Review Article

Taiwan J Ophthalmol 2017;7:15-21

Access this article online

Quick Response Code:

Website:
www.e-tjo.org

DOI:
10.4103/tjo.tjo_17_17

The diagnostic challenge of evaluating papilledema in the pediatric patient

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Abstract:

Pseudopapilledema is a fairly common finding in ophthalmic practice, and in many cases, the diagnosis is straightforward. However, an accurate diagnosis can challenge the most seasoned clinicians, and missing true papilledema can result in life-threatening or vision-threatening consequences. In this review, we describe the clinical findings and a diagnostic algorithm to distinguish pseudopapilledema and papilledema in the pediatric patients. We also describe the clinical evaluation once a diagnosis of papilledema has been established.

Keywords:

Children, intracranial hypertension, optic disc drusen, Papilledema, pediatric, pseudopapilledema, pseudotumor cerebri

Introduction

The evaluation of papilledema in a child is a common, but often stressful endeavor for the patient, parents, and ophthalmologist alike, despite the rarity of papilledema in the pediatric population.[1] Papilledema, or optic disc swelling due to elevated intracranial pressure (ICP), can represent a harbinger of life-threatening etiologies such as intracranial mass lesions or meningitis. Alternatively, pseudopapilledema is classified as the ostensible elevation of the optic disc secondary to local underlying structural conditions, such as optic disc drusen (ODD). An early and accurate diagnosis of pseudopapilledema can avoid anxiety-provoking and expensive testing. Thus, the ability to distinguish between papilledema and pseudopapilledema is an invaluable skill for ophthalmologists. In this review, we will describe a clinical algorithm for the evaluation of pediatric patients with possible papilledema. Furthermore, once a diagnosis of papilledema has been established, we will outline an organized diagnostic approach to confirming an etiology.

Pseudopapilledema

In the evaluation of possible papilledema, the clinician relies on the history, clinical exam, and ancillary tests to establish a definitive diagnosis. Considering they may be inherited in an autosomal dominant fashion, a family history of ODD may support a pseudopapilledema diagnosis. In general, patients without symptoms suggest pseudopapilledema whereas patients with headache make the distinction more difficult. On examination, pseudopapilledema often presents with cupless, elevated optic discs, anomalous vascular branching, including arterial or venous trifurcation, partially visible or surface refractile ODD, and the absence of an obscured disc margin and retinal nerve fibers. Conversely, the absence of papilledema is suggested by the presence of spontaneous venous pulsations and the absence of hyperemia. However, examination findings may overlap when attempting to distinguish mild papilledema from pseudopapilledema. In such cases, supplementary testing is often helpful.

ODD are variably calcified extracellular hyaline deposits in the optic nerve head

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Submission: 11-10-2016
Accepted: 02-12-2016

How to cite this article: McCafferty B, McClelland CM, Lee MS. The diagnostic challenge of evaluating papilledema in the pediatric patient. Taiwan J Ophthalmol 2017;7:15-21.

and are present in an estimated 0.4% of the pediatric population.[2] Typically, they begin as buried deposits and migrate toward the nerve surface in adulthood. Buried drusen can cause disc elevation mimicking papilledema and may appear "lumpy" in appearance compared to a more uniform elevation in papilledema. Undetected drusen are often misinterpreted as early papilledema.

Several imaging modalities can highlight ODD thereby facilitating the diagnosis of pseudopapilledema [Figure 1]. Optical coherence tomography (OCT) of the retinal nerve fiber layer (RNFL) in a patient with drusen often demonstrates thickening of the peripapillary nerve fiber layer. Similar to retinal ganglion cell atrophy exhibited in late papilledema, chronic ODD may also show nerve fiber layer defects on OCT. Orbital computed tomography (CT) and B-scan ultrasonography both may demonstrate calcification within the optic disc though ultrasound is much more sensitive and reliable than CT imaging at detecting ODD and avoids radiation exposure.[3] Acoustic shadowing at the junction of the retina and the optic nerve is a telltale sign of ODD on ultrasound. Another distinguishing sign includes the "30° test" during the B-scan, in which the patient is directed to look 30° laterally. In cases of true papilledema, the intraorbital segment of the optic nerve is enlarged and the fluid will compress with eccentric gaze and the nerve diameter will become smaller.[4] Unfortunately, the 30° test often requires an experienced echographer to perform.

Fundus autofluorescence (FAF) and enhanced depth imaging OCT (EDI-OCT) may be unavailable to a large percentage of practicing ophthalmologists, but offer additional ancillary information to differentiate between ODD and papilledema. FAF may detect buried drusen which may not appear on dilated fundus examination, exhibiting papillary fluorescence corresponding to surface or superficially buried drusen.[3] Autofluorescence can be detected using angiography filters before injection of contrast[5] or using the FAF mode on some OCT imaging equipment. EDI-OCT images deeper structures of the choroid and optic nerve head. Buried drusen appear as hyporeflective lesions with a hyper-reflective border. It offers the potential additional advantage of measuring the dimensions of drusen.[6]

Visual field testing does not distinguish pseudopapilledema and papilledema. A large percentage of patients with ODD will have detectable field loss, and a very small subset may experience severe progressive visual field or acuity loss. One study found that detectable visual field defects are much more common in patients with visible (>70% of cases) as opposed to buried ODD (<40% of cases), with nasal step defects being the most common.[7] Some of the proposed mechanisms by which damage to visual function occurs with ODD include impediment of axonal transport, atrophic degeneration from compressive factors, and focal vascular occlusions.[3] Others suggest that ODD are simply a byproduct of slow axonal degeneration due to underlying structural irregularities of the optic disc and that they represent a structural corollary rather than a direct cause of chronic optic neuropathy progression and vision loss.[3] Typically, visual field deficits are mild to moderate, and most patients remain asymptomatic throughout their lives.

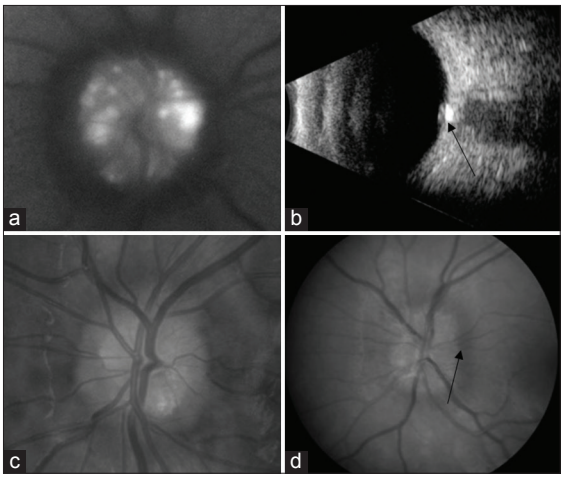


Figure 1: Various imaging modalities demonstrating the presence of optic disc drusen in the pediatric patient. (a) Fundus autofluorescence demonstrating focal hyperfluorescence from drusen. (b) B-scan ultrasonography. Hyperechogenicity at the optic nerve head localizes to the calcified opacities (arrow). (c) Fundus photo with typical "lumpy bumpy" optic disc appearance secondary to multiple drusen. (d) Fundus photo of disc drusen associated with mild optic disc vessel obscuration (arrow), presenting a diagnostic challenge when trying to distinguish between true edema and pseudopapilledema

Papilledema

The evaluation of the patient with possible papilledema mandates a thorough history. Although papilledema may be asymptomatic, certain symptoms should increase suspicion for elevated ICP. Daily nausea, vomiting, and morning headaches increase concern for ICP elevation. Pulsatile tinnitus is a pulse synchronous rhythmic whooshing sound commonly experienced by patients with elevated ICP. Pulsatile tinnitus can also occur in a multitude of other diagnoses, including vascular temporal bone tumors, dural arteriovenous fistulas, semicircular canal dehiscence, and isolated idiopathic pulsatile tinnitus. Nevertheless, the presence of pulsatile tinnitus in a patient with possible optic disc swelling points the clinician toward a diagnosis of papilledema. Binocular horizontal diplopia warrants cover testing to evaluate for 6th nerve palsies secondary to increased ICP. Transient visual obscurations (TVOs) are visual graying epsiodes lasting seconds associated with orthostatic changes. While TVOs occur in about 8.6% of eyes with

pseudopapilledema from optic nerve head drusen,[8] they are more commonly experienced by patients with papilledema.

Medical history can also provide diagnostic clues. Both iron deficiency and aplastic anemia have been associated with idiopathic intracranial hypertension (IIH), with the proposed mechanism being cerebral hypoxia.[9,10] A similar mechanism is described in patients with failure to thrive. Other disorders, such as Addison's disease, are linked to elevations in ICP through unknown mechanisms.[11] Renal disease and many of the methods of managing it can additionally lead to papilledema in the pediatric patient, with renal insufficiency, chronic dialysis, and steroid treatments all potentially contributing to elevated ICP.[12] This is not unsurprising, as renal failure often results in many of the previously mentioned etiologies of IIH, including anemia, hormone abnormalities, and vascular fluid composition changes.

Weight gain and obesity show some of the strongest existing associations with IIH in adults and postpubertal children, particularly among women. Studies have shown a progressively greater risk of IIH with increasing levels of body mass index and percent weight gain.[13] Several studies have also suggested that modest (5%) weight gain among nonobese patients can increase the risk of IIH.[13,14] In prepubertal children, the association with female gender and obesity becomes less evident.

A history of blood clots (in the patient or family), recent head trauma, sinusitis, or otitis media can all serve as indicators of dural venous sinus thrombosis as the potential etiology of papilledema. Recurrent sinusitis or simply sinus pain can result from arteriovenous malformation emptying into a venous sinus as well. Fever, malaise, or neck stiffness could suggest meningitis. Further history should include focused questions regarding medications known to be associated with increased ICP, including danazol, amiodarone, cyclosporine, growth hormone, levothyroxine, sulfonamides,-cycline antibiotics, Vitamin A, as well as corticosteroids (through withdrawal).[3]

Several studies have elucidated the changes that occur to the optic nerve and vasculature when elevated ICP occurs. This increased pressure results in disruption of axonal transport at the level of the lamina cribosa and subsequent increased thickness of the RNFL.[15] As the axons swell, they compress the retinal veins and cause venous engorgement and capillary leakage.[3] Fundus examination characteristically shows variable findings, including elevation of the optic disc, blurring of the disc margin, opacification of the RNFL, and blurring of the retinal vessels. The presence of a physiologic cup and retinal or choroidal folds [Figure 2] strongly support the diagnosis of true papilledema versus pseudopapilledema.[16] Peripapillary lipid and cotton wool spots would also indicate a likely diagnosis of papilledema. The presence of one or two peripapillary intraretinal or subretinal hemorrhages can occur in either scenario, but the presence of multiple intraretinal hemorrhages or of vitreous hemorrhage point toward true papilledema.[3] Imaging modalities may show increased RNFL thickness, total retinal thickness, and optic nerve head volume.[15] However, the presence of these findings may not distinguish mild papilledema and pseudopapilledema based on a single measurement. A follow-up scan weeks to months later may show increase in these parameters in true papilledema and stable measurements in pseudopapilledema. Additional testing including a line OCT scan through the optic nerve head may show inward deflection of the retinal pigment epithelium/basement membrane toward the vitreous in true papilledema [Figure 3].[17]

As opposed to many other types of optic neuropathy, visual acuity and color vision often remain normal in cases of papilledema until late in the course of disease. Rarely, patients may present with rapidly progressive visual loss from papilledema. Occasionally, early visual acuity loss may occur due to papilledema-related macular edema, retinal pigment epithelium changes, choroidal neovascularization, or choroidal folds; however, color vision is typically spared.[18] Therefore, one should consider alternative diagnoses to papilledema in a child with visual acuity loss, dyschromatopsia, severe visual field loss, or afferent pupillary defect. Such a patient may be more likely to have optic neuritis or other forms of optic neuropathy (Leber hereditary optic neuropathy, neuroretinitis, etc.).

However, despite visual acuity and color vision often remaining unaffected, visual field defects are not uncommon among eyes with papilledema, even in the

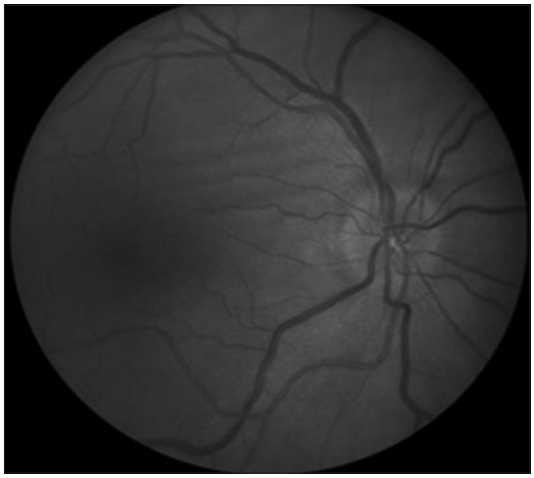


Figure 2: Choroidal folds in a child with mild papilledema

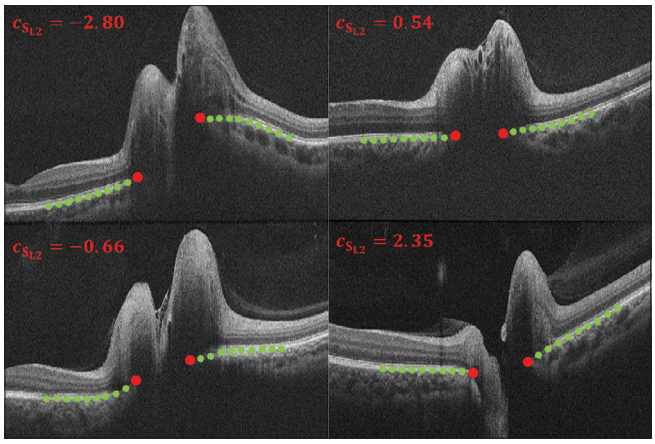


Figure 3: Line optical coherence tomography scan through the optic nerve head demonstrating inward deflection of the retinal pigment epithelium (upper left and lower left) toward the vitreous in a patient with papilledema. Upper right and bottom right are the same patient after treatment with acetazolamide

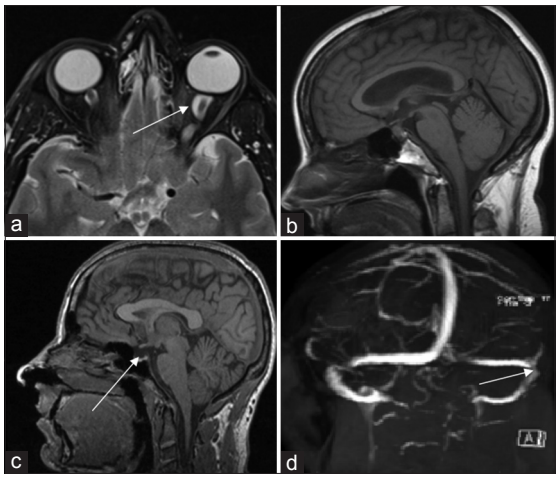


Figure 4: Magnetic resonance imaging highlighting the features associated with idiopathic intracranial hypertension. (a) Note the posterior globe flattening and widened perioptic space, most prominent on the left (arrow). (b) A patient without papilledema and a normal pituitary gland. (c) A partially empty sella (arrow) in a patient with idiopathic intracranial hypertension. (d) Venography demonstrating transverse sinus stenosis at the junction of the transverse and sigmoid sinuses (arrow)

acute phase.[3,19] Nearly, any variety of field defect can occur, with concentric enlargement of the blind spot being the most common and earliest defect, thought to be attributable to a papilledema related anterior shift of the peripapillary retina.[3] Alternatively, a central scotoma should raise a red flag that this is not papilledema. In the pediatric patient, especially those under the age of six or seven, obtaining an accurate visual field may not be possible. In these instances, confrontational visual fields provide a crude measure of field loss. Eyes with significant visual field loss may show sluggish pupils.

After initial in-office evaluation has identified edematous optic discs, neuroimaging is the next critical step in diagnosis. In our academic center, we utilize magnetic resonance imaging (MRI) and venography to evaluate for the presence of intracranial mass lesions, cerebral venous sinus thrombosis, and nonspecific indicators of increased ICP. The presence of three of four neuroimaging findings suggests likely increased ICP. These findings include posterior globe flattening, distention of the perioptic cerebrospinal fluid (CSF) space, an empty or partially empty sella, and transverse venous sinus stenosis.[3,20,21] A montage of these findings is shown in Figure 4. CT and CT venography are less desirable because of the radiation exposure in this age group.

When neuroimaging fails to identify a clear etiology, lumbar puncture is indicated to assess CSF opening pressure, protein, glucose, and cell counts. Although some argue that patient positioning can significantly affect opening pressure;[22] other studies have demonstrated that opening pressure measured in the prone position as essentially equivalent to the lateral decubitus position.[23] Thus, some recommend performing lumbar puncture with the patient in the lateral decubitus position to avoid this error, but we utilize prone positioning under fluoroscopy at our center. The average CSF opening pressure is higher in the pediatric patient relative to adults, with recent diagnostic criteria for pseudotumor cerebri defining a pressure greater than 28cm H_20 as elevated. This is most likely related to the use of sedation in the pediatric population.[24]

The most widely utilized diagnostic criteria are the revised criteria proposed by Friedman *et al*. in 2013.[24] A definitive diagnosis is established as the presence of:

- Papilledema
- A normal neurological examination aside from 6th cranial nerve palsy
- Normal CSF composition associated with an elevated opening pressure (>250 mm CSF in adults and > 280 mm CSF in children)
- Neuroimaging (MRI typically, or CT if MRI is contraindicated) showing normal brain parenchyma and no evidence of mass or structural lesion, hydrocephalus, or meningeal enhancement
- In the absence of papilledema, a definitive diagnosis requires a 6th nerve palsy
- In the absence of papilledema and a 6th nerve palsy, a suggestive diagnosis requires 3 of 4 neuroimaging findings
- A diagnosis is deemed "probable" if all other criteria are met but no lumbar puncture is performed to determine opening pressure.

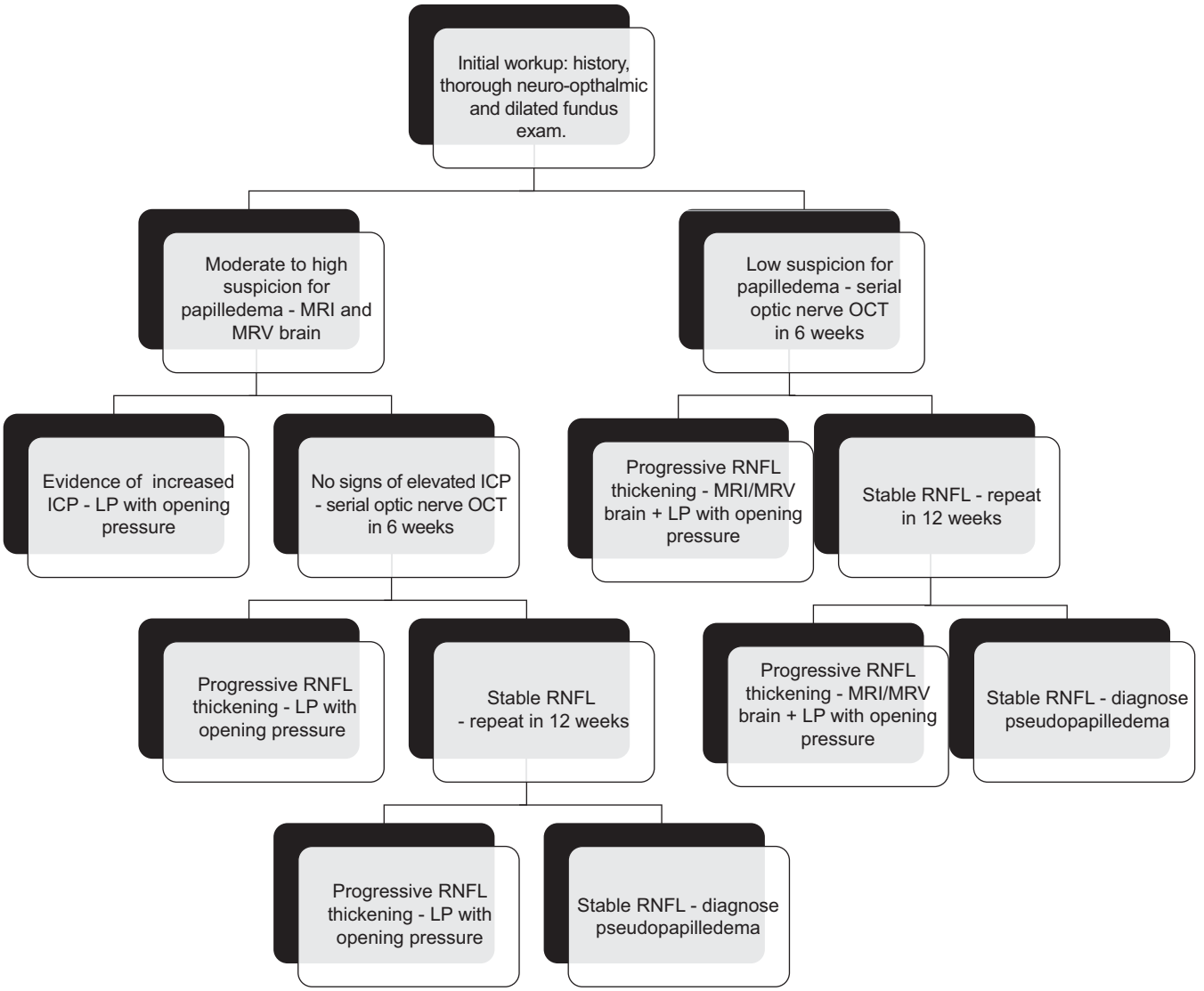
These updated criteria differ from previous iterations, which did not require papilledema. It is important to note that the spinal fluid composition must be normal. Certain conditions may closely mimic pseudotumor cerebri in symptoms and presentation. Spinal cord tumors causing

elevated ICPs and papilledema may resemble cases of IIH. Differentiating factors that should raise a red flag are elevated protein levels in the CSF,[25] back pain, and other symptoms that may correlate with the level of a spinal cord tumor, such as limb weakness, limb paresthesias, or incontinence. If any of these symptoms are present, MRI should be extended from the brain and orbits to the entire spine as well. Infectious meningitis is another, in which CSF studies and MRI of the spine can elucidate the diagnosis, showing white blood cells in the CSF, and meningeal thickening on imaging.

Treatment should be aimed at correcting any underlying factors, such as reversal of anemia and cessation of any potentially contributive medications. While modest weight loss can also result in resolution or improvement of symptoms of IIH in adults, this does not apply to prepubertal children. With respect to directly reducing ICP, acetazolamide is safe to use in the pediatric patient; it has been safely used for this purpose in children for more than 50 years.[26] The current recommended dosage in children is 15 mg/kg/day divided into 3 daily doses. Adverse effects of acetazolamide include distal paresthesias, fatigue, and metallic taste associated with carbonated beverages, increased urination, stomach upset, and rarely kidney stones.

The general management of IIH is similar to glaucoma. One must follow visual acuity, automated perimetry, and optic nerve appearance. For minimal to no visual field loss, medical management (acetazolamide and weight loss) is utilized. For moderate to severe visual field loss, surgical intervention is considered including ventriculoperitoneal shunting and optic nerve sheath fenestration. Lumboperitoneal (LP) shunts have fallen out of favor in IIH because of increased complications. In large part, choice of surgical option to date has been based on training background, staff and equipment

Table 1: General algorithm used at our institution for evaluating a pediatric patient with possible papilledema



availability, and surgeon preference. In 2014 Lai *et al*.[27] performed a systematic review of the literature in the US and the UK on surgical management of IIH to assess which modality achieves the most consistent improvement of IIH symptoms and visual decline. The results of the study demonstrated similar improvement rates of visual field loss and headache symptoms across all the aforementioned interventional methods, with higher rates of perioperative complications associated with shunting procedures in the form of shunt dislocation and failure, infection, and acquired Chiari malformation (with LP shunts). To date, no randomized controlled clinical trial has been attempted testing different surgical management options, and our accepted conclusion at present agrees that each form of intervention has its role and that each patient should be evaluated on a case-by-case basis to determine the best individual option taking into consideration surgical experience, patient comorbidities, and surgical facility factors.

Diagnostic Approach at the University of Minnesota

Differentiating between papilledema and pseudopapilledema may be challenging in a pediatric patient population. We do not follow a strict diagnostic algorithm when evaluating children with possible papilledema at our institution although general work-up guidelines are outlined in Table 1. At our academic center, evaluation begins with a thorough history focusing on the symptoms of and risk factors for increased ICP. Then, a complete neuroophthalmic examination is performed including careful testing of pupils, the dilated fundus, cranial nerves, and alignment. If we are unable to differentiate, and the suspicion of papilledema is low, then we will follow with serial OCT in 6 weeks then 12 weeks. In our experience, significant changes in average RNFL thickness (±6 microns) indicate progression or resolution of true optic disc swelling. If we cannot differentiate and our suspicion for papilledema is moderate, an MRI of the brain and orbits with and without intravenous contrast is obtained. If there are multiple nonspecific indicators of elevated ICP on MRI without an apparent structural etiology, we will consider a sedated lumbar puncture under radiographic guidance. In the event that the MRI lacks signs of elevated ICP, patients are often followed with serial optic nerve OCTs as above.

Conclusion

In most instances, a careful history, examination, and ancillary testing will allow the clinician to discern between pseudopapilledema and papilledema. However, in some cases, the differentiation can be almost impossible for even the best clinicians. An accurate diagnosis can relieve the family of a child with papilledema and help avoid expensive, anxiety-provoking additional testing. Meanwhile, the child with papilledema will undergo prompt evaluation for an etiology and treatment of elevated ICP and reduce the risk of systemic and visual sequelae.

Financial support and sponsorship
Nil.

Conflicts of interest
The authors have no any conflicts of interest to declare.

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