The Angioarchitecture of the Optic Nerve Head in Patients with Optic Disc Drusen

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ABSTRACT

The aim was to analyse the optic disc angioarchitecture in optic disc drusen (ODD) patients using computer-based fundus analysis in a case–control study. Compared with controls the ODD group had a significantly more centralised central retinal artery (CRA) emergence ($p < 0.001$) and primary CRA branching ($p = 0.008$), a higher number of CRA bifurcations ($p = 0.02$), a larger vertical optic disc diameter ($p = 0.02$) and a smaller cup/disc ratio ($p < 0.001$). The CRA emergence was largely within the nasal zone for both groups. The distinctive angioarchitecture of the optic disc in ODD patients can play a role in understanding the pathogenic cause of ODD.

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Introduction

Optic disc drusen (ODD) occurs in about 2% of the population and are nodules consisting of calcium, mucopolysaccharides, amino and nucleic acids.¹ The pathophysiology is perceived to be an abnormal preliminary axonal metabolism leading to axonal damage, extrusion of mitochondria to the extracellular space and gradual ongoing calcium deposition.² During childhood ODD are often buried beneath the surface of the optic disc and can imitate papilloedema,^{3,4} however the most sensitive method to diagnose ODD appears to be enhanced depth imaging optical coherence tomography (EDI-OCT).⁵ In the adolescent years, ODD becomes increasingly calcified and visible using simple ophthalmoscopy or ultrasound.^{6,7}

ODD are often asymptomatic, however, up to 87% of cases are associated with visual field defects.⁸ There are reports of AION^{9,10} occurring in young patients with ODD, but the causal relationship has yet to be proven.

The optic disc is perfused mainly by the posterior ciliary artery, and its branches including any cilioretinal arteries and the central retinal artery (CRA) emerging through the optic disc.¹¹ A previous study

using colour Doppler imaging showed that individuals with ODD had lower blood flow velocities in the vessels around the optic nerve head and that this correlated with the extent of the visual field defects.¹² Increased presence of cilioretinal arteries, early bifurcation and increased tortuosity of the central vessels in children with ODD has previously been described¹³ and another study observed a significant difference in number of bifurcations of arteries and veins in ODD individuals compared with controls.¹⁴ However, the latter two studies looked at vessel structure across all of retina rather than on the optic disc itself.

A significant difference in anomalous vascular branching and number of cilioretinal arteries was found when comparing patients with superficial and buried ODD¹⁵ pointing towards a gradual change in vascularity alongside ODD development. However, this does not determine whether vascular dysplasia is secondary to ODD development or the direct cause of the disease perhaps already present during embryonic development. One study proposed that the pathology behind ODD is a predisposition caused by an inherited dysplasia of the optic disc and its blood supply.⁷

Quantifying anomalous vessel patterns in ODD individuals using a systematic tool could contribute to defining certain vascular characteristics in this group and therefore shed a new light on the pathogenesis and potential vascular complications of ODD.

The aim of this study was to analyse the difference in angioarchitecture of the optic disc between a group of ODD patients and a group of healthy controls with normal optic discs.

Methods

Participants

The population cohort in this case-control study included 30 healthy volunteers (10 males and 20 females) with normal optic nerve heads and 50 ODD patients (16 men and 34 females) with no complications apart from visual field defects. The right eye was used for analysis in the control group except in one case due to poor photograph quality. No control eyes had ODD or hyper-reflective lines, that have been suggested to represent early ODD or ODD precursor lesions.⁵ The eye chosen for examination in the ODD group was the one with the larger perimetric mean deviation in visual field analysis obtained using automated perimetry (Octopus, Haag-Streit, Switzerland) with a 30–2 test pattern.

The ODD cases were recruited from an already available ODD-database at Rigshospitalet-Glostrup and had either visible ODD or buried ODD identified with EDI-OCT. A clinical examination including IOP measurement and best corrected visual acuity was performed on all subjects.

The study was approved by the Scientific Ethics Committee of the Capital Region, Denmark (H-4-2013-040), and the Danish Data Protection Agency, and informed consent was obtained from all the subjects. The research followed the tenets of the Declaration of Helsinki.

Fundus imaging and analysis

Fundus photographs were taken using a Topcon camera TRC 50 DX (Topcon, Tokyo, Japan) and creation of the grid and image analysis was performed using Inkscape Version 0.92.2 (Inkscape Developers, GNU

General Public License). Spectral domain OCT (EDI; Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany) was performed on all participants.

On each fundus image, the outline of the optic disc and the point of the emerging CRA was marked (Figure 1a). Point of emergence was defined as the point where the vessel takes the same colour as the superficial vessel. In two cases the CRA emergence could not be identified accurately due to bulging ODD and were instead found using OCT. A standardised grid (Figure 1b) based on the Garway-Heath map, an anatomical map dividing the optic nerve head into sectors,¹⁶ was aligned as closely as possible to the outline (Figure 1c) by one blinded observer (JV). The grid was made using vector-based graphics and divided the optic disc into six zones with a 90° temporal and nasal zone and 45° superotemporal, inferotemporal, superonasal and inferonasal zones. The dotted lines of the grid marked distance points from the centre as 5%, 10%, 20%.. 90%. The centre of the grid was taken to be the centre of the optic disc. The zone and the distance from the centre from which the CRA emerged were noted by two blinded independent observers (LM and SH). Subjective estimation of $\pm 5\%$ was tolerated when the CRA emerged halfway between two dotted lines. The two observers also noted the number of bi- and trifurcations on the optic disc of the CRA and the central retinal vein (CRV) and the distance from the centre for the first bifurcation using the same grid as well as the numbers of cilioretinal arteries in each case. Branchings (bi- and trifurcations) were noted, when the vessel divided into two or three branches having approximately the same thickness, otherwise they were considered an offshoot. The point of branching was defined as the point where a drawn line through the middle of the vessel would split. Cilioretinal arteries were defined as a retinal

Figure 1. Fundus photograph with point of CRA emergence and outline marked (a) and the standardized grid (b) aligned with the outline (c).

artery branch emerging at the rim of the optic disc making a 180° turn, and non-contiguous with the CRA (Figure 2).¹⁷ In case of disagreement in any of the gradings, a consensus was subsequently reached between the two blinded observers.

The cup/disc ratio (C/D ratio) was measured horizontally using an available C/D tool in Topcon's IMAGENet i-base (3.21.0). The horizontal and vertical diameter was measured using the aforementioned software and in Topcon's IMAGENet6 except in the case of two controls and one ODD patient due to the fundus photos no longer being available in these program databases. All cases were analysed by the same observer (JV).

Statistics

Statistical analysis was performed using RStudio 1.1.419 (RStudio, Inc.). The Mann-Whitney U test was used to compare the controls and ODD patients including range. A p-value of ≤ 0.05 was considered a statistically significant difference. To control for the effect of age, gender and C/D ratio on the CRA branching multiple linear regression was performed.

Results

The general characteristics of the ODD group and the control group (Table 1) showed no significant difference in age ($p = 0.81$), gender ($p = 0.91$), and

Figure 2. Fundus photograph of a patient with visible ODD and two cilioretinal arteries.

Table 1. General characteristics.

	Controls (n = 30)	ODD individuals (n = 50)	p-value
Age (years)	32.5 (20– 61)	33 (19– 78)	0.81
Gender	37	42	0.91
IOP (mmHg)	14 (10– 19)	13 (9– 21)	0.009
Visual acuity	1 (0.9– 1.2)	1.1 (0.4– 1.6)	0.24

Results reported in median values and range. Gender = % male, IOP = intraocular pressure, Visual acuity = Snellen visual acuity, ODD = optic disc drusen, $p < 0.05$ considered statistically significant.

visual acuity ($p = 0.24$) for the two groups. The control group had a significantly higher IOP than the ODD group ($p = 0.009$).

In total, four cilioretinal arteries were found in the ODD group, however, one individual presented with two of these alone. One cilioretinal artery was found in the control group.

The point of emergence of the CRA was significantly closer to the centre of the optic disc in the ODD group compared with the control group ($p < 0.001$). The ODD group also had a significant higher number of bifurcations of the CRA on the optic disc ($p = 0.02$) and the point of the first bifurcation was also significantly closer to the centre of the optic disc compared with the controls ($p = 0.008$). For the CRV there was no significant difference in the number of bifurcations on the optic disc ($p = 0.58$) or in the point of the first bifurcation from the centre ($p = 0.87$) (Table 2).

There was a total of two trifurcations of the CRA in the ODD group and a total of five in the control group. No CRV trifurcations were observed in the control group, but two were found in the ODD group.

The point of CRA emergence on the optic disc was observed to be largely within the nasal zone of both groups, with a higher occurrence in the control group compared to the ODD group (77% vs. 42%). The ODD group had a higher occurrence in the infero-temporal zone (16% vs. 0%) and in the inferonasal zone (30% vs. 10%). The distribution within the remaining zones were overall nearly equal (Table 3).

The vertical diameter of the optic disc was significantly larger for ODD individuals compared with the controls (0.02). The horizontal diameter was larger for the ODD group but not significantly so ($p = 0.09$). C/D ratio was significantly smaller for the ODD group compared with the control group ($p < 0.001$).

When controlling for the effect of age, gender, and C/D ratio on the CRA branching it was still significantly closer to the centre ($p = 0.003$) for the ODD group.

Table 2. Angioarchitecture and cup characteristics of optic disc drusen patients.

	Controls	ODD individuals	p-value
CRA			
Distance from OD centre to point of emergence (%)	30 (10–55)	15 (5–40)	<0.001
Number of bifurcations	2 (0–5)	3 (1–5)	0.02
Distance from OD centre to point of first bifurcation (%)	45 (20–85)	32.5 (0–90)	0.008
CRV			
Number of bifurcations	2 (0–3)	2 (0–3)	0.58
Distance from OD centre to point of first bifurcation (%)	40 (15–80)	40 (5–90)	0.87
Diameter of cup			
Horizontal (mm)	1.72 (1.15–1.96)	1.81 (1.26–2.13)	0.09
Vertical (mm)	1.76 (1.30–2.09)	1.89 (1.42–2.58)	0.02
C/D ratio	0.30 (0.17–0.49)	0.14 (0.09–0.26)	<0.001

Results reported in median values and range. CRA = central retinal artery, CRV = central retinal vein, OD = optic disc, ODD = optic disc drusen, $p < 0.05$ considered statistically significant.

Table 3. Percentage distribution of the point of CRA emergence within the zones of the optic disc.

	T	ST	IT	N	SN	IN	Total
Controls	3	7	0	77	3	10	100
ODD individuals	4	4	16	42	4	30	100

ODD = optic disc drusen, T = temporal zone, ST = superotemporal zone, IT = inferotemporal zone, N = nasal zone, SN = superonasal zone, IN = inferonasal zone.

Discussion

The presence of cilioretinal arteries was more common in the ODD group but there were too few in both groups to determine any statistical difference. In contrast, one study found cilioretinal arteries present in 28.8% of eyes in healthy individuals.¹⁷ Cilioretinal arteries were in another study seen in 20 out of 46 ODD children but only in 11 out of 46 healthy children suggesting that the higher incidence was a consequence of a local disturbance during the embryonic development of the central retinal vessels resulting in a need to replace a part of the blood supply to the retina.¹³ The same study also found an earlier branching of the central vessels in ODD patients, which is consistent with our results, where the first CRA branching was significantly closer to the centre for the ODD group.

Our study showed a significantly higher number of arterial bifurcations in ODD patients. A previous study found no difference in a number of CRA and CRV bifurcations for ODD patients and controls.¹⁴ However, this study included all of retina, contrary to our study where only the course of the vessels within the confinement of the optic disc borders was observed. Furthermore, they only found arterial trifurcations in the ODD group and none in the control

group in contrast to our study where five arterial trifurcations were found in the control group and only two in the ODD group. They found no venous trifurcations in the ODD or control group but did observe them in a group with optic disc oedema. In our study, two ODD patients were found to have venous trifurcations and none were seen in the controls. The absence of venous trifurcations in healthy controls could support the theory of an abnormal vascular development in the embryonic period for individuals later developing ODD.

To our knowledge, the point of CRA emergence in ODD individuals has not been investigated previously. A more centralised emergence could be the consequence of the narrower scleral canal found in ODD patients^{18,19} and the ODD themselves pushing the vessel towards the centre. Another possibility is that a more centralised CRA predisposes to ODD as part of an embryonic disturbance. The narrow surroundings then leading to distortion of the blood vessels in the laminary and preliminary region could then potentially predispose to AION.¹⁰ In contrast to this, however, Floyd et al.²⁰ found the scleral canals of ODD patients to be larger than control eyes using OCT, concluding that scleral canal size is unlikely to be involved in ODD pathogenesis.

The smaller C/D ratio for the ODD group cannot solely explain the more centralised emergence of the CRA, but does point towards the narrow surroundings playing a part in ODD development. The C/D ratio of 0.30 in healthy eyes is in good agreement with previous results.²¹ C/D ratio of 0.14 in our ODD group is comparable to the C/D ratio of 0.1 found in ODD patients in a study by Wilkins et al.²² A smaller cup could lead to a CRA trunk located

more centrally independent of the presence of ODD. A smaller disc in general for ODD patients, however, was not evident in this study where the ODD group in contrast to previous studies^{23,24} had a larger diameter than the controls, although the difference in horizontal diameter was not significant. As suggested by Gili²⁴ the calcium deposition in ODD could mask the retinal pigment epithelial layer making the disc diameter appears larger. Another possibility is that the control group had smaller discs compared with the background population. Gili²⁴ found an average horizontal and vertical diameter of 1.86 mm and 1.98 mm, respectively, in 52 normal controls, being considerable larger than in our control group.

In our study, the CRA emerged within the nasal zone for 77% of the controls, but only for 42% of the ODD individuals. On the other hand, 16% of ODD individuals had CRA emergence within the infero-temporal zone, which not a single one of the controls had. The distribution of ODD has been shown to have a nasal zone predominance compared with the temporal zone,⁸ which could lead to the CRA being pushed away from the nasal zone.

The numerous abnormalities in the major retinal vessels quantified in this study and recognised by clinicians in previous studies indicate that a pathogenic cause of ODD could be present during embryological development and with time this leads to the various vascular patterns seen amongst ODD patients. Using the grid ensured a tool that could quantify anomalous vessel emergence and anatomy but not recognise any clear vascular abnormality potentially leading to vascular complications.

One limitation of the study is the subjective element in outlining the optic disc and placing of the grid. Especially in protruding ODD the exact outline of the disc could be difficult to define, which could also have led to an overestimation of the optic disc outline when measuring the diameter. Despite this, the study should be easily reproducible using the standardised grid created here. Another limitation is that 2D fundus photography cannot fully interpret the 3D conformation of the optic disc especially in cases of ODD. A final limitation is that refractive differences between the groups were not taken into account in this study, which could have led to differences in the magnification and, therefore, have had an impact on the

measured size of the cup. Usage of OCT rather than fundus photography could in a future study be the adequate solution to these dilemmas.

In conclusion, our study showed a significant difference in angioarchitecture of the optic disc in ODD patients in terms of point of emergence of the CRA and its first branching point and a number of arterial bifurcations within the optic disc. This characteristic angioarchitecture together with the numerous abnormalities in the vascular pattern found in previous studies points towards an early embryological disturbance that over time could evolve into various vascular differences in ODD patients.

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Declaration of interest

All of the authors declare that they have no conflicts of interest.

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