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Background and purpose: Investigating mutation carriers with Dutch-type hereditary (D-) cerebral amyloid angiopathy (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. The aim of the present exploratory study was to investigate thinning of retinal layers as a possible (early) biomarker in D-CAA mutation carriers.

Methods: Twenty-one D-CAA mutation carriers ($n = 8$ presymptomatic, $n = 13$ symptomatic, median age 50 years) and nine controls (median age 53 years) were scanned using spectral-domain 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 region thickness were measured and analysed, adjusted for age.

Results: The overall median (interquartile range) thickness of pRNFL was lower in symptomatic, but not presymptomatic D-CAA mutation carriers compared with controls [91 (86–95) μm vs. 99 (87–108) μm; $P = 0.006$]. Both presymptomatic [111 (93–122) μm vs. 131 (123–143) μm; $P < 0.001$] and symptomatic carriers [119 (95–128) μm vs. 131 (123–143) μm; $P = 0.034$] had a thinner temporal-superior quadrant of the pRNFL versus controls. TMV or individual macular layer 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 a marker for disease progression.

Introduction

Dutch-type hereditary (D-) cerebral amyloid angiopathy (CAA), also referred to as hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D), is an autosomal dominant neurovascular disease. D-CAA has a similar pathology to the sporadic form of CAA, both leading to intracerebral hemorrhage and vascular dementia. Since D-CAA mutation carriers can also be studied at the presymptomatic stage, they may provide insight into the evolution of CAA pathology. To date, several neuro-imaging and amyloid biomarkers have been suggested [1]. Recently, the optical coherence tomography (OCT) imaging method has shown its potential in evaluating structural changes in the retina in patients with confirmed neuro

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(psycho)logical disorders [2–4]. Given the close relationship between the retina and the brain, studying the retina may provide interesting predictive biomarkers. OCT provides high-resolution cross-sectional images, allowing quantification and follow-up of structural changes in the retina. We investigated the thickness of retinal and macular layers in D-CAA in an exploratory study using spectral-domain OCT.

Methods

Participants

People with D-CAA were recruited from the CAA Heritage Study of the Leiden University Medical Center (LUMC), a study which 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 experienced at least one symptomatic intracerebral hemorrhage. 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 aged ≥18 years. All participants provided written informed consent. The study protocol was approved by the Medical Ethical Committee 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 was measured using Goldmann applanation tonometry after applying topical oxybuprocaine monofree 0.4% and fluorescein dye. Afterwards, participants' 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.

Spectral-domain OCT measurements

Optic disc and macula were analysed in both eyes with dilated pupils using spectral-domain 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° (Fig. 1a and b). Scans were obtained by blinded examiners. The 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 (Fig. 1a); individual layers were automatically demarcated, qualitatively assessed and objectively quantified using segmentation software to measure thickness (Fig. 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). Spectral-domain OCT measurements were analysed using generalized estimating equations (matrix: exchangeable) to account for inter-eye correlations within participants and to correct for age. Generalized estimating equation 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.

Results

We included 21 D-CAA mutation carriers and nine controls (42 and 18 eyes, respectively). Mutation carriers were younger than controls [median (IQR) age 50 (47–57) years vs. 58 (54–64) years], sex distribution was similar (62% vs. 56% women). Of the D-CAA mutation carriers, 13 were symptomatic [median (IQR) age 53 (49–62) years] and eight were presymptomatic [median (IQR) age 49 (44–52) years]. Symptomatic carriers had developed a symptomatic intracerebral hemorrhage at a median (IQR) of 3.8 (0.8–7.8) years previously. Of the eight presymptomatic mutation carriers, six had clinical magnetic resonance imaging (MRI) scans available that were performed after the OCT examination. Of these six, three had no microbleeds, few white matter hyperintensities (Fazekas 1) and no cortical superficial siderosis. The other three had ≤10 strictly lobar microbleeds, varying white matter hyperintensity

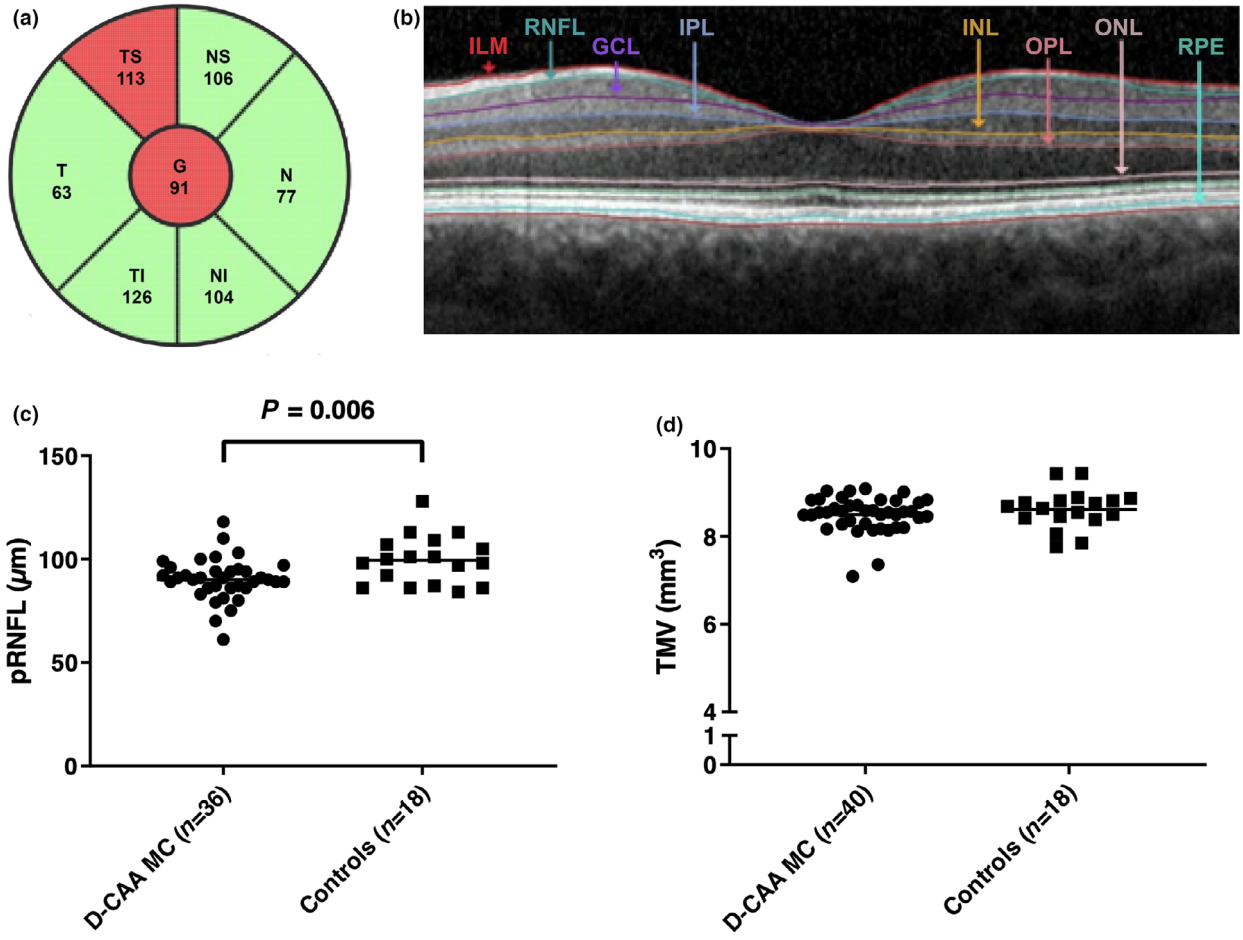

Figure 1 Optical coherence tomography measurements. A circular scan was used to measure the peripapillary retinal nerve fiber layer (pRNFL) with a diameter of 3.5 mm, centered on the optic disc. Sectoral analysis of the pRNFL was performed. Median values for all mutation carriers (MC) per sector are reported (a). Total macular volume (TMV) was measured by using nine sectors using a 1-, 3-, and 6-mm grid, focused on the fovea centralis. Individual layers were automatically demarcated (b). The mean pRNFL thickness was reduced in Dutch-type hereditary cerebral amyloid angiopathy (D-CAA) mutation carriers compared with controls (c). No difference was found in TMV (d). G, global; GCL, ganglion cell layer; ILM, inner limiting membrane; INL, inner nuclear layer; IPL, inner plexiform layer; OPL, outer plexiform layer; ONL, outer nuclear layer; N, nasal; NI, nasal-inferior; NS, nasal-superior; T, temporal; TI, temporal-inferior; TS, temporal-superior; RNFL, retinal nerve fiber layer; RPE, retinal pigment epithelium. [Colour figure can be viewed at wileyonlinelibrary.com]

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 or retinal hemorrhages were observed in D-CAA mutation carriers. One symptomatic mutation carrier had early-stage type 2 diabetes mellitus, but showed no signs of retinopathy. No elevated intraocular pressure was found with a median (IQR) intraocular pressure in D-CAA mutation carriers of 14.0 (13.0–16.0) mmHg and 15.5 (12.8–19.0) mmHg in controls.

Spectral-domain OCT measurements

The pRNFL was thinner in D-CAA mutation carriers compared with controls [median (IQR) 91 (86–95) μm vs. 99 (87–108) μm; P = 0.006 (Fig. 1c)]. This difference was mainly driven by symptomatic mutation carriers who had a thinner pRNFL compared with controls [92 (87–96) μm vs. 99 μm (87–108); P = 0.006 (Table S1)]. Presymptomatic mutation carriers showed a similar trend towards a thinner pRNFL [90 (83–92) μm vs. 99 (87–108) μm; P = 0.05 (Table S1)]. A thinner pRNFL 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 versus controls [113 (95–126) μm vs. 131 (123–143) μm; $P = 0.009$ (Table 1)]. This sector was thinner in both symptomatic mutation carriers compared with controls [119 (95–128) μm vs. 131 (123–143) μm; $P < 0.001$ (Table S1)] as well as presymptomatic mutation carriers [111 (93–122) μm vs. 131 (123–143) μm; $P < 0.034$ (Table S1)]. No differences were found in TMV [8.6 (8.3–8.8) mm^3 vs. 8.7 (8.4–8.8) mm^3; $P = 0.35$ (Fig. 1d)] or individual macula layers (Table 1 and Table S1).

Discussion

In this exploratory study, we demonstrated a thinner pRNFL in symptomatic patients with D-CAA. 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 may 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 some limitations. Firstly, no vascular retinopathy was demonstrated, as no

Table 1 Peripapillary retinal fiber layer and macula layer thickness in Dutch-type hereditary cerebral amyloid angiopathy mutation carriers versus controls

	D-CAA patients ($n = 42$) Median (IQR)	Controls ($n = 18$) Median (IQR)	Coefficient	CI	*P*
Thickness of peripapillary sectors of the pRNFL[a]					
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[b]					
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

CI, confidence interval; D-CAA, Dutch-type hereditary cerebral amyloid angiopathy; GCL, ganglion cell layer; INL, inner nuclear layer; IPL, inner plexiform layer; IQR, interquartile range; mRNFL, macular retinal nerve fiber layer; ONL, outer nuclear layer; OPL, outer plexiform layer; pRNFL, peripapillary retinal nerve fiber layer; RPE, retinal pigment epithelium; TMT, total macular thickness. Analyses conducted using generalized estimating equations to account for inter-eye correlations within participants and to correct for age. [a]In three D-CAA patients the scans were not of sufficient quality for analysis. [b]In one D-CAA patient the scans were not of sufficient quality for analysis. P-values are statistically significant

invasive fluorescence angiography scans were performed because we aimed to find non-invasive biomarkers. We cannot exclude the possibility that invasive fluorescence angiography might have detected vasculopathy in these patients, which is a potential cause of RNFL thinning. However, several neurologic diseases without retinal vasculopathy have also shown thinning of the RNFL [6]. Secondly, the study has a relatively small sample size due to the rareness of the disorder and might be underpowered to detect subtle retinal changes. Finally, even though we performed multiple statistical tests, the significance level was kept at 0.05, which can be justified by the exploratory nature of the study. Future studies should aim to replicate these findings.

Strengths of the present study include the fact that we adjusted for differences in age and inter-eye correlation, and used a 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 a candidate biomarker in CAA, especially since OCT is performed non-invasively in several minutes and with no safety risks.

In 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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Disclosure of conflicts of interest

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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.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Thickness of peripapillary sectors of the peripapillary retinal nerve fiber layer in presymptomatic and symptomatic Dutch-type hereditary cerebral amyloid angiopathy (D-CAA) mutation carriers and controls.

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