REVIEW

Optic Nerve Head Drusen: An Update

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ABSTRACT

Optic nerve head drusen are benign acellular calcium concretions that usually form early in life, just anterior to the lamina cribrosa. Improving imaging using optical coherence tomography suggests they are common and may be present in many clinically normal discs. These drusen may change in appearance in early life, but are generally stable in adulthood, and may be associated with visual field defects, anterior ischaemic optic neuropathy, or rarer complications. Based on long-term clinical data and optical coherence tomography, we propose a refined hypothesis as to the cause of optic disc drusen. Here we summarise recent findings and suggest future studies to better understand the forces involved.

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Introduction

Originally described histologically by Müller,¹ optic nerve head drusen (ONHD) derive their name from an old German word for geodes which are rock cavities lined with crystals. These acellular concretions in the optic nerve head change little over lifetimes and are seldom symptomatic. Now modern imaging and long-term clinical observation are breathing life into this most geological of eye conditions, redefining their diagnosis and challenging theories of pathogenesis. Here we review the current developments in ONHD, refine the hypotheses of aetiology, and suggest a prospective trial to understand them better.

Clinical findings

The great preponderance of ONHD are asymptomatic, detected incidentally on eye examination, and thus many cases can be expected to be undiagnosed. When drusen are visible in the superficial layers of the optic disc, they are usually a straightforward clinical diagnosis, but when buried deeper in the disc they frequently give the optic disc an elevated or swollen-looking appearance and can be a difficult to differentiate from optic disc oedema.

Around 60% of discs with drusen have visible ONHD on clinical examination.² Visible ONHD are usually refractile, pale, rounded, and vary between tiny foci and large lobulated clusters occupying sectors of the nerve head (Figure 1). Buried ONHD have a much more variable appearance, ranging from a near normal optic disc to an elevated swollen appearance (mimicking true disc oedema). Visible and buried ONHD are thought to represent the same pathology, and in both types they are more commonly in the nasal part of the disc.^{3–5}

In differentiating buried ONHD from disc oedema, several clinical features are recognised. Symptoms such as headache or visual disturbance are uncommon in ONHD. The disc may be elevated with indistinct margins, but the nerve fibre layer is not thickened and opacified with obscuration of retinal vessels (as in disc oedema). The disc may have a lumpy appearance (localised elevations), and the apparent swelling does not extend out onto the retina, which may create a smooth reflective line of concavity around the disc (Figure 1). On the other hand, microvascular abnormalities such as disc hyperaemia, haemorrhages, telangiectasia, or exudates all indicate true disc oedema. Aside from disc oedema, rarer differentials for buried ONHD include optic nerve

Figure 1. Visible optic nerve head drusen. This 25-year-old woman had infantile strabismus with multiple operations and amblyopia management in childhood. At age 19 she was investigated for a grand mal seizure and a benign left-sided cerebellopontine epidermoid tumour was diagnosed on MRI. Optic nerve head drusen were noted incidentally but she never had hydrocephalus or papilloedema. There were no visual symptoms, and findings were stable. (a) colour photo; (b) autofluorescence; (c) EDI OCT at section shown by green arrow; (d) ultrasound; (e) OCT peripapillary RNFL thickness classification; (f) 24-2 Humphrey visual field greyscale. Note thinning of the nerve fibre layer corresponds to visual field loss.

meningioma, glioma, or astrocytic hamartoma.^{6,7} As disc oedema due to systemic or idiopathic causes can coexist with ONHD, diagnostic uncertainty is not uncommon, particularly in children. This has the potential for both overinvestigation and underinvestigation.^{8–12}

Unusual branching patterns of the major retinal vessels such as trifurcations, tortuosity, and cilioretinal vessels are common in eyes with ONHD and the eyes of relatives.^{3,5,7,13} Objective and quantitative analysis of fundus photographs found that eyes with ONHD had larger arteriolar and venous calibre in the peripapillary retina even compared to eyes with disc oedema.¹⁴ The study used automated analysis of peripapillary retinal vessels, so they may have not detected differences in vessels on the disc surface. They found that veins branched closer to the optic disc and then ran longer without secondary branches, but vascular trifurcations were not increased.¹⁴ These variations in major retinal vascular patterns suggest that in many

cases the drusen, or the underlying origin of drusen, are present during foetal development when retinal vessels emerge from the disc.

Pathology

Histological reports of ONHD^{1,15,16} preceded the first clinical descriptions,¹⁷ and several substantial histological studies have followed.^{18–20} Consistent findings support the contention that most buried or visible ONHD represent the same pathology. With thinner histological sections and more dense sampling of the optic disc, there are more drusen and smaller drusen detected. At most, serial 1–2 μm sections found up to 50 ONHD per eye, between 5 and 1000 μm in diameter, with larger drusen appearing as clusters and concretions of smaller drusen.¹⁹ They are found in the prelaminar optic nerve head, and smaller drusen may tend to be located deeper at the anterior face of lamina cribrosa. When drusen are associated with retinopathy,

they may be simultaneously found in the peripapillary retina.^{21,22}

Using classical Alizarin red or von Kossa stains, drusen consistently demonstrate calcium content.²³ They also stain for glycoprotein and mucopolysaccharides, and for smaller amino and nucleic acids.²⁴ Iron or haemosiderin are inconsistent findings at the edges of drusen that may represent haemorrhage around ONHD.^{20,25} Electron-dispersive spectroscopy confirms calcium phosphate as the predominant mineral salt.²⁶

At a small scale, drusen are acellular, non-capsulated, with concentric laminations.²⁰ The surrounding optic nerve tissue shows variable and localised atrophy, sometimes with overlying neuroretinal gliosis.^{19,23} A common finding are round neurodegenerative structures in the deep peripapillary retina, sometimes described as corpora amylacea or alternatively as cytooid bodies.²⁰ However, the typical description of cytooid bodies are axon swellings in the retinal nerve fibre layer (RNFL), representing arrested axoplasmic flow, and these are on a much smaller scale and unrelated to these deep or subretinal retinal cellular degenerations.^{27,28}

We could find only one report of a drusen-affected optic nerve head that has been subjected to transmission electron microscopy.¹⁹ Needle-shaped electron dense deposits typical of calcium were observed in mitochondria within axons, as well as dilated or ruptured axons with mitochondria present in the interstitium. These extracellular mitochondria had increasing levels of calcification until they degenerated and coalesced into larger calcified bodies. These concretions were surrounded by a matrix of glial cells and filamentous material.¹⁹

Diagnosis of ONHD in the population

The clinical prevalence of ONHD has been consistently estimated at 0.3–0.5% in adults and in children.^{18,24,29–33} The similar prevalence between children and adults indicates that drusen do not develop or change greatly after the first decade of life (see more in visual function, below). However with histological analysis, the autopsy prevalence is up to seven times higher at 2%.^{18,20} Presumably

this difference relates to asymptomatic, small, buried, or misdiagnosed ONHD.

The prevalence of ONHD depends very much on their definition and method of detection. Visible ONHD require no confirmatory testing, but buried drusen often require diagnostic testing and an expanding array of tests have changed the definition and epidemiology of ONHD.

Ultrasonography

Ultrasonography (US) has generally been considered a highly sensitive imaging tool to demonstrate buried ONHD. A highly echogenic focus at the optic disc that persist at low gain can confirm both visible and buried drusen (Figures 1d and 2d), understood to represent calcification.^{34–37} Newer high-resolution 20 MHz ultrasound probes may increase sensitivity to ONHD detection.³⁸ However, false positives are possible and operator experience is important.^{3,34,39} Ultrasound in children may have particular challenges and variation in measurements, and, because true disc oedema can coexist with ONHD in a minority, some patients may yet require further investigation in the presence of echogenic drusen.^{40,41} Ultrasound provides little information about the nerve, besides the existence of ONHD.⁴²

Computed tomography and magnetic resonance imaging

Computed tomography (CT) will show calcified ONHD (as well as other intracranial pathology); however, the usual 1.5 mm slices can reduce sensitivity.³⁴ This reduced sensitivity, inability to detect any non-calcified ONHD, and radiation exposure limit the utility of CT. Magnetic resonance imaging (MRI) is now indispensable in cases of disc oedema but has no ability to detect ONHD.³⁴

Fluorescein angiography

Before US was widely available, fluorescein angiography (FA) was important to distinguish buried ONHD from true disc oedema, but differentiation remained challenging in subtle indeterminate cases or when disc ischaemia is present.²⁴ In one important series, 62 patients with ONHD underwent FA, although only 40 were confirmed with ultrasound,

Figure 2. Buried optic nerve head drusen. This 12-year-old girl had headaches and saw an optometrist who noted asymmetric optic disc elevation. Optic nerve head drusen were confirmed with autofluorescence, OCT and ultrasound. (a) Infrared fundus image; (b) autofluorescence; (c) EDI OCT at section shown by green arrow; (d) ultrasound; (e) OCT peripapillary RNFL thickness classification; (f) 24-2 Humphrey visual field greyscale.

11 with CT scanning.³⁶ Most visible ONHD showed pre-injection autofluorescence, and early nodular staining without leakage. Buried ONHD showed pre-injection autofluorescence in only 12% and early nodular staining in 25%, but late circumferential peripapillary staining was common (80%) and none showed leakage. When true disc swelling coexisted with ONHD, late leakage as well as late nodular staining was present. However, these FA findings can yet be subjective and have not been sufficiently specific or sensitive for widespread use in the era of ultrasound.

In a small recent study, FA was found to be the superior imaging study to differentiate children with papilloedema from pseudo-papilloedema.⁴³ However, there were methodological limitations, and amongst those eyes with suspected buried ONHD, ONHD were confirmed by other imaging in only 30% of cases. It may be that there is a category of pseudo-swollen optic discs who do not have verifiable drusen, but whom do not demonstrate leakage on FA. Fluorescein angiogram criteria to differentiate ONHD and true disc swelling have not been published.³⁶

Optic disc autofluorescence

Fundus autofluorescence uses the same blue excitation filter and green imaging filter as FA, but now autofluorescence imaging is commonly obtained with scanning laser ophthalmoscopy to enhance sensitivity. Visible ONHD will produce bright hyperfluorescent foci in the disc (Figure 1c), understood to be the calcium salts^{44,45} or mitochondrial porphyrins.⁴⁶ With conventional fluorescence photography, bright excitation flashes can identify nearly all visible drusen and many buried drusen.^{34,47} Amongst the buried ONHD the sensitivity of autofluorescence appeared to be approximately half the sensitivity of ultrasound,³⁴ and the sensitivity of autofluorescence presumably relates directly to the thickness of overlying neural tissue (Figures 1 and 2).⁴⁸

Optical coherence tomography

Optical coherence tomography (OCT) has revolutionised ophthalmic diagnosis, and the technology continues to improve in speed, resolution, and penetration of the deep structures. Time-domain OCT has been superseded by spectral-domain (SD-

OCT) and many platforms are offering enhanced depth imaging (EDI) to increase signal from deeper structures. In recent years, swept source (SS-OCT) lasers have offered even greater speeds of scanning to reduce motion artefact and generally longer wavelengths to increase tissue penetration. It appears that SS-OCT and SD-OCT with EDI give similar findings in the deep optic nerve head.^{42,46,49}

A recent publication by a consortium of ONHD experts provides helpful clarity on the diagnosis of ONHD by OCT.⁵⁰ Initial reports of OCT had indicated that ONHD were hyper-reflective bulges in the subretinal space adjacent to the disc margin,^{51–53} which did not correlate well with histological findings.²³ The consortium agrees that these hyper-reflective subretinal bulges are not ONHD and can occur in papilloedema (Figure 3).⁵⁰ Others have described a hyper-reflective cap over a hyporeflective core.^{54,55} With EDI and SS-OCT there are now a collection of clear descriptions of ONHD as irregular or spheroidal hyporeflective structures (indicating a uniform internal structure), with hyper-reflective foci or borders or bands in the surface of the

ONHD.^{42,46,48,49,56–58} The ONHD volume can now be quantified this way.⁵⁹ Similar hyper-reflective bands without a hyporeflective core were believed to indicate small drusen, although this has not been proven with corroborating data.^{49,50}

In 34 adults with visible or suspected of ONHD, Merchant and colleagues found that visible ONHD were always detected by OCT or US investigations, but suspected ONHD were negative on all testing in one-third.⁴⁹ Of the two-thirds of suspected ONHD that were confirmed to have buried drusen by US or OCT, they found that EDI detected 100%, non-EDI OCT detected 82%, and US detected 41%.⁴⁹ Those ONHD that were not confirmed by US were the smaller type without a hyporeflective core. Additionally, amongst clinically normal fellow eyes, 3 of 11 showed these small ONHD on EDI-OCT (one positive also on US or non-EDI OCT).⁴⁹ In a subsequent study of 130 people with normal eyes, ONHD with typical hyper-reflective bands and hyporeflective core were present in 2.3% of subjects (confirmed by US) but another 12.3% of subjects had hyper-reflective bands with no

Figure 3. Papilloedema from idiopathic intracranial hypertension. This 46-year-old man had no symptoms or background medical history. He was noted to have swollen discs by his optometrist. Autofluorescence, ultrasound, computed tomography, and OCT failed to demonstrate drusen. Magnetic resonance imaging and venogram were normal. Lumbar puncture was normal aside from opening pressure of 34 cm H₂O. (a) Colour photo; (b) autofluorescence; (c) EDI OCT at section shown by green arrow; (d) ultrasound; (e) OCT peripapillary RNFL thickness classification; (f) 24-2 matrix visual field total deviation plot.

hyporeflective core (also negative on US).⁵⁶ Hyper-reflective bands >45 µm long were repeatable, genuine findings, not merely artefacts or noise. These authors proposed that these hyper-reflective bands are small subclinical ONHD and proposed a higher prevalence of ONHD (16%).⁵⁶ A representative cohort of Danish 11–12-year children were examined by EDI-OCT and a prevalence of 1.0% was reported (1.8% if the hyper-reflective bands were included as ONHD).³³

A recent study by Traber and colleagues described three types of ONHD on OCT: (1) the ‘subretinal’ peripapillary hyper-reflective bulges described on early OCT reports, (2) hyper-reflective bands (‘granular’ ONHD), and (3) larger ‘confluent’ ONHD with a hyporeflective core.² In this cohort, half of those with buried drusen and no visual field defect were diagnosed based only on the presence of these subretinal lesions, so misclassification may limit some of their conclusions.⁶⁰

The SD-OCT can help to differentiate buried ONHD from optic disc oedema, although the descriptions of how the two can be differentiated have varied.^{42,52,61–64} In disc oedema there is often subretinal fluid around the disc as well as thickening of the nerve fibre layer, and in cases of papilloedema there is close correlation between the peripapillary RNFL thickness, and total retinal thickness around the disc, and clinical papilloedema grading.⁶⁵ In early OCT, this retinal thickening created an artefact known as the subretinal hyporeflective space (SHYPS, which is now better understood as a proxy measure of total retinal thickness), which were both greater in true disc oedema than ONHD.^{53,61} However, the RNFL thickness is most widely used to differentiate ONHD from disc oedema.^{53,64} In children with ONHD there was a higher rate of plotting errors when SD-OCT devices attempted to measure RNFL (41%).⁶⁶ The nasal sector of the disc appears to have greatest sensitivity and specificity, with disc oedema having a thicker RNFL here than ONHD.^{51,53,62–64,67} In the mildest cases of disc oedema, there may be no distinguishable difference in RNFL compared to ONHD.⁵² Note that increased RNFL is not a marker of swelling in every case of papilloedema (Figure 3e).

In summary, these studies with OCT help to reconcile the variable measures of prevalence. We can summarise that around 0.4% of people have

clinically evident ONHD (visible or buried), but around 2% have subtle buried drusen detectable by US, OCT, or standard histology, and up to 16% may have OCT findings indicative of very small ONHD that are not evident on US.^{49,56} In a similar way, the ability to detect subclinical ONHD increases the proportion with bilateral ONHD, with recent studies showing 73–90% of ONHD are bilateral.^{4,5,39,66}

Visual function and prognosis

Visual morbidity from ONHD is usually mild, but visual field defects are common and can be expected to deteriorate to some extent over time.⁶⁸ Visual acuity and colour vision are usually normal throughout life, although rare cases of blindness or severe field loss due to ONHD are reported.^{69,70} Many of these cases with severe vision loss are presumed to be complicated by an ischaemic optic neuropathy (see complications below).

Visual field defects are much more common than visual symptoms. In children there are challenges in visual field testing, but 14–51% of children with ONHD have defects on automated testing.^{29,66} Field defects are more severe with visible ONHD and those with thinning of the peripapillary RNFL on OCT imaging.²⁹ Among adults, up to 87% have visual field abnormalities depending on selection criteria and field testing sensitivity, and those with visible drusen have more field defects.^{4,5,24,71} Arcuate field defects, enlarged blind spots, nasal steps, and constricted visual fields are the most common abnormalities at any age, indicating the damage to axons occurs in the optic nerve head.²⁹ In patients with buried ONHD, a smaller minority (5–25%) have visual field defects, rarely an inferior arcuate defect but more often enlargement of blind spot or peripheral constriction of the field.^{4,72,73}

With increasing age ONHD may become more visible, and visual field defects increase.^{4,74,75} A collection of well-documented cases with very long-term follow-up highlights the likelihood that progression occurs early in life.^{76,77} For example, a 5-year child with anomalous discs developed visible drusen and field defects by age 21 year,⁷⁸ and another 9-year girl showed significant changes over 3 years (although potentially misclassified as

drusen).⁷⁹ Another child showed increasing drusen and field loss from 8 to 16 years but then remained stable to the age of 31 years.⁸⁰ Following these early years of deterioration, a remarkable 56-year follow-up of eight young patients from the original observational work of Lorentzen indicated stability in adulthood (although the rate of deterioration exceeded normal age-related decline).^{76,77}

The rate of progression in adulthood is of great clinical interest but only limited data exist. Lee and Zimmerman reported the rate of visual field loss to be $1.58\% \pm 0.28\%$ each year based on manual perimetry. This result may only apply to those patients with progressive visual loss and otherwise normal eyes.⁶⁸

Electrophysiology

Investigators have used visual-evoked potentials to elucidate the nature of axonal damage at the optic disc, following the concept that increased latency is a sign of compressive optic neuropathy.⁸¹ Using a macular checkerboard, visual evoked potential (VEP) had increased latency in 41% of those with high rates of visual loss from ONHD,⁸² but a study of ONHD with mostly normal visual fields found no change in VEP.⁸³ Multifocal VEP (mfVEP) appeared to have improved sensitivity, with increased latency measurements⁸⁴ and reduced amplitude⁸⁵ in ONHD. As expected, the mfVEP amplitude was correlated with field defect and nerve fibre layer thickness on OCT. These findings have been taken to imply a compressive aetiology of axon damage in ONHD.

Structure–function relationships

A structure–function relationship is helpful for understanding both diagnosis and prognosis in other common optic neuropathies such as glaucoma, papilloedema, and compressive lesions.^{86,87}

It should come as no surprise that the widely used OCT RNFL scan has been shown to correlate with visual field loss and with the location of drusen nasally in the disc.^{2,29,46,47,88} There was association between ONHD volume, RNFL thinning, and visual field loss.^{89,90} This structure–function correlation is less clear with buried than visible drusen.^{47,88} Additional measures of macular

ganglion cell layer thickness have been sensitive to early damage in cases with buried ONHD, as in some cases of early glaucoma.^{74,91} These OCT measures represent loss of ganglion cells or axons and therefore they correlate well with permanent field loss.⁸⁷ The cause of this loss of axons cannot be differentiated from OCT alone.^{92,93} However, in ONHD as with compressive optic neuropathy or papilloedema there is poor correlation between structural measures of swelling or displacement and optic nerve function by electrophysiology or field loss. Scanning laser polarimetry can quantify the loss of functional axons and this also correlates to field loss in eyes with ONHD.⁹⁴

The extent of visual field defects was found to be proportional to blood flow velocity in the central retinal artery, using a Doppler ultrasound technique that is not widely validated or extensively used.⁹⁵ However this may simply be a secondary phenomenon reflecting inner retinal atrophy.

Association with ocular and systemic disease

Heritability and ethnicity

There appears to be a lower prevalence of ONHD in people with Chinese or African heritage than those who identify as Caucasian or white.^{96–99} This may be associated with optic disc diameter, which is smaller in whites than many other racial groups.¹⁰⁰ An increased prevalence among primary family members also supports a genetic contribution to pathogenesis.^{13,18,24}

Glaucoma

Glaucoma and ONHD have been reported to occur together, though clearly less than would be expected from two common optic neuropathies.^{92,101–106} This is probably because glaucoma is diagnosed from the characteristic appearance of the optic disc (cupping, which is excavation of the neuroretinal rim) and the presence of ONHD thus confuses the diagnosis of glaucoma. More often, glaucoma is diagnosed in ONHD from the presence of raised intraocular pressure (IOP) and progressive loss of nerve fibres and field loss.^{92,102} Many authors comment on the uncertainty of diagnosing glaucoma in the presence of ONHD as each may cause the same

pattern of visual loss.^{93,101,103,104} Grippo and colleagues collected 13 cases of ONHD with raised IOP, and compared them to 47 people with ONHD and normal IOP.⁷¹ In this cross-sectional study, the presence of a raised IOP was associated with both visual field loss and with the presence of more visible drusen, and both the extent of visible drusen and IOP were found to be independent predictors of field defects.⁷¹ IOP-induced loss of the nerve fibre layer would be expected to make existing drusen more prominent. In at least one reported case, controlling the IOP to the normal range was associated with stable findings.¹⁰⁵ A recent report found no association between IOP and field defect or nerve fibre thickness in patients with ONHD at presentation.¹⁰⁷

An emerging model of glaucoma pathogenesis is that a posterior translaminar pressure gradient generates mechanical strain in the lamina cribrosa that is detected by astrocytes, which become activated and toxic to the adjacent axons passing through, leading to axon degeneration.¹⁰⁸ The only established treatment for glaucoma aims to address the translaminar pressure gradient. The interaction of ONHD with the remodelling and strain patterns of the lamina, or with the behaviour of astrocytes are not known.

Papilloedema

Like glaucoma, the similar progressive mid-peripheral visual field loss in papilloedema is thought to be due to the effects of an abnormal translaminar pressure gradient, but in the opposite, anterior direction. There have been a large number of cases of ONHD associated with intracranial tumours, pseudotumour cerebri, or idiopathic intracranial hypertension (IIH), particularly in children.^{8–10,24,30,36,72,97,109–115} In one cohort of 216 patients with ONHD, 7 (3.2%) also had a diagnosis of IIH.³⁶ Recently, a large cohort of children with IIH was reported to have a high prevalence of 48% with ONHD detected by EDI-OCT but these were largely misdiagnosed drusen based on subretinal hyper-reflective bulges and only a minority were confirmed with ultrasound.¹¹⁶ Reviewing 372 patients with ONHD or resolved papilloedema from IIH, others found 19% of resolved papilloedema eyes

to have ONHD but this was also based on outdated OCT definitions and uncertain diagnostic criteria.¹¹⁷ Acquired ONHD is not widely recognised as a common outcome after papilloedema. It may simply be that neurological patients with headaches have their optic discs examined closely, and that ONHD may be detected more often in this broad group.

Retinitis pigmentosa

Patients with retinitis pigmentosa (RP) have ONHD at higher than the usual prevalence, and patients with ONHD have a higher prevalence of RP, as well as several reported cases of rarer retinal dystrophies with ONHD.²⁴ In 262 patients with a clinical diagnosis of RP, 23 (9%) had ONHD evident on fundus photography (similar with autosomal and X-linked heritability).²¹ These drusen were histologically similar to other ONHD but more often in the parapapillary area with normal-sized discs.²⁴ Typical ONHD were also more common in Usher syndrome, particularly type 1 (35% with ONHD). The most common genetic cause of Usher type 1, myosin VIIA, is involved in intracellular transport.²²

Pseudoxanthoma elasticum and angioid streaks

There is a substantial association between angioid streaks and ONHD, as each condition is associated with a much higher prevalence of the other compared to the general population.^{24,118,119} This association is present both with and without pseudoxanthoma elasticum.¹²⁰ On the other hand, as a separate example, pseudoxanthoma elasticum skin changes were found present in 30% of patients with β -thalassaemia, of whom 7% had ONHD.¹²¹ The similarities in histology between Bruch's membrane (which is abnormally calcified and brittle in angioid streaks) and ONHD was recognised early and led to early hypotheses that ONHD were derived from RPE or Bruch's membrane.^{1,23} The underlying abnormal hyper-calcification of extracellular matrix in pseudoxanthoma elasticum is thought to lead to the calcification and enlargement of the nidus of drusen formation.²⁴

Rarer associations

Alagille syndrome is a hereditary dysplasia of arteries and hepatic ducts with numerous ocular associations including a strong association with ONHD.^{30,122} Many other reported associations between neurological conditions and ONHD are an artefact, caused by the fact that patients with neurological conditions have more optic disc examinations.²⁴ Numerous chance associations have been described, particularly (1) retinal findings such as dystrophies, myelination, benign hamartomata, and rare types of uveitis, and (2) neurological syndromes such as phacomatoses, syndromic retinal dystrophies, chromosomal disorders, and craniosynostoses.³⁰

Complications

Anterior ischaemic optic neuropathy

Patients with ONHD appear to be at increased risk of non-arteritic anterior ischaemic optic neuropathy (NAION), although the risk is hard to quantify in this small and varied population.^{24,123,124} Patients are typically younger and have more favourable outcomes than NAION patients without ONHD. Other risk factors for NAION and clinical features such as the risk of bilateral disease, and visual field defects are similar in those with or without ONHD.³

The presentation of NAION with ONHD is sudden painless vision loss, with worsening of optic nerve function and acute optic disc swelling corresponding to the visual loss, often with flame haemorrhages. The swelling may be unusual in appearance due to the presence of ONHD. The presence of ONHD (which can mimic disc oedema) should not distract from the investigation of a sudden-onset optic neuropathy even if the acute swelling is difficult to appreciate on fundoscopy, and modern imaging tools are less important in this context than the history and clinical signs optic nerve function. Management includes identification and management of other contributing causes such as vasculitis (giant cell arteritis) or uncontrolled hypertension or diabetes. Radial optic neurotomy remains a controversial management option, with a recent case of bilateral NAION and ONHD showing limited recovery in the operated eye.¹²⁵

Retinal vascular occlusions

Occlusions of central retinal vein or central retinal artery have both been reported in association with ONHD, sometimes at a young age. As with NAION, it is common for patients to have concomitant risk factors such as altitude,¹²⁶ hormonal contraceptives,¹²⁷ and hypertension.²⁴ In central retinal artery occlusion, ultrasound may be used to identify a calcific thrombus at the optic disc, and ONHD may confuse this investigation.³⁷

Choroidal neovascular membrane

Peripapillary choroidal neovascular membranes (CNV) have a prevalence as high as 25% in children with ONHD, although the presence of CNV was not associated with loss of field or nerve fibre layer.^{66,128} While most peripapillary CNV are benign, often asymptomatic, progression under the macula may result in loss of acuity. When vision is threatened treatment is warranted, and the modern anti-vascular endothelial growth factor (VEGF) medications, photodynamic therapy, and surgical removal have each shown success in this context.^{129–133}

Retinal haemorrhage

Haemorrhagic complications were found in 7% of patients with ONHD.¹³⁴ Patients with haemorrhagic complications had smaller disk diameters and were more often myopic. Subretinal haemorrhages were more common than intraretinal or vitreous haemorrhages, suggesting they usually arise from the ONHD or peripapillary CNV.^{128,134,135} Haemorrhages that are not due to CNV are quickly reabsorbed. Lee and colleagues hypothesised that ONHD in small discs and myopic eyes can create strain and lacquer cracks in Bruch's membrane, resulting in self-limiting leakage of blood from choriocapillaris.¹³⁴

Pathogenesis

Several characteristic observations should be explained by theories of ONHD pathogenesis.

Location and the translaminar pressure gradient

All ONHD are located anterior to the lamina cribrosa, and drusen are generally not present in the RNFL or posterior to lamina cribrosa. This implies that the translaminar pressure gradient is relevant to the formation of ONHD. Specifically, the location implies hold up of axoplasmic flow in the orthograde direction (i.e. leaving the eye, toward lateral geniculate nucleus).

Another similar important observation is that both papilloedema and ONHD tend to occur most at the nasal aspect of the disc, particularly when mild.^{2,18} Similar to glaucoma, both papilloedema and ONHD spare the temporal part of the optic disc and spare the central vision and colour vision unless severe or advanced.

These optic neuropathies are understood to arise from the unique feature of the optic nerve crossing a pressure gradient at the optic disc. Specifically the location of ONHD anterior to the lamina and in a geographic pattern resembling papilloedema implicates a translaminar pressure gradient pushing anteriorly in their origin.

Onset and life course

The underlying cause of ONHD occurs at the beginning of life, probably in embryogenesis, because of the association with retinal vessel branching. Drusen can also progress and become more visible in the first two or three decades but are then stable in most cases. This would indicate that the conditions supporting origin of ONHD are during the period of growth.

The translaminar pressure difference during prenatal and early life is not known, but in neonates and infants the ICP is understood to be low (from a limited data set)^{136,137} and may decrease in the transition from a 'weightless' intrauterine environment to the external world. The emergence of visual impairment and intracranial pressure syndrome in astronauts after prolonged weightlessness could support the concept that an antero-grade translaminar pressure gradient may be common in foetal life.^{138,139}

Calcium phosphate composition of drusen

Analyses of ONHD indicate they are largely calcium phosphate.²⁶ Electron microscopy of one case suggested abnormal calcification of intra-axonal mitochondria, with rupture of axons and release of calcified mitochondria into the interstitium where they are further calcified.¹⁹ This is further highlighted by the association with angioid streaks where extracellular proteins are abnormally calcified.²⁴ Early investigators also noted similarities between calcified acellular Bruch's membrane and ONHD, suggesting a common origin.^{1,23}

Mitochondria accumulate calcium in both physiology (normal mitochondria contain calcium at many times the cytoplasm and several times the extracellular concentration) and in disease (mitochondria act as calcium traps to take up excess calcium from cytoplasm, and excessively calcified mitochondria develop apatite crystals and become dysfunctional).^{140–143} Indeed normal cartilage calcification may involve crystallisation of calcium in the mitochondria, and exportation of crystals to the extracellular space as nuclei for further calcium apatite formation.

That is, the observed calcification of axonal mitochondria in ONHD is not atypical in other cell types undergoing ischaemia or toxicity or degeneration.¹⁴¹ Furthermore, the exportation of calcified mitochondria to the extracellular matrix or into glia may be physiological processes too. The electron micrography observations of Tso in 1981 may reflect what is now recognised as calcium phosphate nucleation.^{19,143,144} The intracellular and developmental signals that regulate these processes are not well known.

Small scleral canal

Small optic disc diameter has been associated with ONHD, and from this observation, a small scleral canal has been hypothesised to be a pathogenic factor.^{5,24} Likewise, racial differences in optic disc size were hypothesised to underlie racial differences in ONHD prevalence.^{96,98} It is not clear how a small canal diameter affects pressures and forces in the optic nerve head, although a small canal is associated with NAION and this mechanism is thought to be akin to a compartment syndrome.¹⁴⁵ It has been

proposed that optic nerve axons are relatively compressed in a small scleral canal, leading to failure of axoplasmic flow, axon degeneration, and collections of degenerate calcified mitochondria that form a nidus for ONHD.^{5,26,146,147}

In re-examining this theory using OCT and some methodological improvements, it was found that control subjects or unaffected eyes had the smallest disc areas, next smallest were unaffected relatives of those with ONHD, then eyes with buried ONHD, and visible ONHD had the largest disc areas.¹⁴⁶ It may be possible that the presence of drusen causes secondary enlargement of the canal, but it would be surprising if a small canal was important in the pathogenesis. In the recently hypothesised redefinition of small ONHD as hyper-reflective bands on EDI-OCT of clinically normal optic discs, it was found that eyes with these bands had a slightly smaller disc diameter but with highly overlapping distributions (no bands mean 1592 μm , range 1134–2182 μm ; with bands mean 1458 μm , range 1184–1805 μm).⁵⁶ In 11–12-year children, 92% of those with ONHD had a smaller scleral canal on EDI-OCT (below 25th percentile), and it was suggested that ONHD may arise in a small canal but then cause remodeling of the canal during growth into adulthood, as well as measurement artefacts.³³ Thus, some of the previously reported differences in optic disc size may relate to the relative appearance of discs with ONHD and the way in which ONHD have been clinically detected in the past.⁶²

Abnormal axonal metabolism

Abnormalities of axonal metabolism, or abnormalities of axonal transport, have been suggested as precursors of ONHD, but without hypotheses to explain why axoplasmic flow is impaired.^{2,19,23,24,46,148,149}

It is worth noting that metabolic optic neuropathies such as mitochondrial diseases, toxic or nutritional optic neuropathies, all affect the optic nerve in a different way to ONHD with bilateral loss of acuity, central scotoma, and loss of colour vision. That is, the temporal disc and papillomacular bundle are first affected in metabolic disorders and spared in ONHD, glaucoma, and papilloedema. In glaucoma the superior and inferior areas are thought to be vulnerable due to larger lamina

cribrosa pores (less mechanical support),¹⁰⁸ while in mitochondrial optic neuropathy the papillomacular bundle is thought to be vulnerable due to a high surface area to volume ratio of these finest axons.¹⁵⁰

Summary

In reconciling the location, timing, and clinical behaviour of ONHD with the electron micrographs from one specimen, it appears that ONHD arise from the excessive accumulation of highly calcified mitochondria in the optic nerve head. Like papilloedema, this process tends to occur most in the nasal part of the optic disc, just anterior to the lamina cribrosa, suggesting these calcified mitochondria are held up by a translaminal pressure gradient in early life. The detection of hyper-reflective bands on OCT in up to 16% of normal eyes suggests that this may be a common issue in development, frequently of little clinical significance.

Within a cell soma, mitochondria are understood to be an active syncytium, fusing and dividing in order to share energy, maintain quality control of metabolism and genomes, and to isolate irreparable mitochondria for destruction through mitophagy.^{151–153} Within an axon, mitochondria are transported in both directions so that they can be refreshed or destroyed in the soma, and to distribute healthy mitochondria along the axon where required.¹⁵⁴ Recently, a new transcellular mitophagy has been shown in the optic nerve head, by which astrocytes remove many of the degraded mitochondria from the axons of retinal ganglion cells.¹⁴⁴ This process may also be different in the myelinated portion of the optic nerve. Derangement of transcellular mitophagy could result in abnormal accumulation of degraded or calcified mitochondria in the prelaminar nerve.

Management

Therapy for ONHD can focus on complications or on progressive visual field loss.

Complications such as ischaemic optic neuropathy or retinal vein occlusion are treated as they would be without ONHD, with similar results. Likewise, choroidal neovascularisation is managed in the same way as other causes of choroidal

neovascularisation, with intravitreal injections of antibodies against VEGF, laser photocoagulation, photodynamic therapy, or subretinal excision.³⁰

Surgical excision of ONHD can have poor visual consequences.^{26,155} Radial optic neurotomy has been attempted with success, but few cases reported and no trials published.¹⁵⁶

When there is progressive field loss from ONHD, there have been attempts to alter the translaminar pressure gradient by reducing IOP with glaucoma treatment⁷¹ or by reducing the retro-laminar tissue pressure through optic nerve sheath fenestration.¹⁵⁷ There have not been trials or retrospective comparisons to evaluate these strategies, and these authors do not discuss the mechanism by which altering the translaminar gradient in either direction could be helpful or harmful.

Future directions

Much remains unknown about ONHD, including the crucial factors that relate to progressive visual loss in adulthood. As with glaucoma it has previously been time consuming and expensive to collect prospective data on a slowly progressive condition. Available data suggest that ONHD cause faster-than-normal loss of retinal ganglion cells through life, and fastest in early life. With highly repeatable OCT and clustering of visual fields, it was recently possible to examine the effect of latanoprost on glaucoma progression within 2 years.¹⁵⁸ It may be possible to conduct trials in ONHD using similar methods, such as a trial of IOP-lowering medication to identify the relevance of the translaminar gradient to ONHD progression. This design would have a greater chance of detecting a clinical effect if participants were at greater risk of progression, for example, younger participants.

Conclusions

Developments in imaging and long-term follow-up have improved our understanding of ONHD. We hypothesise that an anterior-pushing translaminar pressure gradient in early life contributes to the accumulation of mitochondria in the nerve head and that these stalled mitochondria accumulate calcium as they become degenerate. Uncertainty remains about the role of a

translaminar pressure gradient later in life, and it may be possible to study this with a clinical trial design.

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