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REVIEW

Current concepts and strategies in the diagnosis and management of idiopathic intracranial hypertension in adults

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Abstract Since obesity has become an epidemic in industrialized nations, idiopathic intracranial hypertension (IIH) is now a more common neuro-ophthalmic disorder that causes visual loss and headaches. This review highlights the new diagnostic criteria for IIH and the new insights into the pathophysiologic mechanisms of IIH. Key diagnostic and monitoring techniques for papilledema include not only neuroimaging and the measurement of cerebrospinal fluid (CSF) pressure, but also perimetry, optical coherence tomography, and ocular sonography. The main findings of the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) support acetazolamide as the mainstay for medical therapy. CSF diversion procedures, endovascular venous sinus stenting, and optic nerve sheath fenestration are all surgical options when IIH is refractory to medical treatment or when it presents fulminantly. Future clinical trials comparing these procedures will help develop better paradigms in the surgical management of IIH.

Keywords Idiopathic intracranial hypertension · Diagnosis · Therapy · Adults

Introduction

Idiopathic intracranial hypertension (IIH) is caused by elevated cerebrospinal fluid (CSF) pressure of unknown etiology. The annual incidence has been estimated in the literature to be at most 3/100,000. It usually affects obese women of childbearing age with female-to-male ratio of 4.3–1.0. Since obesity is a major risk factor for the development of IIH, the increasing prevalence of IIH parallels the rising epidemic of obesity that also contributes to the socioeconomic burden in the United States (US). Recent estimates of more than $444 million/year was expended for medical costs in the US. Between 1998 and 2002, a threefold increase in new cerebrospinal fluid (CSF) shunt procedures was performed for IIH. About 57% of those affected with IIH went on disability, and 31% changed occupations [1].

Less frequently, IIH can occur in children with no gender predilection for females and no higher prevalence of obesity in prepubescent children [2, 3]. After puberty, females are more often affected, similar to adult onset IIH.

In the IIHTT, headache, usually constant or daily, was the most common presenting symptom in 84% of patients [4]. The headache in IIH can mimic chronic daily headaches or chronic tension-type headaches and can be aggravated by Valsalva maneuvers and physical exertion [5, 6]. In the IIHTT, transient visual obscurations occur in 68%, back pain in 53%, pulsatile tinnitus in 52%, visual loss in 32%, followed by dizziness, photophobia, neck pain, nocturia, cognitive dysfunction, radicular pain, and, finally, diplopia. Papilledema and visual field defects are the hallmark signs [4].

This review will highlight the most recent theories in the pathogenesis of IIH, new diagnostic criteria for IIH, current ocular imaging techniques for the measurement of papilledema, and updated strategies in the medical and surgical management of IIH.

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Updated clinical diagnostic criteria for IIH

The diagnostic criteria for IIH continue to evolve as new clinical findings are recognized in this disorder. The difference in elevated CSF opening pressures for adults and children is now accepted as ≥250 mm H_2O and ≥280 mm H_2O, respectively. The diagnosis is also based on the presence of papilledema, normal neurological examination, neuroimaging, and CSF composition. The diagnosis of IIH without papilledema can be made only if a unilateral or bilateral sixth nerve palsy is present. If neither of these features are present, then IIH is just suggestive if there are additional neuroimaging findings of an empty sella, flattening of the posterior globe, distension of the perioptic subarachnoid space with or without a tortuous optic nerve, or transverse venous sinus stenosis [7] (Table 1).

Secondary causes of IIH

Secondary causes of intracranial hypertension must be excluded to make the diagnosis of IIH. Slowly enlarging mass lesions can cause increased intracranial pressure as the only presenting sign. Any other lesions that cause decreased flow in the arachnoid granulations (scarring from the previous meningitis, elevated CSF protein, and hemorrhage) and obstruction to venous drainage (venous sinus thrombosis from hypercoagulable states, glomus tumor, bilateral radical neck dissection, and increase right heart pressure); arteriovenous malformations, and dural shunts need to be ruled out [8]. Other risk factors for increased intracranial pressure include drugs (lithium carbonate, sulfa antibiotics, tetracycline and its derivatives, and oral contraceptives) and endocrinologic disorders (steroid withdrawal, growth hormone use in children, hyperthyroidism, Addison's disease, and hypoparathyroidism). Most recently, hypervitaminosis A was found to be an unlikely contributory factor in the causation of IIH, according to the IIHTT [9]. Obstructive sleep apnea, iron deficiency anemia, sarcoidosis, and uremia are other causes to consider in adult IIH [8].

Intracranial hypertension without papilledema in chronic migraine patients

Another less common presentation of increased intracranial pressure is IIH without papilledema (IIHWOP) which has been considered a risk factor for the progression of migraine. In a prospective study of 62 chronic migraine patients with a body mass index (BMI) >30, a CSF opening pressure of >200 mm H_2O was found in about 10%. They had no papilledema and no venous sinus stenosis on magnetic resonance venography (MRV) [10]. In another study, about half of patients with bilateral venous sinus stenosis on MRV of the brain were found to have IIHWOP [11]. De Simone et al. [12] have proposed that IIHWOP should be considered in all patients with chronic daily headache with evidence of venous sinus stenosis and unresponsiveness to medical treatment. These patients

Table 1 Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children [2]

1. Required for diagnosis of pseudotumor cerebri syndrome[a]
   - (A) Papilledema
   - (B) Normal neurologic examination except for cranial nerve abnormalities
   - (C) Neuroimaging: normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion and no abnormal meningeal enhancement on MRI, with and without gadolinium, for typical patients (female and obese), and MRI, with and without gadolinium, and magnetic resonance venography for others; if MRI is unavailable or contraindicated, contrast-enhanced CT may be used
   - (D) Normal CSF composition
   - (E) Elevated lumbar puncture opening pressure (250 mm CSF in adults and 280 mm CSF in children; 250 mm CSF if the child is not sedated and not obese in a properly performed lumbar puncture)
2. Diagnosis of pseudotumor cerebri syndrome without papilledema

In the absence of papilledema, a diagnosis of pseudotumor cerebri syndrome can be made if B–E from above are satisfied, and in addition, the patient has a unilateral or bilateral abducens nerve palsy

In the absence of papilledema or sixth nerve palsy, a diagnosis of pseudotumor cerebri syndrome can be suggested but not made if B–E from above are satisfied, an in addition at least three of the following neuroimaging criteria are satisfied:

- (i) Empty sella;
- (ii) flattening of the posterior aspect of the globe;
- (iii) distention of the perioptic subarachnoid space with or without a tortuous optic nerve;
- (iv) transverse venous sinus stenosis.

[a] A diagnosis of pseudotumor cerebri syndrome is definite if the patient fulfills criteria A–E. The diagnosis is considered probable if criteria A–D are met, but the measured CSF pressure is lower than specified for a definite diagnosis

should undergo a lumbar puncture for the diagnosis and CSF withdrawal for the normalization of CSF pressure to help treat their chronic pain.

The role of neuroimaging in the diagnosis of IIH

MRI of the brain and orbits with gadolinium and MRV of the brain can rule out secondary causes of elevated CSF pressure, such as a space-occupying mass lesion and venous sinus thrombosis. When the IIH diagnostic criteria are not fulfilled, or are partially fulfilled, neuroimaging findings typically seen in IIH can also help to support the diagnosis of IIH, but none are pathognomonic for this condition.

Regarding the optic nerve abnormalities that can be observed in IIH, optic nerve head protrusion is more commonly observed in severe cases of IIH, and posterior globe flattening is not specific for IIH, since it is also an MRI feature of ocular hypotony [13]. Posterior globe flattening has a sensitivity of about 66% and specificity of about 36% (Fig. 1); optic nerve head protrusion has a sensitivity of about 98% and a specificity of about 99% [13]. Enhancement of the optic disc on axial T1-weighted MRI with contrast is not specific for papilledema and occurs in other causes of optic disc edema [13].

Osseus erosion and remodeling from the chronic intracranial hypertension are postulated to cause widening of the bony canals of the skull base. Prolonged intracranial hypertension increases the size of the bony pituitary fossa with minimal effect on the pituitary size which leads to the partial empty sella turcica on MRI that is postulated to be a result of herniation of the subarachnoid space to the anterior sella turcica diaphragm [14, 15]. The area of sellar enlargement was highly sensitive at 100% and specific at 90% in distinguishing IIH from normal controls (Fig. 2) [15]. The area of the pituitary gland was found to be only sensitive at 100% for detecting treatment changes [15]. Enlargement of the optic canal is a more recent MRI finding associated with the severity of papilledema and poor visual function in IIH. Each millimeter increase in the bony optic canal size was associated with a 0.50 dB decrease in Humphrey visual field mean deviation and with a higher chance of having grade 4–5 papilledema or optic atrophy. It was postulated that local CSF flow could be increased to cause bony remodeling at the optic canals [16]. Other bony canals that are widened include the foramen ovale with 81% specificity and 50% sensitivity for IIH [17], the jugular foramen and hypoglossal canal [18, 19], both of which are less specific for IIH.

Enlargement of CSF spaces, such as distention of the optic nerve sheaths, or meningoceles from chronic intracranial hypertension might be supportive findings of IIH [19]. Based on the width of the perioptic CSF with a CSF ring >2 mm, the sensitivity of this feature in IIH is about 58% and the specificity is about 89% [13]. In addition to the enlargements of Meckel's cave, distention of the optic nerve sheaths, a more recent finding of narrowing of the trigeminal cave, an arachnoid pouch containing CSF and the trigeminal ganglion, has recently been found [20].

Transverse venous sinus stenosis is commonly seen in IIH based on ATECO MRV, not by cerebral venous pressure gradient measurement. This obstruction to venous outflow in the dural sinus system occurs in about 30–93% of IIH patients [21]. Transverse and sigmoid sinus stenosis on MRV has the same sensitivity and specificity of 93% as a reliable imaging marker of IIH (Fig. 3) [21]. After LP drainage of CSF, the dural sinus system volume increases

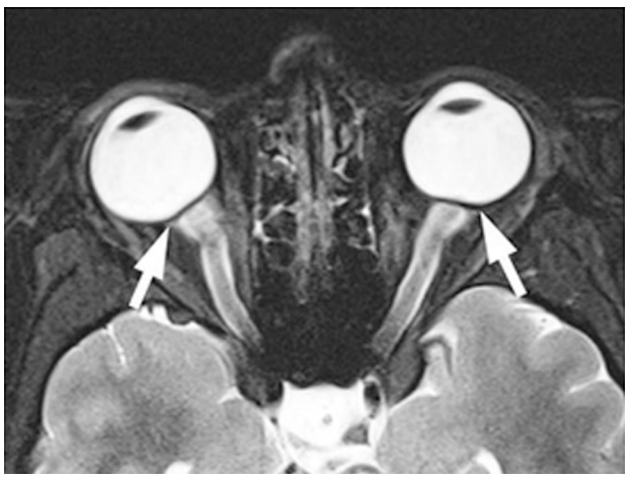

Fig. 1 Axial T2 fat-saturated MRI showing flattening of the posterior globes (*white arrows*) around the insertion of the optic nerve [13]

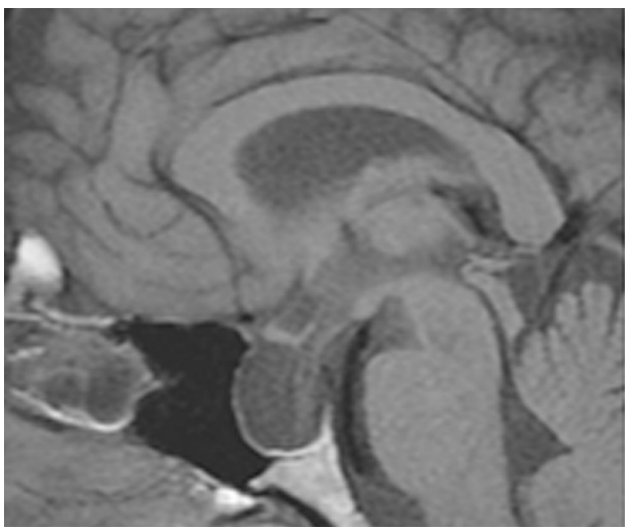

Fig. 2 Non-contrast sagittal T1 MRI of an empty sella with no pituitary tissue [15]

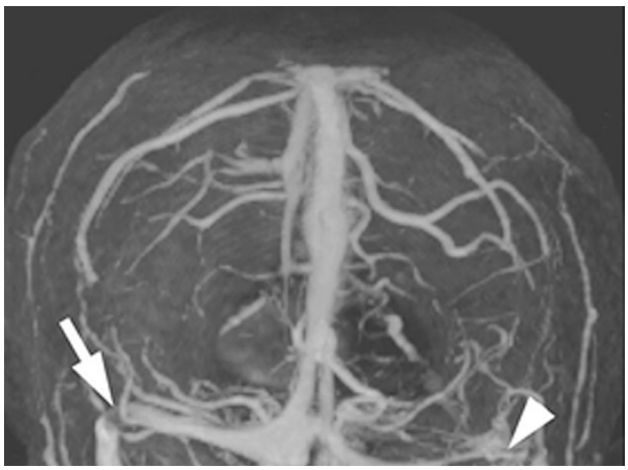

Fig. 3 Postcontrast MRV of the brain showing bilateral transverse venous sinus stenoses [21]

after ICP normalization, [22, 23] and the transverse sinus stenosis can still persist [24].

Intraorbital imaging features that can be seen in IIH include enlarged optic nerve sheath, posterior globe flattening, and optic nerve head elevation. Transorbital ultrasound techniques can reliably detect optic nerve sheath diameter enlargement with a sensitivity of 90% and a specificity of 84% at a cut-off value of 5.8 mm in detecting IIH. An optic nerve sheath diameter of >5 mm predicted CSF pressure greater than or equal to 20 cm H_2O with both a sensitivity and specificity of 100% [25]. Optic disc elevation can also be qualitatively seen and usually requires a longer period to recede after ICP is lowered [26–28]. MRI has a sensitivity of 72–80% and specificity of 96% in detecting increased optic nerve sheath distension and tortuosity [29].

Therefore, these neuroimaging features can be helpful in distinguishing patients with intracranial hypertension from any cause, including IIH, from those with normal ICP.

New theories in the pathophysiologic mechanisms of IIH

The pathophysiology of IIH still remains uncertain, but new theories into the mechanisms of elevated intracranial pressure continue to evolve in our understanding of this disorder. CSF hypersecretion by the choroid plexus has been thought to be a possible mechanism of IIH. The choroid plexus and ciliary epithelium in the eye both have 11 β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) that drives secretion of aqueous humor [30] and may have a role in CSF secretion. Inhibitors to 11β-HSD1 decrease intraocular pressure and a low-calorie diet lowers ICP that correlates with a decreased 11β-HSD1 activity [31]. A selective inhibitor of 11β-HSD1 has been developed to treat obesity, metabolic syndrome, and diabetes mellitus type 2 [32], and this drug may also have the potential to decrease the ICP in IIH [33].

Another new concept of dysregulation of fluid transport across the blood–brain barrier might also be a likely pathophysiologic mechanism for IIH. Water transport channels located in the astrocyte foot processes control fluid transport in cerebral edema. Aquaporin 1, located mostly in the choroid plexus, might be upregulated by retinoids, such as vitamin A, and glucocorticoids can cause elevated intracranial pressure (ICP). Conversely, aquaporin 1 might be downregulated by medications, such as acetazolamide to lower ICP [34].

In addition to the CSF drainage from the subarachnoid space through the arachnoid granulations into the superior sagittal sinus, a more recent finding in mice of the glymphatic pathways, lying along blood vessels, might promote exchange of fluid between the CSF in the subarachnoid space and the interstitial fluid in the brain [35]. Either reduced drainage of CSF through glymphatic pathways or decreased CSF absorption by arachnoid granulations can lead to increased outflow resistance causing elevated ICP. Vitamin A deficiency can cause thickening of the extracellular matrix in the arachnoid villi leading to elevated ICP [35]. Radioisotopic techniques to study CSF circulation have shown decreased CSF absorption in patients with IIH [36]. Therefore, these new findings in CSF fluid dynamics will give insights into more novel therapies for IIH.

Structural abnormalities in the cerebral venous sinus system have been attributed to IIH. Stenosis of the dominant or both transverse sinuses can be due to external situations causing a graduated narrowing tapered stenosis, or can be due to arachnoid granulations or fibrous septae obstructing within the venous sinus [21]. Elevated ICP has also been demonstrated to lead to a focal region of decreased venous sinus gradient pressure, as measured by venography to then cause impaired CSF drainage in the arachnoid granulations. This elevated ICP is treated by transverse venous sinus stenting [37].

The risk of the development of IIH increases as a function of body mass index (BMI) and weight gain over the preceding year. The risk of IIH-induced visual loss increases with BMI >40 kg/m [38]. Berdahl et al. [39] showed that BMI has a linear relationship with CSF pressure. From a BMI of 18 to a BMI of 39, the CSF pressure increased by 37.7% (from 8.6 ± 2.1 to 14.1 ± 2.5 mmHg).

Not all obese persons develop IIH, so there are other risk factors, especially gender and endocrinologic abnormalities that predispose to this disorder. Increased waist-to-hip ratio in which fat is located mostly in the hips rather than in the

waist, as in central obesity, is associated with IIH [40]. Because IIH predominantly affects obese women of reproductive age, adipose signaling factors, such as adipokines, steroid hormones, and their effects on ICP regulation, have been studied. Leptin, an adipokine that regulates satiety in the hypothalamus, appears to be elevated in IIH compared with controls matched for age and gender, but not for BMI [3, 41]. Hyperandrogenism has recently been shown to be correlated with IIH. Increased levels of circulating androgens are associated with earlier age of onset of IIH in women, and polycystic ovarian syndrome (PCOS), a disorder that causes hyperandrogenism, has been associated with IIH [42].

No clear evidence of any genes has been found to be associated with IIH, such as the aquaporin-4 gene variants [43]. It has been hypothesized that upregulation of the aquaporin-1 gene might cause increased intracranial pressure and downregulation might reduce CSF pressure [44].

Improved understanding of the pathophysiologic mechanisms of IIH will help guide future management of this disorder. Biomarkers in the CSF that are related to its pathogenesis will be the focus of future research. In a recent study of the CSF proteome by Brettschneider et al. [45], angiotensinogen was found to be a validated biomarker in which its downregulation contributed to increased CSF production. Upregulated CSF proteins included element-binding protein 1, zinc-α-2-glycoprotein, immunoglobulin heavy constant α-1, α-1-antitrypsin, serotransferrin, and haptoglobin. The other downregulated CSF proteins included hemopexin, vitamin-D-binding protein, and transerythretin. An immunologic abnormality, such as higher levels of IL-2, IL-4, IL-10, IL-17, and IFN-γ in IIH compared to multiple sclerosis and other non-inflammatory neurologic conditions, has also been postulated to underly IIH [46].

The evolving role of perimetry, optical coherence tomography, and ocular sonography in IIH

Perimetry

Visual loss correlates with the severity of papilledema and affects the entire visual field and even more with eccentricity, especially nasally and around the blind spot. Since visual field defects improve with treatment of IIH, the main outcome measure in the IIHTT was the change in the average perimetric mean deviation from baseline to 6 months. Localized nerve fiber bundle defects were found in 60% of the IIH patients at baseline. A partial arcuate defect with an enlarged blind spot was most commonly seen at baseline of the study. These field defects affected the inferior hemifield more often than the superior one, and the visual loss was greater in the left eye [47].

At the end of 6 months, statistically significant mean change in dB improvement occurred in the nasal region and around the blind spot, especially in the acetazolamide group compared to the placebo group [48]. Papilledema causes anterior elevation of the optic disc and peripapillary retina. Unlike the nerve fiber bundle defects representing damage, this region of the retina becomes hyperopic and represents a refractive scotoma that can be eliminated with plus lenses [49].

Since perimetry can be affected by behavior, such as fatigue and poor attention from headache in IIH, retesting should be done when the mean deviation worsens in patients who have been clinically stable or who have been improving. In the IIHTT, performance failure in the visual field testing occurred in 21% of the study patients [50].

Optical coherence tomography (OCT)

Some useful features of OCT to characterize papilledema are disc volume, degree of subretinal fluid, degree of buried disc drusen, and thickness of the retinal ganglion cell layer (RGCL) [51]. In the IIHTT, changes in peripapillary retina and optic nerve head closely correlated with Frisèn grading of papilledema. These OCT parameters did not correlate with severity of clinical symptoms or visual dysfunction, especially visual acuity, in patients with newly diagnosed IIH and mild vision loss [52].

In papilledema, the degree of upward angling and displacement of Bruch's membrane changes after the intracranial pressure is reduced (Fig. 4). This deformation of Bruch's membrane to angle toward the vitreous, especially notable in the nasal and temporal borders of the neural canal opening, can help in monitoring the force differential at the optic disc over time as the intracranial pressure changes. The deflection of Bruch's membrane may represent the hydrostatic pressure in the retrobulbar space onto the optic nerve head. This translaminar pressure gradient represents the difference between the CSF pressure and the intraocular pressure. This OCT finding can also help in differentiating papilledema from other causes of optic disc edema or pseudopapilledema. This OCT feature can also be observed in eyes with atrophic papilledema that do not have much RNFL or optic nerve head swelling [53, 54].

Buried disc drusen can also be differentiated from papilledema by SD OCT. With enhanced depth imaging-optical coherence tomography (EDI-OCT), structures can be seen 500–800 μm deeper than in the conventional OCT. The entire circumference of the drusen can be delineated and the cross-sectional area of drusen beneath the optic nerve head can be measured [55] (Fig. 5).

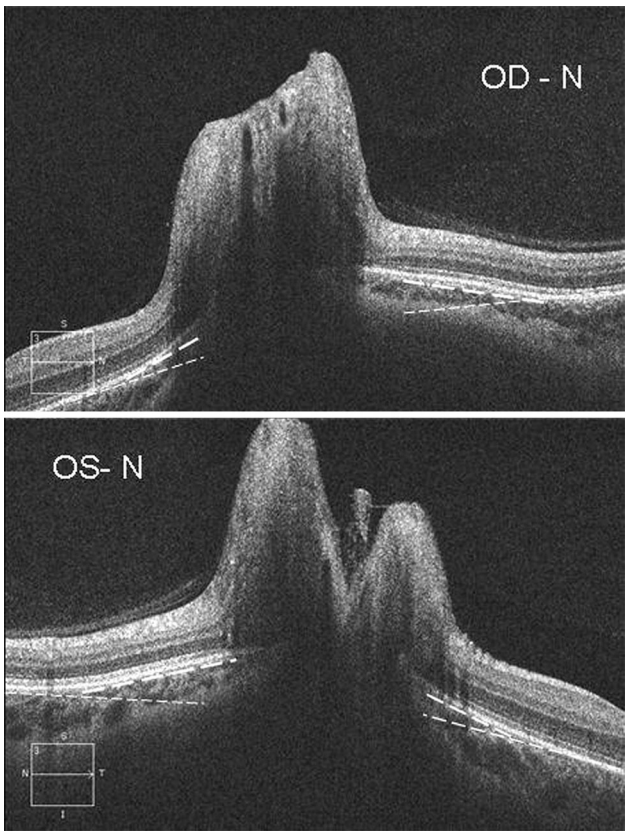

Fig. 4 Spectral domain OCT showing Bruch's membrane is elevated in papilledema (*top*). It is displaced in the same eye before and after treatment of elevated intracranial pressure [42]

OCT is useful for monitoring the effects of papilledema from IIH and for measuring the effects of medical treatment. In the IIHTT, acetazolamide and low-sodium weight loss were shown to improve RNFL thickness, total retinal thickness (TRT), and optic nerve head (ONH) volume swelling measurements the most during the first 6 months. Retinal ganglion cell loss appears to be uncommon in treated patients. After 6 months of treatment, there is minimal RGCL and IPL thinning [56]. It has also been shown to be an effective parameter for monitoring the optic nerve after optic nerve sheath fenestration (ONSF) [57].

Macular thickness and RNFL thickness both can quantify axonal loss in IIH.

In a prospective study of 52 eyes with chronic papilledema, which was defined as clinically resolved papilledema of Frisen grade 0 with stable VF defect for at least 6 months after medical and/or surgical treatment and CSF pressure of <25 cm H_2O after papilledema resolution, macular thickness and RNFL thickness were both significantly reduced compared with normal controls. These OCT parameters correlated with VF sensitivity loss. Macular thickness measurements might be used to estimate and monitor the degree of retinal ganglion cell loss in chronic

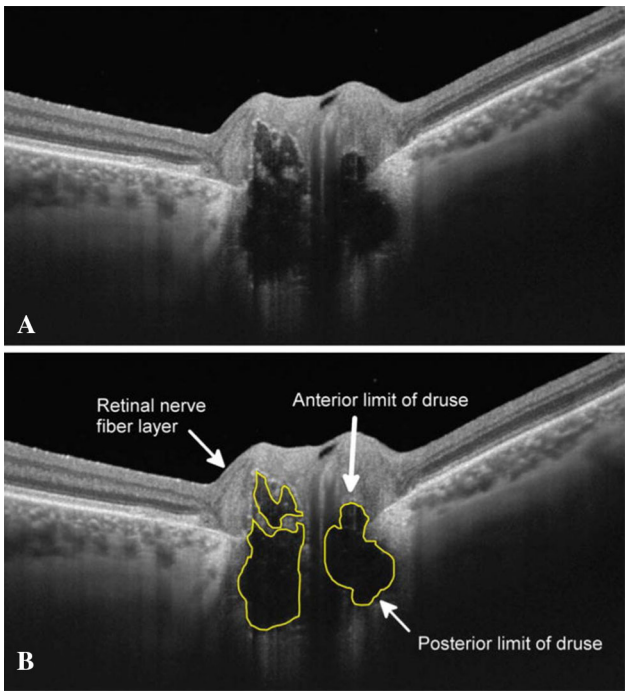

Fig. 5 Optic nerve head drusen, a differential diagnosis of papilledema, can be seen in enhanced depth imaging-optical coherence tomography (**a**). Posterior border of drusen outlined (**b**) [44]

papilledema (resolved papilledema at Frisen grade 0 stage) [58]. Further visual functional testing showed that pattern ERG measurements to detect RGC dysfunction correlated with macular thickness, RNFL thickness, and VF measurements in patients at the chronic papilledema stage. PERG may be useful in monitoring retinal ganglion cell loss after papilledema has resolved [59].

Segmentation of the retinal layers in the macula in resolving papilledema can further help quantify subclinical atrophy. Photoreceptor loss and inner nuclear layer cysts can be seen in atrophic papilledema (Fig. 6). In addition to mechanical compression leading to ischemia in the retina, retrograde transsynaptic degeneration might occur leading to retinal ganglion cell and inner nuclear neuronal loss followed by thinning of the outer plexiform layer and outer nuclear layer cell loss [60].

Ocular sonography

Other techniques to detect increased intracranial pressure include ocular sonography to measure the diameter of the optic nerve sheath, which has good diagnostic accuracy compared to CT. This non-invasive technique is a sensitive test for ruling out raised intracranial pressure in a low-risk population and a specific test for ruling in raised ICP in a higher risk population. Ocular sonography might have a role in an emergent clinical setting or during transport of a patient where no CT is available [61].

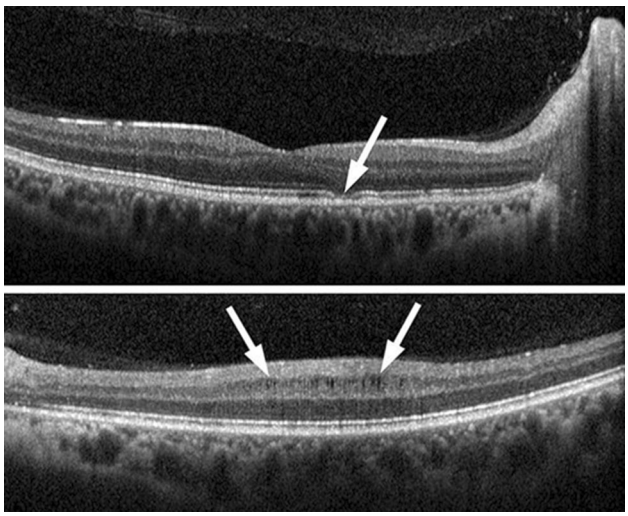

Fig. 6 Photoreceptor loss (*top*) and inner nuclear layer cysts can be seen in atrophic papilledema (*bottom*), as seen in spectral domain OCT [49]

Recent evidence for the medical management of IIH

Acetazolamide

Acetazolamide is considered the first-line medication for the treatment of IIH. It inhibits carbonic anhydrase in the choroid plexus to decreased CSF production, and thereby, reduces ICP. The most common side-effects include transient myopia, paresthesias, loss of appetite, and metabolic acidosis [62].

The Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) was the first multicenter, randomized, double-blinded, placebo-controlled trial to compare the efficacy of acetazolamide and a weight-reducing diet vs. dieting alone in 165 patients with IIH and mild visual loss [63]. In patients with mild IIH, those with mild visual acuity loss and predominantly arcuate loss and enlarged blind spots, acetazolamide up to a maximum of 4 g/day with a low-sodium weight-reduction diet compared with diet alone resulted in modest improvement in visual field function. These visual field results were statistically significant, particularly in the nasal areas and around the blind spot, but the difference between the two groups was less than expected. The group treated with both acetazolamide (2.5 g/day on average) and diet had a significant reduction in weight (7.5 kg on average). They showed significantly improved papilledema, especially the high-grade type, and improved visual-related quality of life, but no significant treatment effects were noted in regard to headache disability. The patients in both treatment groups who lost at least 6% of their baseline weight at 6 months had demonstrable reduction of papilledema on OCT. Although a decrease in BMI was not correlated with a decrease in RNFL thickness in this large study, small amounts of weight loss alone can improve some IIH-associated findings, as shown in a smaller retrospective study [64].

Other medications

Topiramate is a mild carbonic anhydrase inhibitor. The most common side-effects include distal paresthesias, loss of appetite, difficulty in concentration, and nephrolithiasis [62]. Myopia and acute angle-closure glaucoma have also been reported [65–67]. It has been shown to be effective in the treatment of IIH, especially in those with concomitant migraines. In an open-label, randomized study comparing the efficacy of topiramate (100–150 mg/day) in 20 IIH patients with acetazolamide (1–1.5 g/day) in another 20 IIH patients, there was no significant difference in the improvement of the visual fields, degree of papilledema, nor relief of headache between the two groups at month 3, 6, and 12 [68]. A larger multicenter, randomized, double-blinded, placebo-controlled trial will be required to confirm these results.

Other medications that may have a weak carbonic anhydrase inhibitor effect, such as methazolamide, have not been as extensively studied as acetazolamide in clinical trials. Some abortive (sumatriptan, dihydroergotamine, and ergotamine) and prophylactic (beta blockers, tricyclic antidepressants, and calcium channel blockers) migraine medications are used as adjunctive therapy for the treatment of pain in chronic refractory headaches associated with IIH [69]. For refractory chronic daily headaches with migrainous features, a lumbar puncture to rule out elevated ICP without papilledema might be prudent. No reliable data from clinical trials or practice guidelines are available to provide specific recommendations for drug treatment duration. Based on the author's clinical experience, the medication(s) are usually tapered slowly when the CSF pressure is normal, when a 5–10% weight loss is achieved, and when IIH symptoms, papilledema, and visual field defects improve. Regularly scheduled follow-up visits monitor whether patients have a relapse and appropriate medical or surgical treatments are then given. According to a study by Yri et al. [70], the relapses, defined as recurrence of either papilledema or symptoms with elevated ICP, occurred in 28% of 18 newly diagnosed IIH patients who were followed over about 21.1 (±8.0) months. Relapses were associated with regaining of weight. Headache continued in 67% of all patients and was unrelated to relapse, despite improvement in visual function and visual fields after treatment with acetazolamide and dietary weight loss regimen. Therefore, headache was a poor marker of active disease.

New insights into the surgical management of IIH

Optic nerve sheath decompression (ONSD)

For sudden and severe visual loss from papilledema refractory to medical treatment, optic nerve sheath fenestration (ONSF) is the treatment of choice. This procedure reduces CSF pressure on the retrolaminar optic nerve to mainly prevent further visual loss and to have some effect on decreasing ICP and headaches.

Based on a meta-analysis of case series published from 1988 to 2014 [71], ONSF can rapidly improve visual function. This procedure has been shown to improve visual acuity (59%) or stabilize it (95%), improve visual fields (68%), papilledema (80%), and headache (44%). Although bilateral ONSD may eventually be required in some patients, most have adequate visual improvement from only a unilateral procedure. Most postoperative complications, such as diplopia and anisocoria, were transient and resolved without any sequelae. More serious ones included central retinal artery occlusion, acute angle-closure glaucoma, infection, and iatrogenic traumatic optic neuropathy [71]. Overall, ONSD is a safe and effective procedure for patients with acute and/or severely reduced visual acuity and visual field loss.

Long-term postoperative blindness with occasional recovery can occur after ONSD in those who have apparent remission, so long-term follow-up is required after this procedure [72]. Furthermore, risk factors for failure after ONSD have recently been studied in relation to degree of intracranial pressure. A retrospective study in 174 patients showed that male gender, pre-operative visual acuity, and a CSF opening pressure of $\geq$50 cm H_2O increased the risk by threefold for ONSD failure, causing continued visual loss and eventual LP or VP shunting [73].

CSF shunting

For acute and more severe presentations of IIH, repeated lumbar punctures, CSF diversion by ventriculoperitoneal shunting (VP shunting), or lumboperitoneal shunting (LP shunting) are usually considered. Most patients with IIH headache improve within 1 month of a spinal tap [6]. Immediate headache relief typically occurs after the diagnostic lumbar puncture with CSF removal [5]. CSF diversion by ventriculoperitoneal shunting (VPS) and lumboperitoneal shunting (LPS) is the most common procedures to rapidly decrease increased ICP and to improve papilledema, headache, and visual loss. CSF diversion techniques are usually preferred for patients who have headaches with or without visual loss who are refractory to medical treatment.

In a meta-analysis of 17 case series published from 1988 to 2014 with 435 patients (85% females) who underwent CSF diversion [71], 86% of patients had CSF diversion as their initial procedure. The mean CSF opening pressure was 41.4 cm H_2O. Headache (80%), papilledema (70%), and visual acuity (54%) all improved postoperatively. Most of the patients required additional shunt revisions, such that 43% underwent one revision, and 154 of the 435 patients underwent an additional 428 revisions. Shunt obstruction (41%) was the main reason for revision. Some other reasons included low-pressure headache (15%), shunt failure (11%), radicular pain, valvular dysfunction, shunt malposition, subdural hematoma, and CSF fistula.

VP shunts are technically more challenging to perform because of the insertion of the catheter into normal or small ventricles of IIH patients and often required stereotactic guidance [74, 75]. Although LP shunts might be technically easier and faster, shunt obstruction is the most common complication in more than 50% of cases and low-pressure headache from overdrainage. Excess abdominal fat in patients with high BMI can also cause difficulty in the intraperitoneal insertion of the shunt tube. Based on a 2-year prospective study in 2016 on 12 female patients (BMI >30 kg/m^2) who failed the initial LP shunts [76], lumbopleural shunts have been shown to improve headache and visual acuity. This variation of the shunt procedure was safe and effective, especially in patients with excessive abdominal fat.

Endovascular venous stenting

Although CSF diversion procedures have traditionally been considered the preferred first surgical option for IIH refractory to medical treatment, endovascular venous stenting has also become an initial treatment option for patients with IIH who present with worsening headaches and visual loss, and who have cerebral venous sinus stenosis. Focal venous sinus stenosis with a cerebral venous pressure gradient (CVPG) of $\geq$8 mmHg has been demonstrated in IIH and has been shown to be a consequence of increased ICP [37]. Venous sinus stenoses in IIH have recently been found to be not as common as previously thought (“non-pressure gradient-related “stenosis detected by ATECO MRV was observed in 90% of IIH patients vs. only 6.7% of controls) [21]. In a 2016 retrospective analysis of 164 venograms performed on 155 patients with and without IIH, 96 procedures (58.5%) were for patients with IIH. CVPG was present in 35.4% of patients with IIH (34 of 96 procedures) and 11.8% (8 of 68 procedures) in non-IIH patients. It was concluded that CVPG is uncommon in IIH patients, rare in those with pre-existing shunts, and absent in those with normal ICP [37]. If there is a venous sinus pressure gradient across the

stenotic region, then endovascular venous stenting can decrease it, thereby decreasing the overall ICP. Even in bilateral venous sinus pressure gradients from stenosis, unilateral stenting is sufficient in reducing this gradient [77].

Based on a meta-analysis of 8 studies published from 1988 to 2014 [71], 136 patients (88% females) with mean BMI of 34 kg/m^2 and mean CSF opening pressure of 34.3 cm H_2O underwent endovascular venous sinus stent placement. Seventy-three percent of patients with IIH had the stent procedure as their initial intervention. The mean pre-stent pressure gradient was 20.6 mmHg and the mean poststent pressure gradient was 2.7 mmHg. Postoperative improvement in headache (83%), papilledema (97%), and visual acuity (78%) was observed. The complication rate was 7.4% and the repeat procedures were done in 10.3%. Of the patients initially receiving stents, 2.2% required conversion to CSF diversion.

A 2016 prospective study of 13 patients with IIH who were refractory or intolerant to medical treatment showed that venous sinus stenting decreased CSF opening pressure on LP at 3-month postop by >10 cm H_2O in all patients, even those who presented with fulminant visual field loss. By this time, the thickened RNFL in all eyes also decreased back to normal, except for 1 patient who improved several months later. Visual symptoms and papilledema improved more than headaches after stenting. The complication rate and repeat procedure rate were both comparable to that calculated in the previously mentioned meta-analysis [78].

The most common complications of venous sinus stenting include transient postop headaches that last for several days, stent migration, venous sinus perforation, thrombosis in the stent, subdural hemorrhage, and recurrent stenosis proximal to the stent [77, 79, 80].

Bariatric surgery

Obesity, or a high body mass index, is a common chronic risk factor that can perpetuate IIH. When medical treatment with weight loss by dieting is not successful and CSF shunting or endovascular venous stenting is not an option, bariatric surgery is an alternative that can be considered. Patients with IIH who undergo this procedure have an average weight loss of 20–35% after 2–3-year postop and maintain a 14–37% greater weight loss than non-surgical controls [81]. Those who undergo gastric bypass and who maintain their weight loss at 2–3-year postop have a higher likelihood of maintaining that the same weight range at 10-year postop compared to those who undergo gastric banding [81].

In a systematic review by Handley et al. [82], 17 of 85 publications were reviewed which showed overall improvement of symptoms of IIH after bariatric surgery in 60 of 65 patients (92%). Postoperative lumbar puncture CSF opening pressure was shown to decrease by an average of 18.9 cm H_2O in the 12 patients who had this done. Although the main limitations of these case series were the lack of randomization, lack of blinding, and small sample size, it was concluded that there was level 3 and level 4 evidences that bariatric surgery is an effective treatment for IIH, especially when patients had already failed medical therapies of weight loss by dieting and VP shunting.

Besides the rare surgical postoperative complications, the neuro-ophthalmic complications of bariatric surgery are usually asymptomatic but are detectable as laboratory abnormalities. Most commonly encountered are vitamin and mineral deficiencies, such as Wernicke's encephalopathy from thiamine deficiency, optic neuropathy from copper, Vitamin B12, and/or thiamine deficiency; nyctalopia from vitamin A and/or zinc deficiency; and ophthalmoparesis from vitamin E deficiency [83].

Conclusion

Novel diagnostic and monitoring techniques with OCT pave the way for greater understanding of the in vivo histologic changes in papilledema and its effect on the optic nerve and retina. Neuroimaging techniques also continue to evolve for better visualization of the effects of IIH on the brain. Improved understanding of the pathophysiologic mechanisms of IIH will help guide future management of this disorder. The investigation of CSF biomarkers and the search for the genes responsible for IIH will probably be the next frontier in research.

New endocrinologic medications for the treatment of disorders related to obesity also hold promise for better management of IIH. The clinical trial currently assessing a selective competitive inhibitor of 11β-HSD1, AZD4017, used to treat obesity, metabolic syndrome, and diabetes mellitus type 2 [32] and its effects on the ICP in IIH will be completed in 2017 [33].

In the past 10 years, the increasing prevalence of IIH has paralleled the rise in percentage of obese persons with a BMI >30 kg/m^2 in the US. Between 1998 and 2002, a threefold increase in new CSF shunt procedures was performed for IIH. The total cost of repeat procedures of CSF diversion also contributed to this socioeconomic burden [1]. Since endovascular stenting is a safe and effective technique for moderate-to-severe visual loss and headaches with a much lower rate of revision and is less costly, the evaluation for venous sinus stenosis by catheter venography with pressure measurements should be part of the initial workup of IIH patients.

Practice guidelines for risk stratification of IIH patients for surgical procedures will be needed to determine which

procedures are best suited for a patient with particular risk factors in his/her clinical situation. The cost and risks of such procedures must be weighed against the benefits for each patient. A randomized clinical trial comparing the efficacy and visual outcomes of LP or VP shunting vs. endovascular venous stenting is being organized (ClinicalTrials.gov Identifier: NCT02513914). In addition, a randomized clinical trial for the comparison of the efficacy of and visual outcomes of ONSD vs. venous sinus stenting is also being considered by NORDIC (Neuro-Ophthalmology Research Disease Investigator Consortium) (personal communication).

Compliance with ethical standards

Conflicts of interest No competing or conflicts of interest and no funding sources declared.

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