REVIEW

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Updates on ophthalmic imaging features of optic disc drusen, papilledema, and optic disc edema

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Purpose of review
Optic nerve head elevation can be associated with vision loss. This review provides an update regarding key features of optic disc drusen (ODD) compared with papilledema from increased intracranial pressure and optic disc edema from other causes.

Recent findings
Clinical history and funduscopic examination are not sufficient to correctly diagnose different causes of optic nerve head elevation. Multimodal ophthalmic imaging is noninvasive and should be used as first-line diagnostic testing to distinguish optic disc edema or papilledema from pseudoedema. Advanced ophthalmic imaging, including enhanced depth imaging optical coherence tomography (EDI-OCT) and autofluorescence imaging, can visualize ODD at high resolution and determine whether there is optic disc edema. OCT angiography does not require contrast and can rapidly visualize papillary, peripapillary, and macular microvasculature and identify important vascular biomarker of ischemia and, potentially, visual prognosis.

Summary
Multimodal ophthalmic imaging can help in the diagnosis of ODD and optic disc edema and identify patients at high risk of vision loss and neurological issues in order to ensure appropriate diagnosis and treatment.

Keywords
anterior ischemic optic neuropathy, multimodal imaging, optic disc drusen, optical coherence tomography, papilledema

INTRODUCTION

Optic nerve head elevation is an important physical examination finding in the evaluation of patients with visual disturbances or vision loss. It may be associated with optic disc edema or not (pseudoedema). Common causes of optic nerve head elevation because of optic disc edema include elevated intracranial pressure (papilledema), optic neuritis (papillitis), diabetic or hypertensive papillitis, anterior ischemic optic neuropathy (AION), neuroretinitis, uveitis, compression, or infiltration [1–3]. Excellent reviews on different causes of optic disc edema have been published elsewhere [1,4,5].

An important cause of optic disc pseudoedema is optic disc drusen (ODD), which are acellular, extracellular concentric mucoprotein deposits that are often calcified and found in the unmyelinated optic nerve [6–8,9▪]. An apparent fullness of the optic disc may also be because of congenitally anomalous optic disc. These structural changes of the optic disc are not neurological emergencies and do not require extensive and sometimes invasive testing, in contrast to optic disc edema or papilledema. However, careful ophthalmic assessment is important as these patients are at risk of vision loss.

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KEY POINTS

- In most cases of optic nerve head elevation, clinical history, and ophthalmoscopic examination of the optic nerve may be not sufficient to make the correct diagnosis. Multimodal ophthalmic imaging, especially EDI-OCT, can help distinguish optic disc edema from pseudoedema.
- Optic nerve head elevation because of ODD is a common cause of pseudoedema and is not a neurological emergency. However, these patients are at risk of vision loss, such as young-onset anterior ischemic optic neuropathy (ODD-AION).
- Optical coherence tomography angiography, which does not require contrast, can detect microvascular changes in papillary, peripapillary, and macular regions. Vascular compromise can occur in severe ODD, papilledema, and optic disc edema, leading to secondary anterior ischemic optic neuropathy and irreversible vision loss.

Multimodal imaging provides information beyond the physical examination and can help narrow down differential diagnosis.

This review aims to: describe key characteristics of ODD, compare clinical characteristics and key ophthalmic imaging features of ODD, papilledema, and optic disc edema, and provide an update regarding ODD and patients with concurrent ODD and optic disc edema. Evaluation and recognition of key features of ODD and different causes of optic disc edema will ensure that patients receive appropriate diagnostic workup and treatment.

OPTIC DISC DRUSEN AS A COMPRESSIVE OPTIC NEUROPATHY

ODD are present in 0.3–2.0% of general population [10–12]. ODD may be found incidentally in patients with no visual symptoms as part of a routine ophthalmic examination, or during workup for headache and optic nerve head elevation. ODD are by far most common in Caucasians [12]. They are typically idiopathic but can occur in families with an autosomal dominant inheritance pattern. In addition, ODD can occur in the setting of systemic or ocular genetic syndromes (Table 1) [12–17].

Although the cause is unknown, ODD formation may be related to axonopathy or abnormal axonal transport in congenitally crowded optic discs, leading to axonal rupture and release of abnormal mitochondria that serve as a nidus for drusen formation [6–8]. ODD is more common in congenital optic nerve dysplasia or genetically determined small scleral canal [18]. ODD is typically present at birth or early childhood and increases in size and number over the adolescence and move from deep to superficial with increasing age [17]. Over time, enlarged ODD can compress and compromise neighboring axons and blood supply, leading to visual field loss.

Table 1. Clinical characteristics of optic disc drusen, papilledema, and optic disc edema

Features	Optic disc drusen	Papilledema	Optic disc edema
Visual symptoms	May have none Associated with transient visual obscuration May have peripheral visual field constriction or decreased visual acuity in severe cases Associated with sudden vision loss with vascular complications	May have none early Associated with transient visual obscuration, diplopia May have peripheral visual field constriction or decreased visual acuity in severe cases Associated with sudden vision loss with vascular complications	Depends on etiology Optic neuritis associated with severe vision loss, dyschromatopsia AION may have dense inferior, superior, or central vision loss Visual disturbance may vary with eye movement in severe edema
Visual field defect	May be normal Most common: enlarged blind spot, nasal step, altitudinal visual field loss, constricted visual field	May be normal Most common: enlarged blind spot, nasal step, altitudinal visual field loss, constricted visual field	Depends on etiology. May have central scotoma or altitudinal visual field defect. Often abnormal in optic neuritis and AION. Sometimes normal
Other neurological symptoms or syndrome	None in idiopathic ODD Rarely, ODD is associated with conditions, such as retinitis pigmentosa, Joubert syndrome, Alagille syndromes, DiGeorge syndrome, and pseudoxanthoma elasticum	Commonly associated with pulsatile tinnitus, dizziness, nausea/vomiting, cranial neuropathies Can be due to idiopathic intracranial hypertension, brain tumor, hemorrhage, meningoencephalitis, venous thrombosis, and trauma	Optic neuritis may be associated with multiple sclerosis or other neurological issues

AION, anterior ischemic optic neuropathy; ODD, optic disc drusen.

DISC EDEMA OR PSEUDOEDEMA?

Clinical history and fundoscopic examination cannot reliably distinguish disc edema from pseudoedema

In most cases of optic nerve head elevation, clinical history and optic nerve examination are not sufficient to make the correct diagnosis. There are many overlapping clinical characteristics, and patients can present with normal vision or relatively nonspecific visual disturbances (Table 1). Patients with ODD or papilledema commonly have normal central vision, whereas those with optic disc edema because of optic neuritis or AION typically have symptomatic vision loss.

On funduscopic examination, most causes of optic nerve head elevation look similar – the optic disc is full and elevated, and there is blurred disc margin and small cup-to-disc (C/D) ratio (Table 2). There may be venous congestion and dilation, peripapillary arteriolar irregularity or narrowing, and signs of ischemia. These are important signs of vascular compromise that should heighten awareness for risk of sudden vision loss.

Typical appearance of optic disc drusen on color fundus photography and fluorescein angiography

Eyes with ODD have a lumpy-bumpy, raised appearance with blurred disc margins, and visible ODD may appear strikingly optically refractile during ophthalmoscopy (Fig. 1) (Table 2). Buried ODD are not visible on ophthalmoscopy but may mimic papilledema, especially in pediatric bilateral cases (Frisén grades 1 or 2). On fluorescein angiography, ODD have early or late nodular staining of the disc and late circumferential peripapillary staining without any early or late leakage [19].

Typical appearance of papilledema and optic disc edema on color fundus photography and fluorescein angiography

Optic disc in papilledema typically exhibits hyperemia, dilated and tortuous veins, and splinter hemorrhages in acute cases, or smooth, champagne cork-like elevation in chronic cases. Different causes of optic disc edema may look slightly different [1]. Severe papilledema and optic disc edema may be associated with narrowed or

Table 2. Optic disc appearance and imaging features of optic disc drusen, papilledema, and optic disc edema

Features	Optic disc drusen	Papilledema	Optic disc edema
Optic nerve head appearance	Full, raised optic disc with irregular, lumpy bumpy appearance, blurred disc margin. ODD may be highly refractile. C/D ratio: absent to very small. Color: yellow to slightly pale Vascular: venous dilatation, papillary/peripapillary arteriolar irregularity or narrowing, typically no hemorrhage SVP: typically present Typically bilateral Do not have exudate, cotton wool spots, Paton's lines, retinal and choroidal folds.	Full, raised optic disc with blurred disc margin. Acute papilledema is more raised, chronic, more diffuse. C/D ratio: absent to very small. Color: normal or hyperaemic. Vascular: venous dilatation, papillary/peripapillary arteriolar narrowing or obscuration. May have splinter hemorrhages. SVP: subtle or absent. Typically bilateral May have exudate, cotton wool spots, Paton's lines, retinal and choroidal folds.	Full, raised optic disc with blurred disc margin. Variable depending on condition. C/D ratio: absent to very small. Color: normal or hyperemic, pale in arteritic AION. Vascular: venous dilatation, papillary/peripapillary arteriolar narrowing or obscuration. May have splinter hemorrhages. SVP: typically present Unilateral or bilateral May have exudate, cotton wool spots, Paton's lines, retinal and choroidal folds.
Multimodal ophthalmic imaging	Autofluorescence: bright FA: early, late nodular staining, late circumferential staining, no optic disc leakage unless has superimposed disc edema OCT B-scan: irregularly raised optic disc contour. ODD has hyporeflective core with bright anterior edge. hyperreflective horizontal lines. Typically V-shaped or flat RPE/BM layer. PHOMS: common *En face* NIR: gray to white pearl-like structures on the disc. PHOMS appear as hyperreflective ring or cresent around the disc. RNFL: not typically thickened, maybe thinned. B ultrasonography: presence of hyperechogenic focus at low gain in calcified ODD.	Autofluorescence: dark. FA: prominent disc leakage OCT B-scan: raised optic disc contour. Peripapillary edema and exudate. Inverted U-shape or flat RPE/BM layer. PHOMS: may be present *En face* NIR: Optic disc appears as a dark zone or a hyperreflective ring depending on the severity of disc elevation. May have Paton's lines, retinal or choroidal folds. RNFL: thickened in acute papilledema. B ultrasonography: optic disc elevation and increased optic nerve sheath diameter.	Autofluorescence: dark FA: prominent disc leakage OCT B-scan: raised optic disc contour. May have peripapillary edema and exudate. Typically V-shaped or flat RPE/BM layer in papillitis and AION, and inverted U-shaped in optic nerve sheath meningioma. PHOMS: may be present *En face* NIR: Optic disc appears as a dark zone or a hyperreflective ring depending on the severity of disc elevation. May have Paton's lines, retinal or choroidal folds RNFL: thickened in acute optic disc edema. B ultrasonography: May exhibit optic disc elevation.
Orbit CT/MRI	Typically normal on MRI ODD may be bright on CT.	Flatten posterior globe, increased optic nerve sheath diameter, optic nerve tortuosity.	Enhancement of optic nerve or optic nerve sheath.

AION, anterior ischemic optic neuropathy; C/D: cup-to-disc ratio; CT, computed tomography; FA, fluorescein angiography; MRI: magnetic resonance imaging, NIR: near infrared reflectance, OCT, optical coherence tomography; ODD, optic disc drusen; PHOMS, peripapillary hyperreflective ovoid mass-like structures; RNFL: retinal nerve fiber layer, RPE/BM: retinal pigment epithelium/Bruch's membrane, SVP, spontaneous venous pulsation.

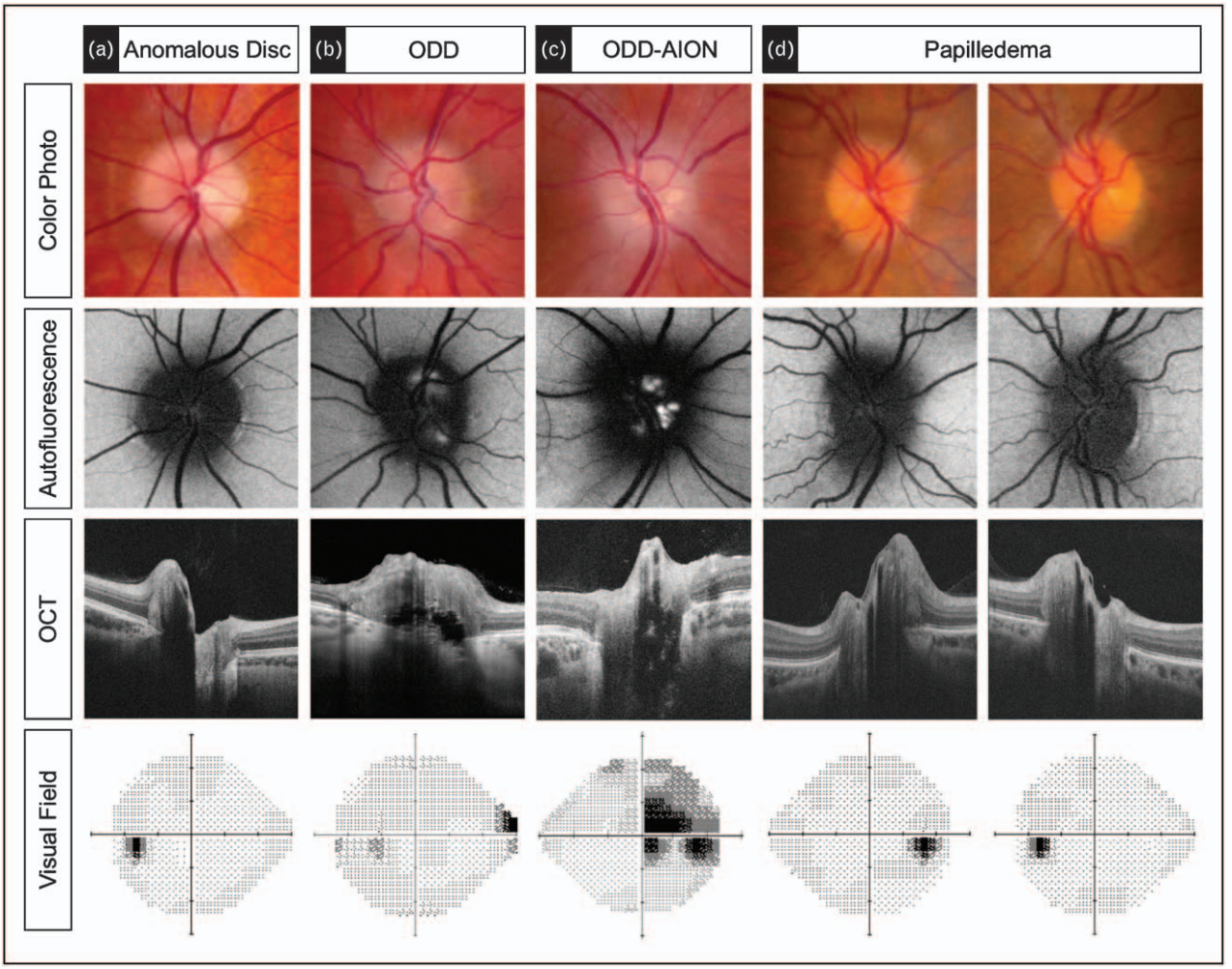

FIGURE 1. Multimodal ophthalmic imaging and static perimetry in five eyes with pseudoedema or papilledema, including color fundus imaging, optical coherence tomography, and fundus autofluorescence imaging. (a) Anomalous optic disc (left eye) of a patient with myopia and normal visual field. Color fundus imaging shows nasal optic disc is elevated with blurred margin, and there is no disc hyperautofluorescence or visual field defect. Optical coherence tomography (OCT) shows peripapillary hyperreflective ovoid mass-like structures (PHOMS) and a V-shaped retinal pigmental epithelium/Bruch's membrane (RPE/BM) layer. (b) ODD (left eye) with diffuse blurring of the disc margin and no visible superficial drusen. On autofluorescence imaging, there are slightly bright clusters of ODD. On OCT, there is prominent elevation of the optic nerve head on OCT. OCT shows ODD have signal poor core with anterior hyperreflective margin, and horizontal hyperreflective lines. There is a V-shaped RPE/BM layer and minimal visual field loss (c) ODD (right eye) with nonarteritic anterior ischemic optic neuropathy (ODD-AION). Same patient as (b). On color imaging, there is diffusely blurring of the disc margin involving the entire peripapillary area because of optic disc edema superimposed on ODD. ODD look like yellowish refractile deposits on the disc, which look like bright clusters on AF imaging. OCT shows characteristic findings of ODD and a V-shaped RPE/BM layer. Static perimetry revealed superior visual field defect involving central vision because of ODD-AION. (d) Right > left papilledema (right eye is shown on the left) showing blurred nasal disc margin, no hyperautofluorescence, inverted U-shaped RPE/BM layer in both eyes, and no visual field loss. AF, autofluorescence; AION, anterior ischemic optic neuropathy; OCT, optical coherence tomography; ODD, optic disc drusen; ODD-AION, ODD-associated AION; PHOMS, peripapillary hyperreflective ovoid mass-like structures; RPE/BM, retinal pigment epithelium/Bruch's membrane.

obscured papillary arterioles (optic disc ischemia), cotton wool spots (nerve fiber layer ischemia), exudates, Paton's lines, and retinal and choroidal folds [20]. Spontaneous venous pulsation may be subtle or absent in papilledema but visible in at least one eye in optic disc edema. On fluorescein angiography, papilledema is associated with normal perfusion, excess vascularity, and early as well as late staining of the optic disc [21,22]. Nonischemic optic disc edema is also associated with normal perfusion of the optic disc, whereas most cases of optic disc edema from AION have significantly delayed filling of the optic disc [23].

OPTICAL COHERENCE TOMOGRAPHY IMAGING OF OPTIC NERVE HEAD ELEVATION

The role of ophthalmic imaging is to provide high resolution imaging of the eye that is not readily available on fundoscopic examination [24]. Figure 1 shows examples of common causes of optic nerve head elevation, including anomalous optic disc, ODD, non-arteritic AION in ODD (ODD-AION), and papilledema (Fig. 1). On color fundus imaging, they all show blurring of disc margins, whereas optical coherence tomography (OCT) shows clear differences among them. OCT imaging of anomalous optic disc shows elevation of optic nerve head because of peripapillary hyperreflective ovoid mass-like structures (PHOMS) (Fig. 1a), and OCT imaging of ODD shows elevation because of multiple masses with signal poor core and anterior hyperreflective margin typical of ODD (Fig. 1b). In ODD-AION and papilledema, optic nerve head swelling is because of thickening of the retinal nerve fiber layer and edema (Fig. 1c and d).

Enhanced-depth imaging optical coherence tomography as gold standard for diagnosis of optic disc drusen

Since its introduction in the 1990s, OCT has allowed easy visualization of optic nerve head and quantification of various parameters, such as optic disc volume, subretinal fluid, thickness of the retinal nerve fiber layer, ganglion cell complex, and posterior pole structures [5,24,25]. On spectral-domain OCT, enhanced-depth imaging OCT (EDI-OCT) was initially described for imaging the choroidal circulation [26]. In 2018, the Optic Disc Drusen Studies (ODDS) Consortium recommended EDI-OCT as the new gold standard for the diagnosis of ODD [27▪▪]. On EDI-OCT, ODD look like deposits of variable sizes located in the anterior optic nerve, and they are often associated with PHOMS and horizontal hyperreflective lines [18]. PHOMS can be seen in 74% of eyes with ODD [27▪▪], which are localized peripapillary dysmorphic retinal ganglion cell axons but not drusen [9▪]. PHOMS can also exist in congenital anomalous discs (Fig. 1), high myopic eyes with tilted discs, and papilledema [28]. EDI-OCT can quantify drusen volume and anatomic location, although this is relatively time consuming and requires some training. Larger ODD volume was demonstrated to be associated with worse visual field [29]. ODD are associated with decreased retinal nerve fiber layer thickness in corresponding sectors [30]. A study including 47 eyes with ODD used three-dimensional reconstruction software assessed ODD volume using EDI-OCT scans and shows that ODD volume is correlated with retinal nerve fiber layer thickness and static perimetry mean deviation [31]. Another study uses three-dimensional swept-source OCT to quantify ODD volume and show that ODD ranges from 0.24 to 1.05 mm^3, and volume is correlated with visual field loss [32].

Peripapillary retinal pigment epithelium and Bruch's membrane shapes

On OCT, different causes of optic nerve head elevation have different peripapillary retinal pigment epithelium (RPE) shape at the Bruch's membrane opening. The RPE/ Bruch's membrane (BM) layer in papilledema has an inverted U shape that turns toward the vitreous [33] (Fig. 1d). This altered RPE/BM shape turning toward the vitreous is thought to be the result of altered translaminar pressure, with relatively higher intracranial pressure relative to the intraocular pressure. In contrast, in normal controls and in patients with ODD or optic disc edema other than papilledema, the RPE/BM layer is either flat or has a V-shape pointed away from vitreous [33,34] (Fig. 1b and c).

Eye movement induced mechanical distortion of the peripapillary retina

Eye movement induces mechanical distortion, shearing, and strains on the peripapillary tissue, and this may be differentially impacted by optic nerve head pathology. A study of 45 eyes with papilledema, 15 eyes with AION, and 20 controls shows that adduction leads to a relative posterior displacement of the RPE/BM layers temporal to the optic disc and a relative anterior displacement of the RPE/BM layers nasal to the disc, which reverses with abduction [35]. This seesaw-like distortion with horizontal eye movement was more prominent in papilledema than normal and AION eyes [35] and causes peripapillary choroidal folds [36]. Another study from the same group shows that this seesaw-like distortion because of horizontal eye movement is also present in eyes with ODD and induces significant shearing deformations of the peripapillary retina and intrapapillary tissues [37]. The clinical importance of gaze-induced optic disc deformations is unknown but repetitive motion may be a factor in the genesis or progression of optic neuropathies.

EN FACE OPHTHALMIC IMAGING OF OPTIC DISC DRUSEN AND PAPILLEDEMA

Autofluorescence imaging of optic disc drusen

En face ophthalmic imaging is readily available at point-of-care locations. Fundus autofluorescence imaging uses blue or green filter sets to detect

ODD [38▪,39]. Autofluorescence imaging is noninvasive (no contrast used), easy to interpret, and quick to obtain. The optic disc is normally dark on autofluorescence imaging (Fig. 1a and d), whereas ODD appear bright or hyperautofluorescent (Fig. 1b and c). Autofluorescence imaging can most easily identify visible ODD, which displays focal autofluorescence with irregular edges in 93–100% of eyes [19,40] (Fig. 1b and c). For buried ODD, the sensitivity varies from 12 to 92% depending on the location of the drusen [19,40,41]. Larger drusen volume and more superficial anatomic location significantly affected the sensitivity of autofluorescence imaging [42]. Using a novel confocal scanning device, which enables acquisition without pharmacologic pupillary dilation, the location of hyperautofluorescence in ODD was found to be associated with thinning of the RNFL and visual field defects [38▪].

Sometimes, multimodal imaging instrument is built as part of OCT devices and capable of scanning with three wavelengths of light simultaneously: 488 nm (blue), 536 nm (green), and 786 nm [near infrared reflectance (NIR)] [43]. It can also be used to distinguish papilledema and optic disc edema from pseudoedema. In papilledema, there is consistently a green shift and an elevated green ring [43]. This ring is also hyperreflective on the blue and green images and surrounded a central shadow, which is seen best on near infrared reflectance (NIR) [43]. In optic disc edema, the optic disc has a greenish hyperreflectance that extends beyond the optic disc margins with irregular blurry margins and obscured disc vasculature, whereas pseudoedema has a greenish hyperreflectance with clear and distinct margins and well delineated disc vasculature [44].

Vascular imaging of optic disc drusen using optical coherence tomography angiography

Retinal vasculature is often affected in optic nerve head swelling. Historically, fluorescein angiography is the most commonly used method, although it requires an intravenous fluorescein injection which carries risk of adverse reaction. Optical coherence tomography angiography (OCTA) is an emerging vascular imaging technique that does not require contrast. OCTA images vessels based on flow characteristics and can different layers of retinal vasculature can be segmented individually. Comparison of fluorescein angiography and OCTA revealed that OCTA was superior in imaging the radial peripapillary and deep capillary networks [45]. Image averaging can improve noisy OCTA data [46] and detailed vascular measurements are possible, including vessel area density, vessel skeleton density, vessel diameter index, vessel perimeter index, and vessel complexity index [47].

OCTA studies have found that focal peripapillary microvascular attenuation corresponds to ODD [48,49] and that large ODD volume is associated with lower peripapillary superficial capillary plexus vessel density [50]. Several studies show that in general, ODD are associated with significantly reduced peripapillary vessel density, and that this reduction correlates with the OCT retinal nerve fiber layer or ganglion cell complex thickness [51,52] and visual field defect [53]. Yan *et al.* performed hierarchical clustering of 5 key OCT and OCTA parameters in ODD patients with different severities of visual field loss and found that *increased* macular vessel diameter and flow were associated with mild visual field defect [54▪]. In contrast, decreased peripapillary vessel density, retinal nerve fiber layer, and ganglion cell complex thickness were associated with moderate to severe visual field loss, suggesting that a combination of OCTA and OCT changes may serve as early and late biomarkers in patients with ODD [54▪].

OPTIC DISC DRUSEN WITH CONCURRENT OPTIC DISC EDEMA

Optic disc drusen with superimposed optic disc edema

A minority of patients with ODD may have concurrent optic disc edema. In a study of 102 patients with ODD (mean 37 years, range 8–90 years), 11% was found to have coexistent optic disc edema because of papilledema (46%), nonarteritic AION (30%), or uveitis (7%) [36]. Although thickening of the retinal nerve fiber layer analysis on OCT is a common finding in papilledema, this measurement alone does not adequately identify those with ODD and concurrent optic disc edema. In contrast, the presence of retinal and choroidal folds in *en face* imaging may be more specific for optic disc edema in ODD [36].

Optic disc drusen with anterior ischemic optic neuropathy

Eyes with ODD are at risk for acute visual loss because of vascular compromise and ischemia. An example of AION in the setting of ODD (ODD-AION) is shown in Fig. 1c. On color imaging, there is prominent optic disc edema that spreads into the peripapillary area, and on autofluorescence imaging, the optic disc border is much enlarged and indistinct because of optic disc edema and displacement of the normally bright lipofuscin-containing RPE (Fig. 1c).

AION is the most common ischemic complication in young patients with bilateral and buried ODD [55,56,57▪▪,58], and ODD eyes are also at risk for retinal artery or vein occlusion and choroidal neovascularization. Nonarteritic AION is the most common acute optic neuropathy in patients older than 50 years old, with incidence of 2.3–10.2 cases per 100,000 persons 50 years of age or older [59,60]. In studies of young onset nonarteritic AION (range 15–50 years), slightly more than 50% of patients had ODD-AION compared with 2% in general population [58,61▪▪]. Comparison of patients with ODD-AION and nonarteritic AION (similar age) reveals that significantly more ODD-AION patients have no vascular risk factors, consistent with ODD as an independent risk factor for AION [57▪▪,61▪▪].

CONCLUSION

The diagnosis of patients with optic nerve head elevation should focus on a combination of history, neuro-ophthalmic examination, and multimodal ophthalmic imaging. This careful approach can help distinguish ODD, papilledema, and optic disc edema of various types and avoid unnecessary brain MRI and invasive lumbar puncture procedure in those without optic disc edema. Patients with ODD may have concurrent optic disc edema from papilledema or AION, so clinical suspicion and multimodal ophthalmic imaging are critical to correctly identify these patients who are at high risk of vision loss. In the future, more studies are needed to validate imaging biomarkers of optic nerve head elevation and identify features that are not just diagnostic but also prognostic of visual outcome.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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