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REVIEW

Diagnosis of Optic Disc Oedema: Fundus Features, Ocular Imaging Findings, and Artificial Intelligence

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ABSTRACT

Optic disc swelling is a manifestation of a broad range of processes affecting the optic nerve head and/or the anterior segment of the optic nerve. Accurately diagnosing optic disc oedema, grading its severity, and recognising its cause, is crucial in order to treat patients in a timely manner and limit vision loss. Some ocular fundus features, in light of a patient's history and visual symptoms, may suggest a specific mechanism or aetiology of the visible disc oedema, but current criteria can at most enable an educated guess as to the most likely cause. In many cases only the clinical evolution and ancillary testing can inform the exact diagnosis. The development of ocular fundus imaging, including colour fundus photography, fluorescein angiography, optical coherence tomography, and multimodal imaging, has provided assistance in quantifying swelling, distinguishing true optic disc oedema from pseudo-optic disc oedema, and differentiating among the numerous causes of acute optic disc oedema. However, the diagnosis of disc oedema is often delayed or not made in busy emergency departments and outpatient neurology clinics. Indeed, most non-eye care providers are not able to accurately perform ocular fundus examination, increasing the risk of diagnostic errors in acute neurological settings. The implementation of non-mydriatic fundus photography and artificial intelligence technology in the diagnostic process addresses these important gaps in clinical practice.

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Introduction

Optic disc swelling is a broad subject that concerns not only neuro-ophthalmologists but also general ophthalmologists and neurologists, and emergency department (ED) providers and other medical personnel because of the neurological and systemic implications of optic disc oedema. Thus, this review is intended as both a state-of-the-art review for a broad audience of physicians and trainees, and an update on new developments for neuro-ophthalmologists.

When faced with apparent optic disc swelling, a crucial initial distinction is whether the appearance reflects papilloedema (i.e., disc oedema from raised intracranial pressure), other acute anterior optic neuropathies, or pseudo-optic disc oedema, as investigations and immediate management will not be the same. The diagnosis of optic disc oedema is most often made when patients become symptomatic and seek medical care, whereas the diagnosis of pseudo-optic oedema is often incidental on a routine ocular examination. Papilloedema occurs when cerebrospinal fluid pressure in the subarachnoid space of the optic nerve sheath is increased because of raised intracranial pressure from a space-occupying lesion, a meningeal process, venous sinus thrombosis or idiopathic intracranial hypertension (IIH).[1] Other acute anterior optic neuropathies that warrant urgent management can result from various mechanisms and are summarised in Table 1.[2–6] If not treated in a timely manner, true optic disc oedema may lead to ganglion cell loss and subsequent permanent vision loss; it may also reveal an underlying life-threatening disorder associated with intracranial hypertension. Such sinister outcomes highlight the crucial importance of ocular fundus examination.[7,8]

The ocular fundus features currently used to diagnose optic disc oedema and classify its severity are most often insufficient to determine the underlying cause and are always interpreted in light of a patient's history and the constellation of visual

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Table 1. Causes of optic disc oedema from acute anterior optic neuropathies other than papilloedema that warrant urgent management.

Localisation	Mechanism	Aetiology	Other clinical findings
Anterior optic nerve	Compression or infiltration	Rapidly expansive orbital process; Graves orbitopathy; infiltrative optic neuropathy from leukaemia, lymphoma, or carcinoma	Orbital syndrome, including proptosis, extraocular muscle palsies; retinal haemorrhages and Roth spots
Anterior optic nerve	Demyelination	Multiple sclerosis; MOGAD; NMOSD	Can be isolated or accompanied by other neurological symptoms
Anterior optic nerve or optic nerve head	Infectious or non-infectious inflammation	Bartonella; syphilis; tuberculosis; Lyme disease; sarcoidosis; viral	Intraocular inflammation, extraocular muscle palsies, neuroretinitis with retinal infiltrates, delayed macular star, vasculitis
Optic nerve head	Venous stasis	CRVO, venous papillopathy	Isolated disc oedema (venous papillopathy), venous tortuosity and dilation with scattered retinal flame haemorrhages distant from the optic disc
Optic nerve head	Sectoral or diffuse ischemia	Non-arteritic AION; incipient non-arteritic AION; diabetic papillopathy	Contralateral 'disc-at-risk'; diabetic retinopathy
Optic nerve head	Diffuse ischaemia and infarction from inflammatory arteriolar occlusion	Arteritic AION	Pallid disc oedema, cilioretinal occlusion, CRAO, choroidal ischemia
Optic nerve head	Ischaemia; may be associated with raised intracranial pressure	Hypertensive retinopathy	Copper-wired retinal arterioles, arteriovenous nicking, cotton-wool spots, haemorrhages
Optic nerve head	Toxic/metabolic and mitochondrial dysfunction	Methanol or ethylene glycol poisoning; amiodarone; phosphodiesterase inhibitors; tacrolimus or tetracycline toxicity; thiamine or biotinidase deficiency	Medical history, medication list

AION = anterior ischaemic optic neuropathy; CRVO = central retinal vein occlusion; MOGAD = myelin-oligodendrocyte glycoprotein-associated disease; NMOSD = neuromyelitis optica spectrum disorder.

symptoms and their evolution over time. Brain and orbital imaging are frequently ordered, but may not be helpful if the pathology is isolated to the optic nerve head. The emergence of modern ocular imaging has partly addressed these diagnostic gaps in clinical practice.[9,10] Multimodal ocular imaging includes ocular fundus photography, retinal fluorescein/indocyanine green angiography, fundus autofluorescence, ocular ultrasound, optical coherence tomography (OCT), enhanced depth imaging OCT (EDI-OCT), and OCT angiography (OCTA), and are nowadays routinely utilised to diagnose, grade, and follow-up papilloedema; to identify accompanying retinal and choroidal features associated with other acute anterior optic neuropathies; and to distinguish true disc oedema from pseudo-disc oedema, especially when the swelling is mild (Table 2).[9]

The diagnosis of optic disc oedema is traditionally achieved on ocular fundus examination using ophthalmoscopy. Many patients with optic disc oedema present to non-eye care providers such as neurologists and ED providers because of accompanying symptoms such as headaches or other neurological or systemic complaints.[11] However, ocular fundus examination is often poorly performed or not performed at all by non-eye care providers,[10,12] resulting in missed optic disc oedema.[13,14]

We review diagnostic clinical and funduscopic features of optic disc oedema, the contribution of ocular fundus imaging in diagnosis and management, how to distinguish disc oedema from pseudo-disc oedema, and how artificial intelligence (AI) can assist ocular fundus examination and improve diagnostic yield, especially among patients seen outside the eye clinic.

Part 1 : clinical and funduscopic features of optic disc oedema

Optic disc swelling is a non-specific response to injury of the anterior portion of the optic nerve. Various mechanisms of optic nerve injury often coexist, including axoplasmic stasis, ischaemia, inflammation and compression.

Clinical features

Visual acuity loss is usually encountered in acute anterior optic neuropathies but not in most patients with papilloedema. However, it is not uncommon to observe vision loss with severe papilloedema and only mild visual impairment with some other acute anterior optic neuropathies.

Table 2. Multimodal ocular imaging of optic disc oedema.

Purpose of imaging	Modalities used	Structure imaged	Potential findings
Routine diagnosis, grading, and follow up of papilloedema	Fundus photography	Optic disc	Severity (Frisén scale) and chronicity (Hoyt and Beeston classification)
	OCT	pRNFL and mGCIPL	Change in thickness
Identify accompanying retinal and choroidal features associated with other acute anterior optic neuropathies	Fundus autofluorescence	RPE	Macular or peripheral hyper- or hypo-autofluorescence
	OCT	pRNFL, mGCIPL, and macular outer and inner layers	Change in pRNFL and mGCIPL thickness; macular oedema, subretinal fluid, outer retinal morphological changes
	OCTA	Macular choroid	Neovascularisation
	Retinal fluorescein angiography	Retinal vasculature, choroid (very early phases)	Arm-to-retina delay, arteriolar occlusion, venous drainage, retinal ischaemia, vascular leakage, neovascularisation
	Indocyanine green angiography	Choroid	Inflammatory choroidal foci
Distinguish true disc oedema from pseudo-disc oedema	Fundus photography	Optic disc	Vessel obscuration in disc oedema, mineral elevation in disc drusen
	OCT	pRNFL, mGCIPL, and optic nerve head cube	Change in thickness and morphology of the optic nerve head (e.g mass, PHOMS)
	EDI-OCT	Prelaminar portion of the optic nerve	Buried disc drusen, PHOMS
	Optic disc autofluorescence	Optic disc	Disc drusen hyper-autofluorescence
	Ocular ultrasound (B-scan)	Optic disc	Optic nerve head deep hyper-reflectivity
	Retinal fluorescein angiography	Optic disc	No fluorescein dye leakage in pseudo-optic disc oedema

EDI-OCT = enhanced depth imaging optical coherence tomography; mGCIPL = macular ganglion cell-inner plexiform layer; OCT = optical coherence tomography; OCTA = optical coherence tomography angiography; PHOMS = peripapillary hyper-reflective ovoid mass-like structures; RPE = retinal pigment epithelium; pRNFL = peripapillary retinal nerve fibre layer.

Papilloedema

Papilloedema is a specific term used to describe optic disc oedema specifically secondary to intracranial hypertension. Papilloedema is usually bilateral, although very asymmetric papilloedema (at least 2 Frisén grade difference between the two eyes) has been reported to occur in 3.6[15] to 7%[16] of IIH cases. Unilateral papilloedema is possible but rare.[17] Patients often present with other symptoms and signs of intracranial hypertension, such as headaches and neurological symptoms. Transient visual obscurations, defined as brief, seconds-long reductions in vision, usually precipitated by changes in posture, are common in patients with papilloedema. Binocular diplopia related to divergence insufficiency or sixth nerve palsies occurs at presentation in about one-fifth of cases.[16] Visual function is usually preserved in the acute stages, especially when the swelling is mild to moderate. There is usually no deficiency of visual acuity or colour vision, and visual field testing may initially be normal or show enlargement of the physiological blind spots, eventually progressing to nasal defects and constriction of the visual field if papilloedema is severe and the intracranial hypertension not treated in a timely manner. Refractive errors, such as hyperopic shift are common and are related to posterior flattening of the globes from the increased intracranial pressure transmitted along the perioptic subarachnoid space.[18] Less commonly, severe acute papilloedema results in profound visual loss such as seen with fulminant IIH or other intracranial disorders that result in severe intracranial hypertension, such as cerebral venous sinus thrombosis.[19] If left untreated, papilloedema can evolve into optic atrophy and visual function can deteriorate with progressive constriction of visual fields.

Other acute anterior optic neuropathies

Acute anterior optic neuropathies are usually unilateral, but bilateral simultaneous or sequential insults to the optic nerve head may occur. Unlike papilloedema, other acute anterior optic neuropathies typically present with decreased visual acuity, impaired colour vision and contrast sensitivity, and visual field defects that are often central or altitudinal.[2,20] The diagnosis of an acute anterior optic neuropathy other than papilloedema is even more likely when the visual loss is out of proportion to the severity of disc oedema. The site of injury is either the optic nerve head or the anterior part of the intraorbital portion of the optic nerve (Table 1).[20] While most acute anterior optic neuropathies cause vision loss, they can sometimes

manifest with unilateral isolated pauci-symptomatic optic disc oedema, adding to the diagnostic complexity of such cases.[17] The differential diagnosis in this setting most commonly includes incipient non-arteritic anterior ischaemic optic neuropathies (NAION), compression such as from optic nerve sheath meningioma, vitreopapillary traction, so-called venous papillopathy, and papilloedema.

Pathophysiology of optic disc oedema

Papilloedema builds up progressively as intracranial pressure increases, but the exact onset of papilloedema is unknown in most cases and may vary based on the cause of intracranial hypertension and a patient's individual anatomical features. In a prospective study of 37 patients with acute elevation of intracranial pressure on continuous intracranial pressure monitoring after intracranial bleeding or trauma, papilloedema appeared on funduscopy with a delay of 5 to 6 days.[21] The seminal work by Hayreh et al using in vivo imaging and histopathological studies of an experimental model of papilloedema in rhesus monkeys demonstrated that the first sign of raised intracranial pressure was swelling of the optic discs that resulted directly from swollen axons and axoplasmic flow stasis in the prelaminar portion of the optic discs.[22–26] Vascular changes, such as optic disc hyperaemia, capillary dilation, microaneurysms, peripapillary haemorrhages, and venous dilation, appeared later than the optic disc oedema itself. Depending on when optic disc oedema is diagnosed in its natural evolution, it can appear similar in papilloedema and other causes of acute anterior optic neuropathies, despite different pathophysiological mechanisms and initial clinical presentations (Figure 1). All mechanisms of optic disc oedema, whether from increased cerebrospinal fluid pressure, ischaemia, compression, inflammation, or metabolic dysfunction, have a common final pathway of axoplasmic stasis.[23] Disc oedema eventually shifts towards varying amounts of optic atrophy depending on the mechanism, severity, and duration of swelling, as the number of viable nerve fibres decreases.[27] This secondary optic atrophy can appear falsely reassuring because disc oedema seems to resolve on fundus examination. However,

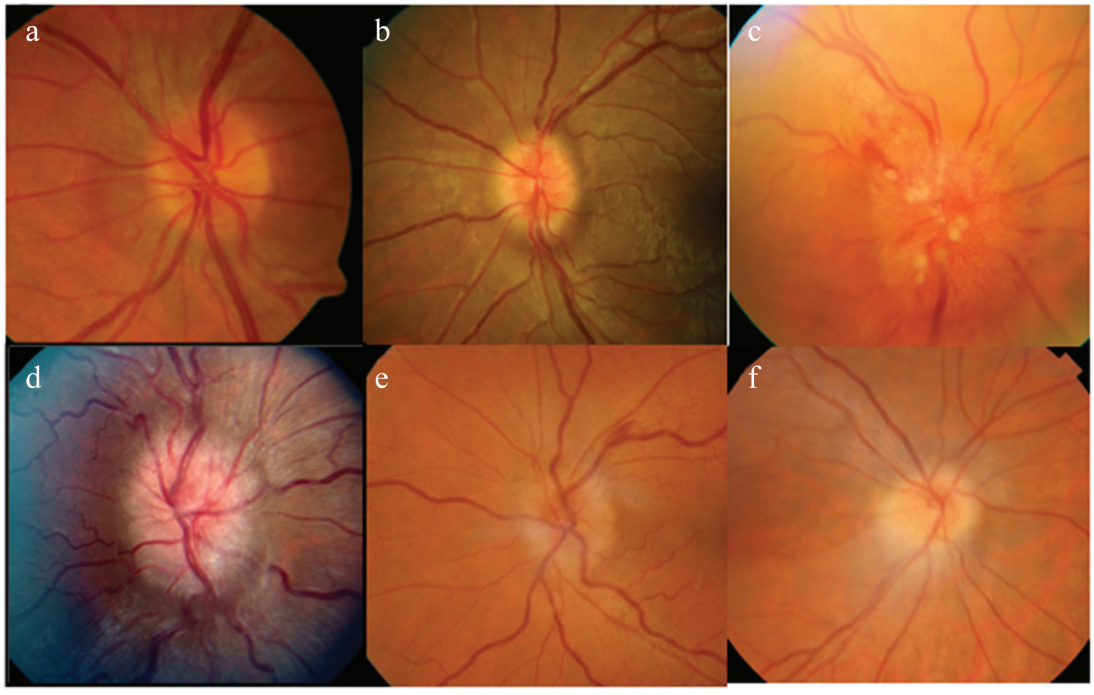

Figure 1. Apparent optic disc swelling from various aetiologies. Papilloedema (a) Frisén grade 1, (b) grade 2, and (c) grade 5 with cotton-wool spots on the disc. (d) Optic disc oedema from compressive optic neuropathy (optic nerve sheath meningioma). (e) Circumferential optic disc oedema with venous dilation and distal peripapillary splinter haemorrhage from myelin-oligodendrocyte glycoprotein-associated optic neuropathy. (f) Predominantly inferotemporal sectoral disc oedema from non-arteritic anterior ischaemic optic neuropathy.

it is important to remember that 'dead axons do not swell', and only viable axons will remain to reflect disc oedema. The absence of disc oedema in patients with secondary optic atrophy from chronic papilloedema does not rule out intracranial hypertension and is not always reassuring.

Ocular fundus features

The visible appearance of optic disc oedema depends on when the observation is made during the course of the swelling, with very few findings specific for given aetiologies.

Papilloedema

Vascular and nerve fibre layer changes are observed on fundus examination in papilloedema. The optic disc appears elevated, and vessels are obscured by the swelling of nerve fibres. The retina and choroid can also manifest visible abnormalities accompanying papilloedema, such as macular exudates, subretinal fluid, and retinal or choroidal folds from adjacent pressure to the posterior globe. These changes can induce visual acuity loss, even when optic nerve function is relatively preserved.

The chronicity of oedema can be described by a four-stage clinical classification of vascular changes based on Hoyt and Beeston's work (Table 3).[28,29] Another classification of papilloedema, the modified Frisén scale, focuses more on nerve fibre layer changes that reflect the severity of the oedema (Table 3).[30] The Frisén classification is the most used in clinical practice and research, and allows for monitoring over time. It is important to highlight that the Frisén scale is better suited for description of early and acute stages of papilloedema, whereas Hoyt and Beeston's classification includes a description of more chronic, resolving papilloedema. One study evaluated the ability of the Frisén scale to monitor changes in the appearance of the optic discs in IIH and found low reproducibility among six observers (36.1%).[31] This study also found that a system of disc ranking, whereby the observers were asked to compare the severity of papilloedema in pairs of photographs, had higher sensitivity (75.3%) than Frisén gradings (53.2%) in the evaluation of optic disc changes. A recent study showed that Frisén grades may not correlate with intracranial pressure measured on lumbar puncture or telemetric monitoring with an invasively implanted device in patients with

Table 3. Clinical classifications of papilloedema.

Vascular changes (based on Hoyt and Beeston classification)[28,29]	Nerve fibre layer changes (modified Frisén scale)*[30]
Early : hyperaemia	**Stage 0: normal optic disc**
	Prominence of the retinal nerve fibre layer at the nasal, superior, and inferior poles in inverse proportion to disc diameter.
	Radial nerve fibre layer striations, without tortuosity.
Acute : haemorrhages, exudates and small infarcts of peripapillary nerve fibre layer (cotton-wool spots)	**Stage 1 : minimal degree of oedema**
	C-shaped halo that is subtle and greyish with a temporal gap; obscures underlying retinal details[a]
	Disruption of normal radial nerve fibre layer arrangement striations
	Temporal disc margin normal
Chronic : no haemorrhages or exudates; vessels undergo structural changes such as telangiectasias and retinochoroidal collaterals, punctate white glistening dots on the disc that may be a manifestation of long-standing neurodegeneration	**Stage 2 : low degree of oedema**
	Circumferential halo[a]
	Elevation (nasal border)
	No major vessel obscuration
	Stage 3 : moderate degree of oedema
	Obscuration of ≥ 1 segment of major blood vessels leaving disc[a]
	Circumferential halo
	Elevation (all borders)
	Halo (irregular outer fringe with finger-like extensions)
Atrophic : pallid and flat disc	**Stage 4 : marked degree of oedema**
	Total obscuration on the disc of a segment of a major blood vessel on the disc[a]
	Elevation (whole nerve head, including the cup)
	Border obscuration (complete)
	Halo (complete)
	Stage 5 : severe degree of oedema
	Obscuration of all vessels on the disc and leaving the disc[a]

*Note that the modified Frisén scale does not include secondary optic atrophy.
[a]Key feature (major findings) for each grade.

active IIH participating in an interventional trial requiring iterative measures of intracranial pressure.[32]

Other acute anterior optic neuropathies

Anterior optic neuropathies acutely present with optic disc oedema in addition to various degrees of visual loss. When occurring secondary to inflammation, the term 'papillitis' is sometimes used.

Bilateral disc oedema, with or without vision loss, can be a manifestation of severe hypertensive retinopathy caused by malignant hypertension (≥180 mmHg systolic blood pressure or ≥110 mmHg diastolic pressure). Because it can mimic papilloedema, it is important to always measure blood pressure in all patients who present with bilateral disc oedema.[5]

In acute anterior ischaemic optic neuropathies (AION) optic disc oedema is by definition always present on fundus examination. Sectoral disc oedema strongly suggests NAION, whereas pallid, more diffuse oedema indicating optic disc infarction raises suspicion for an arteritic mechanism.[4] Interestingly, some patients with or without AION in one eye may present with an asymptomatic sectoral disc oedema in the other eye, reflecting so-called 'incipient' NAION, considered a form of very early NAION.[33,34] This can also be seen in diabetic patients (so-called 'diabetic papillitis' or more accurately, 'papillopathy', as the mechanism is probably microvasculopathic, akin to incipient NAION, rather than inflammation).[35] Thus, ischaemic insults to the optic nerve head may present along a continuum: on one end, massive ischaemia such as arises from arteritic mechanisms causing optic nerve head infarction with profound vision loss; on the other end, mild oedema from asymptomatic incipient NAION or diabetic papillopathy.

The diagnostic distinction between AION and anterior optic neuritis (with disc oedema) can be difficult despite the classic age difference,[36,37] In 'idiopathic' optic neuritis or the optic neuritis associated with multiple sclerosis, disc oedema is only present in one-third of patients and is usually mild, without peripapillary haemorrhages. However, the recently identified optic neuritis associated with myelin-oligodendrocyte glycoprotein (MOG) antibodies, representing about 5% of all optic neuritis in a population-based study,[38] is frequently associated with prominent optic disc oedema and peripapillary haemorrhages.[39] A retrospective study of 45 eyes from 25 patients eventually diagnosed with MOG-optic neuritis found that four eyes (8%) received an initial diagnosis of NAION,[40] thus highlighting the potential diagnostic confusion between the two entities when based solely on acute clinical presentation and presence of optic disc oedema.[41] Magnetic resonance imaging of the orbits with contrast and fat suppression techniques should help in these cases, since at least 90% of acute optic neuritis cases, including those secondary to MOG antibodies, will have optic nerve enhancement, while no enhancement is the rule in cases of NAION.[9] The presence of optic nerve enhancement usually indicates breakdown of the blood-brain barrier within the optic nerve, such as seen in active inflammation or infiltrative processes.[9]

Metabolic optic neuropathies, such as from thiamine deficiency, and toxic optic neuropathies such as from methanol or tacrolimus, will have a suggestive patient history and usually manifest with bilateral mild optic disc oedema at the time of diagnosis in acute stages, although unilateral involvement has been reported. Although the clinical course is more insidious than NAION, metabolic and toxic optic neuropathies with disc oedema are often accompanied by peripapillary haemorrhages that can sometimes be confused with NAION, especially those associated with amiodarone.[42–44]

Part 2 : differentiating optic disc oedema from pseudo-optic disc oedema

It is important to distinguish pseudo-optic disc oedema from the true optic disc oedema of papilloedema and other acute anterior optic neuropathies. Pseudo-optic disc oedema is a general term used to describe anomalous appearing optic nerves, usually with elevated disc margins, typically resulting from congenital configurations, peripapillary hyperreflective ovoid mass-like structures (PHOMS), or optic disc drusen (ODD), all of which can easily be mistaken for mild optic disc oedema, but do not usually require further workup as detailed below.[45]

Congenitally small optic discs

Small optic discs with a small scleral canal such as in hyperopic eyes can be mistaken as swollen, because of physiological thickening of the prelaminar nerve fibre layer that makes the optic disc appear hyperaemic and elevated, especially nasally. When optic discs are small because of pathological congenital axonal deficiency, such as in optic nerve hypoplasia, the discs do not appear elevated, but the disc margins can seem blurred because the lamina cribrosa appears yellowish beneath the abnormal overlying retina, around the actual pathologically small optic disc.[46]

Tilted optic discs

Tilted optic discs are normal developmental variants caused by an excessively oblique angle between the anterior optic nerve and the globe. They are usually bilateral and seen most often in myopic patients. The disc appears oval because its superotemporal portion is elevated and the inferonasal portion is posteriorly displaced and bears chorioretinal degenerative changes. The superotemporal elevation can be mistaken for disc oedema. Patients are usually asymptomatic.[47]

Myelinated nerve fibres

Myelinated nerve fibres result from ectopic myelination of the nerve fibres anterior to the lamina cribrosa into the retina. The appearance is very characteristic, ranging from obvious and impressive white opacities within the nerve fibre layer that radiate from the optic disc, engulfing vessels from beneath, to mild peripapillary whitening that can be confused with optic disc oedema. In all cases, the borders appear feathery and follow the nerve fibre layer anatomy. Fundus examination is usually sufficient for diagnosis.[48] However, small patches of myelinated nerve fibres might occasionally be mistaken for cotton wool spots. In this case, OCT on this region can show thickened nerve fibre layer and inner plexiform hyper-reflectivity and rule out focal inner layer thinning from ischaemia.[49]

Optic disc drusen

ODD are usually bilateral, bright yellow hyaline bodies that lie on and/or beneath the surface of the optic disc, conferring an elevated disc appearance on funduscopy, present in around 2% of the general population.[50] They are most often asymptomatic, although visual field defects, NAION and peripapillary choroidal neovascularisation may occur. The diagnosis is easy when they are superficial but can be challenging when ODD are buried, in which case they are often mistaken for mild disc oedema. Occasionally, ODD and papilloedema can coexist.[51,52] Classically, ODD appear as round autofluorescent structures on the optic disc, deep hyper-echogenic masses within the optic nerve head on B-mode ultrasound, and may stain in early phases of FA, but these modalities are sensitive only when the ODD are superficial and calcified. EDI-OCT of the optic nerve head is very useful for the diagnosis of ODD, which appear as round hypo-reflective structures with hyper-reflective anterior margins located anterior to the lamina cribrosa and below Bruch's membrane (Table 2).[45]

Peripapillary hyperreflective ovoid mass-like structures (PHOMS)

It has recently been suggested that the blurred margin aspect of some cases of pseudo-disc oedema may be conferred by PHOMS. These structures are visible most clearly on EDI-OCT and are composed of herniated nerve fibres bulging into the peripapillary region because of axonal distension and crowding.[53] They are non-specific findings as they often accompany optic disc oedema, ODD, and anomalous discs, such as seen in myopia and tilted discs.[54]

Part 3 : ocular fundus imaging for optic disc oedema

Multimodal ocular fundus imaging has allowed for better characterisation and quantification of optic disc oedema and has provided some insight about pathophysiological mechanisms (Table 2). Widespread implementation of non-invasive and cost-effective ocular imaging has allowed for routine integration of multimodality imaging into the clinical evaluations of patients with suspected disc oedema.[9]

Ocular fundus photography

Colour ocular fundus photography is a simple, inexpensive, and widely available tool that allows for detailed evaluation of the optic disc and the posterior pole and documentation for further comparison in both adults and children.[55,56] Photographs are routinely used to monitor patients with papilloedema and various causes of optic neuropathies. Depending on the camera, they can be obtained without pharmacological dilation of the pupils and can be stored and easily transmitted electronically for remote interpretation if necessary. Widefield fundus cameras are not ideal for imaging of optic disc oedema, which is better evaluated on 30–45 degrees ocular fundus photographs.[9]

Retinal fluorescein angiography

Fluorescein angiography (FA) is an invasive ancillary examination technique that explores the retinal and choroidal vasculature and usually involves intravenous injection of fluorescein dye. Oral ingestion of fluorescein dye can be performed in children or in patients with poor intravenous access, in which case only late phases are usually reliably assessed.[57] The vascularisation of the prelaminar portion of the optic disc arises primarily from the posterior ciliary arteries that also supply the peripapillary choroid.[4] This circulation fills quickly in the very early phases of FA, resulting in a mild physiological disc hyper-fluorescence, or disc staining.[58] Although FA is rarely necessary in patients with disc oedema, it may be useful in differentiating true mild papilloedema from pseudo-optic disc oedema, by showing the late leakage manifested only by truly swollen nerves.[25] ODD may show early staining, but there is usually no dye leakage in the absence of true disc oedema.[51] Similarly, there is no leakage on FA in Leber's hereditary optic neuropathy, which often presents with elevated and congested optic nerve heads acutely.[25,59]

In patients with disc oedema suggesting acute AION, FA may also be used to look for associated early diffuse choroidal hypoperfusion, which may suggest an arteritic mechanism such as from giant cell arteritis.[4,60] FA is also often used when the disc oedema is thought to be related to chorioretinitis, retinal vasculitis or posterior uveitis, in conjunction with OCT and fundus autofluorescence imaging that can reveal active lesions and chronic damage in the outer retinal layers.[61]

Optical coherence tomography of the optic nerve head

OCT provides objective measurements of the thickness of the peripapillary retinal nerve fibre layer (pRNFL), which is a very reliable and reproducible way to monitor mild-to-moderate optic disc swelling regardless of the aetiology.[30,62–64] It must be remembered, however, that measures of pRNFL thickness will reflect both thickening due to swelling and thinning due to atrophy. Therefore, pRNFL measurements should not be used in isolation to follow patients with papilloedema, as normalisation of the pRNFL thickness may be falsely reassuring in a patient developing secondary optic atrophy.[9] In papilloedema, pRNFL thickness correlates with Frisén grades,[64] and provides an objective way to monitor disc oedema.[9] However, layer segmentation may not reliable for high grades of swelling.[30,64] Tomographic slices of the optic disc, also called 'cube OCT', allow for quantification of the optic nerve head volume and the central thickness of the optic nerve head, both of which have been shown to correlate with intracranial pressure.[32] Cube OCT allows for more precise appreciation of the anatomical structure of the optic nerve head, helps diagnose ODD and PHOMS,[65] and can rule out optic disc masses, such as inflammatory granulomas or astrocytic hamartomas, which can be mistaken for optic disc oedema on funduscopy.[66,67]

Optical coherence tomography of the macula

Macular OCT with segmentation of the macular ganglion cell and inner plexiform layers (mGCIPL) is useful to detect and monitor the loss of retinal ganglion cells over time and should be systematically obtained with pRNFL OCT when evaluating and following patients with optic disc oedema. The loss of mGCIPL is visible more rapidly than the loss of pRNFL in all optic neuropathies.[3] Unlike pRNFL, macular OCT is usually not affected by the severity of optic disc oedema, although

segmentation of mGCIPL is often unreliable when papilloedema is severe. mGCIPL is very useful to detect early retinal ganglion cell loss prior to the development of visible optic atrophy on funduscopic examination.[62,64] Although some studies have suggested that the severity, speed, and pattern of mGCIPL loss could help differentiate among the different aetiologies of optic neuropathies,[68,69] the presence of mGCIPL loss in optic disc oedema can only point to a subacute onset of at least 3–4 weeks or to previous episodes of optic neuropathy. In promptly treated papilloedema with resolution of disc oedema, ganglion cell loss should remain minimal.[70] Macular OCT can also detect alteration of the outer macular layers in patients with optic disc oedema and inflammatory outer retinal and choroidal diseases.[71–73]

Optical coherence tomography angiography of the optic nerve head

The more recently developed OCTA is a non-invasive modality that infers the presence of retinal and choroidal blood vessels from detection of motion contrast of blood flow, combined with the retinal segmentation capabilities of OCT.[74] Compared with FA, OCTA allows visualisation of optic disc vasculature in optic disc oedema (which is often obscured by dye leakage on FA), is more sensitive in visualising radial peripapillary capillaries that run along the nerve fibre layer, has superior axial resolution allowing segmentation of superficial and deep plexuses, and is suitable for vasculature quantification. In papilloedema, the peripapillary capillary network density decreases as Frisén grade and pRNFL thickness increase.[75,76] In AION, OCTA shows reduction of the peripapillary flow density and vascular flow density in the peripapillary choroid in NAION[77] as well as sectorial peripapillary capillary network reduction surrounded by tortuous capillaries and telangiectasia.[78] One study showed loss of the peripapillary capillary network radiating pattern within 10 days of NAION onset, often with peripapillary non-perfused areas, which was not the case in inflammatory/infectious optic neuropathy and papilloedema.[79] Another study showed that when compared with controls, NAION eyes had the lowest vessel density, followed by optic neuritis, then papilloedema.[80] However, limited numbers of patients and several limitations across OCTA studies make these results difficult to apply in clinical practice.[81]

Part 4 : improving diagnostic yield in non-ophthalmology settings using ocular fundus photography

Non-mydriatic fundus photography with table-top or handheld devices can readily be performed by ED personnel and other non-eyecare practitioners, such as neurologists.[82,83] Failure to accurately perform an ocular fundus examination can have severe consequences on visual, neurological, and general health prognosis.[84] For example, in the ED and outpatient neurology clinics, an ophthalmologist is not always available, and most providers lack the skills to perform examination of the ocular fundus with ease.[10] Widespread implementation of non-mydriatic ocular fundus cameras is changing the way most providers examine the ocular fundus and several studies have highlighted the preferred use of fundus photography over funduscopy to teach medical students how to examine the ocular fundus.[85,86]

The prospective Fundus photography versus Ophthalmology Trial Outcomes in the Emergency Department (FOTO-ED) studies compared direct ophthalmoscopy with non-mydriatic fundus photography in an ED in the United States.[13,87,88] The three phases of the FOTO-ED study confirmed that most ED providers rarely use the ophthalmoscope, and, when they do, they usually fail to correctly identify relevant ocular funduscopic findings. The FOTO-ED study showed that non-mydriatic fundus photography is an effective alternate way of providing access to the ocular fundus in the ED. A total of 1,291 patients with headaches, focal neurological deficits, acute visual changes, or diastolic blood pressures ≥ 120 mmHg, (symptoms and signs generally accepted as warranting ocular fundus examination) were included in the three phases of the FOTO-ED study, among whom 12% had relevant findings (including disc oedema) on fundus photographs that altered the ED management of these patients. The ED providers were not able to identify any of the relevant findings in phase I (when they did not have access to the

photographs but could perform ophthalmoscopy if they wished), but they recognised 36.7% of the relevant findings when given access to fundus photographs in phases II and III. Importantly, they also correctly identified 87% of normal optic nerves, which was believed to be very helpful, particularly in patients with headaches in whom papilloedema could be easily and reliably excluded. Similar results were subsequently shown in Australian EDs[89] and in an outpatient neurology clinic.[85] Despite these results, this readily available technology remains largely underused and relatively few EDs and neurological clinics have acquired the equipment necessary to obtain routine ocular fundus photographs. This may be explained by the low confidence of non-ophthalmology trained health-care providers in interpreting ocular fundus photographs without the help of an eyecare provider; additional contributing constraints likely include technical issues regarding uploading of the images to electronic medical records, administrative difficulties regarding billing for the photographs and their interpretation, the cost of implementation and maintenance, and fear of legal repercussions in cases of misinterpretation. Lack of awareness of the potential value of funduscopic findings for diagnostic assistance likely also plays an important role. Some of these issues could be solved by remote interpretation of ocular fundus photographs by an eyecare provider, or by the use of AI for immediate interpretation of the ocular fundus findings.

Tele-neuro-ophthalmology

Non-mydriatic fundus photographs can be easily transmitted to an eye care provider for expert review.[88] This can be done remotely and in real-time in e-consultations. The COVID-19 pandemic has catalysed remote interpretation of fundus photographs. In a 2021 survey among 135 neuro-ophthalmologists mainly in the US, while visual fields and OCTs were the leading tests being interpreted in the pre-COVID era (28.3% and 28.0% respectively, versus only 17.5% for fundus photography), the percentage of providers who remotely interpreted fundus photographs more than doubled in this interval of time (36.7% versus 17.5%).[90] Remote interpretation of fundus photographs can even be implemented through existing networks such as tele-stroke facilities.[91,92] However, remote interpretation of fundus photographs via telemedicine can be difficult and requires additional clinical information from the ocular examination.[93–95]

Automated detection of optic disc oedema on fundus photographs with artificial intelligence/deep learning systems

Early efforts to automatically detect papilloedema from ocular fundus photographs date to the early 2010s.[96–98] The emergence of deep learning systems (DLS) in ophthalmology has enabled computers to automatically learn image features from large colour fundus photograph datasets with robust ground truths and predict such extracted features on subsequent datasets.[99] Over the past decade, photograph-based DLS have been used for the autonomous screening of diabetic retinopathy and glaucomatous optic neuropathy. It is likely that similar tools implemented in non-mydriatic fundus cameras could assist non-eye care providers in instantly interpreting whether an optic nerve is swollen or not and circumvent delayed neuro-ophthalmologists' interpretation from in-person or tele-consultations.[100] A small study conducted in a single centre showed that machine learning classifiers could distinguish papilloedema from normal discs and other causes of optic disc oedema with accuracies ranging from 95.9 to 98.7%.[101] In the large international collaborative study from the BONSAI consortium, a DLS was successfully trained to classify 14,341 fundus photographs as 'normal', 'papilloedema', or 'other optic disc abnormalities', with 96% sensitivity and 85% specificity.[102] A subsequent study showed that the diagnostic performance of the validated DLS was faster and as good as that of two expert neuro-ophthalmologists.[103] Additionally, the BONSAI DLS proved capable of discriminating mild to moderate (Frisén 1 to 3) from severe (Frisén 4 or 5) papilloedema with a sensitivity of 91.8% and a specificity of 82.6%. The algorithm sensitivity was comparable to that of three independent neuro-ophthalmologists (91.8%).[104] Another smaller study on 944 colour fundus photographs from one centre validated a DLS capable of distinguishing abnormal

from normal optic discs across a wide range of optic anomalies, with a sensitivity of 94% and specificity of 96%. Interestingly, when tested on fundus photographs taken by smartphone cameras, this algorithm achieved a sensitivity of 100% and a specificity of 50%, suggesting a possible application as a readily available screening tool.[105]

Currently, DLSs capable of distinguishing papilloedema from ODD and normal optic discs on ocular fundus photographs and on OCT are being developed, emphasising the potential for such applications in the future.[106] Ongoing studies are validating these DLSs on non-mydriatic fundus photographs, on photographs obtained with handheld cameras and in the paediatric population. Attempts at automatic diagnosis of various subtypes of optic neuropathies are underway. The implementation of a DLS capable of recognising papilloedema and other optic neuropathies in ocular fundus cameras will be of great help as diagnostic aids to screen patients with headaches or vision loss in EDs and neurology and paediatric practices.

Conclusion

Prolonged severe optic disc swelling results in permanent and irreversible ganglion cell damage, adding to the underlying primary ischaemic, inflammatory, toxic/metabolic, or compressive insult to optic nerve fibres and resulting in deterioration of vision. Despite our evolving understanding of the pathophysiology of optic disc oedema from different mechanisms, accurate diagnostic criteria and classification scales of optic disc oedema still require refinement. There remains significant overlap among underlying mechanisms and current diagnostic criteria are non-specific and insufficient to precisely identify the underlying cause of the oedema. The development of multimodal ocular fundus imaging has enabled better appreciation of the structural anatomy of the optic disc and quantification of swelling on a continuous scale, thus allowing for more reliable follow up. Despite these advances, many aetiologies remain indistinguishable, especially in the acute stages.

Non-eye care providers, especially those in acute care settings, must be able to appreciate optic disc oedema and its systemic and neurological associations. The barriers of ophthalmoscopy with accurate interpretation of ocular fundus findings could be overcome by readily available non-mydriatic ocular fundus cameras providing high-quality fundus photographs that can be interpreted in real-time by teleophthalmology or DLS algorithms. Indeed, the development of DLS capable of detecting and grading optic disc oedema and differentiating papilloedema from other anterior optic neuropathies and pseudo-optic disc oedema has proven powerful in large studies. Because such emergent methods require robust reference standards (i.e., 'ground truths'), more refined diagnostic criteria for optic disc oedema from various aetiologies will be needed. Future directions include the implementation of these systems in real-world settings and with non-mydriatic cameras, both table-top and handheld. The goal is not to replace the ophthalmological consultation, but as a diagnostic aid in the patient's immediate assessment of the presence of disc oedema and its cause.

Search strategy and selection criteria

We identified references for this review through searches of our own files, and through PubMed for publications in English between January 1, 1977 and December 1, 2022. The general search terms "optic disc oedema", "papilloedema", "fundus photography", and "machine learning" were combined with more specific search terms related to optic disc oedema, including "OCT" and "angiography". References from identified papers were included if they were scientifically relevant to the topic. The final reference list was generated based on relevance to the purpose of this review.

Disclosure statement

WB declares no competing interest. VB is consultant for GenSight Biologics and Neuro-phoenix, and receives research support from GenSight Biologics and Santhera/Chiesi. NJN is consultant for GenSight Biologics, Santhera/Chiesi, Stoke, and Neurophoenix; receives research support from GenSight Biologics and Santhera/

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WB designed the manuscript, prepared the first draft, figures and tables.
VB and NJN designed the manuscript, contributed to the discussion, critically edited thereview, and approved its final version.

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