Current Neurology and Neuroscience Reports (2024) 24:55–64
https://doi.org/10.1007/s11910-023-01327-6

REVIEW

Advantages and Pitfalls of the Use of Optical Coherence Tomography for Papilledema

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Accepted: 11 December 2023 / Published online: 23 January 2024

Abstract

Purpose of Review Papilledema refers to optic disc swelling caused by raised intracranial pressure. This syndrome arises from numerous potential causes, which may pose varying degrees of threat to patients. Manifestations of papilledema range from mild to severe, and early diagnosis is important to prevent vision loss and other deleterious outcomes. The purpose of this review is to highlight the role of optical coherence tomography (OCT) in the diagnosis and management of syndromes of raised intracranial pressure associated with papilledema.

Recent Findings Ophthalmoscopy is an unreliable skill for many clinicians. Optical coherence tomography is a non-invasive ocular imaging technique which may fill a current care gap, by facilitating detection of papilledema for those who cannot perform a detailed fundus examination. Optical coherence tomography may help confirm the presence of papilledema, by detecting subclinical peripapillary retinal nerve fiber layer (pRNFL) thickening that might otherwise be missed with ophthalmoscopy. Enhanced depth imaging (EDI) and swept source OCT techniques may identify optic disc drusen as cause of pseudo-papilledema. Macular ganglion cell inner plexiform layer (mGCIPL) values may provide early signs of neuroaxonal injury in patients with papilledema and inform management for patients with syndromes of raised intracranial pressure.

Summary There are well-established advantages and disadvantages of OCT that need to be fully understood to best utilize this method for the detection of papilledema. Overall, OCT may complement other existing tools by facilitating detection of papilledema and tracking response to therapies. Moving forward, OCT findings may be included in deep learning models to diagnose papilledema.

Keywords Papilledema · Pseudopapilledema · Optical Coherence Tomography · Idiopathic Intracranial Hypertension · Peripapillary Retinal Nerve Fiber Layer · Macular Ganglion Cell Inner Plexiform Layer

Introduction: Opening Statement

Papilledema is a syndrome of optic disc swelling caused by raised intracranial pressure. The causes of papilledema are protean (Table 1) and may be both vision and life-threatening in nature [1–6]. Unfortunately, deleterious effects of papilledema may go unrecognized in the absence of dedicated ophthalmic oversight. While many patients fare well with medical management, cerebrospinal fluid (CSF) pressure-lowering procedures may be needed for those with rapidly deteriorating vision. Detecting papilledema is a "real world" challenge for many physicians because performing reliable ophthalmoscopy is a diminishing skill [7]. Thankfully, advances in ocular imaging techniques offer promise, by facilitating early recognition of papilledema and providing early clues to impending vision loss that may be readily interpreted, even by clinicians who lack specific expertise in ophthalmic care. The goals of this review are to discuss the clinical spectrum of papilledema, consider key features that herald risk for visual loss, and highlight the role of optical coherence tomography (OCT) in identifying and managing syndromes of raised intracranial pressure.

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Table 1 Causes of papilledema [1–6]

Cause or mechanism	Example(s)
Mass effect	Large intracranial tumor, abscess, AVM
CSF flow obstruction	Obstructive hydrocephalus, spinal tumors (possibly)
Focal or generalized cerebral edema	Large vessel ischemic stroke, trauma
Impaired CSF resorption	Cerebral venous sinus thrombosis, meningitis
Increased CSF production	Choroid plexus tumor
Cranial vault abnormalities	Craniosynostosis
Medications	Tetracyclines
Idiopathic	Idiopathic intracranial hypertension

AMV arteriovascular malformation, *CSF* cerebrospinal fluid

Papilledema: Standard Methods of Detection, Classification, and Implications

Papilledema arises when axoplasmic flow stasis caused by raised intracranial pressure leads to edema in the retinal nerve fibers around the optic nerve head [3, 5]**.** Frisén developed a scale for papilledema which in its modified version is used by eye care specialists to characterize optic nerve swelling as mild, moderate, or severe [3, 8, 9]. Grading papilledema has value, because higher levels may be associated with increased of risk of vision loss in conditions such as idiopathic intracranial hypertension (IIH) [3]. Frisén grade I (barely detectable) papilledema appears as a C-shaped optic nerve head elevation that spares the temporal margin of the disc; grade II (mild papilledema) causes a full "halo" of edema around the optic nerve head; grade III (moderate papilledema) includes circumferential optic disc edema with obscuration of at least one major blood vessel segment *leaving* the optic disc; grade IV (marked papilledema) involves edema of the entire optic nerve head, with obscuration of at least one segment of a major blood vessel feature *on* the optic disc; and, grade V (severe papilledema) results in optic disc swelling with total obscuration of all blood vessels *on* and *leaving* the optic disc [3]. In the setting of papilledema, funduscopy may also reveal retinal abnormalities including hemorrhages, cotton wool spots, peripapillary wrinkles, and folds [3, 5, 10]. Occasionally patients develop peripapillary choroidal neovascularization and subretinal fluid as accoutrements of papilledema [3]. It is important to recognize retinal manifestations of raised intracranial pressure both to facilitate diagnosis and elucidate mechanisms of visual dysfunction that may not directly implicate optic nerve injury. Specifically, a patient with papilledema and vision loss secondary to retinal folds and hyperopic shift may respond quickly to medical management, whereas a patient with severe optic nerve dysfunction is more likely to require an urgent surgical procedure to reduce intracranial CSF pressure.

Ophthalmoscopy—a Diagnostic Challenge

In reality, grading papilledema and identifying associated retinal pathologies are specialized skills that require proficient ophthalmoscopy, or access to fundus photography. In most clinical environments, there is a paucity of both, as demonstrated in the FOTO-ED I (Fundus Photography vs. Ophthalmoscopy Trial Outcomes in the Emergency Department) experience [11]. In this study, investigators enrolled 350 adult patients who presented to the emergency department with headaches (65%), acute focal neurologic deficits (29%), or acute visual changes (26%), and/or, with diastolic blood pressures of 120 mm Hg or higher (6%) [11]. Unfortunately, even among individuals with potential manifestations of raised intracranial pressure, ophthalmoscopy was performed by emergency department physicians for only 48/350 (14%) of patients [11]. As per the study protocol, non-mydriatic fundus photos obtained with trained nurse practitioners were reviewed by a neuro-ophthalmologist within 24 h of procurement. Strikingly, 44/350 (13%) of enrolled patients had relevant ocular findings including optic disc edema, intraocular hemorrhages, hypertensive retinopathy, arterial vascular occlusion, and optic atrophy [11]. The findings of the FOTO-ED I study highlight the fact that ophthalmoscopy is unreliably performed in high yield clinical circumstances and emphasize the need for better tools to detect papilledema in settings where patients with raised intracranial pressure are likely to seek care.

The Role of Optical Coherence Tomography in Evaluating Papilledema

Optical coherence tomography (OCT) is a non-invasive ocular imaging technology that has been routinely used in ophthalmic practice for over two decades. This user-friendly tool may readily help with the identification and management of papilledema across a variety of clinical environments, as long as its pros and cons are well understood (Table 2).

Table 2 Advantages and pitfalls of OCT in the evaluation of papilledema [9, 12–32]

OCT feature	Advantages	Pitfalls	Key points
Peripapillary retinal nerve fiber layer (pRNFL) thickness	In clinical practice OCT may detect cases of mild papilledema by showing increases in pRNFL thickness. These features may escape detection with ophthalmoscopy alone	OCT software segmentation errors cause inaccuracies in quantifying high grades of papilledema. Increased pRNFL thickness is not specific for papilledema and may be seen in any cause of optic disc edema. Floor effects with OCT mean that this tool may be insensitive to detecting new neuroaxonal loss superimposed on pre-existing optic nerve injury	Since elevated pRNFL measures may be seen with any cause of optic disc edema other investigations (clinical, radiological, and lumbar puncture findings) may be needed to investigate the mechanism of raised intracranial pressure
Macular ganglion cell inner plexiform layer (mGCIPL) thickness	Preserved mGCIPL measures indicate intact neuroaxonal integrity and provide an indirect structural measure of optic nerve health in patients with papilledema. Decreasing mGCIPL values may provide early evidence of optic nerve injury, and prompt more aggressive therapy for papilledema. mGCIPL measures may play a role in predicting visual outcomes in IIH. Cross-sectional OCT scans centered on the macula are also useful for identification of outer retinal contributions to vision loss such as subretinal fluid, chorioretinal folds, and choroidal neovascularization	Software segmentation errors seen in high grades of papilledema may cause inaccuracies in quantifying mGCIPL thickness	mGCIPL measures may be impacted by a myriad of retinal pathologies and are not specific for papilledema
Optic nerve head (ONH) volume	ONH volume correlates with mean pRNFL thickness, total retinal thickness, and Frisén grades of papilledema. ONH values increase with papilledema and decrease with successful treatment of raised intracranial pressure	There may be inconsistent correlations between ONH volume and Frisén grades of papilledema over time, potentially due to due to floor effects with OCT and the ordinal nature of the Frisén scale	Caution is needed when attributing decreasing ONH values over time to improving papilledema, because these findings may reflect evolving optic atrophy
Peripapillary hyperreflective ovoid mass-like structure(s) (PHOMS)	PHOMS may be found in papilledema	PHOMS have been misinterpreted as representing drusen	PHOMS can be found in association with multiple disorders affecting the optic nerve head and are not specific for papilledema
Retinal pigment epithelium/Bruch's membrane (RPE/BM)	Normally, the RPE/BM around the optic nerve is "V-shaped" and angled away from the vitreous, but in patients with papilledema it may show an inverted U shape toward the vitreous. Peripapillary RPE/BM shape changes may correlate with decreased pRNFL thickness after CSF pressure lowering treatments. RPE/BM shape changes may serve as a marker of increased intracranial pressure	A limitation of utilizing peripapillary BM/RPE changes to guide clinical care is the lack of a commercially available algorithm to reliably detect and quantify morphometric changes	Study of RPE/BM changes requires intensive image processing stages

Table 2 (continued)

OCT feature	Advantages	Pitfalls	Key points
En face spectral domain OCT imaging	OCT readily detects peripapillary wrinkles and chorioretinal folds. Recognition of these findings may help localize papilledema as a cause of optic disc swelling	Retinal folds may be found in other optic nerve pathologies including optic disc drusen	Retinal folds may resolve whereas. choroidal folds may persist
OCT angiography (OCTA)	Quantitative analysis of vessel density around the edematous optic nerve may show dilation and tortuosity of large vessels and tangling and/or curling of capillaries	Optic disc edema may induce artifacts during the image acquisition	This OCT technique may help explore the pathophysiological differences that distinguish different causes of optic disc edema

OCT optical coherence tomography, *IIH* idiopathic intracranial hypertension

While early OCT iterations relied upon time domain techniques, current spectral domain machines employ low-coherence interferometry to generate cross-sectional images of inner retinal structures, including the peripapillary retinal nerve fiber layer (pRNFL) and macular ganglion cell-inner plexiform layer (mGCIPL) [12]. Structural changes in these retinal layers may be quantified and compared to normative data in the longitudinal evaluation of patients with papilledema [12]. Importantly, OCT findings for any patient need to be considered with a view to scan quality, myopic correction, and comorbidities that might impact results.

In the context of papilledema, OCT measures of mGCIPL thickness provide a surrogate structural measure of retinal ganglion cell integrity in the afferent visual pathway and may be used to detect early evidence of neuronal loss. The pRNFL harbours the axons of deeper lying retinal ganglion cells [12]. As a marker of axonal structure, pRNFL thickness increases in the setting of papilledema, and regresses with its resolution [12]. Together, pRNFL and mGCIPL values may be used to detect papilledema and monitor treatment response to CSF pressure lowering interventions. Specifically, elevations in pRNFL thickness which improve over time are reassuring when mGCIPL values are well maintained, because these observations indicate improved papilledema with well-preserved optic nerve integrity. In contrast, the finding of mGCIPL thinning and persistently high pRNFL values (or even decreasing pRNFL measures) is concerning and suggests evolving optic atrophy.

Recent advances in enhanced depth imaging (EDI) OCT techniques enable better visualization of the deeper structures of the retina and choroid than standard SD-OCT [13]. Accordingly, EDI OCT may be used to identify buried optic disc drusen as a cause of pseudo-papilledema and obviate the need for other investigations in some patients with an elevated optic nerve appearance [13–17]. With EDI OCT, optic disc drusen appear as rounded, hypo-reflective structures with a full or partial hyper-reflective anterior margin and have different imaging features than peripapillary hyper-reflective ovoid mass-like structures (PHOMS) (Fig. 1) [14]. In contrast to drusen, PHOMS, which likely represent herniated nerve fibres, have a hyper-reflective appearance, lack of clearly defined margins, and are devoid of a hypo-reflective core (Fig. 1) [14]. Similarly, swept-source OCT (SS-OCT) techniques use a longer wavelength (approximately 1050 nm) and allow robust resolution of deeper retinal structures, thus facilitating drusen diagnosis [16]. Finally, the introduction of OCT angiography (OCTA) has enabled in vivo assessment of retinal and choroidal vascular networks. This angiographic technique does not require contrast and allows indirect evaluation of retinal blood flow [16, 18–21]. There is emerging evidence that OCTA may be used to help differentiate cases of papilledema from pseudo-papilledema, predict visual outcomes in IIH patients, and

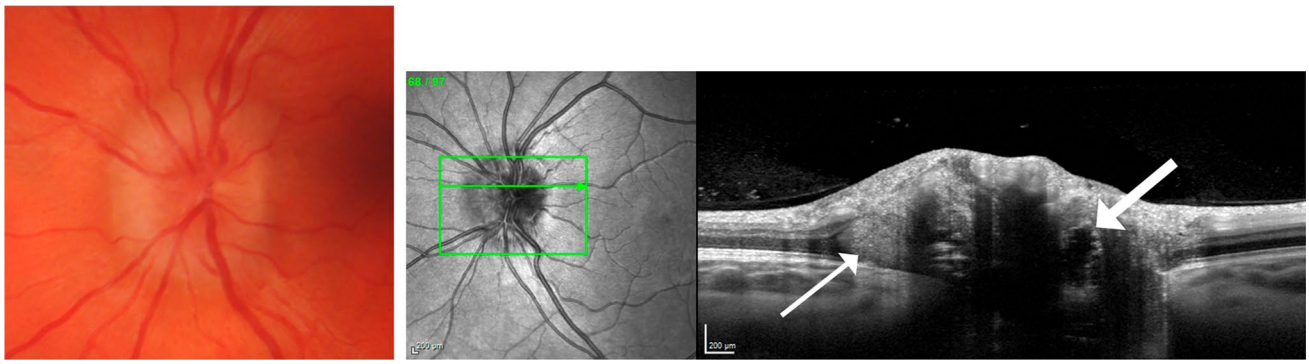

Fig. 1 Fundus photo and enhanced depth imaging optical coherence tomography (EDI-OCT) scan of the optic nerve head from the left eye of a 20-year-old man with optic disc drusen (ODD). The fundus photo shows pseudo-papilledema with evident blurring of the nasal margin of the optic disc. There are no visible ODD. The EDI-OCT shows a peripapillary hyperreflective ovoid mass-like structure (PHOMS), thin arrow, and several ODD, the largest shown by the thick arrow. The PHOMS is responsible for the blurred disc margin, hence the pseudopapilledema, and not the ODD itself

serve as a clinical marker for optic nerve injury caused by papilledema [16, 18–21].

Using Optical Coherence Tomography to Address Key Clinical Questions about Papilledema

Optical coherence tomography has a role to play in the diagnosis and management of patients with suspected papilledema. It is important to avoid the perils of over-diagnosis (confusing other causes of an elevated disc appearance with papilledema) and the consequences of misdiagnoses (overlooking papilledema as a mechanism causing optic disc swelling) to optimize clinical outcomes.

Question 1: Does This Patient Have Papilledema, Pseudo-papilledema, or Neither?

Many acute and chronic disorders of the optic nerve may cause an elevated optic disc appearance. The first step to localizing papilledema as the pathogenic mechanism of optic disc swelling is to perform a focused history, since symptoms of raised intracranial pressure may vary with cause. Patients with meningitis for example may complain of new headaches, fever, and neck stiffness whereas patients with cerebral venous sinus thrombosis (CVST) may present with seizures and encephalopathy. Ingestion of certain agents including tetracyclines may precipitate a syndrome of raised intracranial pressure in some individuals (Table 1). Similarly, for reasons unknown, weight gain is associated with the onset of IIH, particularly in young women. Symptoms to inquire about in cases of suspected IIH include headache, neck or back pain, transient visual obscurations, blurred vision (due to hyperopic shift or shortening of the globe), metamorphopsia (distortion of vision secondary to retinal folds), visual field loss, pulsatile tinnitus, and binocular horizontal diplopia [3, 5]. It bears mentioning that up to a quarter of patients with IIH are asymptomatic [3]. These individuals may manifest optic disc swelling that is incidentally detected during a routine eye examination.

On initial assessment, most patients with papilledema have well preserved high contrast visual acuity. Since deficits of central vision are late sequelae in papilledema, visual acuity decrements not otherwise explained by subretinal fluid, or hyperopic shift caused by retinal folds are reason for concern. Visual field function may initially be explored with confrontation testing, but the most accurate way to ascertain the impact of papilledema on visual function is with formal perimetry techniques [3]. Typically, patients with papilledema will have enlarged blind spots, reflecting the morphology of their edematous optic nerve heads. With severe papilledema and associated optic nerve injury, the visual fields may be markedly constricted [3]. Prominent visual field loss is a serious concern even in patients with well-preserved central visual acuity. In these cases, medical therapy may need to be escalated, and surgical options exercised, to address the immediate threat to optic nerve function. At times, IIH patients may demonstrate evidence of abducens nerve dysfunction, which may range from a subtle esophoria to frank abduction deficits in both eyes [3]. While other cranial nerve deficits including third, fourth, and seventh nerve palsies may occur in IIH [3], alternative diagnoses should be considered for patients presenting with these clinical findings.

At the diagnostic stage, OCT may be particularly useful in detecting papilledema by showing mild or markedly elevated pRNFL values (Table 2). For lower Frisen grades of papilledema, OCT compares favorably with expert review of optic nerve photographs [9]. With higher

grades, however, OCT processing algorithms often fail to reliably quantify the extent of optic disc swelling [3]. This means that papilledema may be detected, but pRNFL values may be imprecisely measured [9]. For suspected mild cases of papilledema, longitudinal follow-up with OCT provides invaluable insights by showing test–retest variability in pRNFL measurements that falls outside the normal range of the machine (5 to 6 microns). This observation is particularly useful if the optic nerve elevation is subtle because OCT is sensitive to subclinical pRNFL elevations that would potentially be missed with ophthalmoscopy alone. Importantly, performing OCT may alleviate concerns for papilledema by showing consistently stable, and normal pRNFL values, or alternatively revealing other reasons for an elevated optic nerve appearance. Optic disc drusen, for example, may be directly diagnosed with OCT by using a protocol developed by the Optic Disc Drusen Studies (ODDS) Consortium [15, 22]. In this respect, OCT findings may prevent unnecessary invasive and costly investigations for patients who do not have papilledema.

If the clinical assessment and OCT findings raise concern for papilledema, the patient's CSF opening pressure should be determined by lumbar puncture, particularly if there are no obvious reasons for raised intracranial pressure revealed by cranial or spinal imaging studies (Table 1). As a general rule, the normal CSF opening pressure in adults is considered to be 10 to 25 cm of water, with measures above 25 cm of water considered high [3, 5]. The normal range of CSF opening pressures in children is higher than in adults, and measures less than 28 cm H_2O are considered normal in the former [3]. That said, issues such as use of sedation, leaky manometers, and suboptimal positioning during the lumbar puncture procedure may cause spurious results. Of note, CSF analysis will also help identify potential inflammatory and infectious causes of papilledema, or alternatively provide support for the diagnosis of IIH if other reasons for raised intracranial pressure are excluded.

Key Points

- OCT may help confirm the presence of papilledema, particularly in mild cases, by detecting subclinical pRNFL thickening that would otherwise potentially be missed with ophthalmoscopy alone.
- The observation of normal OCT-measured pRNFL and mGCIPL values may alleviate concerns for papilledema, particularly if these measures are stable over time and fall within the test–retest variability of the machine (typically 5–7 microns).
- Newer EDI and Swept Source OCT techniques facilitate direct detection of optic disc drusen as a cause of pseudopapilledema. Using these OCT techniques may obviate the need for costly and invasive investigations in patients who have a low risk for true papilledema.

Question 2: If a Patient Has Papilledema, What Is the Cause?

Importantly, irrespective of papilledema severity, it is important to exclude potential life or vision-threatening etiologies for raised intracranial pressure, because these conditions need emergent management. A patient with a malignant brain tumor, for example, may have relatively mild papilledema, whereas a patient with fulminant IIH may not have a life-threatening condition but could nonetheless experience severe visual impairment. Unfortunately, when used in isolation, OCT cannot unequivocally confirm the presence of papilledema or elucidate potential causes since pRNFL values increase with any cause of optic nerve head swelling. Furthermore, while OCT-measured morphometric deflections of the retinal pigment epithelium-Bruch's membrane (RPE/BM) towards the vitreous, and the detection of peripapillary wrinkles (Fig. 2) and retinal folds suggest raised intracranial pressure as a basis of optic disc edema (Table 2) [23–25], other investigations are needed to confirm or refute this hypothesis. Cranial magnetic resonance imaging (MRI) and computed tomography (CT) studies should be

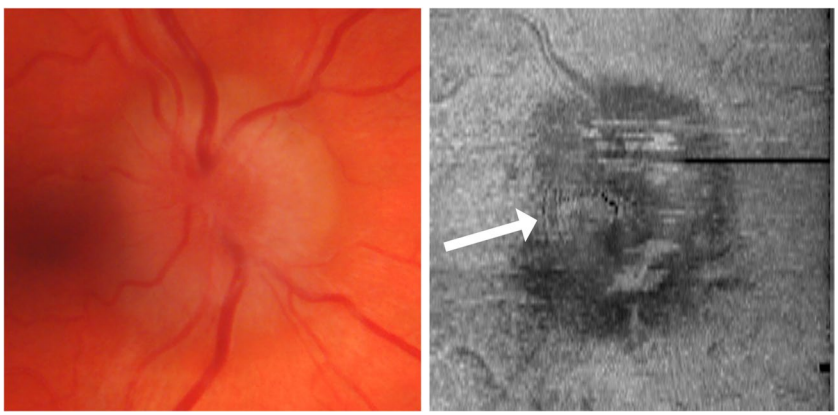

Fig. 2 Fundus photo and en face optical coherence tomography (OCT) scan of the optic nerve head from the right eye of a 44-year-old woman with idiopathic intracranial hypertension (IIH). The fundus photo shows optic disc edema in the clinical context consistent with Frisén grade 2. The en face OCT reveals peripapillary wrinkles or Paton's folds, closely spaced and concentric to the disc, arrow, confirming that it is not pseudo-papilledema

considered to exclude intracranial mass lesions (Table 1). In addition, neuroimaging protocols may be tailored to include the spinal cord and evaluate vascular structures, since spinal lesions and vascular abnormalities (cerebral venous sinus thrombosis, internal jugular vein occlusions, arteriovenous fistulas/malformations/thrombosis) may cause raised intracranial pressure (Table 1). As an important caveat, radiological signs including tortuosity of the optic nerve sheaths, stenosis of the transverse sinuses, an empty sella, and flattening of the posterior globes may be seen in cases of IIH, but these signs are also detected among normal individuals [3, 5, 26].

Key Point

- OCT findings may help detect papilledema but do not disclose cause. For this reason, other investigations are needed.

Question 3: What Is the Threat to Vision from Papilledema?

It can be difficult to predict which patients presenting with papilledema are at risk of vision loss, and which are not. The threat of visual impairment may vary with the etiology of the papilledema [28–43] . In the authors' experience, adult patients with congenital hydrocephalus and shunt malfunction are at significant risk of visual morbidity from raised intracranial pressure. Dire outcomes related to delayed diagnosis, and untimely shunt revision have been well established in this patient population [30, 33–35]. Factors that may contribute to poor visual outcomes include over-reliance on sub-optimal imaging studies that fail to show evidence of shunt malfunction, inadequate ophthalmic oversight, deficient understanding regarding clinical manifestations of raised intracranial pressure, and potentially, selective vulnerability of the patient population [30, 33–35]. Specifically, patients with congenital hydrocephalus may have a "fragility of the visual system" that increases their risk of vision loss from papilledema due to anatomically small optic discs, anomalous vascular configurations, or pre-existing optic nerve injury [30]. It is important to have a low threshold to investigate and treat patients with a history of congenital hydrocephalus because early shunt revision or endoscopic third ventriculostomy may salvage vision and prevent severe neurologic injury [36]. Optical coherence tomography may complement clinical surveillance efforts by detecting spikes in pRNFL values reflecting elevated intracranial CSF pressures. Unfortunately, significant optic atrophy may obscure detection of hydrocephalus with ophthalmoscopy alone because there are not enough viable axons to augment visible optic disc swelling. Similarly, floor effects of the OCT machine make it challenging to identify new optic nerve injury superimposed on chronic optic atrophy. In this setting, morphological deflections of the peripapillary RPE/BM complex towards or away from the vitreous may serve as proof of increased and then decreased intracranial pressure, respectively, in patients tested pre- and post-intracranial pressure lowering interventions (Table 2) [27].

Patients with rapidly progressing, or so-called "fulminant IIH" are also at high risk of severe vision loss, and valiant efforts have been made to identify potential predictors of poor visual outcomes associated with this condition. Individuals with fulminant IIH may present with severe optic disk swelling and profound visual field constriction. Without effective treatment, blindness may ensue. That said, it bears mentioning that many IIH patients who present with severe disc edema, have well preserved vision, respond well to aggressive medical management, and do not need CSF diversion procedures. The conundrum is that no single biomarker reliably predicts which IIH patients are at imminent threat of vision loss, and which will have a favourable natural history. Historically, variables associated with poor visual outcomes in IIH patients have included male sex, anemia, morbid obesity, African American race, paucity of headaches, and sub-optimal ophthalmic surveillance [31, 32, 37–43]. The IIH Treatment Trial showed that male sex, high Frisén grades of papilledema, and decreased visual acuity at baseline were factors linked to treatment failure [31]. For this reason, individuals with suspected IIH who display any of these potential "red flags" at presentation should be carefully monitored. In a recent study, Mikkilineni and colleagues [32] retrospectively reviewed the automated visual field mean deviations at diagnosis and at final visit in 79 IIH patients with papilledema. Among thirteen of 79 (21%) patients who entered the study with prominent visual field loss (mean deviations worse than − 7 dB), 11/13 (85%) ended up with poor visual outcomes (final mean deviations ranging from − 5 to − 32 dB). Over half of these patients required surgery for IIH, often within 3 weeks of diagnosis, as evidence of their fulminant course [32]. Takkar et al. [28] conducted a prospective study of 40 IIH patients and reported that no specific factor including CSF opening pressure, or pRNFL thickness accurately identified patients at risk of vision loss. These investigators observed that severe vision loss at presentation increased the likelihood of poor final outcomes, whereas relatively mild visual dysfunction at the time of diagnosis was associated with a favorable prognosis for visual recovery [28].

Importantly, not all vision loss in IIH patients is due to optic nerve injury. Optical coherence tomography may reveal different mechanisms of visual impairment and indicate when CSF diversion procedures are needed, or alternatively when medical therapy will suffice. In the authors' experience, a patient presenting with newly discovered IIH and central vision loss, will often have subretinal fluid in the macula, detectable with OCT, as the underlying cause. This

mechanism of vision loss is reversible with medical management; recognition thereof will help prevent unnecessary CSF diversion procedures. Chen and colleagues [29] performed a retrospective review of 660 patients with IIH to determine etiologies of vision loss. They also aimed to identify objective predictors of visual recovery [29]. In this study, 31 individuals (4.7%) (48 eyes) had a best-corrected visual acuity of 20/25 or worse on initial presentation. Outer retinal changes alone were responsible for visual loss in 22 eyes (46%). Specific factors contributing to central vision loss included: subretinal fluid (16 eyes), chorioretinal folds (5 eyes), and peripapillary choroidal neovascularization (1 eye) [29]. In most cases, visual loss caused by outer retinal pathology responded well to medical therapy, with the exception of chorioretinal folds [29]. Among patients with optic nerve injury secondary to IIH, a mGCIPL measure ≤ 70 microns at presentation, or progressive loss ≥ 10 microns of mGCIPL thickness within 2 to 3 weeks of initial evaluation correlated with poor visual outcomes [29].

Key Points

- Among patients with papilledema secondary to IIH, the best-predictor of vision loss is poor vision at presentation due to optic nerve injury.
- In patients with established papilledema being followed over time, OCT measures of pRNFL and mGCIPL may be partnered with tests of visual function to gauge response to therapy.
- Macular ganglion cell inner plexiform layer thinning is an early indicator of optic nerve injury.
- Evidence suggesting progressive optic nerve injury should prompt escalation of medical and/or surgical therapy.
- Not all causes of vision loss are due to optic nerve injury in cases of papilledema. OCT testing may help identify outer retinal causes of visual dysfunction that do not implicate optic nerve injury and could forestall CSF diversion procedures.

Idiopathic Intracranial Hypertension—Specific Considerations

While IIH is not the only cause of papilledema it does deserve special mention, because it is a relatively common problem encountered in eye care settings. Paradoxically, IIH is both an under-recognized and over-diagnosed condition [44]. The rising rates of obesity in many parts of the world mean that the overall prevalence of IIH is increasing, for both children and adults [45]. That said, increasing obesity rates are also a variable contributing to overdiagnosis of IIH, particularly among young women affected by primary headache disorders [44]. Other factors that may lead to overdiagnosis of IIH include anchoring bias, over-weighting non-specific radiological findings, and deficient fundus examinations.

Chen et al. [26] performed a prospective cross-sectional study of outpatients undergoing cranial MRI, with concurrent ocular fundus photography. Among 296 patients (median age = 49.5 years; 188/296 (63.5%) females), 145 individuals (49.0%) had at least one radiographic sign of IIH [26]. Yet, in this study, only 5 patients (1.7%) had papilledema. Those with papilledema were more likely to have radiological evidence of an empty sella accompanied by optic nerve tortuosity and transverse venous sinus stenosis [26]. Importantly, the prevalence of papilledema increased from 2.8% among patients with at least one potential MRI sign of IIH to 40.0% among patients with 4 or more MRI features of raised intracranial pressure [26]. The findings of this study illustrate the perils of relying on radiological features alone to render a diagnosis of IIH.

The risks IIH overdiagnosis were highlighted in a study conducted by Fisayo and colleagues [44], who reviewed 165 patients referred for neuro-ophthalmic evaluation with either a pre-existing diagnosis or with the intent to rule out IIH. Among patients with a pre-existing diagnosis of IIH, 34/86 (39.5%) were determined to not carry the diagnosis, and only 15/79 (19%) of patients referred with a suspicion of IIH were confirmed to harbour the condition [44]. The most common sources of diagnostic error identified this study included inaccurate ophthalmoscopic examinations and cognitive biases held by evaluating clinicians [44].

Certainly, it is reasonable to suspect IIH when evaluating a young overweight woman presenting with headaches. Yet, the incidence of primary headache disorders is also high in this patient population [44]. The ability to perform reliable ophthalmoscopy is critical to rendering the correct diagnosis. Unfortunately, in the study by Fisayo and colleagues, 44% of those who examined the ocular fundus misinterpreted the optic nerve appearance as papilledema [44]. Based on their findings, Fisayo and colleagues [44] proposed non-mydriatic fundus photography as a potential solution to the real-world challenge of identifying papilledema with ophthalmoscopy.

Unfortunately, it is the authors' experience that many physicians struggle not only to reliably perform ophthalmoscopy but also have difficulty in discriminating photographic features of optic disc pathology from normal findings. For this reason, OCT may have utility in non-vision care settings by providing a quantitative analysis of the optic nerve, with clear diagnostic indicators of optic disc edema, normal optic nerve findings, and optic atrophy. In addition to facilitating diagnosis of IIH, OCT may be used in concert with serial perimetry measures to monitor disease control over time.

Key Points

- OCT-measured pRNFL values may provide structural evidence for papilledema and identify patients who should undergo additional investigations for IIH.
- Normal OCT measures of pRNFL thickness and mGCIPL thickness may obviate concerns for IIH with papilledema.
- Serial OCT measures may be paired with tests of visual function to monitor disease control in IIH patients.

Conclusions

It is challenging for many physicians to perform reliable ophthalmoscopy in real-world clinical settings. For this reason, patients with true papilledema may experience diagnostic delays whereas others without papilledema may be subjected to inappropriate investigations and treatments. Optical coherence tomography may complement other emerging tools, including non-mydriatic photography to fill the care gap. Moving forward, OCT may also be included in emerging deep learning models to differentiate papilledema from normal optic discs and other optic neuropathies based on fundus photos alone [46–48]. Employing OCT in common clinical care settings may aid in the recognition of papilledema, providing there is a solid understanding of the advantages and pitfalls of the technology.

Author contributions F.C. wrote the main manuscript with input from S.H. The figures were prepared by S.H. All authors reviewed the manuscript.

Declarations

Competing interests The authors declare no competing interests.

Conflict of Interest Dr. Costello has received speaker fees or advisory board honoraria from Alexion, Novartis, Horizon Therapeutics, Sanofi, Vindico, and Healio Live.
Dr. Hamann has nothing to disclose.

References

1. Rigi M, Almarzouqi S, Morgan M, Lee A. Papilledema: epidemiology, etiology, and clinical management. Eye Brain. 2015;7:47–57.
2. Costello F, Kardon RH, Wall M, Kirby P, Ryken T, Lee AG. Papilledema as the presenting manifestation of spinal schwannoma. J Neuroophthalmol. 2002;22(3):199–203.
3. Thurtell MJ. Idiopathic intracranial hypertension. Continuum (Minneap Minn). 2019;25(5):1289–309.
4. Crum OM, Kilgore KP, Sharma R, Lee MS, Spiegel MR, McClelland CM, Bhatti MT, Chen JJ. Etiology of papilledema in patients in the eye clinic setting. JAMA Netw Open. 2020;3(6):e206625.
5. Markey KA, Mollan SP, Jensen RH, Sinclair AJ. Understanding idiopathic intracranial hypertension: mechanisms, management, and future directions. Lancet Neurol. 2016;15(1):78–91.
6. Pinto VL, Tadi P, Adeyinka A. Increased intracranial pressure. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482119/ . Accessed 26 Dec 2023.
7. Mackay DD, Garza PS, Bruce BB, Newman NJ, Biousse V. The demise of direct ophthalmoscopy: a modern clinical challenge. Neurol Clin Pract. 2015;5(2):150–7.
8. Frisén L. Swelling of the optic nerve head: a staging scheme. J Neurol Neurosurg Psychiatry. 1982;45(1):13–8.
9. Scott CJ, Kardon RH, Lee AG, Frisén L, Wall M. Diagnosis and grading of papilledema in patients with raised intracranial pressure using optical coherence tomography vs clinical expert assessment using a clinical staging scale. Arch Ophthalmol. 2010;128(6):705–11.
10. Nichani P, Micieli JA. Retinal Manifestations of Idiopathic Intracranial Hypertension. Ophthalmol Retina. 2021;5(5):429–37.
11. Bruce BB, Lamirel C, Biousse V, Ward A, Heilpern KL, Newman N, Wright DW. Non-mydriatic ocular fundus photography in the emergency department. N Engl J Med. 2011;364:387–9.
12. Costello F, Chen JJ. The role of optical coherence tomography in the diagnosis of afferent visual pathway problems: a neuroophthalmic perspective. Handb Clin Neurol. 2021;178:97–113.
13. Spaide RF, Koizumi H, Pozzoni MC. Enhanced depth imaging spectral-domain optical coherence tomography. Am J Ophthalmol. 2008;146(4):496–500.
14. Costello F, Rothenbuehler SP, Sibony PA, Hamann S. Optic disc drusen studies consortium. Diagnosing optic disc drusen in the modern imaging era: a practical approach. Neuroophthalmology. 2020;45(1):1–16.
15. Costello F, Malmqvist L, Hamann S. The role of optical coherence tomography in differentiating optic disc drusen from optic disc edema. Asia Pac J Ophthalmol (Phila). 2018;7(4):271–9.
16. De Carvalho ER, Maloca PM. Review of optical coherence tomography in neuro-ophthalmology. Ann Eye Sci. 2020;5:14.
17. Yan Y, Liao YJ. Updates on ophthalmic imaging features of optic disc drusen, papilledema, and optic disc edema. Curr Opin Neurol. 2021;34(1):108–15.
18. Fard MA, Sahraiyan A, Jalili J, Hejazi M, Suwan Y, Ritch R, Subramanian PS. Optical coherence tomography angiography in papilledema compared with pseudopapilledema. Invest Ophthalmol Vis Sci. 2019;60(1):168–75.
19. Pahuja A, Dhiman R, Aggarwal V, Aalok SP, Saxena R. Evaluation of peripapillary and macular optical coherence tomography angiography characteristics in different stages of papilledema. J Neuroophthalmol. 2023. https://doi.org/10.1097/WNO.0000000000001908.
20. Rougier MB, Le Goff M, Korobelnik JF. Optical coherence tomography angiography at the acute phase of optic disc edema. Eye and Vis. 2018;5:15.
21. Rodriguez Torres Y, Lee P, Mihlstin M, Tomsak RL. Correlation between optic disc peripapillary capillary network and papilledema grading in patients with idiopathic intracranial hypertension: a study of optical coherence tomography angiography. J Neuroophthalmol. 2021;41(1):48–53.
22. Malmqvist L, Bursztyn L, Costello F, Digre K, Fraser JA, Fraser C, Katz B, Lawlor M, Petzold A, Sibony P, Warner J, Wegener M, Wong S, Hamann S. The optic disc drusen studies consortium recommendations for diagnosis of optic disc drusen using optical coherence tomography. J Neuroophthalmol. 2018;38(3):299–307.

23. Malhotra K, Padungkiatsagul T, Moss HE. Optical coherence tomography use in idiopathic intracranial hypertension. Ann Eye Sci. 2020;5:7.
24. Sibony PA, Kupersmith MJ, Feldon SE, et al. Retinal and Choroidal Folds in Papilledema. Invest Ophthalmol Vis Sci. 2015;56:5670–80.
25. Sibony PA, Kupersmith MJ, Kardon RH. Optical coherence tomography neuro-toolbox for the diagnosis and management of papilledema, optic disc edema, and pseudopapilledema. J Neuroophthalmol. 2021;41(1):77–92.
26. Chen BS, Meyer BI, Saindane AM, Bruce BB, Newman NJ, Biousse V. Prevalence of incidentally detected signs of intracranial hypertension on magnetic resonance imaging and their association with papilledema. JAMA Neurol. 2021;78(6):718–25.
27. Gampa A, Vangipuram G, Shirazi Z, Moss HE. Quantitative association between peripapillary Bruch's membrane shape and intracranial pressure. Invest Ophthalmol Vis Sci. 2017;58(5):2739–45.
28. Takkar A, Goyal MK, Bansal R, Lal V. Clinical and neuro-ophthalmologic predictors of visual outcome in idiopathic intracranial hypertension. Neuroophthalmology. 2018;42(4):201–8.
29. Chen JJ, Thurtell MJ, Longmuir RA, Garvin MK, Wang JK, Wall M, Kardon RH. Causes and prognosis of visual acuity loss at the time of initial presentation in idiopathic intracranial hypertension. Invest Ophthalmol Vis Sci. 2015;56(6):3850–9.
30. Oyama H, Hattori K, Kito A, Maki H, Noda T, Wada K. Visual disturbance following shunt malfunction in a patient with congenital hydrocephalus. Neurol Med Chir (Tokyo). 2012;52(11):835–8.
31. Wall M, Falardeau J, Fletcher WA, Granadier RJ, Lam BL, Longmuir RA, Patel AD, Bruce BB, He H, McDermott MP, NORDIC Idiopathic Intracranial Hypertension Study Group. Risk factors for poor visual outcome in patients with idiopathic intracranial hypertension. Neurology. 2015;85(9):799–805.
32. Mikkilineni S, Trobe JD, Cornblath WT, De Lott L. Visual field mean deviation at diagnosis of idiopathic intracranial hypertension predicts visual outcome. J Neuroophthalmol. 2019;39(2):186–90.
33. Qiu S, Jifang Qu, Yang Bo, Song Y. Nan Bao; Permanent visual impairment due to delayed diagnosis of shunt malfunction in case of lack of typical features of increased intracranial pressure and unchanged ventricular size. Pediatr Neurosurg. 2022;57(5):306–31.
34. Newman NJ. Bilateral visual loss and disc edema in a 15-year-old girl. Surv Opthalmol. 1994;38(4):365–70.
35. Pople IK. Hydrocephalus and shunts: what the neurologist should know. J Neurol Neurosurg Psychiatry. 2002;73:i17–22.
36. Das S, Montemurro N, Ashfaq M, Ghosh D, Sarker AC, Khan AH, Dey S, Chaurasia B. Resolution of papilledema following ventriculoperitoneal shunt or endoscopic third ventriculostomy for obstructive hydrocephalus: a pilot study. Medicina (Kaunas). 2022;58(2):281.
37. Bruce BB, Preechawat P, Newman NJ, Lynn MJ, Biousse V. Racial differences in idiopathic intracranial hypertension. Neurology. 2008;70:861–7.
38. Digre KB, Corbett JJ. Pseudotumor cerebri in men. Arch Neurol. 1988;45:866–72.
39. Bruce BB, Kedar S, Van Stavern GP, Monaghan D, Acierno MD, Braswell RA, Preechawat P, Corbett JJ, Newman NJ, Biousse N. Idiopathic intracranial hypertension in men. Neurology. 2009;72:304–9.
40. Biousse V, Rucker JC, Vignal C, Crassard I, Katz BJ, Newman NJ. Anemia and papilledema. Am J Ophthalmol. 2003;135:437–46.
41. Orcutt JC, Page NGR, Sanders MD. Factors affecting visual loss in benign intracranial hypertension. Ophthalmology. 1984;91:1303–12.
42. Wall M, Purvin V. Idiopathic intracranial hypertension in men and the relationship to sleep apnea. Neurology. 2009;72:300–1.
43. Lim M, Kurian M, Penn A, Calver D, Lin JP. Visual failure without headache in idiopathic intracranial hypertension. Arch Dis Child. 2005;90:206–10.
44. Fisayo A, Bruce BB, Newman NJ, Biousse V. Overdiagnosis of idiopathic intracranial hypertension. Neurology. 2016;86(4):341–50.
45. Kilgore KP, Lee MS, Leavitt JA, Mokri B, Hodge DO, Frank RD, Chen JJ. Re-evaluating the incidence of idiopathic intracranial hypertension in an era of increasing obesity. Ophthalmology. 2017;124(5):697–700.
46. Milea D, Najjar RP, Zhubo J, Ting D, Vasseneix C, Xu X, AghsaeiFard M, Fonseca P, Vanikieti K, Lagrèze WA, La Morgia C, Cheung CY, Hamann S, Chiquet C, Sanda N, Yang H, Mejico LJ, Rougier M-B, Kho R, Thi Ha Chau T, Singhal S, Gohier P, Clermont-Vignal C, Cheng C-Y, Jonas JB, Yu-Wai-Man P, Fraser CL, Chen JJ, Ambika S, Miller NR, Liu Y, Newman NJ, Wong TY, Biousse V, BONSAI Group. Artificial intelligence to detect papilledema from ocular fundus photographs. N Engl J Med. 2020;382(18):1687–95.
47. Leong YY, Vasseneix C, Finkelstein MT, Milea D, Najjar RP. Artificial intelligence meets neuro-ophthalmology. Asia Pac J Ophthalmol (Phila). 2022;11(2):111–25.
48. Biousse V, Newman NJ, Najjar RP, Vasseneix C, Xu X, Ting DS, Milea LB, Hwang JM, Kim DH, Yang HK, Hamann S, Chen JJ, Liu Y, Wong TY, Milea D, BONSAI (Brain and Optic Nerve Study with Artificial Intelligence) Study Group. Optic disc classification by deep learning versus expert neuro-ophthalmologists. Ann Neurol. 2020;88(4):785–95.