability seen in glaucoma and optic neuritis patients.^{57,58}Two clinical features were associated with post-operative outcome. A visual field defect outside of 10 degrees from fixation was associated with an improved post-operative visual field (p=0.042). Surgery greater than 6 months from the diagnosis was associated with a worse outcome (p=0.027). Another retrospective review, by Banta and Farris in 2000, reported ONSF surgical outcome in a larger cohort of 86 patients (158 eyes).³⁷ A similar medial transconjunctival approach was used to fenestrate the optic nerve. Eighty-one patients had pre and post-operative visual field data. Visual fields stabilized or improved in 71 (88%) and worsened in 10 (12%). One eye had a permanent decrease of

vision to the count finger level from a presumed iatrogenic traumatic optic neuropathy. Another patient had an orbital apex syndrome with no light perception vision and complete ophthalmoplegia post-operatively which recovered after 1 month to 20/15 vision and full motility. Sixteen eyes in 11 patients had progression of vision loss after the ONSF. Two patients who underwent repeat ONSF eventually required CSF diversion procedures to halt the progression of visual loss, giving support for the 3 compartment theory of Hayreh and Keltner. Only 8 of 61 patients who presented with headache as the chief complaint had improvement after ONSF. Banta and Farris recognized in their case series, that some patients will require both ONSF and CSF diversion to halt the progression of vision loss. Plotnik and Kosmorsky reviewed the complications seen in 38 eyes of 31 patients.⁵⁹ These complications ranged from the transient double vision seen by Banta and Farris in 29%, pupillary abnormalities similar to those reported by Kersten et al in 11% and 4 patients with post-operative visual loss secondary to vascular complications.^{17,59}

Complications can be thought of in several broad categories which may be considered and reduced by surgical planning and method. These injuries include soft tissue, nerve, globe, vascular and in some techniques to the orbital bone. The incidence of complications have been reported to vary as much as 4.8–45%.⁵⁹These complications are very much related to surgical technique. For instance, post-operative diplopia requiring strabismus surgery is much more likely if a rectus muscle has been dis-inserted from the globe or if posterior retraction compromising innervation of the recti muscle has been performed. In the Banta and Farris cohort in which the medial rectus was dis-inserted, thirty patients (35%) had post-operative double vision with 87% (26) resolving spontaneously and 4 patients requiring prismatic correction (2) or strabismus surgery (2).³⁷ Plotnik and Kosmorsky reviewed the complications seen in 38 eyes of 31 patients.⁵⁹ These complications ranged from the transient double vision in 29%, similar to the 35% seen by Banta and Farris, pupillary abnormalities in 11%, similar to the 14% reported by Kersten et al and 4 patients with post-operative visual loss secondary to vascular complications.^{17,37,59}

Author	Year	Age; M/F	Number Patients	VA improved eyes	VA stabilized eyes	VA worsened eyes	VF improved eyes	VF stabilized eyes	VF worsened eyes
Alsuhaibani	2011	32; 10/52	62*	NR	NR	NR	NR	NR	NR
Chandrasekaran	2006	33.4; 3/29	32	13		26	13	17	1
Banta	2000	32.1; 16/70	86	148		10	71		10
Corbett	1988	29; 8/20	28	12	22	6	21	10	9
Total			146	173 (73%)	22 (0.9%)	42 (18%)	105 (69%)	27 (18%)	20 (13%)

*N not included in tally as visual acuity (VA) and visual fields (VF) results not reported.

PERSPECTIVE

ONSF should be considered early in the process rather than when prolonged loss of vision has been established.²⁸ In the acute phase when complete primary injury has not occurred the opportunity to rescue those axonal fibers at risk from progression of the injury exists. Consequently, surgical indication includes those IIH patients with clinical data to support an expectation for recovery of some of the compromised axons. Literature in other surgical specialties supports the notation that this complex surgery within the orbit, on the key neurologic structure in the orbit, the optic nerve, should be performed by those most experienced in orbital surgery. Consideration of minimally invasive surgery with avoidance of torque or traction on the optic nerve or globe may limit surgical complications. A fenestration of the dura with a window like opening of the arachnoid rather than linear slits in the dura may allow for a more adequate fistula. The future of this surgery may include an image guided endoscopic approach. Ultimately for treatment of IIH to be successful, a multifaceted management must be followed with ONSF being only one facet of care.

CME ANSWERS

1. b
2. c
3. c

REFERENCES

1. DeWecker L. On incision of the optic nerve in cases of neuroretinitis. *Int Ophthalmol Congress Rep.* 1872;4:11–14.
2. Patel BC, Flaharty P, Hunts J, Anderson RL. Optic nerve sheath decompression. In: Naugle TC, Hesse RJ, Fry CL, eds. *Diagnosis and Management of Oculoplastic and Orbital Disorders: Proceedings of the 43rd Annual Symposium, New Orleans, LA, USA, February 18–30, 1994, organized by the New Orleans Academy of Ophthalmology.* New York: Kugler; 1995:355–367.
3. Corbett JJ. Optic nerve sheath fenestration for treatment of idiopathic intracranial hypertension. *North American Neuro-ophthalmology Society.* Montreal, Quebec, Canada: North American Neuro-Ophthalmology Society; 2000.
4. Carter RB. On retrobulbar Incision of the optic nerve in cases of swollen disc. *Brain.* 1887;10:199–209.
5. Carter RB. Operation of opening the sheath of the optic nerve for the relief of pressure. *Br Med J.* 1889;1:399–401.
6. Müller L. Die Trepanation der Optikusscheide: Eine neue Operation zur Heilung der Stauungspapille. *Wien Klin Wochenschr.* 1916;2:1001–1003.
7. Müller L. Demonstration von vier durch Schnervenscheiden-Trepanation geheilten Faen von Stauungspapille und Hirndruck. *Wien Klin Wochenschr.* 1917. 1917;5:154–155.
8. Gomez-Marquez M. Traitement chirurgical local de la stase papillaire. *Bull Soc Ophthalmol Paris.* 1935;5:814–827.
9. Smith JL, Hoyt WF, Newton TH. Optic nerve sheath decompression for relief of chronic monocular choked discs. *Am J Ophthalmology.* 1969;68:633–639.
10. Davidson SI. The surgical approach to pleocephalic disc edema. *Eye (Lond).* 1969;89:669–690.
11. Galbraith JEK, Sullivan JH. Decompression of the perioptic meninges for relief of papilledema. *Am J Ophthalmology.* 1973;76(5):687–692.
12. Galbraith JEK. Optic nerve decompression in benign intracranial hypertension. *Trans Fourth Asia-Pacific Congress Ophthalmol.* 1973;4:165–170.
13. Billson FA, Hudson RL. Surgical treatment of chronic papilloedema in children. *Br J Ophthalmol.* 1975;59:92–95.
14. Kaye AH, Galbraith JEK, King J. Intracranial pressure following optic nerve decompression for benign intracranial hypertension. *J Neurosurg.* 1981;55:453–456.
15. Smith CH, Orcutt JC. Surgical treatment of pseudotumor cerebri. *Int Ophthalmol Clin.* 1986;26:265–275.
16. Tse DT, Nerad JA, Anderson RL, Corbett JJ. Optic nerve sheath fenestration in pseudotumor cerebri. A lateral orbitotomy approach. *Arch Ophthalmol.* Oct 1988;106(10):1458–1462.
17. Kersten RC, Kulwin DR. Optic nerve sheath fenestration through a lateral canthotomy incision. *Arch Ophthalmol.* Jun 1993;111(6):870–874.
18. Spoor TC, McHenry JG, Shin DH. Optic nerve sheath decompression with adjunctive mitomycin and meltano device implantation. *Arch Ophthalmol.* 1994;112:25–26.
19. Adenis JP, Salomon JL, Robert PY. A valve for optic nerve sheath fenestration. *Orbit.* 1995;14(1):37–41.
20. Spoor TC, McHenry JG, Shin DH. Long-term results using adjunctive mitomycin C in optic nerve sheath decompression for pseudotumor cerebri. *Ophthalmology.* 1995;102:2024–2028.
21. Pelton RW, Patel BC. Superomedial lid crease approach to the medial intraconal space: a new technique for access to the optic nerve and central space. *Ophthal Plast Reconstr Surg.* Jul 2001;17(4):241–253.
22. Plan UHCC. Bilateral Procedures Policy. 2012; [http://www.uhcccommunityplan.com/assets/Bilateral-Procedures-Policy-\(R0023\)-1-10-11.pdf](http://www.uhcccommunityplan.com/assets/Bilateral-Procedures-Policy-(R0023)-1-10-11.pdf). Accessed October 7, 2012, 2012.
23. Services DoHaH. Medicare Program; Payment Policies Under the Physician Fee Schedule and Other. *Centers for Medicare & Medicaid Services* 2012; http://www.ahcancal.org/facility_operations/Federal%20Regulations/FedReg201011MCarePhysicianFeeSchedule.pdf. Accessed October 7, 2012.
24. Hayreh SS. Pathogenesis of Oedema of the Optic Disc (Papilloedema). A Preliminary Report. *Br J Ophthalmol.* 1964;48:522–543.
25. Keltner JL, Albert DM, Lubow M, Fritsch E, Davey LM. Optic nerve decompression. A clinical pathologic study. *Arch Ophthalmol.* Jan 1977;95(1):97–104.
26. Keltner JL. Optic nerve sheath decompression. How does it work? Has its time come? *Arch Ophthalmol.* Oct 1988;106(10):1365–1369.
27. Sergott RC, Savino PJ, Bosley TM. Modified optic nerve sheath decompression provides long-term visual improvement for pseudotumor cerebri. *Arch Ophthalmol.* Oct 1988;106(10):1384–1390.
28. Corbett JJ, Nerad JA, Tse DT, Anderson RL. Results of optic nerve sheath fenestration for pseudotumor cerebri. The lateral orbitotomy approach. *Arch Ophthalmol.* Oct 1988;106(10):1391–1397.
29. Killer HE, Laeng HR, Flammer J, Groscurth P. Architecture of arachnoid trabeculae, pillars, and septa in the subarachnoid space of the human optic nerve: anatomy and clinical considerations. *Br J Ophthalmol.* Jun 2003;87(6):777–781.
30. Killer HE, Jaggi GP, Flammer J, Miller NR, Huber AR. The optic nerve: a new window into cerebrospinal fluid composition? *Brain : a journal of neurology.* Apr 2006;129(Pt 4):1027–1030.
31. Killer HE, Jaggi GP, Flammer J, Miller NR, Huber AR, Mironov A. Cerebrospinal fluid dynamics between the intracranial and the subarachnoid space of the optic nerve. Is it always bidirectional? *Brain : a journal of neurology.* Feb 2007;130(Pt 2):514–520.

32. Jaggi GP, Harlev M, Ziegler U, Dotan S, Miller NR, Killer HE. Cerebrospinal fluid segregation optic neuropathy: an experimental model and a hypothesis. *Br J Ophthalmol*. Aug 2010;94(8):1088–1093.
33. Killer HE, Jaggi GP, Miller NR, et al. Cerebrospinal fluid dynamics between the basal cisterns and the subarachnoid space of the optic nerve in patients with papilloedema. *Br J Ophthalmol*. Jun 2011;95(6):822–827.
34. Mauriello JA, Jr., Shaderowfsky P, Gizzi M, Frohman L. Management of visual loss after optic nerve sheath decompression in patients with pseudotumor cerebri. *Ophthalmology*. Mar 1995;102(3):441–445.
35. Goh KY, Schatz NJ, Glaser JS. Optic nerve sheath fenestration for pseudotumor cerebri. *J Neuroophthalmol*. Jun 1997;17(2):86–91.
36. Acheson JF, Green WT, Sanders MD. Optic nerve sheath decompression for the treatment of visual failure in chronic raised intracranial pressure. *J Neurol Neurosurg Psychiatry*. Nov 1994;57(11):1426–1429.
37. Banta JT, Farris BK. Pseudotumor cerebri and optic nerve sheath decompression. *Ophthalmology*. Oct 2000;107(10):1907–1912.
38. Wilkes BN, Siatkowski RM. Progressive optic neuropathy in idiopathic intracranial hypertension after optic nerve sheath fenestration. *J Neuroophthalmol*. Dec 2009;29(4):281–283.
39. Knight RS, Fielder AR, Firth JL. Benign intracranial hypertension: visual loss and optic nerve sheath fenestration. *J Neurol Neurosurg Psychiatry*. Mar 1986;49(3):243–250.
40. Kelman SE, Sergott RC, Cioffi GA, Savino PJ, Bosley TM, Elman MJ. Modified optic nerve decompression in patients with functioning lumboperitoneal shunts and progressive visual loss. *Ophthalmology*. Sep 1991;98(9):1449–1453.
41. Chandrasekaran S, McCluskey P, Minassian D, Assaad N. Visual outcomes for optic nerve sheath fenestration in pseudotumour cerebri and related conditions. *Clin Experiment Ophthalmol*. Sep-Oct 2006;34(7):661–665.
42. Eggenberger ER, Miller NR, Vitale S. Lumboperitoneal shunt for the treatment of pseudotumor cerebri. *Neurology*. Jun 1996;46(6):1524–1530.
43. Johnston I, Besser M, Morgan MK. Cerebrospinal fluid diversion in the treatment of benign intracranial hypertension. *J Neurosurg*. Aug 1988;69(2):195–202.
44. Rosenberg ML, Corbett JJ, Smith C, et al. Cerebrospinal fluid diversion procedures in pseudotumor cerebri. *Neurology*. Jun 1993;43(6):1071–1072.
45. McGirt MJ, Woodworth G, Thomas G, Miller N, Williams M, Rigamonti D. Cerebrospinal fluid shunt placement for pseudotumor cerebri-associated intractable headache: predictors of treatment response and an analysis of long-term outcomes. *J Neurosurg*. Oct 2004;101(4):627–632.
46. Russo RR, Ha L, Emmett L, Magee M, Mansberg R. Progressive visual loss due to obstruction of an optic nerve sheath fenestration demonstrated on SPECT/CT radionuclide cisternography. *Clin Nucl Med*. Mar 2010;35(3):208–210.
47. Wall M. Idiopathic intracranial hypertension. *Neurol Clin*. Aug 2010;28(3):593–617.
48. Alsuhaibani AH, Carter KD, Nerad JA, Lee AG. Effect of optic nerve sheath fenestration on papilledema of the operated and the contralateral nonoperated eyes in idiopathic intracranial hypertension. *Ophthalmology*. Feb 2011;118(2):412–414.
49. Hayreh SS. Pathogenesis of oedema of the optic disc. *Documenta Ophthalmologica*. 1968;24:289–411.
50. Brouman ND, Spoor TC, Ramocki JM. Optic nerve sheath decompression for pseudotumor cerebri. *Arch Ophthalmol*. 1988;106:1378–1383.
51. Seiff SR, Shah L. A model for the mechanism of optic nerve sheath fenestration. *Arch Ophthalmol*. Sep 1990;108(9):1326–1329.
52. Yazici Z, Yazici B, Tuncel E. Findings of magnetic resonance imaging after optic nerve sheath decompression in patients with idiopathic intracranial hypertension. *Am J Ophthalmol*. Sep 2007;144(3):429–435.
53. Mittra RA, Sergott RC, Flaharty PM, et al. Optic nerve decompression improves hemodynamic parameters in papilledema. *Ophthalmology*. Jul 1993;100(7):987–997.
54. Hammond JW, Queale WS, Kim TK, McFarland EG. Surgeon experience and clinical and economic outcomes for shoulder arthroplasty. *J Bone Joint Surg Am*. Dec 2003;85-A(12):2318–2324.
55. Nazarian SM, Yenokyan G, Thompson RE, Griswold ME, Chang DC, Perler BA. Statistical modeling of the volume-outcome effect for carotid endarterectomy for 10 years of a statewide database. *J Vasc Surg*. Aug 2008;48(2):343–350; discussion 350.
56. Chen K, Cheung K, Sosa JA. Surgeon volume trumps specialty: outcomes from 3596 pediatric cholecystectomies. *J Pediatr Surg*. Apr 2012;47(4):673–680.
57. Wall M, Johnson CA, Kutzko KE, Nguyen R, Brito C, Keltner JL. Long- and short-term variability of automated perimetry results in patients with optic neuritis and healthy subjects. *Arch Ophthalmol*. Jan 1998;116(1):53–61.
58. Heijl A, Lindgren A, Lindgren G. Test-retest variability in glaucomatous visual fields. *Am J Ophthalmol*. Aug 15 1989;108(2):130–135.
59. Plotnik JL, Kosmorsky GS. Operative complications of optic nerve sheath decompression. *Ophthalmology*. May 1993;100(5):683–690.

ENDOVASCULAR VENOUS STENTING FOR IDIOPATHIC INTRACRANIAL HYPERTENSION (IIH)

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LEARNING OBJECTIVES

1. The attendee will be able to discuss the evidence for venous sinus stenosis in patients with idiopathic intracranial hypertension (IIH) and the theoretical rationale for evaluating venous stenting as a potential therapy
2. The attendee will be able to list the available retrospective and anecdotal evidence so far in support or against the use of venous stenting for patients with IIH
3. The attendee will be able to list the possible complications and their frequency in patients who undergo venous stenting for IIH

CME QUESTIONS

1. Current models of cerebrospinal fluid (CSF) absorption at the arachnoid granulations show a relationship with all of the following except:
 - a. Blood pressure
 - b. CSF pressure
 - c. Superior sagittal sinus pressure
 - d. Resistance of CSF outflow across the arachnoid villi
2. Which of the following statements is true?
 - a. Intracranial pressure has decreased in some patients following venous sinus stenting
 - b. Venous sinus stenosis has improved in some patients following CSF diversion procedures
 - c. Both A and B
 - d. Neither A or B
3. Observed complications of venous sinus stenting include all of the following except:
 - a. Reversible hearing loss
 - b. Meningitis
 - c. Stent thrombosis
 - d. Subdural hemorrhage
 - e. Anaphylaxis

KEYWORDS

1. Idiopathic Intracranial Hypertension
2. Venous Sinus Stenosis
3. Venous Stenting
4. Venous Sinus Hypertension
5. Pseudotumor Cerebri

INTRODUCTION

Venous sinus stenosis has been observed in patients with idiopathic intracranial hypertension (IIH) over the last two decades. Uncertainty remains as to whether this stenosis is the result or cause of intracranial hypertension in certain patients with the disease or whether it may be both. The association of venous sinus stenosis with IIH has led to multiple case reports and retrospective studies detailing the outcomes of patients following venous sinus stenting. The rate of serious irreversible complications appears to be relatively small, but more studies with long-term follow up are needed to fully evaluate its safety. Rates of post-procedure improvement in symptoms, papilledema and visual field defects are promising, but a controlled, prospective trial is needed to properly evaluate its efficacy in stabilizing or reversing symptoms and visual loss in patients with IIH.

1. INTRODUCTION

Idiopathic intracranial hypertension (IIH) is a disease of elevated intracranial pressure in the absence of a structural lesion, venous sinus thrombosis or meningitic process that occurs primarily in obese woman of childbearing age. Recognition of an association of IIH with transverse sinus stenosis has led to the theory that this stenosis contributes to intracranial hypertension or might even be the primary cause, but a causative relationship remains controversial.¹ Stenting of the transverse sinus has emerged as a potential therapy for IIH, based on theoretical evidence and an accumulation of retrospective, uncontrolled data over the last decade. However, prospective, controlled studies are needed to truly understand the safety and efficacy of this procedure in stabilizing or even reversing visual loss.

2. CASE PRESENTATION

A 25 year old woman with a history of obesity and nephrotic syndrome with end stage renal disease on hemodialysis presented with several weeks of transient visual obscurations, intermittent headaches in the setting of a 20 pound weight gain.

Automated Perimetry using Humphrey Visual field analyzer showed significant enlargement of the blind spot in both eyes and mild nasal and inferior depressions in the left eye. There was Frisén grade IV papilledema on funduscopy. She was admitted to the hospital where MRI was normal but MRV showed focal bilateral narrowing at the transverse sinus/sigmoid sinus junction. Lumbar puncture showed normal contents but opening pressure was >55 cm of water.

Acetazolamide was started, but was kept at a low dose of 250 mg a day at the request of nephrology. There was an improvement in the frequency of visual obscurations but they worsened again at three weeks in the setting of non-compliance with the medication. Visual fields demonstrated new inferonasal defects in both eyes and papilledema had progressed in severity. Acetazolamide was restarted but repeat lumbar puncture several days later still demonstrated opening pressure of 45 cm of water.

Audience Response Question: What would you do next?

- Increase acetazolamide gradually to 4 grams a day despite nephrology's protests, closely monitoring for acetazolamide toxicity
- Institute maximal dose furosemide and a low sodium diet
- Optic nerve sheath fenestration
- CSF diversion procedure
- Venous stenting

Surgical options were discussed with the patient including placement of a ventriculoperitoneal shunt and optic nerve sheath fenestration, and venous stenting was presented as a potentially beneficial experimental procedure. After consulting with her family, she consented for angiogram and stenting, if indicated. Conventional angiogram demonstrated stenosis at the transverse-sigmoid sinus junctions and pressure gradients between the sinuses of 20 mm Hg on the right and 23 mm Hg on the left. Balloon angioplasty was performed on the right transverse sinus and a stent was placed across the sinus junction. Post-stent pressure measurements showed a resolution of the gradient.

In the week that followed, headaches, pulsatile tinnitus and visual obscurations all resolved. Repeat funduscopy 1 month later showed significant improvement in the papilledema but there were still blurred margins at the poles. Visual fields at 1 month showed that the defects had not improved. Funduscopic examination at 6 months showed resolution of papilledema and Humphrey visual fields showed improvement although not resolution of field defects. Repeat lumbar puncture at 2 months showed an improved opening pressure of 24 cm of water.

The procedure was complicated by a retroperitoneal hemorrhage that resolved without any permanent effects.

The indications in this case included progression of field defects and papilledema despite treatment with the maximal medication dose deemed safe by nephrology. While alternative medications could have been attempted, the patient had demonstrated poor compliance with acetazolamide, and there was concern that vision would deteriorate further during a medication trial that she might not comply with. The patient was a candidate for stenting as angiogram confirmed the transverse-sigmoid junction venous stenosis seen on MRV and demonstrated a cross-sinus pressure gradient.

The outcome of the case demonstrated resolution of symptoms within a few days, but papilledema took months to improve. Visual field defects also took more than a month to improve and never resolved completely. While these results suggest a positive effect of venous stenting, it is important to note that some, if not all of this improvement may have occurred anyway with time.

3. THEORETICAL RATIONALE FOR STENTING

The theoretical underpinnings of venous sinus stenosis as a contributor to high intracranial pressure in IIH, begin with the long-held knowledge that venous sinus thrombosis or compressive occlusions are well-known causes of increased intracranial pressure. This resulted in the addition of venography in the diagnosis of IIH to rule out thrombosis.² Although the Dandy criteria for IIH require a "normal" MRI, in fact it has been recognized for years that venous sinus stenosis is common patients with IIH, specifically along the transverse sinuses.

In 1995, King et al demonstrated venous hypertension in the superior sagittal sinus and proximal transverse sinuses of 7 patients with IIH, with a drop in the lateral third of the sinus. Interestingly, they reported that this was not the case in 2 patients with minocycline-induced IIH.³ In 1996, Karahalios found dural sinus outflow obstruction in only 5/10 patients with IIH but 8/8 patients who underwent manometry demonstrated elevated venous sinus pressures, suggesting that venous hypertension is common in IIH, although whether it was cause or effect was not elucidated.⁴

The absorption of cerebrospinal fluid (CSF) at the arachnoid granulations has been modelled by the equation: $CSF \text{ absorption} = (P_{CSF} - P_{SSS}) / R_{out}$, where P_{CSF} is the CSF pressure, P_{SSS} is the SSS pressure, and R_{out} is the resistance of CSF outflow across the arachnoid villi.⁵ Thus, CSF absorption is dependent on the venous pressure in SSS. According to this model, relieving a venous sinus obstruction responsible for venous hypertension in the SSS will therefore promote CSF absorption and eventually reduce CSF pressure. In 2007 however, Rohr et al demonstrated reversibility of sinus stenosis in patients after CSF-diversion procedures, arguing that in these patients the stenosis is *secondary* to the elevated ICP, and cautioning that venous sinus stenting should not be performed in such patients.⁶ Proponents of

stenting have countered that sinus stenosis may be both secondary to elevated ICP and a contributor to elevated ICP, thus participating in a vicious cycle. Venous stenting as a means to breaking that cycle may still be efficacious even in patients where the stenosis would be reversible with lowering of the ICP by shunting, they argue.⁷ Furthermore, venous stenosis may recur in some patients who experienced resolution with a drop in ICP.

Patients with IIH who are refractory to medical management may undergo optic nerve sheath fenestration or ventricular or lumbar-shunt placement, but these procedures are not without risk of complication or failure.^{8,9} Based on the early findings of manometry and in the context of the limitations of alternative surgical therapies, some groups have set out to examine the safety and utility of cerebral venous sinus stenting for IIH.

Data from uncontrolled retrospective studies of venous stenting will be presented below. At this time however, venous stenting for IIH remains an experimental procedure, without controlled, retrospective data proving its safety and efficacy. *At this time, there are no randomized controlled trials and all data is anecdotal. The studies that have been performed, for the most part, do not address long term efficacy: the longest follow up is 136 months¹⁰ but the mean clinical follow up time was just under a year at 11.9 months.*

4. PROCEDURE

It is important that practitioners understand what is involved in the procedure of venous stenting (video). Since there is a risk of peri and post-procedural stent thrombosis, an anti-thrombotic regimen is generally prescribed prior to and after the procedure. In our institution, patients receive daily aspirin 81mg and clopidogrel 75 mg for 5 days prior to the intervention. The procedure may be divided into 5 steps:

- 1) Direct Retrograde Cerebral Venography (DRCV): Vascular access is obtained from the femoral vein with placement of a 6 French sheath. Systemic heparin is administered and a catheter is inserted through the iliac vein and brought to the right or left (depending on the location of the stenosis on the MRV or CTV) internal jugular vein and cerebral venous sinuses under fluoroscopic guidance.
- 2) Manometry: A smaller catheter is further advanced to the area of stenosis and pressures are measured before and after the stenosis.
- 3) Angioplasty: This procedure, along with stenting, may immediately follow the DRCV or can be done on separate day. Subjects will be placed under general anesthesia to prevent peri-operative movement. A catheter is again brought to the point of stenosis and a balloon is advanced through the catheter and positioned across the stenosis. The balloon is carefully inflated for a few seconds to partially re-open the stenosis, making room for the stent. The balloon is removed.
- 4) Stenting. The stent will be advanced through the catheter in neck across the stenosis and carefully deployed.

- 5) Repeat Manometry. After stent placement, the pressure gradient across the stenosis is measured again.

Anesthesia: Direct Retrograde Cerebral Venography and manometry are performed with local anesthetic and moderate sedation because general anesthesia may cause artificially elevated venous sinus pressure, confounding the results.¹¹ If angioplasty and stenting are indicated, we convert to general anesthesia (GA) before proceeding, as these procedures are painful. If necessary, patients may return the next day for angioplasty and stenting under GA, but the former protocol is preferable as it requires only one venipuncture.

Post-procedure care: After the procedure the subject will stay in the intensive care unit for 24 hours for observation. Clopidogrel 75mg is continued for 1 month and ASA 81mg for a total of 6 months. We ask patients to avoid contact sports for the period in which they are on both anti-platelet medications. We also ask female patients to avoid becoming pregnant during the month in which they are taking both medications. Other than emergency surgeries or procedures, we ask patients not to schedule any elective surgeries for the first month because they are at high risk for in-stent thrombosis if either the clopidogrel or ASA is stopped. We also ask that elective procedures requiring ASA cessation be avoided in the first 6 months, since stopping the ASA would confer a mild risk of thrombosis, especially in the first few months.

5. FOLLOW-UP

Follow-up goals are to ensure stent patency and efficacy in lowering ICP and to monitor for long-term complications. The follow-up in our study includes:

- a. Neurological and ophthalmological evaluation including perimetry will be performed at 1, 3, 6, 12, 18, and 24 months after treatment, or more frequently if indicated.
- b. Non-invasive imaging studies: Computed tomography venogram (CTV) will be performed at 3, 12 and 24-months after treatment. If there is clinical concern about stent patency, an expedited or intermediate CTV will be performed.
- c. Invasive Procedures: Follow-up DRCV will be performed if there is clinical or imaging (CTV) concern for restenosis or decreased stent patency.
- d. A lumbar puncture will be repeated between 2–3 months and at or around 24 months after treatment to measure the intracranial pressure.

6. RISKS / SAFETY DATA

Venous stenting is not without risk. Based on a literature review inclusive to July, 2012, there were 17 reported complications among 151 patients. They included:

- a. Stent thrombosis: 2 (1.26%)—treated with thrombolytics and were asymptomatic.¹²
- b. Subdural hematoma: 3 (1.9%) One was associated with an AVM.

- c. Transient contrast extravasation: 1 (0.63%)¹³
- d. Transient headache: 1 (0.63%)¹³
- e. Allergic reaction: 2 (1.26%)¹⁴
- f. Anaphylaxis to general anesthesia: 1 (0.63%)
- g. Transient hearing loss: 2 (1.26%)¹⁴
- h. Anaphylaxis to GA: 1 (0.63%)¹⁴
- i. Thrombosis R TS: 1 (0.63%)¹⁰
- j. UTI: 1 (0.63%)¹⁰
- k. Syncope next day: 1 (0.63%)¹⁰
- l. Retroperitoneal hemorrhage: 2 (including 1 of our patients, unpublished) (1.3%)¹⁵
- m. Femoral artery Pseudoaneurysm: 1 (0.63%)

7. EFFICACY DATA

After-stent results are reported, based on a literature review inclusive to July, 2012. There were a total of 158 cases identified, 55 of which were from the US. (35%)

- a. Headache: 142 with headache pre-stent are described in the literature. Among them, 117 (82%) resolved or improved.
- b. Objective visual defects: 66 with visual field defects pre-stent are described
 - Resolved/ improved: 45/66 (68%)
 - Unchanged 7/66 (11%)
 - Worsened: 1/66 (2%)
 - No data: 13/66 (19%)
- c. Elevated CSF pressure: 109 with elevated ICP pre-stent are described
 - Resolved / improved: 26/109 (24%), 26/27 checked (96%)
 - Unchanged: 1/109 (0.09%)
 - No data: 81/109 (74.3%).
- d. Papilledema: 128 with papilledema pre-stent are described
 - Resolved / improved: 118/128 (92%)
 - Unchanged: 4/128 (3.1%)
 - No data: 6/128 (4.6%)

Please reference table #1 on page 358 for a review of the safety and efficacy of venous sinus stenting in the literature.

8. BEST INDICATIONS

As venous sinus stenting has not been proven to be an long-term effective therapy for IIH, and the long term risks have not been clearly established, there is no clear indication as of yet. As such, it is reasonable to conclude that at present it is best reserved for patients with IIH who have shown a decline in reliable perimetry (in the setting of persistent or worsening papilledema) either despite maximal medical therapy, or who are unable to tolerate or are non-compliant with best medical therapy. Patients with IIH who present with severe visual loss initially and are deemed to require urgent and persistent lowering of intracranial pressure may theoretically benefit from the procedure, although the latency between reduction in stenosis and any effect on intracranial pressure is as of yet unclear.

9. WEILL CORNELL VENOUS STENTING TRIAL

Along with co-investigator Athos Patsalides, MD, we have set out to evaluate the safety and efficacy of venous stenting for patients with IIH in our institution.¹⁷ Our primary objectives include evaluating the safety of sinus venous sinus stenting in patients with refractory IIH and evaluating the efficacy of venous stenting in improving visual function in patients with refractory IIH. (Refractory IIH is defined as absence of stabilization or improvement in visual function after one month of best medical treatment or intolerance to the medical regimen) In this study, which is the first FDA-approved trial in US, we aim to quantify change in mean deviation after stenting and quantify changes in papilledema on clinical examination and using optical coherence tomography (OCT).

10. FUTURE DIRECTIONS

While the available retrospective and anecdotal data on venous stenting suggests that it may be an effective alternative therapy for IIH, a prospective, randomized head to head trial of venous stenting vs. ventriculoperitoneal shunting vs. optic nerve sheath fenestration is ultimately needed to truly assess its value in the therapeutic options for this disease. While the interventional radiologist and surgeons will know the treatment used, evaluating neuro-ophthalmologists should be blinded as they assess visual function and improvement in papilledema.

Audience Response Question: After this talk, would you consider sending a patient with IIH refractory to acetazolamide with a worsening visual field for treatment with venous stenting at an institution with several years of experience with the procedure?

- a. Yes
- b. No

CME ANSWERS

1. A. Blood pressure is not directly related to csf absorption at the arachnoid granulations
2. C. Venous stenting has been followed by a decrease in intracranial pressure in some patients and csf shunting has been followed by an improvement in venous sinus stenosis in others.
3. B. Meningitis has not been reported as a complication of venous sinus stenting as of august, 2012.

REFERENCES

1. Ahmed R, Friedman DI, Halmagyi GM. Stenting of the Transverse Sinuses in Idiopathic Intracranial Hypertension, *J Neuro-ophthalmology*, 31, 374–380, 2011.
2. Friedman DI, Jacobson DM: Diagnostic criteria for idiopathic intracranial hypertension, *Neurology* 59(10), 1492–5, 2002.
3. King JO, Mitchell PJ, Thomson KR et al.: Cerebral venography and manometry in idiopathic intracranial hypertension, *Neurology*

45(12), 2224–2228, 1995.

4. Karahalios DG, ReKate HL, Khayata MH et al.: Elevated intracranial venous pressure as a universal mechanism in pseudotumor cerebri of varying etiologies, *Neurology* 46(1), 198–202, 1996.
5. Davson H, Welch K, Segal MB, eds. *Physiology and pathophysiology of the cerebrospinal fluid*. New York: Churchill Livingstone: 485–21, 1987.
6. Rohr A, Dorner L, Stingele R et al.: Reversibility of venous sinus obstruction in idiopathic intracranial hypertension, *Am J Neuroradiol* 28(4), 656–659, 2007.
7. Bateman GA. Stenoses in idiopathic intracranial hypertension: to stent or not to stent? *Am J Neuroradiol* 29(2), 215, 2008.
8. Banta JT, Farris BK. Pseudotumor cerebri and optic nerve sheath decompression, *Ophthalmology* 107(10), 1907–12, 2000.
9. McGirt MJ, Woodworth 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* 101(4), 627–32, 2004.
10. Kumpe DA, Bennett JL, Seinfeld J et al.: Dural sinus stent placement for idiopathic intracranial hypertension, *J Neurosurg* 116(3), 538–48, 2012.
11. McGonigal A, Bone I, Teasdale E. Resolution of transverse sinus stenosis in idiopathic intracranial hypertension after L-P shunt, *Neurology* 62(3), 514–515, 2004.
12. Higgins JN, Cousins C, Owler BK et al.: Idiopathic intracranial hypertension: 12 cases treated by venous sinus stenting, *J Neurol Neurosurg Psychiatry* 74(12), 1662–1666, 2003.
13. Bussière M, Falero R, Nicolle D et al.: Unilateral transverse sinus stenting of patients with idiopathic intracranial hypertension, *Am J Neuroradiol* 31(4), 645–50, 2010.
14. Ahmed RM, Wilkinson M, Parker GD et al.: Transverse sinus stenting for idiopathic intracranial hypertension: a review of 52 patients and of model predictions, *Am J Neuroradiol* 32(8), 1408–14, 2011.
15. Albuquerque FC, Dashti SR, Hu YC et al.: Intracranial venous sinus stenting for benign intracranial hypertension: clinical indications, technique, and preliminary results, *World Neurosurg* 75(5–6), 648–52, 2011.
16. Fields JD, Javedani PP, Falardeau J et al.: Dural venous sinus angioplasty and stenting for the treatment of idiopathic intracranial hypertension, 2011.
17. Venous sinus stenting for idiopathic intracranial hypertension refractory to medical therapy. Available at: <http://www.clinicaltrials.gov/ct2/results?term=NCT01407809>. Accessed August 13, 2012.

TABLE 1. REVIEW OF EFFICACY AND SAFETY DATA OF VENOUS STENTING

Author	n	Age (y)	HA	FE	VD	PHI	OC	PROX procedure	F/U (months)	EBSD on HA	EBSD on VSD	EBSD on Visual Acuity	EBSD on Ocular Motility	Long term (year)	Adverse Effect	
Higgins 2002	1	30	1	1	1	1	1	0	12	improved 1	improved 1	improved 1	improved 1	Patient 1	Adverse Effect: Commissioning	
Higgins 2003	12	19-62	12	8	5	11	11	9 (LPS) 3, VPS 2, ONSF 1, BSTD 1	2-26 (14)	Resolved 5 Improved 2 Unchanged 5	Resolved 2 Improved 1 Unchanged 3	Resolved 1 Improved 1 Unchanged 10	Resolved 1 Improved 1 Unchanged 10	Patient 11 Not stable 1	Start thrombus in 2 patients - treated with thrombolytic - asymptomatic	
Owler 2003	4	17-36	4	4	3	3	3	3	5-12 (8)	Resolved 1 Improved 3	Resolved 2 Worse 1 Not stable 1	Improved 1	Improved 3	Patient 4		
Cyganok 2003	1	37	1	1	0	1	0	0	12	improved 1	improved 1	improved 1	improved 1	Patient 1		
Rajjar 2005	1	15	1	1	1	1	0	0	6	improved 1	Resolved 1	Resolved 1	Not stable 1	Patient 1		
Messias 2005	1	51	1	1	1	1	0	0	3	Resolved 1	Resolved 1	Resolved 1	Not stable 1	Patient 1		
Messias 2007	6	22-45	6	7	5	6	1	1	12-30 (18)	Resolved 7 Improved 1	Resolved 3 Not stable 2	Resolved 3	Resolved 6	Patient 3		
Rohr 2007	1	28	1	1	1	1	0	0	1	Unchanged 1	Unchanged 1	Unchanged 1	Unchanged 1	Resentous 1		
Cross 2007	1	38	1	1	1	1	0	0	1	improved 1	NOT stable 1	NOT stable 1	NOT stable 1	NOT stable 1		
Pasquet 2008	1	60	1	1	1	1	0	0	0	improved 1	Resolved 1	Resolved 1	Resolved 1	NOT stable 1		
Dornier 2008	10	28-60	10	10	6	10	0	0	6-36(17)	Resolved 6 Improved 2 Unchanged 2	Resolved 4 Improved 3 Unchanged 1	Resolved 4	Resolved 10	Patient 10		
Alar 2009 (US)	1	51	1	1	0	1	0	0	2	Resolved 1	Not stable 1	NC 1	Not stable 1	Patient @ 2 mos 1		
Eusebio 2010	10	16-65	10	10	4	10	0	0	4-80 (17.6)	Resolved 2 Improved 8 Unchanged 2	Resolved 2 Improved 4	Improved 4	Not stable 10	Patient 10 F/U venogram not performed	Contrast extravasation 1 Transient HA 2.	
Zheng 2010 (China)	1	54	1	1	0	1	0	0	3	Resolved 1	Resolved 1	Resolved 1	Resolved 1	Not stable	Retroposterior hemorrhage	
Albuquerque 2010	16	12-51	16	NA	NA	NA	0	0	2-40 (20)	Resolved 2 Improved 10 Not stable 3 Unchanged 2 Worse 1	Not stable 18	Not stable 18	Not checked 18	Patient 14/16 NA 4/16	Retroposterior hemorrhage with drop in HCT	
Amied 2011	52	10-64 (54)	43	46	30	41/41	0	9/4 ONSF 2 (48%), LPS 1 (19%), LPO 1 (19%), VPS 3 (20%)	2-108 (24)	Resolved 35 Resolved later 5 Unchanged 3	Resolved 23	Resolved 23	Checked in 4 but measurements not stable	Resolved same 6	Quality 2 Transient HL 2 Anaphylaxis to SA 1 Pseudoaneurysm 1 (FR) SOHSAHICH 1 (FR) Femoral Pseudoaneurysm 1	
Fisher 2011	15	30-56 (54)	15	15	NA	NA	0	0	1-49 (14) median 9	Resolved 2 Improved 8 Unchanged 3 Worsened 2	NA	NA	NA/15	14/14		
Raviary 2011	2	NA	1	2	NA	NA	0	0	NA	NA 2	NA 2	NA 2	NA 2	NA	0	
Kump 2012	16	16-62	12	17	4	17	1 NC	10 (7 ONSF, 3 VPS)	11-136 (43.7)	Resolved 2 Improved 8 Unchanged 2	Worsened 0 Stable/Improved 16	Worsened 0 Stable/Improved 16	NC 16	15/16	SOHSAH 1 (venous, rec AMM) Thrombosis R 15, L 1 UTI 1 Syncope next day 1	
TOTAL	139 (65 USA)	10-65	142	136	86	105	5†	5†	0-135	Resolved 129 Improved 48 Unchanged 16 Worsened 2 Not stable 9 UTI/HA 1 Improved/Resolved	Resolved 32 Improved 18 No change 7 Worse 1 Not stable 6 UTI/HA 1 Improved/Resolved	Resolved 30 Improved 16 No change 7 Worse 1 Not stable 6 UTI/HA 1 Improved/Resolved	Resolved 30 Improved 16 No change 7 Worse 1 Not stable 6 UTI/HA 1 Improved/Resolved	Patient 30†		

Legend: PE: papilledema, HA: headache, VD: visual field defect, CSF: cerebrospinal fluid, ONSF: optic nerve sheath fenestration, VPS: ventriculoperitoneal shunt, LPS: lumboperitoneal shunt, BSTD: bilateral subtemporal decompression, HL: hearing loss, SDH: subdural hematoma, SAH: subarachnoid hemorrhage, ICH: intracerebral hemorrhage, GA: general anesthesia, R TS: right transverse sinus, UTI: urinary tract infection