Unraveling the genetic architecture of migraine: exploring the vascular components

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CHAPTER 8

Optical Coherence Tomography Detects Retinal Changes in Hereditary Cerebral Amyloid Angiopathy

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Abstract

Background: Investigating mutation carriers with Dutch-type hereditary Cerebral Amyloid Angiopathy (D-CAA), offers the possibility to identify markers in pre- and symptomatic stages of CAA. Optical Coherence Tomography (OCT) has shown potential to detect retinal changes in several neurodegenerative diseases. We performed an exploratory study on the thickness of retinal layers as possible (early) biomarker in D-CAA mutation carriers.

Methods: D-CAA mutation carriers (n=8 presymptomatic, n=13 symptomatic, median age 50 years) and (n=9, median age 53 years) controls were scanned using Spectral Domain OCT (SD-OCT). Symptomatic mutation carriers were defined as having a history of ≥1 symptomatic intracerebral hemorrhage. D-CAA mutation carriers and controls were recruited from our D-CAA cohort and a healthy control cohort. Total peripapillary Retinal Nerve Fiber Layer (pRNFL) thickness, six regions of pRNFL, total macular volume (TMV), and individual macular regions thickness were measured and analyzed adjusted for age.

Results: The overall median (IQR) thickness of pRNFL was decreased in symptomatic, but not presymptomatic D-CAA mutation carriers compared with controls (91µm (86-95) versus 99µm (87-108),p=0.006). Both presymptomatic (111µm (93-122) versus 131µm (123-143),p<0.001) and symptomatic carriers (119µm (95-128) versus 131µm (123-143),p=0.034) had a thinner temporal-superior quadrant of the pRNFL versus controls. TMV or individual macular layers thickness did not differ between carriers and controls.

Conclusions: Thinning of the Retinal Nerve Fiber Layer may be a candidate marker of disease in hereditary CAA. Further studies are needed to determine whether retinal thinning is present in sporadic CAA and estimate its value as marker for disease progression.

Introduction

Dutch-type hereditary Cerebral Amyloid Angiopathy (D-CAA), also referred to as Hereditary Cerebral Hemorrhage With Amyloidosis-Dutch type (HCHWA-D), is an autosomal dominant neurovascular disease. D-CAA shares a similar pathology with the sporadic form of CAA, both leading to intracerebral hemorrhages (ICH) and vascular dementia. Since D-CAA mutation carriers can be studied also at the presymptomatic stage, they may provide insight in the evolution of CAA-pathology. To date, several neuro-imaging and amyloid biomarkers have been suggested.[1] Recently, the imaging method of Optical Coherence Tomography (OCT) has shown its potential in evaluating structural changes in the retina in patients with confirmed neuro(psycho)logical disorders.[2-4] Given the close relationship between the retina and the brain, studying the retina may provide an interesting predictive biomarker. Optical coherence tomography (OCT) provides high resolution cross-section images allowing quantification and follow-up of structural changes in the retina. We investigated the thickness of retinal and macular layers in D-CAA with an exploratory study using Spectral Domain (SD)-OCT.

Methods

Participants

D-CAA patients were recruited from the *'CAA-Heritage study'* of the Leiden University Medical Center.. This study identifies mutation carriers and follows them over time. Mutation carriers were diagnosed using DNA-analysis of the Glu693Gln mutation in the *APP*-gene. Mutation carriers were considered symptomatic if they suffered at least one symptomatic ICH. Exclusion criteria were age-related macular degeneration, eye trauma, macular dystrophy and primary glaucoma. Controls were included from a healthy ophthalmological control cohort at the LUMC. Controls were excluded if they had any ocular, cerebrovascular, neurodegenerative, metabolic or systemic disease. Participants were ≥18years old**.** All participants provided written informed consent. The study protocol was approved by the Medical Ethical Committe of the LUMC in accordance with the Declaration of Helsinki.

Ophthalmologic examinations

A neuro-ophthalmologist (I.C.N.) performed or supervised ophthalmologic examination of all participants, including slit lamp examination and ophthalmoscopy. Intraocular pressure (IOP) was measured using Goldmann applanation tonometry after applying topical oxybuprocaine monofree 0.4% and fluorescein dye. Afterwards, pupils were dilated with tropicamide monofree 0.5% and phenylephrine monofree

5.0%. Subsequently, color and red-free photographs of optic disc and macula were taken to be assessed for retinopathy (TRC-50DX, Topcon Europe Medical BV). Controls underwent standard ophthalmologic examination and fundus photography.

SD-Optical Coherence Tomography measurements

Optic disc and macula were analyzed in both eyes with dilated pupils using SD-OCT (Heidelberg Spectralis; Heidelberg Engineering) and image alignment eye tracking software (TruTrack ActiveEyeTracking, Heidelberg Engineering). Retinal images were created using software (Heidelberg Eye Explorer v1.9.10.0) with a minimum resolution of 768x768 pixels and field of view of 30° (figure 1A and B). Scans were obtained by blinded examiners. Peripapillary Retinal Nerve Fiber Layer (pRNFL) was measured with a circular scan with a diameter of 3.5 mm centered on the optic disc. Total macular volume (TMV) was measured using nine sectors using a 1-, 3-, and 6-mm grid focused on the fovea. Sectoral analyses of the pRNFL were performed (figure 1A); individual layers were automatically demarcated, qualitatively assessed and objectively quantified by segmentation software to measure thickness (figure 1B) as several neurological diseases have been shown to affect the retina in certain geometric locations and cellular layers.[5,6]

Statistical analyses

Demographics were described as median (interquartile range (IQR)) and count (percentages). SD-OCT-measurements were analyzed using generalized estimating equations (matrix: exchangeable) to account for inter-eye correlations within participants and to correct for age. GEE analysis is an extension of the generalized linear model. A p-value of <0.05 was considered significant. The APOSTEL recommendations for reporting quantitative OCT studies were applied.[7] Symptomatic and presymptomatic mutation carriers were also separately compared with controls.

Data Availability Statement

The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

Results

We included n=21 D-CAA mutation carriers and n=9 controls (42 eyes and 18 eyes, respectively). Mutation carriers were younger (median 50 years (IQR 47-57) vs. 58 years (IQR 54-64)), sex distribution was similar (women 62% vs. 56%). Of the D-CAA

mutation carriers, n=13 were symptomatic (median age 53 (IQR 49-62)) and n=8 were presymptomatic (median age 49 (IQR 44-52)). Symptomatic carriers developed a symptomatic intracerebral hemorrhage previously with a median of 3.8 years (IQR 0.8-7.8)). Of the eight presymptomatic mutation carriers, six had clinical MRI scans available that were performed after the OCT examination. Of these six, three did not have any microbleeds, little white matter hyperintensities (Fazekas 1) and no cortical superficial siderosis.. The other three had ≤10 strictly lobar microbleeds, varying white matter hyperintensity volumes (Fazekas 1-3), and no cortical superficial siderosis.

Ophthalmologic examinations

Besides slight narrowing of arterioles in one presymptomatic and four symptomatic mutation carriers (n=10 eyes), no retinopathy was observed in D-CAA mutation carriers. One symptomatic mutation carrier had early stage diabetes mellitus type II, but showed no signs of retinopathy. No elevated intraocular pressure was found with a median intraocular pressure in D-CAA mutation carriers of 14.0mmHg (13.0-16.0) and 15.5mmHg (12.8-19.0) in controls.

SD-Optical Coherence Tomography measurements

The pRNFL was thinner in D-CAA mutation carriers compared with controls (median (IQR) 91µm (86-95) vs. 99µm (87-108), p=0.006, figure 1C). This difference was mainly driven by symptomatic mutation carriers who had a thinner pRNFL compared with controls (92µm (87-96) vs. 99µm (87-108) , p=0.006, supplementary table). Presymptomatic mutation carriers showed a similar trend towards a thinner pRNFL (90µm (83-92) vs. 99µm (87-108), p=0.05, supplementary table). A thinner RNFL was also seen in two of the three presymptomatic carriers without presence of lobar microbleeds on MRI.

Sectoral analyses demonstrated that the pRNFL was thinner in the peripapillary temporal-superior sector in mutation carriers vs. controls (113µm (95-126) vs. 131µm (123-143),p=0.009, table 1). This sector was thinner in both symptomatic mutation carriers compared with controls (119µm (95-128) vs. 131µm (123-143),p<0.001, supplementary table) as well as presymptomatic mutation carriers (111µm (93-122) vs. 131µm (123-143),p<0.034, supplementary table). No differences were found in TMV (8.6mm^3 (8.3-8.8) vs. 8.7mm^3 (8.4-8.8), p=0.35, figure 1D) or individual macula layers (table 1 and supplementary table).

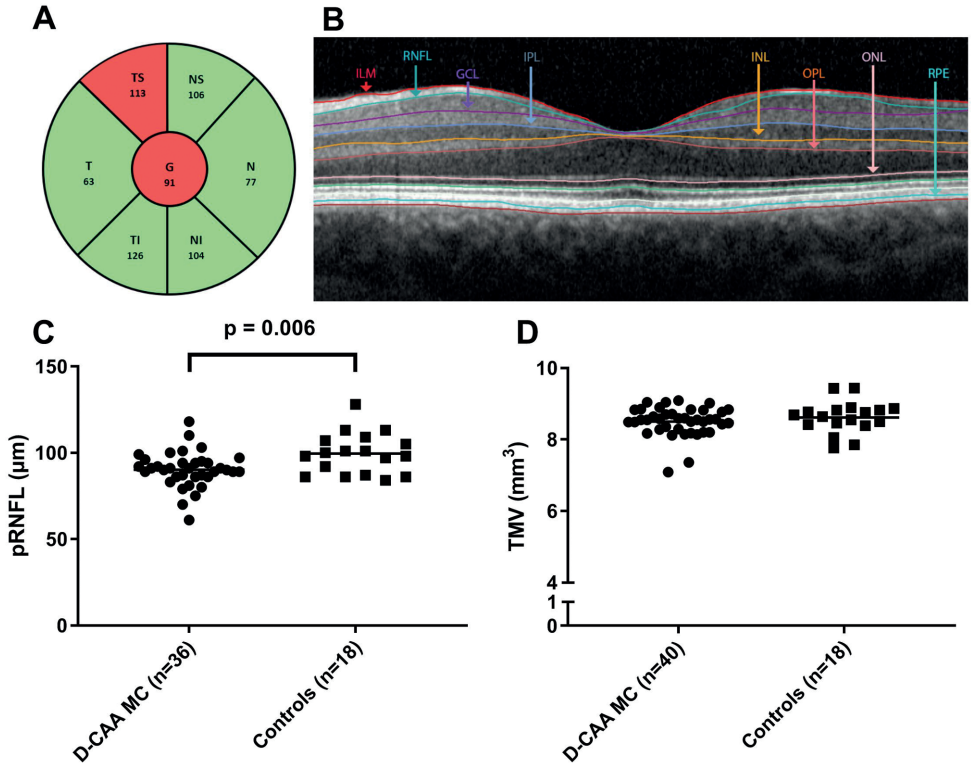

Figure 1. Optical Coherence Tomography measurements.

A circular scan measured the Peripapillary Retinal Nerve Fiber Layer (pRNFL) with a diameter of 3.5 mm centered on the optic disc. Sectoral analysis of the pRNFL was performed. Median of all mutation carriers per sector are reported (figure 1A). The total macular volume was measured by using nine sectors using a 1-, 3-, and 6-mm grid focused on the fovea centralis. Individual layers were automatically demarcated (figure 1B). The mean pRNFL thickness was reduced in D-CAA mutation carriers compared with controls (figure 1C). No difference was found in TMV (figure 1D). Global (G); temporal-superior (TS); temporal (T); temporal-inferior (TI); nasal-inferior (NI); nasal (N); nasal-superior (NS); inner limiting membrane (ILM); retinal nerve fiber layer (RNFL); ganglion cell layer (GCL); inner plexiform layer (IPL); inner nuclear layer (INL); outer plexiform layer (OPL); outer nuclear layer (ONL); retinal pigment epithelium (RPE).

Table 1. Peripapillary retinal fiber layer and macula layer thickness in D-CAA vs. controls.

	D-CAA patients median (IQR) (n=42)	Controls median (IQR) (n=18)	Coefficient	CI	P-value
Thickness of peripapillary sectors of the pRNFL†					
Mean pRNFL (µm)	91 (86-95)	99 (87-108)	-11.4	-19.5;-3.3	**0.006**
nasal-superior (µm)	106 (90-126)	102 (90-114)	-7.4	-25.7;10.9	0.43
nasal (µm)	77 (66-95)	79 (68-104)	-8.1	-26.2:10.1	0.39
nasal-inferior (µm)	104 (91-120)	124 (90-143)	-16.5	-37.0:4.0	0.11
temporal-inferior (µm)	126 (107-135)	135 (120-144)	-15.1	-33.7:3.5	0.11
temporal (µm)	63 (55-71)	62 (57-70)	-3.6	-10.7:3.5	0.32
temporal-superior (µm)	113 (95-126)	131 (123-143)	-23.2	-40.5:-5.8	**0.009**
Thickness of the macula layers ‡					
TMV (mm^3)	8.6 (8.3-8.8)	8.7 (8.4-8.8)	-0.2	-0.5;0.2	0.35
TMT (µm)	311 (305-321)	317 (306-320)	-2.6	-14.3:9.0	0.66
mRNFL (µm)	26 (25-28)	25 (23-27)	1.2	-0.6:2.9	0.19
GCL (µm)	40 (37-41)	40 (36-41)	-0.0	-2.5:2.5	1.00
IPL (µm)	34 (31-35)	34 (32-35)	-0.5	-2.6:1.6	0.65
INL (µm)	35 (34-37)	35 (33-38)	0.2	-1.9:2.4	0.84
OPL (µm)	29 (27-31)	29 (28-29)	-0.9	-2.1:0.3	0.15
ONL (µm)	68 (65-73)	71 (64-74)	-1.8	-8.5:4.9	0.60
RPE (µm)	15 (14-15)	15 (13-15)	0.3	-0.7:1.3	0.56

Interquartile range (IQR); confidence interval (CI); peripapillary retinal nerve fiber layer (pRNFL); total macular thickness (TMT); macular retinal nerve fiber layer (mRNFL); ganglion cell layer (GCL); inner plexiform layer (IPL); inner nuclear layer (INL); outer plexiform layer (OPL); outer nuclear layer (ONL); retinal pigment epithelium (RPE). Analyzes with generalized estimating equations to account for inter-eye correlations within participants and to correct for age. † In three D-CAA patients the scans were not of sufficient quality for analysis. ‡ In one D-CAA patient the scans were not of sufficient quality for analysis.

Discussion

In this exploratory study we demonstrated a thinner pRNFL in symptomatic D-CAA patients. Sectoral analyses showed that the temporal-superior sector of the pRNFL was thinner in both presymptomatic and symptomatic mutation carriers, which might indicate that changes to retinal nerve fibers occur before symptomatic intracerebral hemorrhage.

The pRNFL contains largely unmyelinated axons of the macular ganglion cells, thus mutation carriers demonstrate a loss of intraocular axonal integrity. RNFL thinning of the temporal sector indicates predominant damage of the papillomacular bundle, consisting of smaller, thinly myelinated axons. In several neurological disorders, including other hereditary arteriopathies,[4] it was observed that these thinner axons are more susceptible to injury.[8,9] Thinning of the RNFL is therefore not specific for CAA, although it does add to understanding CAA pathology. The RNFL forms the most inner retinal layer connecting the neuroretina with visual tracts leading to the visual cortex. The visual cortex is of particular interest in CAA, since CAA-pathology predominantly appears in the lobar regions of the brain, and mostly in the occipital lobe in both sporadic CAA[10] and D-CAA.[11] Damage in areas covering the visual tract may lead to retrograde degeneration of the optic nerve causing retinal changes starting with thinning of the RNFL.[3] It will be interesting to investigate if these peripapillary changes correlate with the clinical course as has been demonstrated in other diseases or with other biomarkers.[3,12,13] We investigated a hereditary form of CAA. So far, retinal changes in sporadic CAA have only been reported in case reports.[14,15]

This exploratory study has limitations. No vascular retinopathy was demonstrated in our study, but no invasive fluorescence angiography scans were performed as we aimed to find non-invasive biomarkers. We cannot rule out that invasive fluorescence angiography might have detected vasculopathy in these patients, which is a potential cause of RNFL thinning. However, several neurologic disease without retinal vasculopathy have shown thinning of the RNFL as well.[6] Secondly, our study has a relative small sample size due to the rareness of the disorder and might have been underpowered for subtle retinal changes., Additionally, even though we did multiple statistical tests, the significant level was kept at 0.05 which can be justified by the exploratory nature of this study. Future studies should aim to replicate these findings. Strength of our study are that we adjusted for differences in age and intereye correlation, and used an unique hereditary model for sporadic CAA in which the presymptomatic disease stage can be studied.

In CAA-related research, especially early markers are needed for future prevention trials. To date, several (early) markers in D-CAA have been demonstrated including reduced cerebrovascular reactivity and reduced amyloid-β concentrations in cerebrospinal fluid.[1] This study shows that thinning of the pRNFL measured with OCT might also serve as an early biomarker in CAA, especially since OCT is performed noninvasively in several minutes and with no safety risks.

Conclusion

Thinning of the pRNFL might serve as a marker for early and later phases of CAA-pathology. These results raise the possibility that OCT may be used as a rapid, non-invasive tool to detect early CAA-pathology.

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Supplementary table 1. Thickness of peripapillary sectors of the pRNFL in presymptomatic and symptomatic D-CAA mutation carriers and controls.

	Presymptomatic D-CAA patients median (IQR) (n=16†)	Symptomatic D-CAA patients median (IQR) (n=26‡)	Controls median (IQR) (n=18)	Coefficient§	CI§	P-value§	Coefficient¶	CI¶	P-value¶
Thickness of peripapillary sectors of the pRNFL									
pRNFL (µm)	90 (83-92)	92 (87-96)	99 (87-108)	-12.4	-25.0:0.1	0.05	-11.4	-19.4:-3.3	**0.006**
nasal-superior (µm)	104 (88-125)	106 (87-131)	102 (90-114)	-9.3	-28.5:9.8	0.34	-7.5	-28.0:12.9	0.47
nasal (µm)	73 (66-88)	83 (65-97)	79 (68-104)	-3.0	-20.3:14.2	0.73	-7.3	-27.6:13.0	0.48
nasal-inferior (µm)	109 (71-122)	103 (92-116)	124 (90-143)	-13.2	-42.4:15.9	0.37	-17.2	-37.7:3.3	0.10
temporal-inferior (µm)	126 (109-132)	127 (104-137)	135 (120-144)	-22.7	-54.6:9.3	0.16	-15.4	-34.6:3.7	0.11
temporal (µm)	64 (56-76)	62 (55-68)	62 (57-70)	-5.4	-15.2:4.4	0.28	-4.1	-12.2:3.9	0.32
temporal-superior (µm)	111 (93-122)	119 (95-128)	131 (123-143)	-33.3	-51.2:-15.4	**<0.001**	-21.1	-40.5:-1.6	**0.034**
TMV and thickness of the macula layers									
TMV (mm^3)	8.6 (8.5-8.8)	8.5 (8.2-8.7)	8.7 (8.4-8.8)	-0.1	-0.5:0.3	0.53	-0.2	-0.5:0.2	0.41
TMT (µm)	313 (310-322)	308 (303-318)	317 (306-320)	0.8	-12.4:14.2	0.90	-3.0	-15.4:9.4	0.64
mRNFL (µm)	27 (25-28)	26 (25-28)	25 (23-27)	0.9	-1.1:3.0	0.38	1.2	-0.8:3.1	0.24
GCL (µm)	40 (37-41)	40 (36-41)	40 (36-41)	0.0	-2.8:2.9	0.98	0.0	-2.7:2.7	0.99
IPL (µm)	34 (32-35)	34 (31-35)	34 (32-35)	-0.0	-2.4:2.4	0.99	-0.7	-2.9:1.6	0.57
INL (µm)	35 (34-37)	36 (34-38)	35 (33-38)	0.6	-1.7:2.9	0.60	0.5	-1.8:2.9	0.66
OPL (µm)	29 (27-32)	29 (27-31)	29 (28-29)	-0.6	-2.7:1.5	0.57	-0.9	-2.2:0.4	0.19
ONL (µm)	69 (66-74)	68 (61-73)	71 (64-74)	0.9	-5.3:7.1	0.78	-2.4	-9.9:5.0	0.52
RPE (µm)	15 (13-15)	15 (14-15)	15 (13-15)	0.2	-1.1:1.4	0.81	0.4	-0.6:1.4	0.46

Interquartile range (IQR); confidence interval (CI); peripapillary retinal nerve fiber layer (pRNFL); total macular thickness (TMT); macular retinal nerve fiber layer (mRNFL); ganglion cell layer (GCL); inner plexiform layer (IPL); inner nuclear layer (INL); outer plexiform layer (OPL); outer nuclear layer (ONL); retinal pigment epithelium (RPE). Analyzes with generalized estimating equations to account for inter-eye correlations within participants and to correct for age. † In one presymptomatic D-CAA patient the scans of the pRNFL were not of sufficient quality for analysis. ‡ Macula scans of one symptomatic D-CAA patient and the pRNFL scans of two symptomatic D-CAA patients were not of sufficient quality for analysis. § Analyses of presymptomatic patients and controls. ¶ Analyses of symptomatic patients and controls.