Systematic Approch and Ancillary Testing for Diagnosis of Papilledema and Differential Diagnosis from Pseudopapilledema

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ABSTRACT

Papilledema resulting from elevated intracranial pressure is one of the important entities that need urgent evaluation in ophthalmology practice. Although diagnosis can readily be made in established clinical presentations with advanced papilledema by experienced clinicians, differential diagnosis should be made meticulously in pediatric patients and in case of subtle edema. In particular, early papilledema must be distinguished from pseudopapilledema by clinical findings and ancillary testing.

In this review, we attempted to present important approaches that could be used for diagnosis, differential diagnosis and follow-up of papilledema and pseudopapilledema, including ancillary testing (optical coherence tomography, sonography, magnetic resonance imaging and magnetic resonance venography) in diagnosis of papilledema, differential diagnosis of papilledema-pseudopapilledema and follow up of these two diseases.

Key words: Papilledema, Pseudopapilledema, Optical coherence tomography, Sonography, Magnetic resonance venography.

INTRODUCTION

The optic disc edema caused by elevated intracranial pressure (ICP) is defined as "papilledema". The term "optic disc edema" or "papillitis" is used to define optic disc edema due to local or systemic causes or other etiologies. The ICP is the most important factor for development of papilledema. The papilledema does not develop without elevated ICP but elevated ICP can be present without papilledema.

The ICP and cerebrospinal fluid (CSF) dynamics are explained by Alexander Monro and George Kellie (Monto-Kellie hypothesis).[1] According to Monro-Kellie hypothesis, brain tissue, ICP, perfusion pressure and blood volume interact within in a fixed intracranial space. As cranial volume is fixed, there should be compensating alterations in other component in case of elevation or reduction in one of these components. If compensation does not occur in a complete and timely manner, it results in either intracranial hypertension or hypotension. The intracranial hypertension can develop through one or more than one of following mechanisms.[2]]:

1. Intracranial space occupying lesions (mass, abscess, hemorrhage)
2. Increased intracranial tissue volume (focal or diffuse brain edema)
3. Decreased intracranial space (craniosynostosis, thickened cranial bones)
4. Blockade in CSF circulation (ventricular system obstruction, non-communicating hydrocephalus)
5. Increased CSF production (choroidal plexus papilloma, idiopathic intracranial hypertension)
6. Decreased CSF absorption (venous sinus thrombosis, meningitis, increased protein concentration in CSF, communicating hydrocephalus)

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As cerebral parenchyma, optic nerve is also covered by 3 meninges (dura mater, arachnoid mater and pia mater) and subarachnoid space has a continuum around optic nerve via basal cisterns at optic chiasm. Thus, elevated ICP is directly reflected on optic nerve through CSF. The elevated CSF pressure disrupts equilibrium between intraocular pressure (IOP) and retrolaminar tissue pressure, resulting in increased pressure at optic nerve tissue. This leads impaired axoplasmic flow, vascular leakage secondary to venous stasis and extracellular fluid accumulation, resulting in papilledema.[3] In electron microscopy, enlarged axons at laminar region and mitochondrial accumulation within axons can be seen. Also, irregular mitochondria and micro-tubules are observed. Clinically, the tissue accumulation leads elevation and effacement of physiological pit in optic disc. Lamina cribrosa is a fenestrated connective tissue extension arising from peripapillary sclera, which is the most important structural component of optic disc. Wang et al. demonstrated that ICP alterations lead changes in thickness of lamina cribrosa and sizes of fenestra. The changes in the pressure gradient over lamina cribrosa are linked to IOP and ICP. In cases with elevated intracranial pressure, the development of papilledema, presence of asymmetrical papilledema and ICP elevation without papilledema are associated with compartments surrounding optic nerve and pressure gradient of translaminar cribrosa resulted from difference between IOP and ICP. In papilledema, there is pressure gradient caused by ICP elevation while a pressure gradient occurs due to low IOP in eyes with hypotonia, both resulting in optic disc edema.[5]

According to grading scale proposed by Lars Friesen, 5 grades were defined for papilledema.[6]]:

Grade 1. C-shaped halo with normal appearance of temporal disc, slightly impaired retinal nerve fiber layer and mildly obscured retina.

Grade 2. Circumferential halo without major retinal vessel obscuration and elevation and nasal margin of disc

Grade 3. Obscured one major retinal vessel and elevation in all margins of disc with circumferential halo

Grade 4. Completely obscured on major retinal vessel and circumferential halo with elevation in whole disc and disc pit

Grade 5. All major retinal vessels over disc and at disc margins are obscured

Papilledema is typically bilateral and symmetrical (Figure 1). Unilateral papilledema is rarely seen; in general, it is secondary to a congenital anomaly of optic nerve sheath or develops due to atrophy of contralateral optic nerve.[7] However, the subarachnoid space surrounding optic nerve is a tubular system consisting of many segments rather than being an uniform structure. These segments are termed as bulbar, intraorbital and canalicular it is thought that the complex trabecular and septal structure is involved in regulation of pressure around optic nerve. It is also thought that the arachnoid trabecular structure displaying individual variation is one of the underlying causes of asymmetrical papilledema.[8, 9] In a study evaluating optic canal size in cases with papilledema by computed tomography, Farrokhi et al. reported no significant difference with asymmetrical cases.[10]

Evaluation and Differential Diagnosis

In the ophthalmology practice, idiopathic intracranial hypertension (IHH) is the most common cause of

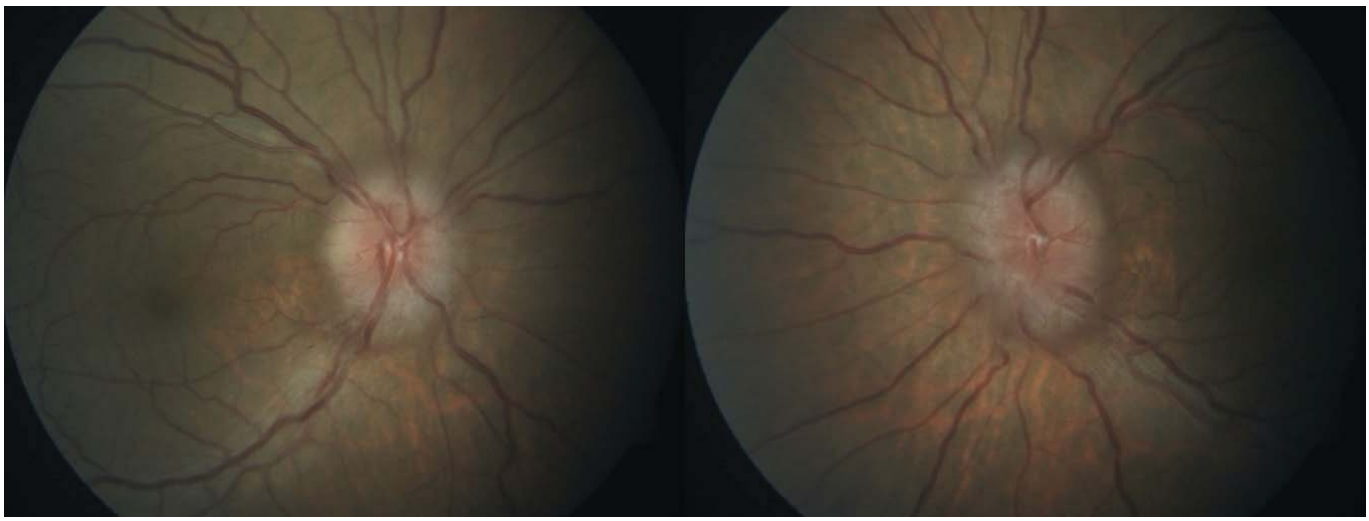


Figure 1: *Typical bilateral papilledema image. In this case, it is seen that one segment of major retinal vessels at optic disc margin was obscured and that there was elevation at whole optic disc margin together with circumferential halo, and disappearance of optic pit (Grade 3-4).*

papilledema. The diagnosis of IHH is made using Dandy criteria: symptoms of ICP elevation (e.g. headache), findings of ICP elevation (e.g. papilledema), high CSF opening pressure (>250 mmH_2O in adults and >280 mmH_2O in children), normal CSF analysis and normal neuroimaging studies. The IHH is seen in obese women aged 15-45 years.[11] Besides IHH, there are many disorders that can cause papilledema. These can be assessed under 5 categories:

1. Disrupted venous drainage

2. Endocrine and metabolic dysfunction

3. Exogenous agents

4. Systemic diseases

5. Central nervous system lesions

However, clinical presentations resembling papilledema but resulting distinct etiologies are termed as "pseudopapilledema". It is highly important to distinguish papilledema and pseudopapilledema since papilledema may require urgent evaluation and invasive modalities. For discrimination, fundus examination should be performed in the first place. The pseudopapilledema findings include lack of physiological optic pit, abnormal vascular branching, refractive bodies in optic disc drusen (ODD) and obscured disc margins. Although it is lacking in 10-20% of normal population, detection of spontaneous venous pulsation and non-hyperemic disc favor pseudopapilledema. This group includes ODD (most common cause), congenital anomalies (tilted disc, myelinated nerve fiber, optic nerve hypoplasia, Bergmeister's papilla, epipapillary glial tissue, Morning glory anomaly, small and compressed optic disc, orbital hypertelorism), mass lesions, vitreopapillary traction (Figure 2A and B) and systemic causes.[12, 13]

The ODD is a disorder associated with calcified hyaline depositions on optic nerve, which is seen in approximately 0.4% of pediatric population and up to 12% by histopathological examination and OCT studies.[14] These depositions are generally advanced towards surface at adulthood. Particularly, embedded ODD can be confused with early papilledema. Clinically, prominent optic disc margins are the most important finding favoring pseudopapilledema. Observation of physiological pit and presence of choroidal folds are suggestive of papilledema in edematous disc.[15] However, peripapillary lipid and cotton wool spots also favor papilledema. Although peripapillary hemorrhage can be seen in both papilledema and pseudopapilledema, presence of substantial numbers is compatible with papilledema. There are several modalities used in differential diagnosis including optical coherence tomography (OCD), enhanced depth imaging (EDI)-OCT), fundus autoflorescence FOF), computed tomography (CT) and B-mode sonography. Chang et al. suggested that fluorescein angiography (FA) is most successful modality in differential diagnosis.[16] Visual field testing is generally inadequate to make discrimination between papilledema and ODD. The visual field defects are generally seen in

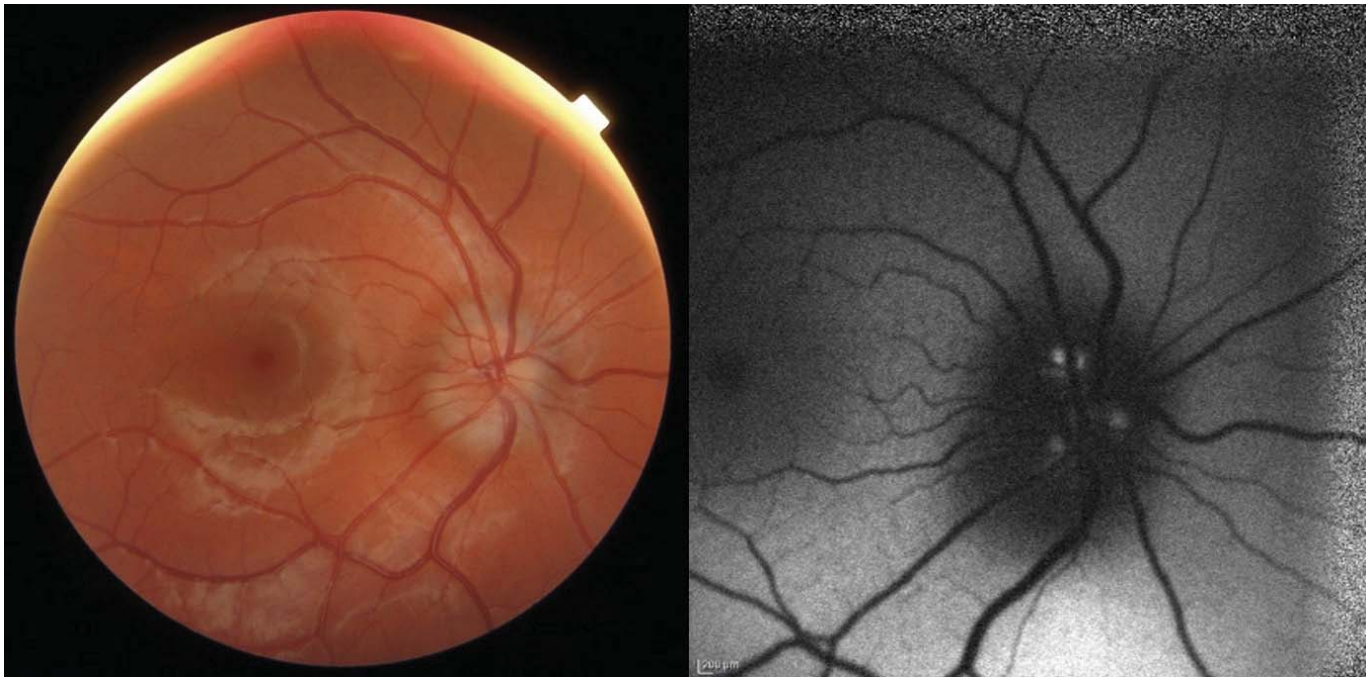


Figure 2 A: *Disc image of a case with pseudopapilledema (ODD);* **B.** *In the same case, autoflorescence areas belonging to ODD on FOF imaging.*

superficial ODD and it is most commonly seen in the form of nasal step defect.[17]

The diagnosis of papilledema requires urgent evaluation. The blood pressure measurement and neuroimaging studies are initial studies that should be undertaken after detection of papilledema in ophthalmological examination. Magnetic resonance (MR) imaging can generally identify etiology in most patients. MR venography (MFV), CT venography (CTV) and catheter venography may be required in case of venous sinus thrombosis. Lumbar puncture is performed if imaging studies are normal. Opening pressure is carefully measured in lumbar puncture. In addition, CSF sampling and analysis are performed to rule out infectious, inflammatory and neoplastic processes. For accurate measurement of opening pressure, the patient is placed to lateral decubitus position. Sedation is generally needed in children and opening pressure tends to be high under sedation. The normal opening pressure is ≤250 mmH_2O in adults and ≤280 mmH_2O in children. Opening pressure >76 mmH_2O at neonatal period and >180 mmH_2O in children aged <8years are proposed as IHH criterion.[18]

Ancillary methods

Despite well-defined criteria such as Frisen grading, there is variation in grading by ophthalmoscopy among clinicians. Similar variation has also been reported in the assessment of fundus photographs.[19] However, differences in the experience of clinicians, difficulties in discrimination between papilledema and pseudopapilledema and desire to avoid unnecessary testing in pediatric patients drive neuro-ophthalmologists to more objective methods reducing human factor. Given these challenges, techniques such as OCT, sonography, MR imaging and MRV have been introduced.

Optical Coherence Tomography (OCT)

The OCT has become an ancillary method that is increasingly used in the diagnosis and follow-up of optic nerve disorders by ability to quantify thickness of specific layers such as total retina, retinal nerve fiber layer (RNFL) and ganglion cell layer and provision of subjective data regarding neuroretinal as a result of advances in OCT technology in last decade. In addition to diagnosis and follow-up of optic nerve disorders, OCT is also used in differential diagnosis of optic nerve disorders and discrimination of optic nerve disorders from retinal diseases. The OCT has been introduced into clinical practice for diagnosis and follow-up of papilledema by its ease of application and reproducibility. However, it was observed that, n patients with moderate to severe papilledema (Frisen grade≥3), severe thickening in peripapillary RNFL caused software-related error in one-third of patients. To address such problem, retinal layer segmentation was performed by 3-dimensional approach on OCT image and errors in retinal thickness measurement were markedly decreased.[20] Wang et al. reported that volumetric results obtained by 3-dimensional segmentation method are compatible with Frisen grading and 2-dimensional RNFL-total retinal thickness measurements.[20] Another limitation is failure to measure RNFL thickness below 30 µm, which is termed as "base effect".[21] Due to non-neuronal retinal structures, retinal thickness never decreases below 30 µm regardless of severity of optic nerve injury. Thus, RNFL thickness measurement is less helpful in monitoring novel injuries in cases with severe optic nerve injury. Based on these fundamental data, the goal in clinical practice is to diagnose and monitor papilledema and distinguish papilledema and pseudopapilledema by monitoring disc volume, RNFL thickness, ganglion cell/inner plexiform layer (GC/IPL) thickness and Bruch's membrane image together with fundoscopy findings.

Savini et al. defined hypo-reflective space (subretinal hypo-reflective area-SHA) between sensory retina and retinal pigment epithelium-choriocapillaris complex around optic nerve on OCT images of optic disc edema while Johnson et al. described qualitative and quantitative parameters to aid clinician in distinguishing papilledema from pseudopapilledema.[22] Qualitative findings provide indirect insight in favor of either papilledema or ODD by interpreting retinal changes on OCT images. Such changes do not demonstrate ODD directly but they are considered as signs for presence of ODD. In quantitative measurements, assessment is made through mean and standard deviation. In the study, it was seen that SHA and RNFL thickness were higher in all quadrants in cases with papilledema. In cases with optic disc edema, qualitative and quantitative OCT characteristics include:

1. Optic nerve head elevation with flattened inner contour
2. Lazy V pattern resulting from >2-folds higher SHA measurement on 2 mm distance from optic disc centre than measurement on 1.5 mm distance (Figure 3)
3. Increased RNFL thickness as being more than 86 µm in nasal region
4. Increased SHA thickness (widest measurement >169 µm at 2-mm diameter and second widest measurement>127 µm)

On the other hand, following parameters were detected in cases with ODD:

1. Optic nerve head elevation with lumpy-bumpy inner contour

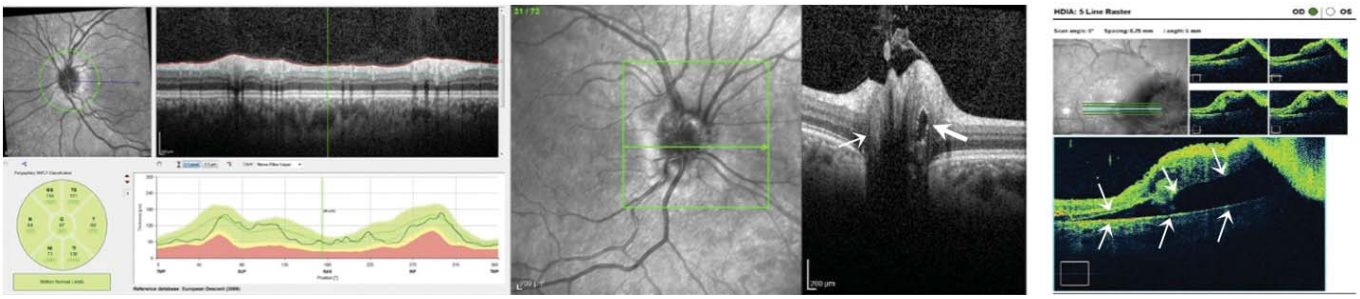


Figure 3: A. *OCT image of normal optic disc.* **B.** *In the case with ODD, lumpy-bumpy appearance within optic disc, superficial ODD at left side of disc and hypo-reflective band image (thin arrow) beneath superficial ODD and hypo-reflective ovoid area (thick arrow) demarcated by hyper-reflective band;* **C.** *Lazy V pattern in which subretinal hypo-reflective area was slowly decreased on OCT in a younger patient with fulminant papilledema (arrows).*

2. >5-folds higher SHA measurement on 0.75-mm diameter than 1.5-mm diameter
3. Normal or slightly increased RNFL thickness as being less than 86 µm in nasal region
4. Normal SHA thickness at 2-mm diameter (mean: 60.7 µm)

In conclusion, qualitative criteria aided differential diagnosis by sensitivity of 63% while sensitivity is increased to 80% by>86 µm RNFL thickness in nasal region and over 90% by >169 µm SHA thickness at 2-mm diameter.

Similarly, in a large series, Rodriguez et al. reported that sensitivity and specificity of quantitative parameters were higher when compared to qualitative parameters.[23] Authors emphasized that RNFL increase in nasal quadrant has high sensitivity and specificity to distinguish papilledema from ODD.

In randomized, controlled IHHTT (Idiopathic Intracranial Hypertension Treatment Trial), RNFL thickness, total retinal thickness, optic nerve volume and GC/IPL were assessed using 3-dimensional segmentation technique in order to assess treatment efficacy in IHH cases with mild loss of vision.[24] RNFL thickness, total retinal thickness and optic nerve volume were decreased more markedly in treatment group when compared to placebo group. Thus, it has been reported that OCT may play role in the follow-up by close ophthalmologic monitoring.

Regarding use of Oct for differential diagnosis and follow-up of papilledema, another qualitative parameter is associated to peripapillary retinal pigment epithelium (RPE) and Bruch's membrane angulation.[25] The angle can be positive (towards vitreous), neutral (horizontal) or negative (towards retrobulbar compartment). Marked positive angle is helpful for diagnosis in an eye with suspected papilledema. However, neutral or negative angulation does not rule out diagnosis. Sibony et al. observed that anterior deformation of retinal pigment epithelium-Bruch's membrane was diverged to neutral angulation following pressure-lowering procedures in patients with papilledema who were followed using OCT after treated by lumbar puncture, CSF shunt and medical therapy.[26] Authors suggested that, together with RNFL thickness, changes in Bruch's membrane angulation on OCT can be helpful to monitor effects of elevated ICP and treatment efficacy. However, it is thought that orientation of Bruch's membrane complex (peripapillary RPE and Bruch's membrane) on OCT can be monitored as real-time image of translaminar perfusion pressure. In the same study, posterior displacement from Bruch membrane was observed by reduction in ICP. Same finding was also observed in IHHT cases receiving acetazolamide.[24] Following ICP-lowering procedures, as similar to Bruch's membrane complex, it was observed that lamina cribrosa was displaced towards posterior on OCT.[27]

The OCT is also helpful to detection and characterization of choroidal folds accompanying to papilledema in IHH cases. Sibony et al. detected 3 distinct types of fold in cases with IHH.[28]]: peripapillary wrinkles, retinal fold and choroidal fold (Figure 4). The wrinkles and fold can be detected in 41% of cases by fundus images while in 73% of cases by OCT. Particularly, en face modality has an important contribution to observation of folds. In en face technique, axial C-screening deep raster OCT images are reconstructed in coronal plane using a software. The major advantage of en face OCT is ability to detect lesions at specific subretinal layer by high sensitivity. Thus, in cases with IHH, detection rate for choroidal changes is increased by OCT; in addition, it helps distinguishing IHH from pseudopapilledema.

The OCT can be useful in the early diagnosis of mild papilledema which is clinically subtle with normal visual acuity and regressed symptoms of elevated ICP. Besides,

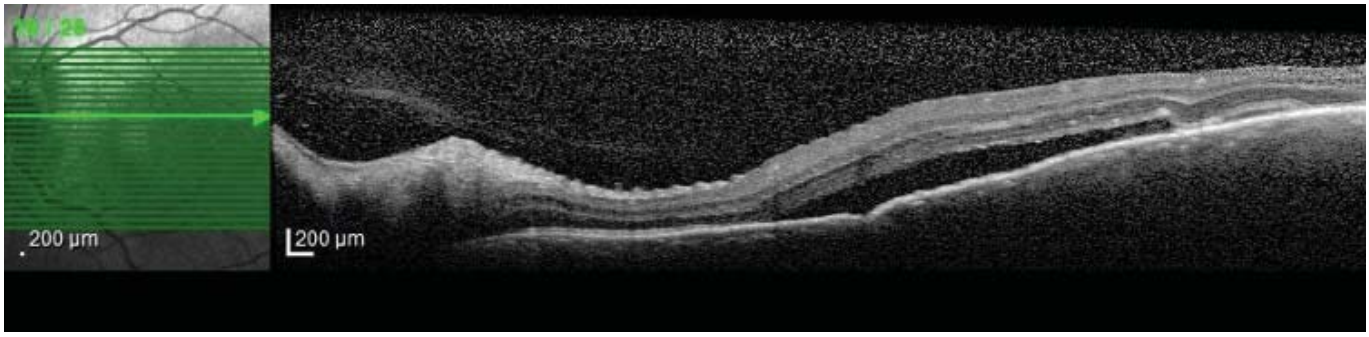


Figure 4: *Retinal folds and macular edema are seen in OCT imaging of a patient with a diagnosis of pseudotumor cerebri.*

it is though that OCT may play role in early detection of neuronal loss (GC/IPL thinning). After controlling papilledema, GC/IPL thickening during normalization of RNFL may indicate optic nerve damage.[29] Again, use of 3-dimensional algorithm in these measurements may prevent errors seen in 2-dimensional B-screenings. It is most likely that future studies will focus on GC/IPL measurement by OCT in the follow-up of papilledema.

In the absence of neurological or systemic symptoms, it becomes more difficult to distinguish between low-grade papilledema and embedded ODD. By advances in OCT technique, discrimination between papilledema and pseudopapilledema can be possible without need for further evaluations such as MR image/MRV or lumbar puncture. In spectral domain (SD)-OCT, reduction distance between each B-screening (from 8-10 µm to 5-7 µm) has facilitated to visualize smaller structures such as ODD. It should be kept in mind that IHH may also develop in cases with ODD, resulting in overlapping presentations.

Lee et al. classified ODDs as small (<300 µm) moderate (300-500 µm) and large (500 µm).[30] In large ODD, hyper-reflectivity at margins, lobulation and intraretinal cysts are seen more commonly. Despite high-resolution, SD-OCT does not have 100% sensitivity in the imaging of embedded ODD. Deep retinal structures become visible by swept source OCT devices using longer wavelength. By enhanced depth imaging (EDI)-OCT, deeper disc lesions such as embedded ODD can be readily visualized. Merchant et al., using EDI-OCT, described ODD as ovoid areas with low hyper-reflectivity encased by hyper-reflective bands perpendicular to OCT beam or clusters of hyper-reflective bands without central hypo-reflectivity. Also, they reported that EDI-OCT was more sensitive than B-mode sonography which is considered as gold standard in the diagnosis of ODD.[31] Traber et al. described three morphological types of ODD: peripapillary subretinal ODD (hyper-reflective), granular ODD (hyper-reflective) and confluent ODD (hypo-reflective). The three types of ODD can be seen in same optic nerve head.

ODD can predispose ischemic injury in optic disc; particularly, it may lead to non-arteritic anterior ischemic optic neuropathy (NAAION)-like presentation in the presence of small-compressed optic disc and vascular risk factors. Unlike typical NAAION, it is seen younger adults and visual prognosis is better. In this entity, overlapping true disc edema and ODD during acute phase may cause confusion in fundus and OCT imaging. By advances in COT techniques, the relationship between ODD-type visual field defects and RNFL loss. In cases with visual defect, greater, confluent and autofluorescent ODD is more common. Malmqvist et al. found that optic nerve disc dysfunction is increased by increasing ODD volume regardless of anatomic location.[33] Peripapillary RNFL thickness is increased in initial stages; followed by RNFL loss by enlarging ODD. As similar to visual field loss, RNFL loss progresses in parallel to ODD size. Temporal RNFL is generally preserved and central vision is not affected even in advanced stages.

In deeply located ODD, RNFL thickening can mask axonal injury. The thinning in macular GC/IPL analysis can be alarming about axonal injury earlier than RNFL. Casado et al. found thinning in GC-IPL despite normal RNFL thickness in 26% of patients with embedded ODD.[34] Based on these findings, it can be suggested that GC/IPL analysis is more useful for early detection of damage.

Together with thorough ophthalmological examination, non-invasive modalities such as OCT reduce need for unnecessary invasive methods in both differential diagnosis and follow-up

Sonography

The use of B-mode sonography in ODD was described in 1970s; both superficial and deep ODDs can be visualized by this method.[35] Particularly, it is frequently used in discrimination between papilledema and pseudopapilledema to diagnose ODD and to prevent invasive examinations for diagnosis of ODD and

prevention of invasive techniques in pediatric cases. In B-mode sonography, due to calcium deposits, ODD appears as a lesion with high-echogenicity at optic nerve head and remains to be visible at low-gain (Figure 5). The major advantage of sonography is its ability to visualize posterior margin of ODD. Although axial approach is the easiest method, signal intensity is decreased due to double cross of sonography waves from lens. Transverse and longitudinal approaches have been described to obtain high-resolution via bypassing lens. The disadvantage is low-resolution and not providing information about neural retina. It is attempted to address resolution problem by recent use of 20 Hz ultrasound probes. Besides, false-positive results can be seen in pseudodrusen in chronic papilledema, vascular lesions and astrocytoma.[36]

Raghunandan et al. recently published a study on role of optic nerve sheath diameter (ONSD) measurement by B-mode sonography in non-invasive diagnosis and follow-up of papilledema.[37] In elevated ICP, another diagnostic modality is to measure enlargement of optic nerve sheath at 3 mm posterior to globe. Due to continuity in subarachnoid space, enlargement in optic nerve sheath is seen in elevated ICP by sonography, even it is reported that enlargement is started before development of papilledema.[38] In above-mentioned study, it was reported that together with symptoms of ICP elevation, ONSD>4 mm on sonography is diagnostic. In addition, it can be used in follow-up as ONSD is correlated with severity of papilledema. Since papilledema is not clinically apparent in cases with optic atrophy, ONSD measurements can be used to monitor ICP in optic atrophy with concurrent ICP elevation without need for invasive tests. This emphasizes importance of sonography in diagnosis and follow-up as well as preventing use of invasive tests.

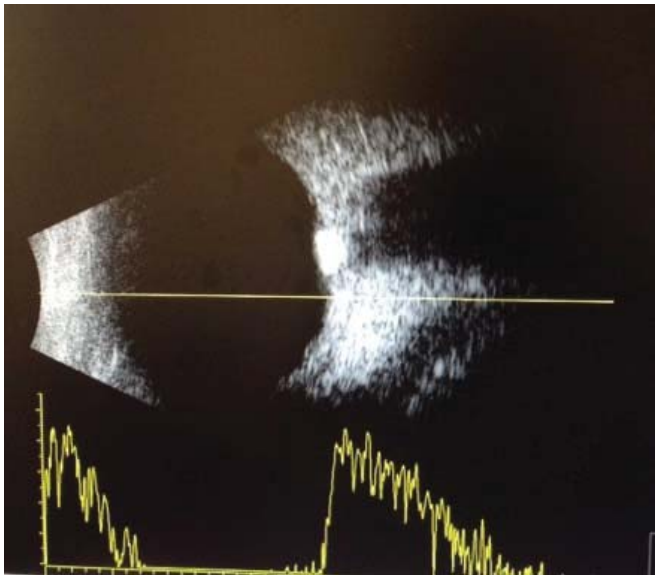
The Doppler sonography is also used in the ophthalmology. Since 19802, Doppler sonography has been used to assess retrobulbar blood flow and carotid arteries. In addition, it can detect ophthalmic artery or central retinal artery embolus by using sonographic contrast material. Adding Power Doppler (PD) on color Doppler sonography has increased sensitivity, facilitating imaging of intrabulbar mass lesions.[39] Transcranial Doppler sonography is used for imaging ophthalmic artery, central retinal artery and posterior ciliary arteries. This method can assess collateral circulation and determine auto-regulatory capacity of retinal and cerebral circulation. Superb micro-vascular imaging (SMI), developed over conventional Doppler technique, makes it possible to visualize smaller blood flow. At time of this review, there is no study about its use in ocular vascularity in the literature.

MR imaging and MRV

Given that MR imaging provides high-resolution images of soft tissues, it provides detailed data about globe, optic nerve, orbit and optic tract. Despite these advantages, highly smaller diameter of optic nerve (0.4-0.6 mm) makes it difficult to assess the nerve by MR imaging. It has been reported that fat-suppressed T2-weighted sequences are optimal method to image optic nerve and peri-optic CSF.[40]

In patients with papilledema, most common MR imaging findings are:

1) Optic nerve sheath dilatation (Figure 6A)



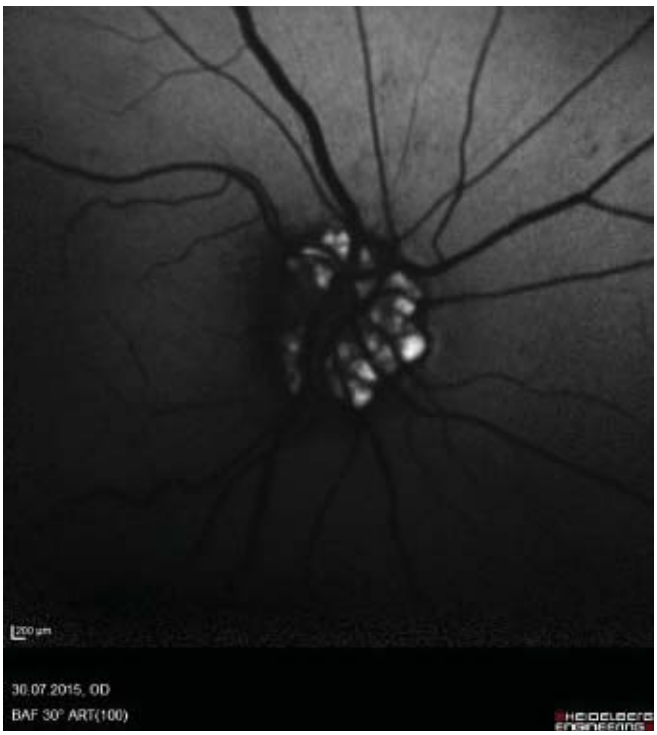


Figure 5: A. *Hyperechogenic image of ODD obtained at 75dB on sonography;* **B.** *SD-OCT FOFF image of same case.*

2) Flattening in posterior sclera (Figure 6A)

3) Enlargement in perioptic subarachnoid space

4) Optic nerve wrinkles (Figure 6A)

5) Empty sella (Figure 6B).[40, 41]

6) Protrusion of optic nerve head towards glob (Figure 7A)

In MR imaging studies on patients with IHH, posterior sclera flattening was observed by 80% whereas empty sella by 70%, enlarged perioptic subarachnoid space by 45% and dilatation in prelaminar optic nerve by 30%.[40] In a study on IHH cases without papilledema, Mallery et al. reported that the sensitivity and specificity were %80 and %64 for pituitary height whereas 51% and 83 for increased optic nerve sheath diameter, 97% and 57% for posterior scleral flattening, respectively.[42] In addition, Transverse sinus stenosis showed sensitivity of 78%. In conclusion, it was suggested that sensitivity of 100% and specificity of 64% can be achieved by presence of 3 of 4 MRI findings. Authors showed that ≥3 MRI findings were present in 30% of patients having headache and elevated opening pressure but not papilledema.

By MR imaging, normal optic nerve sheath diameter is measured as 5.52±1.11 mm just beneath glob and 5.2±0.9 mm at 4 mm posterior to glob.[41] Seitz et al. showed that optic nerve sheath diameter was increased to 7.54±1.05 mm just beneath globe in pathological conditions. In addition, they suggested that CSF surrounding optic nerve can remain visible up to 6.3 mm distance from glob to optic chiasm in healthy individuals and that the length was increased up to 12.4 mm in pathological conditions. In general, the length>5 mm is considered as abnormal. In pediatric patients with suspected IHH, Ozturk et al. measured optic nerve sheath diameter as 6.62±0.70 mm in cases with papilledema and 4.62±0.64 mm in cases with pseudopapilledema.[43] In addition, they found a significant correlation between CSF opening pressure and optic nerve sheath diameter. Besides, MR imaging is used to monitor treatment efficacy following optic nerve sheath fenestration in IHH patients.

In several studies, posterior scleral flattening was shown in cases with ICP elevation, suggesting that it is one of the mildest radiological changes in papilledema.[44] In a case with elevated ICP and unilateral papilledema, Jacobson et al. reported posterior scleral flattening together with dilatation in perioptic subarachnoid space.[44] On normal MR images, optic nerve is seen as a flat, hyper-intense area at posterior sclera. In IHH cases, intraocular protrusion of optic nerve head can be shown by MR imaging. In addition, hyper-intensity can be observed in protrusion area due to impaired blood flow in prelaminar capillary by contrast-enhanced studies.[40]

The increased wrinkling and tortuosity in optic nerve can be associated with ICP elevation. Owing sensitivity of axial imaging, horizontal tortuosity is considered as relatively

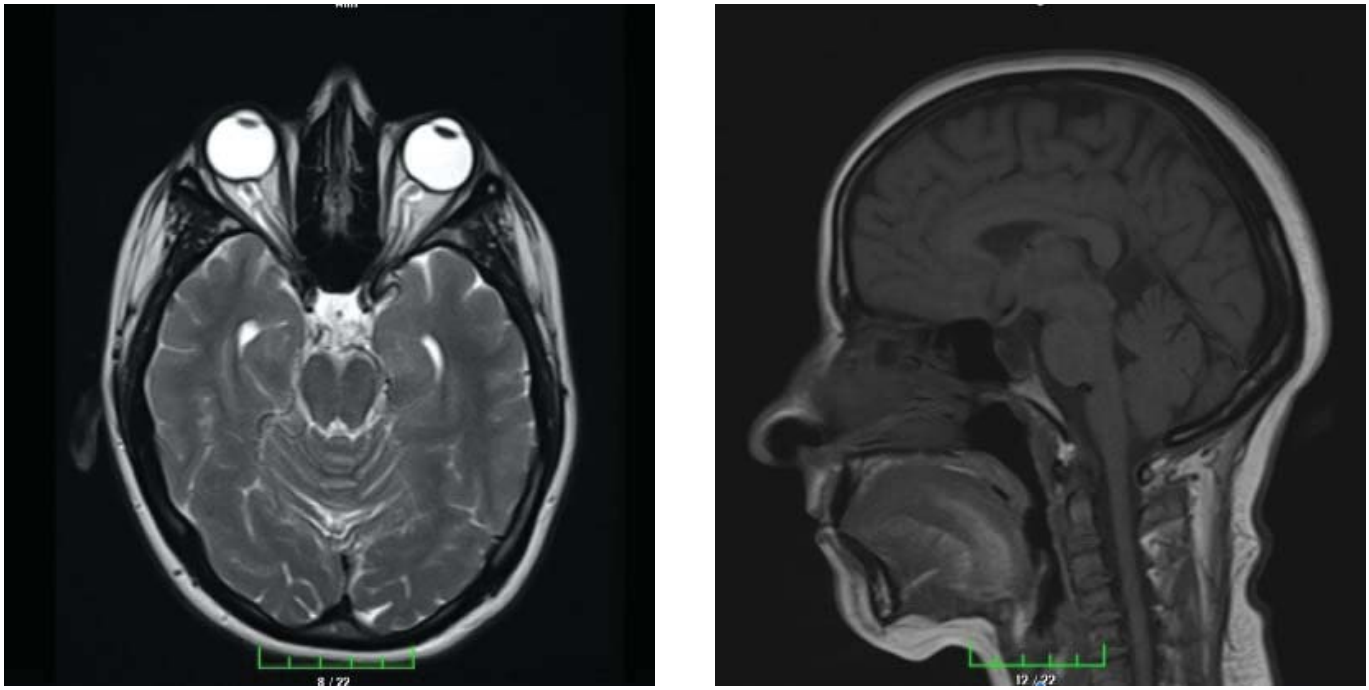


Figure 6: A. *Contrast enhancement around optic nerves and thickening, flattened posterior sclera and increased tortuosity in left optic nerve are seen on T2-weighted axial MRI sections in a case with a diagnosis of pseudotumor cerebri;* **B.** *Empty sella finding is seen on T1-weighted sagittal section in another case.*



Figure 7: A. *Protrusion of optic nerve head to vitreous on axial MRI section in a patient with papilledema;* **B.** *Marked occlusion is seen in left transverse sinus on MRV in the same case.*

non-specific finding. However, tortuosity on axial plane has higher diagnostic value. The reason for wrinkling is that failure in anterior displacement of globe by increased pressure around optic nerve results in folding of optic nerve sheath.[40]

Given time delay between ICP elevation and papilledema development and the fact that IHH can be present without papilledema, MRI findings providing insight before onset of papilledema makes it valuable in the diagnosis and follow-up.

Given that IHH, most common cause of papilledema in ophthalmology is an exclusion diagnosis, MRV together with MR imaging is important to exclude cerebral venous sinus thrombosis (CVST). The CVST is a rare disease characterized by thrombotic occlusion of venous sinuses (Figure 7). It may lead venous infarction and seizures and neurological deficits secondary to hemorrhages. It can result in permanent sequels and death in approximately 20% of patients. Likewise IHH, the symptoms may include 6th cranial nerve paralysis and papilledema. Again, only finding is ICP in 37% of patients.[45] MR imaging alone is sufficient to diagnosis CVST in the presence of intra-parenchymal hemorrhage; however, the success of MRV in the diagnosis of CVST is consistent with catheter angiography and superior to MR imaging. Although there are evidence that CVST has a more acute course than IHH, subacute presentation was found as 55% in the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). However, the finding that 75% of cases were women and mean age was 37 years suggested that it affects population similar to IHH.[46] As previously mentioned, it is known that iron deficiency anemia, frequently seen in the same age group, predisposes to CVST.

In another study, King et al.[47] and Karahalios et al.[48] found that intracranial venous sinus pressure as measured by jugular venous catheterization was high in majority of patients with IHH. Although the elevation in venous sinus pressure is secondary to central venous pressure, it mostly occurs due to focal stenotic lesions that hampers venous outflow in lateral sinuses, raising the question whether these lesions are reason or result in ICP elevation. The finding that lateral sinus stent and dilatation resulted in recovery of symptoms suggests that it may be reasons.[49] Higgins et al. detected lateral sinus flow abnormalities in more than one-half of IHH cases without thrombosis on static MR imaging. However, lower rate of abnormalities in the control group showed that thrombosis frequency is higher than expected in IHH patients.

Based on these findings, MRV should be performed in situations predisposing to hyper-coagulability such as anemia, dehydration, pregnancy, oral contraceptive use, infection, head trauma, history of malignancy and coagulation disorder and in cases which are consistent with IHH in demographic manner, including male gender, pre-pubertal girls, elder individuals and non-obese women.

CONCLUSION

As papilledema can be seen in potentially life-threatening pathologies, it requires urgent evaluation and meticulous differential diagnosis. Thus, it is important to understand tests that may help clinician in distinguishing papilledema and pseudopapilledema. In several studies, pseudopapilledema or normal variations have been detected in 34-76% of pediatric cases evaluated for suspected papilledema. In cases where pseudopapilledema is excluded, diagnosis is attempted to be made by neuroimaging studies and CSF analysis. However, multiple mechanisms can be present for optic disc elevation in a case with a diagnosis of papilledema. It should be kept in mind that there may be cases with overlapping entities. In particular, accurate diagnosis may prevent troublesome and expensive modalities which lead anxiety in both child and parents. CSF pressure measurement can be affected by height, posture, diurnal variations and anesthesia techniques and may not be necessarily reliable. In addition, ancillary testing is helpful not only in diagnosis and differential diagnosis but also in the follow-up. Given these, it becomes apparent that OCT, sonography, MR imaging and MRV and experience of clinician in using these modalities are of important.

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