Review Article

Advances in origin, evolution, and pathogenesis of optic disc drusen: A narrative review

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Optic disc drusen (ODD) is acellular calcified deposits found mainly in front of the lamina cribrosa within the optic nerve. It can cause chronic or acute vision loss. There has been progress in clinical diagnosis using ophthalmic multimodal imaging in recent years. We conducted a database search on PubMed and Google Scholar (April 2023) with no restrictions on publication year or language. We used the terms: ("optic disc drusen") OR ("optic nerve head drusen") OR ("drusen of optic nerve head"). Other terms included gene, mutation, scleral canal, axonal transport, calcinosis, mitochondria, blood vessel, vasculature, visual field, vision, and optical coherence tomography to identify publications. Etiologically, ODD may stem from congenital genetic defects, aberrant axoplasmic transport, anatomical abnormalities, and mechanical factors during ocular duction. Clinically, ODD is linked to progressive visual field defects and vascular complications. Detection of deeply buried ODD can be challenging, but advances in optical coherence tomography make early identification possible. Structural changes, including retinal nerve fiber layer thinning, can be monitored. Increasing reports indicate vascular complications, including anterior ischemic optic neuropathy, in ODD patients. Currently, ODD-related visual field defects are not effectively treated, and observation remains the primary management approach. Future pathological discoveries or the establishment of animal models may provide new evidence for revealing the pathogenesis of ODD.

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Optic disc drusen (ODD) is calcified deposits within the optic nerve anterior to the lamina cribrosa. They tend to accumulate in the supranasal sectors. Historically, ODD was first observed histologically by Müller in 1858.[1] Lauber first associated ODD with visual field impairment.[2] Sander managed to differentiate from papilledema using fluorescein angiography in 1967.[3] The advent of optical coherence tomography (OCT) improved detection and monitoring, with enhanced depth imaging (EDI-OCT) being especially effective.[4] ODD prevalence varies depending on the diagnostic method used, with higher rates observed using histopathology and EDI-OCT.[5] While the exact etiology remains unknown, theories suggest anatomic abnormalities, metabolic disturbances, and repetitive physical stress as possible factors. Pathogenesis likely involves disturbances in axoplasmic metabolism leading to calcium deposition,[6] often resulting in vascular complications.[7]

Method of literature search

We conducted a database search on PubMed and Google Scholar (April 2023) with no publication year or language restrictions. We used the terms: ("optic disc drusen") OR ("optic nerve head drusen") OR ("drusen of optic nerve head"). Other terms included gene, mutation, scleral canal, axonal transport, calcinosis, mitochondria, blood vessel, vasculature, visual field, vision, and OCT to identify publications. Exclusion criteria were animal studies, articles focusing on treatment, articles discussing other ocular disorders, correspondence, and editorials. Case reports were included only if they contributed novel information about the characteristics or diagnosis of the disease. We supplemented our findings by identifying additional articles listed in the bibliographies of the retrieved articles. While this review mainly refers to English literature, we considered non-English articles if the translated abstracts were sufficient.

Pathogenesis of ODD

Genetic predisposition

Early studies conducted on families and relatives were reported in a small series.[8] Lauber first proposed the possibility of a hereditary predisposition to ODD in two generations.[9] The hypothesis was further refined in ODD patients without other eye diseases.[10] In 1961 and 1966, Lorentzen found that 28 out of 909 relatives of ODD patients suffered from ODD.[11,12] Consequently, he described ODD as "an irregularly dominant hereditary affection". However, 665 relatives failed to carry out the examinations for various reasons. In 1999, Antcliff investigated seven probands with bilateral ODD using B-scan ultrasonography and color photography.[8] It turned out that

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one out of 27 relatives had buried ODD, estimated at 3.7%, higher than the average prevalence estimates in the studies.

Accordingly, researchers have attempted to find candidate genes for ODD [Table 1]. In 1997, Nischal reported a strong correlation between Alagille syndrome (AS) and ODD in young children under ultrasound evidence.[13] The findings showed that the prevalence of unilateral ODD and bilateral ODD in patients with AS was 90% and 65%, respectively. ODD was the most common ophthalmologic abnormality in infants with several types of cholestasis, including AS, with an incidence of 10.7%.[14] Gilbert attributed the causal genes for AS to JAGGED1 within 20p12 and NOTCH2 within 1p12 by disrupting the Notch signaling pathway.[15] Given the critical role of Notch signaling in cellular fate determination and its activity during development and in organ systems, it is hypothesized that ODD may be independently influenced by JAGGED1 and NOTCH2 genes. ODD has recently been identified as a complex ophthalmic syndrome linked to a mutation in the membrane-type frizzled-related protein (MFRP) gene. Studies suggested that MFRP might be involved with

Table 1: Lists of possible genes and syndromes associated with optic disc drusen and related clinical presentations

Associated Genes and Syndromes	Clinical findings	
	Ophthalmologic	Non-ophthalmologic
ABCC6[21-22]	Angioid streaks, optic disc drusen (ODD)	Pseudoxanthoma elasticum
ALMS1 in Alström syndrome[24-25]	Cone-rod dystrophy, optic atrophy, ODD, optic disc pallor, attenuation of retinal vessels, macular pigmentary changes, retinal pigment epithelium atrophy without bone spicules, retinal telangiectasias with exudative retinopathy	Cardiomyopathy, sensorineural hearing loss, obesity, type 2 diabetes mellitus, pulmonary, hepatic, and renal dysfunction with multi-organ fibrosis
Chromosome 22q11.2 duplication syndrome[30]	Megalocornea, congenital cataract, astigmatism, nystagmus, ODD, strabismus, delayed visual maturation	/
Chromosome 22q11.2 microdeletion[31]	Cataract, ODD	Dysmorphic facial features, palate anomalies, heart disease, developmental delay, immune deficiency, hypocalcemia associated with hypoparathyroidism
CRB1[19,36]	Retinitis pigmentosa (RP), cone-rod dystrophy, foveal retinoschisis, Leber congenital amaurosis, isolated macular dystrophy, ODD, nanophthalmos	/
CYP4V2 in Bietti crystalline dystrophy[26]	Visual field constriction, bilateral progressive vision loss, nyctalopia, disruption of outer retinal hyperreflective bands, diffuse retinal crystalline deposit, retinal pigment epithelium atrophy, choriocapillaris atrophy, choroidal sclerosis, choroidal neovascularization, ODD	/
JAGGED1[15,37,38]	Mosaic pattern of iris stromal hypoplasia, microcornea, RP, ODD, Posterior embryotoxon	Characteristic facial features, aortic dysplasia, aortic stenosis, pulmonary artery stenosis, atrial/ventricular septal defect, hepatomegaly, hepatic dysfunction, cholestasis, renal injury, epileptic seizure, butterfly vertebrae, hypercholesteremia
Joubert syndrome[33,34]	Pigmentary fundus changes, retinal dystrophy, severe vision loss, ocular misalignment, ODD, cataract, chorioretinal coloboma, optic nerve hypoplasia, ptosis, ocular fibrosis, pendular nystagmus, vestibulo-ocular reflex latency	Hypotonia, ataxia, developmental delay, “molar tooth sign” on cranial MRI, episodic hyperpnoea
Klippel-Trenaunay syndrome[35]	Orbital varix, heterochromia iridum, retinal varicosities, choroidal angioma and melanoma, glaucoma, bilateral optic nerve and chiasmal gliomas, ODD, acquired retinal nerve fiber layer myelination	Vascular nevus, peripheral varicosities, hemihypertrophy of bone and soft tissue, persistent fetal vasculature
MFRP[16-18]	High hyperopia, RP, peripheral retinoschisis, foveoschisis, ODD, nanophthalmos, posterior microphthalmia	/
PTEN (p.Gly165X) in Cowden syndrome[27-28]	ODD (rare)	Increased risks for malignancies (breast, thyroid, and endometrial) as well as benign hamartomatous overgrowth of tissues (skin, colon, thyroid, etc.), gingival enlargement, dental abnormalities, joint hyperextensibility
SH3BP2 gene in Cherubism[29]	Globe displacement, inner retinal striae, retinoschisis, foveal vitelliform lesions, macular scarring, chorioretinal folds, angioid streaks, optic nerve impairment, ODD, proptosis, strabismus, lower lid retraction, nasolacrimal duct obstruction	Painless multilocular cysts in the jaws and the maxilla in early childhood
Usher syndrome[32]	RP, ODD	Hearing loss

eye development.[16-18] A frame-shift mutation identified in a Mexican family led to dysfunction of the MFRP-encoded protein, which was associated with nanophthalmus, retinitis pigmentosa (RP), foveoschisis, and ODD.[17] A similar disease complex characterized by RP, nanophthalmus, and ODD was attributed to a homozygous missense mutation in crumbs homolog 1 (CRB1) in a Turkish family.[19] Besides, several studies explored the potential correlation between ODD, angioid streaks, and pseudoxanthoma elasticum (PXE). Mansour found that one out of 21 patients with ODD had angioid streaks.[20] Using B-scan ultrasound, Pierro found that ODD was present in 21.6% of the 116 eyes with angioid streaks and in 21.0% of the eyes with streaks and PXE.[21] Pipelart examined 155 patients with PXE and revealed a 24.5% prevalence of ODD in the cohort.[22] However, ABCC6 genotype and linkage analysis related to PXE excluded the ABCC6 gene's involvement in ODD formation.[22,23] Other genetic variants or disorders were reported with findings of ODD, including the ALMS1 gene in Alström syndrome,[24,25] CYP4V2 in Bietti crystalline dystrophy,[26] PTEN (p.Gly165X) in Cowden syndrome,[27,28] SH3BP2 gene in Cherubism,[29] and the chromosome 22q11.2-related syndromes.[30,31] Moreover, ODD were found to have a high prevalence in Usher syndrome, which was typically associated with congenital hearing loss and RP.[32] Among Usher syndrome patients (60 with type I and 100 with type II), the prevalence of ODD was 9% for both types. Joubert syndrome (JS),[33,34] characterized by a distinct cerebellar and brainstem malformation, was found to be accompanied by ocular and oculomotor abnormalities. Sturm found bilateral ODD in two of ten JS patients.[34] Nevertheless, no genetic mutation was detected in them. A case of ODD in Klippel-Trenaunay syndrome has been reported, but no specific chromosomal locus or causative gene has been identified.[35]

Small scleral canals and dysplasia of optic disc

The narrow aperture of scleral canals may generate localized mechanical stress, which will exacerbate the obstruction in axoplasmic flow, resulting in axonal degeneration and retinal ganglion cell injury once the limit is exceeded. [Fig. 1a and b] Mullie employed an indirect method by assessing the non-drusen-containing optic discs in both patients with unilateral ODD and normal individuals.[39] The optic disc surface area in patients with unilateral ODD was, on average, 20–33% smaller than in controls. However, Floyd found no significant difference in the average scleral canal size between eyes with ODD and control eyes or fellow eyes without ODD.[40] Floyd speculated that ODD would cause the scleral canal to show a progression from narrowing to widening with age, which may explain why scleral canal size in adults with ODD was similar or even larger than in controls.[40] In a prospective cross-sectional study involving 98 normal-tension glaucoma patients, Ahmadi identified ODD in six patients (6.1%) using EDI-OCT. Among these, five patients had unilateral buried ODD, while one had bilateral visible ODD.[41] The study found no significant difference in scleral canal size between eyes with and without ODD. Another explanation suggests that ODD displacement of the surrounding structure leads to an

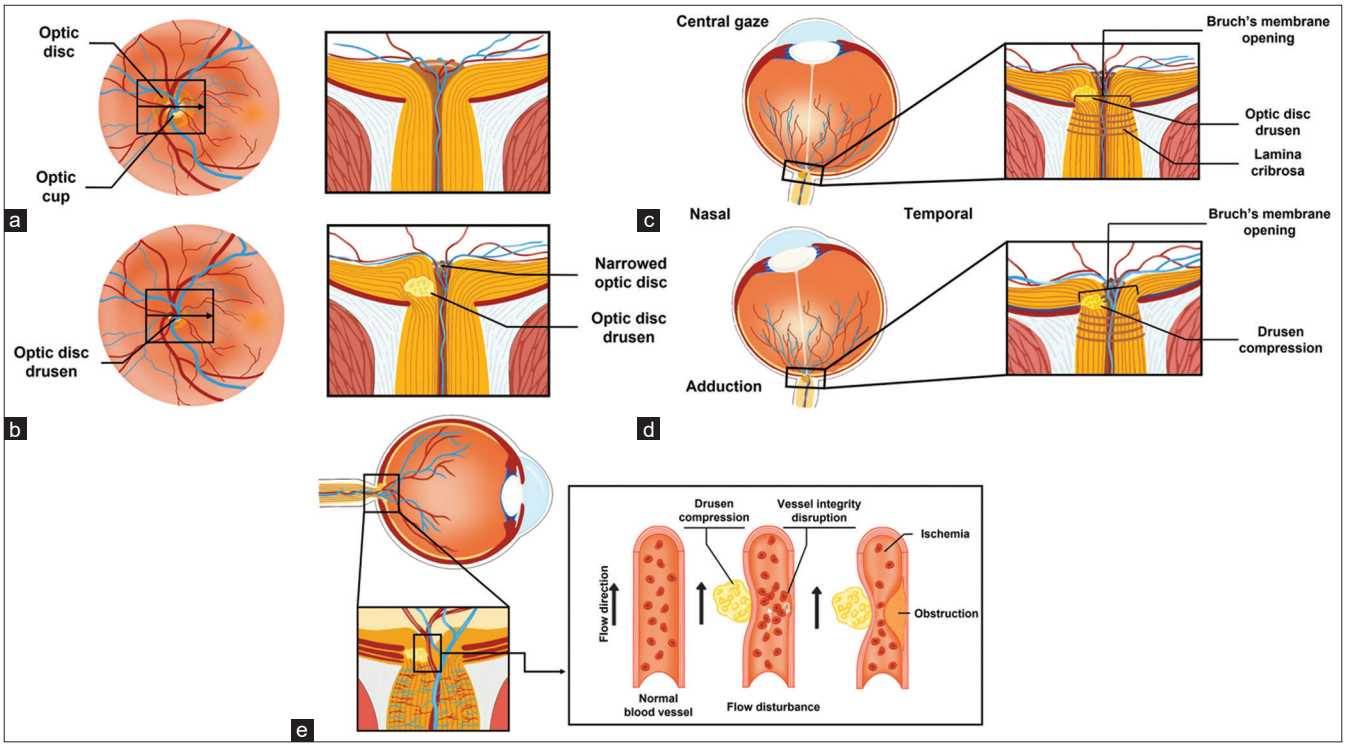

Figure 1: Pathogenesis of complications due to optic disc drusen. (a) Optic disc in a healthy eye with a normal cup-to-disc ratio. (b) A small optic disc and optic canal appeared in an eye with ODD. The vessels were growing crowded in the narrowed optic disc. Nerve fibers adjacent to the drusen were compressed by the ODD. (c) The optic disc drusen was located on the nasal side of the optic disc anterior to the lamina cribrosa. The nasal side of the nerve fibers was relatively thinner due to the drusen compression. (d) In adduction, the ODD produces more compressive strains to the adjacent nerve fibers, vessels, and tissues. The compression caused decreased blood supply to the distal central retinal artery and retardation of the venous flow in the distal central retinal vein. The Bruch's membrane diameter might be decreased in adduction. (e) ODD compressed the vessels and caused blood flow turbulence and endovascular injury. Artery stenosis and vein congestion at the compression will lead to optic nerve and retinal vascular complications

overestimation of the scleral canal diameter. In comparison, younger patients with ODD would eliminate this masking and displacement during early developmental stages.[42]

Jonas investigated 26 patients with visible ODD and observed an association between ODD and abnormally small optic discs.[43] He found that the patients' optic discs and scleral canals were smaller than normal. Antcliff found vascular anomalies were present in 57% of eyes within family members of seven ODD patients, and approximately 50% of eyes lacked optic cups. Some studies observed differences in ODD prevalence among ethnic groups. It was suggested that Caucasians or whites are usually born with smaller optic discs than many other racial groups.[44] The lower prevalence of ODD in blacks may be attributed to their generally larger average cup-to-disc ratio compared to whites. ODD might be a sporadic occurrence in black patients due to the absence of familial connections and other ODD-associated disorders.[45] In Northern China, a population-based cohort study found a statistically significantly smaller optic disc area in ODD eyes than those without ODD (1.97 ± 0.46 mm^2 versus 2.61 ± 0.50 mm^2).[46] Lee suggested that buried ODD formation is linked to a small optic disc as measured by spectral-domain OCT (SD-OCT). Meanwhile, nearly 20% of fellow eyes did not have ODD, indicating that there could be other factors apart from the anatomy involved in ODD genesis.[47]

Abnormal vasculature

Seitz hypothesized that ODD develops due to congenitally anomalous vasculature, which disrupts circulation and impedes the transport of plasma proteins. The gradual accumulation of the proteins contributed to the drusen formation.[48] Sacks observed abnormal vascular patterns and perivascular acellular materials within optic discs in ODD patients. He suggested that the drusen-like materials originated from the blood leakage of plasma proteins, which accumulated to form extracellular calcified deposits.[49] Antcliff found anomalies of cilioretinal arterioles occurring in 57% of the eyes of family members of ODD.[8] As more research progressed, the vascular anomalies became characteristic of ODD. Some attention has been paid to microvascular changes. Optical coherence tomographic angiography (OCTA) analysis of the superficial microvasculature of the optic disc showed a positive correlation between retinal vasculature attenuation, RNFL loss, and ODD.[50] Using fluorescence angiography, Karel observed venostasis in all ODD patients, suggesting circulatory disturbance as a potential pathological factor for ODD.[51] However, not all ODD exhibit vascular changes in electron microscopic analysis,[6] and the role of abnormal vasculature in the pathogenesis of ODD formation awaits further investigation.

Metabolic disturbances and pathological findings

One leading hypothesis suggested that the aberrant axoplasmic transport at the optic disc would lead to nerve fiber defects, resulting in extracellular calcified deposits and finally forming ODD. The pathological findings of ODD are summarized in Table 2. ODD was initially believed to result from chronic degenerative changes in retinal ganglion cell axons.[52] Histochemical studies indicate that ODD originates from axoplasmic derivatives of disintegrating nerve fibers through a prolonged, gradual pathological process.[48] Spencer postulated that ODD was associated with altered axoplasmic transport.[53] Tso supported the idea that the drusen could be found in sites where axoplasmic flow slowed down in normal eyes. He hypothesized that abnormal axoplasmic metabolism led to intracellular mitochondrial calcification, which damaged axons and expelled mitochondria into the extracellular space. The mitochondria calcified profusely in response to the concentration gradient and generated calcified microsomes serving as locations for further calcification and ODD development. During this process, mitochondria in ODD cases remained morphologically and functionally intact, while calcium became the major component of the deposit.[6] Macrophages were missing, so the damaged axons and extracellular mitochondria could remain *in situ* for progressive calcification.[54]

According to the previous findings on the pathological characteristics of ODD [Table 2], ODD is circular and slightly irregularly outlined with various sizes. They are usually located in front of the lamina cribrosa; in some cases, they are anterior to the choroid or extend to the retina.[12,55,59,62-64] They frequently cluster, particularly on the nasal side of the optic disc.[12,55] Atrophy of the optic nerve fibers is found adjacent to the drusen.[56-58,63,64] Besides, ODD may push nerve fibers aside, resulting in swelling of nerve fibers.[56] Histologically, ODD showed a whitish-yellow color with light-reflecting properties marked in superficial ODD.[12] Protein, calcium, and iron were found in the drusen.[56-58,60] Microcalcification could also be observed[59] The presence or absence of pigment in ODD may hint at its origin. The absence of pigment suggested an origin in the papilla or retina, while its presence suggested a pigment epithelial origin.[55] Early ramification of the retinal vessels and abnormal capillary hyperplasia were noticed on the optic disc. A vascular loop may also be present. Such anomalous vascular patterns were likely due to the neuronal ischemic changes caused by the drusen.[49,61]

Research has identified calcium deposits in the brain and other organs of hypocalcemia patients. Ringvold first proposed that human hypocalcemic cataracts contained increased calcium in the lens.[65] Allegrini agreed with the impact of hypocalcemia on the development of cataracts from an osmotic point of view and suggested that calcium deposits in ODD may share similar pathogenesis and that hypocalcemia may increase the risk of ODD.[31]

PXE was considered a systemic metabolic disorder with secondary calcification of elastic fibers. A common process of aberrant mineralization was hypothesized to be involved in ODD.[66] PXE was marked by angioid streaks, likely due to the mineralization and subsequent calcification of the elastin-rich Bruch's membrane. Lack of anti-mineralizing factors such as inorganic pyrophosphate would lead to ectopic mineralization of the elastic fibers and the formation of calcified deposits on the Bruch's membrane.[67,68] Altered metabolism of elastic fibers in the lamina cribrosa may cause thickening and crowding of the optic disc laminar beams, along with dysregulated extracellular calcium homeostasis, leading to the formation of ODD.[20,66]

Birnbaum thought papilledema in idiopathic intracranial hypertension (IIH) may contribute to the ODD formation.[69] The reported prevalence of ODD was 19% among adult eyes with resolved papilledema from IIH using OCT[69] and 14.7% in children and adolescents with IIH using B-mode ophthalmic ultrasound.[70] Papilledema may impair axonal transport in the optic nerve, disrupting calcium metabolism and causing calcium deposits in the mitochondria, which can serve as a nidus for ODD.

Repetitive shearing

The long-term mechanical impact of repetitive shearing from ocular ductions is hypothesized to contribute to both visual and vascular complications of ODD. Sibony identified notable

Table 2: Lists of pathological findings of ODD in previous studies

Year, author	Average age	Number of eyes	Resource of eyes	Pathological findings
1858, Müller[1]	75	2	N/A	Numerous slightly yellowish granules with fibrous tissue were located in the anterior part of the optic nerve, and the nerve fibers were atrophic. Numerous slightly yellowish granules with fibrous tissue were located in the anterior optic nerve, accompanied by atrophic nerve fibers.
1940, Samuels[55]	10 to 42	20	Enucleated	The drusen, characterized by irregularly rough contours, were primarily located on the nasal side of the optic disc, anterior to the lamina cribrosa, except one druse situated posterior to the lamina cribrosa. Small scattered drusen were located in the papilla anterior to the choroid. A layer of endothelial-like cells surrounded the drusen, and there was no pigment. Drusen at the periphery may surround the disc with a narrow, notched, and glittering border.
1952, Chamlin[56]	40	2	Cadaver	Tiny yellow bodies of noncellular drusen were located anterior to the lamina cribrosa. The deposits were a complex protein-rich thickened fluid with a large amount of iron. The lamina cribrosa were pushed backward. The surface optic nerve head was elevated, with swollen nerve fibers shifted on either side. The nerve fibers on the nasal side of the optic nerve were atrophic.
1975, Friedman[57]	55.9	17	Cadaver	The sizes of drusen were from 50~750 μm in diameter, in the prelaminar optic nerve, with the smaller ones closer to the lamina cribrosa. Calcium and iron were deposited in drusen. There was superficial hemorrhage, juxtapapillary retinal scarring with deposition of hemosiderin, exudation in the outer plexiform layer, atrophy of the nerve fibers, cystoid bodies neighboring the optic disc, compression of adjacent nerve fibers, and cellular reaction.
1977, Sacks[49]	N/A	53	Cadaver	The vessels on the optic nerve head branched early, and the number of branched retinal vessels was greater than in the control groups. The number and size of disc capillaries increased without leakage, seemingly interconnected with the superficial disc circulation and that of the deeper portions of the optic nerve. Circumflex was visible in 62% of ODD but in none of controls.
1978, Boyce[58]	N/A	52	Cadaver	The sizes of drusen were from 20 μm to 1200 μm (320 μm on average). Drusen were composed of a mucoprotein substance with excess acid mucopolysaccharides and a small amount of ribonucleic acid and, infrequently, iron. There were optic atrophy, peripapillary fibers crowding, dislocated dilated vessels around drusen, and central retinal vein occlusion.
1978, Spencer[53]	N/A	N/A	Cadaver	The familial ODD was bilaterally located anterior to the lamina cribrosa and within the contours of the scleral ring, and sometimes the superficial drusen overlay the disc margin. The drusen were composed of calcified, concentrically laminated, ball-shaped aggregates. Physiologic cupping is absent in the early stage of drusen; in adulthood, the disc surface is covered with refractile structures. There was progressive atrophy of the nerve fiber layer, especially at the front of drusen, a moderate amount of deformation and compression of adjacent nerve fibers and glia, and focal amorphous deposits.
1981, Tso[6]	50	18	16 enucleated and two cadavers	ODD comprised 2 to 3 small nodules to 40 to 50 colloid bodies. The size ranged from 5 to 1,000 μm in diameter. The larger ones were deeper. Large and multiple ODD made optic disc swollen and disc cup filled. There were irregular angular atrophic axons in the anterior lamina retinalis, acuate calcium deposition within the mitochondria of intact axons, extrusion of mitochondria, laminated dense bodies, and axoplasmic proteins into the interstitial space from axons.
1990, Giarelli[59]	75	18	Cadaver	Multiple, small drusen or isolated, large drusen varied from 50 μm to 700 μm, anterior to the lamina cribrosa within the disc margins. Superficial drusen appeared as roundish multi-lobular translucid concretions. There were microcalcifications, spongiotic edema, apparent gliosis, nerve fibers atrophy, hemorrhages, and hyperaemic with changes of the superficial arterial network.
2008, Kapur[60]	59	2	Vitrectomy	ODD was composed of $Ca_3(PO4)_2$, and decreased blood flow through the retinal vasculature was found.
2008, Frisén[61]	31	1	Enucleated	The peripapillary ring reflex was fragmented and gradually replaced by peripapillary grayish pigmentation. There was loss of nerve fiber bundles. The most central parts of the central retinal vessels were obscured by an overlying opacity. Hemorrhages were seen close to the temporal vascular loop.

Contd...

Table 2: Contd...

Year, author	Average age	Number of eyes	Resource of eyes	Pathological findings
2020, Skougaard[62]	57.6	31	Enucleated	Round aggregated bodies of various sizes and numbers were anterior to the lamina cribrosa. The edema of the optic nerve axons elevated the disc surface, and, in several eyes, the axons were not swollen. The superficial nerve fibers were thickened in the eyes with large drusen under the BMO. The superficial drusen of the same size has thinner nerve fibers. The thickness of nerve fibers was exhibited normally in small drusen.

BMO, Bruch's membrane opening; N/A, not available; ODD, optic disc drusen

gaze-induced deformity in the peripapillary Bruch's membrane and significant strains in the prelaminar optic nerve head in ODD patients. The magnitude of the deformation was found to be similar in the ODD patients and the healthy group. However, for patients with intrapapillary calcifications, long-term exposure to repetitive strains was more likely to damage the axons, border tissues, and blood vessels, progressively leading to visual and vascular complications.[71] The optic disc was compressed during adduction, and the compressive strains induced by the adducted optic disc were much greater than the strains caused by elevated intraocular pressure (IOP) and vascular perfusion. The decomposition of the strains found significantly large compressive strains in the temporal hemi-disc and similar tensile strains in both temporal and nasal hemi-discs. The difference in strains may be attributed to Bruch's membrane opening (BMO) compression, with a significant decrease in BMO diameter observed in adduction but not in abduction. Besides, the retinal vascular volume increased by more than 5% in adduction. Strains of various degrees on the blood vessels could interfere with vascular function or regulation.[72] These findings may demonstrate the possible effect of repetitive shearing on visual and vascular complications caused by ODD [Fig. 1c and d].

Clinical findings

The progression of visual field defects

Initially asymptomatic, ODD can later cause concentric contraction and generalized visual field depression [Table 3].[63] Auw-Haedrich identified visual field defects in ODD as nerve fiber bundle defects (primarily in the inferior nasal quadrant), blind spot enlargement, and concentric narrowing. Arcuate defects, however, were suggested to be the leading pattern of peripheral visual field loss in ODD.[54] Visual field defects were usually observed in adults and patients with large or superficial drusen,[73] whereas children seldom presented with vision loss.[74] Visual field defects can develop slowly during childhood, often undetected in early life. In a 44-month follow-up study of 21 children with a mean age of 10.2 years, visual field defects were identified in 18 out of 35 eyes. Drusen became superficial and visible at an average age of 12.1 years, with visual field defects detected at an average age of 14 years.[75]

Longitudinal studies on visual field defects in ODD indicate a gradual decline in the visual field over time. The time interval for a change ranged from a minimum of 2.5 years to a mean of up to 9 years. Sudden significant visual field loss in ODD is often caused by vascular complications like nonarteritic anterior ischemic optic neuropathy (NAION).[8] A retrospective study with at least 36 months of follow-up included 60 eyes of 32 patients with ODD. The mean age of the patients was 46.4 years at entry. Goldmann visual field testing indicated an annual visual field loss rate of 1.58% ± 0.28, irrespective of sex.[7] Estrela monitored 65 eyes from 43 patients with ODD over an average of 7.6 ± 5.3 years, finding an average standard automated perimetry (SAP) mean deviation (MD) change of −0.23 ± 0.26 dB/year. Slow progression (<−0.5 dB/year) was observed in 57 eyes (87.7%), while only two eyes (3.1%) showed faster progression (> −1 dB/year). Given the above, older age and worse baseline SAP MD could relate to faster rates of change.[84] Visual field defects in ODD may be more common when accompanied by peripapillary RNFL thinning and ocular hypertension.[4]

Application of OCT for detecting and monitoring ODD

History and fundoscopic examinations could be assisted with ophthalmic imaging for more direct evidence. Following B-scan ultrasound, scanning laser ophthalmoscopy, fluorescein angiography, and autofluorescence, OCT has become an attractive nonmydriatic, noninvasive alternative for ODD detection. There are visible and buried ODD based on their appearance found by fundus ophthalmoscopy, and superficial or deep ODD according to their locations above or below the BMO demonstrated on OCT [Fig. 2]. As a next-generation OCT, EDI-OCT has the highest sensitivity in the vicinity of the medial sclera and is capable of obtaining images of the posterior edge of the ODD, making it ideally suited for detecting small, deeply buried ODDs.[4] According to the ODD Studies Consortium, on EDI-OCT, the ODD typically exhibits hyporeflective center with a partial or complete hyperreflective margin, sometimes with small conglomerates. Hyperreflective horizontal lines are possibly found nearby, which indicate early ODD changes. Fig. 3 shows the collection of small ODD conglomerates representing superficial ODD and large deep drusen beneath the BMO. EDI-OCT could assess the shape, structure, size, and extent of ODD to inform their progression. On OCT, peripapillary hyperreflective ovoid mass-like structures (PHOMS) exhibit distinct characteristics compared to ODD. PHOMS are typically situated circumferentially around the optic disc and are most commonly found in the nasal peripapillary region, lying on top of Bruch's membrane. Notably, on the superior aspect of PHOMS, there is usually an upward deflection of at least two of the other retinal layers, resembling a "ski slope" sign. PHOMS is considered a nonspecific OCT marker of impaired axoplasmic flow, corresponding to the herniated optic nerve fibers, which commonly coexist with ODD. Other ophthalmic entities are also found to be associated with the presence of PHOMS, such as papilledema, central retinal vein occlusion, papillitis, and tilted disc.[85]

Fundus autofluorescence (FAF), especially green-light and blue-light FAF, is a valuable tool in the diagnosis and characterization of ODD. PHOMS appear dark on FAF due to

Table 3: Visual field defects in optic disc drusen in the literature

Year, author	Average age (year)	Number of ODD eyes with visual field defects (total eyes)	Visual field defect (number of ODD eyes)	Average period of follow-up (month)
1973, Erkkilä[76]	7	2 (4)	Inferior visual field defect (2), nerve fiber bundle defect (1)	N/A
1978, Spencer[63]	N/A	N/A	Concentric contraction and depression in all quadrants	N/A
1979, Savino[77]	N/A	37 (52)	Nerve fiber bundle defects (29), superior/inferior arcuate/nasal/temporal scotomas (82), enlarged blind spot (25), general constriction (4)	N/A
1981, Stevens[78]	33	27 (38)	Visual field defects (27)	N/A
1981, Brudet-Wickel[79]	Range 10 to 59	43 (46)	Enlarged blind spot and irregular peripheral contraction (16), nerve fiber bundle scotomas (13)	N/A
1988, Hoover[75]	10.2 at presentation	18 (35)	Enlarged blind spot (9), an inferior arcuate/ sector/or altitudinal defect (6), or both (3)	44
2005, Lee[7]	46.4	60	The rate of visual field loss was 1.58% ± 0.28/ year	90
2013, Noval[80]	13	26 (28)	An isolated enlarged blind spot (5), a nasal defect (15), a mild inferior arcuate scotoma (9), and a constricted visual field (6)	N/A
2016, Duncan[81]	10.8±3.3	19 (57)	Enlarged blind spots (12), arcuate scotoma (6), nasal step (1)	> one visual field session (8)
2019, Kelbsch[82]	N/A	6 (208)	Visual field defects ≥50% (6)	N/A
2021, Sustronck[83]	Range 11 to 68 years	11 (16)	Enlarged blind spot (9), and arcuate scotoma (9)	N/A
2023, Estrela[84]	55.8±13.5 at presentation	65 (65)	Mean rate of SAP MD change: −0.23±0.26 dB/year <−0.5 dB/year (57) −0.5 dB/year ~ −1 dB/year (6) >−1 dB/year (2)	91.2±63.6

N/A, not available; SAP, standard automated perimetry; MD, mean deviation

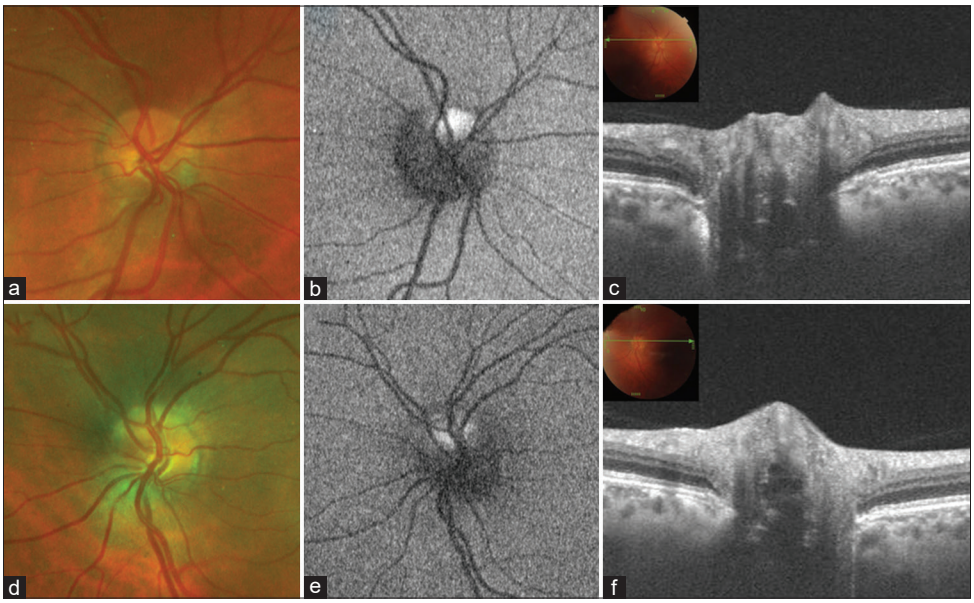

Figure 2: The clinical findings of optic disc drusen (ODD) by multimodal imaging. (a) Color fundus imaging of the right eye showed a small optic disc without visible ODD. (b) Autofluorescence demonstrated the existence of buried ODD. (c) Swept-source optical coherence tomography (OCT) (Triton, DRI-OCT-2, Topcon Co., Tokyo, Japan) showed the hyporeflective center of ODD with hyperreflective margin below the Bruch's membrane opening demonstrating a deep ODD. (d) Color fundus imaging of the left eye showed visible ODD in the superior quadrant of the optic disc. (e) Autofluorescence demonstrated the existence of ODD. (f) Swept-source OCT showed the hyporeflective center of ODD with a hyperreflective margin above the Bruch's membrane opening demonstrating a superficial ODD

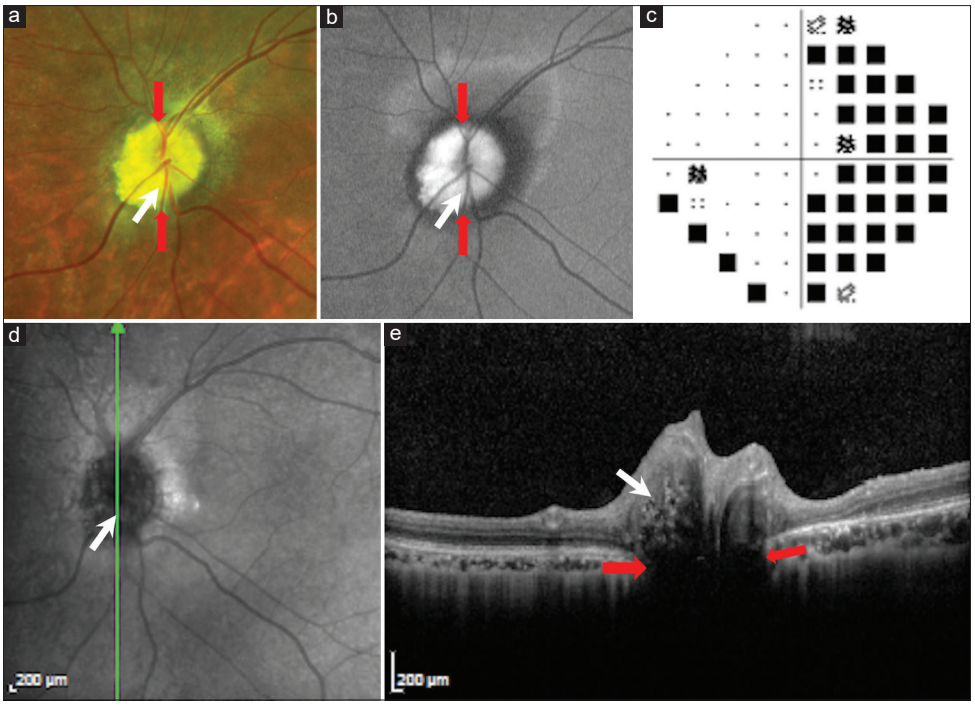

Figure 3: An eye with small optic disc drusen (ODD) conglomerates representing superficial ODD and large deep drusen beneath the BMO. (a) The lumpy-bumpy appearance of superficial ODD (white arrow) in inferornasal quadrant of optic disc and deep ODD in the whole optic disc underneath (between the red arrows) with pigmentation surrounding the optic disc. (b) The hyper-autofluorescence of ODD correponds to the color fundus imaging. (c) The nasal visual field defect was caused by ODD. (d) Infrared imaging of optic disc with ODD indicates the pearls-like ODD conglomerates in the nasal quadrant of the disc. (e) Enhanced depth imaging optical coherence tomography (OCT) (Spectralis, Heidelberg Engineering, Germany) showed the hyporeflective center of ODD below the Bruch's membrane opening demonstrating large deep ODD (between the red arrows) and collection of small ODD conglomerates indicating the presence of superficial ODD (white arrow)

the lack of underlying lipofuscin-containing retinal pigment epithelium (RPE). This characteristic can assist in distinguishing ODD from other conditions that may present with optic disc swelling. In a recent study comparing the diagnostic accuracy of various imaging modalities, FAF demonstrated a sensitivity of 84%, in contrast to 74% for ultrasound and 95% for EDI-OCT.[86] ODD located beneath the BMO might potentially display negative autofluorescence.[87]

Since OCT could be used to monitor and quantify changes in nerve fiber axons and ganglion cells, while OCTA provided a better view of changes in retina and optic disc blood flow, the combination of OCT and OCTA could better predict vision loss in ODD. Research revealed that RNFL thinning was associated with clinically visible ODD and that the OCT parameter could be an early indicator [Fig. 4].[88] Measuring the decrease of RNFL thickness could evaluate the extent of axonal loss, a robust biomarker in determining visual field deterioration.[89] In an OCT-based study of ODD in enucleated eyes, RNFL thickened in young patients with large, deep ODD but decreased in older patients with ODD.[62] In clinical studies, ODD would be more difficult to detect and require more time to follow up on their change. Ocakoglu used OCT to perform a long-term study with 14 to 22 months of follow-up, finding no significant difference in the mean RNFL thickness.[90] A longitudinal study on ODD reported a mean follow-up duration of 5.8 years. This study recorded minimal visual field defects but observed an annual reduction of nearly 1 µm in RNFL and 0.2 µm in GCIPL, with the RNFL loss rate potentially being five times higher than normal aging expectations.[91] Malmqvist analyzed the correlation between RNFL thickness and visual field defects in patients with superficial and deep ODD. Functional and structural defects were more pronounced in superficial ODD, likely due to more significant axonal damage from calcification.[88]

Vascular complications

ODD patients were at a higher risk of vascular occlusions and NAION compared to the general population.[92] ODD complicated central retinal artery (CRA) occlusion usually occurs in younger people. Migraines, high altitude, and oral contraceptives could be predisposing factors.[93] Studies utilizing color Doppler ultrasound have identified disrupted blood flow in the CRA among patients with ODD. Peak-systolic and end-diastolic velocities significantly decreased, with a higher resistivity index observed in ODD patients, particularly females. ODD might cause mechanical compression on CRA, leading to stenosis, which usually reduces blood perfusion and leads to ischemia in the supplying area.[94] ODD-related central retinal vein occlusion is evidenced by the involvement of deep ODD in symptomatic branch retinal vein occlusion.[95] The acellular deposits might produce compression that reduces the venous flow and endothelial cells' growth, increases flow turbulence, disrupts vascular integrity, and causes congestion or ischemia [Fig. 1e].[49] Venous retinal-choroidal collaterals, primarily observed in eyes with superficial ODD, are attributed to elevated pressure in the central retinal vein.[54]

ODD is identified as an independent anatomical risk factor for AION in young patients.[96,97] The location of ODD is hypothesized to be a significant risk factor for visual field

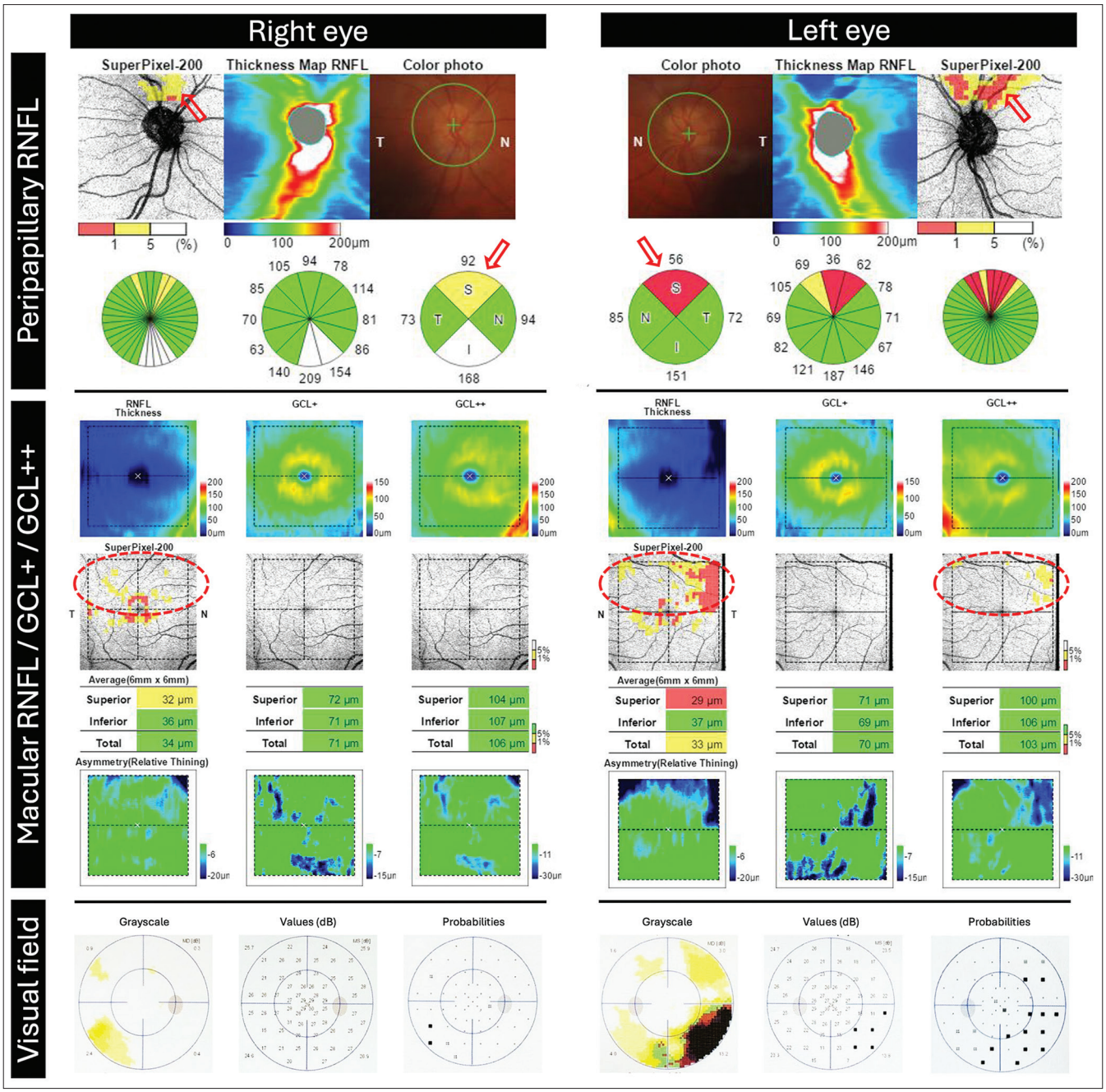

Figure 4: The peripapillary retinal nerve fiber layer and macular ganglion cell layer analysis by optical coherence tomography (Triton, DRI-OCT-2, Topcon Co., Tokyo, Japan) and visual field testing (Octopus 900, Haag-Streit, Köniz, Switzerland) in optic disc drusen (ODD) eyes in Fig. 4. Loss of peripapillary and macular RNFL thickness in the superior quadrant of the left eye (visible and superficial ODD) was worse than that of the right eye (buried and deep ODD). There was subtle thinning of the macular ganglion cell complex in the superior hemifield of the left eye. GCL+: ganglion cell+ inner plexiform layer thickness, GCL++: ganglion cell complex thickness. The octopus visual field test showed an inferior arcuate defect in the left eye corresponding to the thinning of peripapillary RNLF in the superior quadrant

defects. The deep ODD might occupy the space of axons near the lamina cribrosa, compressing the axons and triggering an ischemic cascade.[97] Recent studies proposed that ODD might contribute to the occurrence of diabetic papillopathy.[98] Diabetes could induce microvascular destruction with optic disc edema. It was speculated that a rapid downregulation of glycemia impeded the axon's energy metabolism and led to nerve fiber swelling. The crowded disc in ODD patients would combine to cause hypoperfusion with venous congestion. The development of an optic disc compartment syndrome would exacerbate the ischemic condition due to limited space for expansion.

Choroidal neovascularization (CNV) was a complication of ODD that seemed more common in children.[54,73] Formed due to a Bruch's membrane defect, it was typically located in the peripapillary area and generally did not affect vision.[99] Cases of retinal hemorrhages in connection with ODD have

also been published. The possible mechanisms of hemorrhages without neovascularization in ODD included erosion of blood vessels, venous congestion or circulation disturbance,[51] and ischemia.[100] Most cases complicated with retinal hemorrhages usually had a good visual prognosis.

Conclusion

Researchers have made significant progress in ophthalmic multimodal imaging diagnosis in recent years, yet the pathogenesis of ODD remains unclear. Why calcifications appear in the optic disc from childhood, gradually increase in size, and become shallower over time remains a question to be answered. Future pathological discoveries or the establishment of animal models may provide new evidence for revealing the pathogenesis of ODD. In terms of treatment, how to prevent the increase of calcification lesions and prevent vascular complications is an urgent problem that needs to be resolved.

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