Imaging the Retina in Alzheimer's Disease

den Haan, J.

2019

document version
Publisher's PDF, also known as Version of record

CHAPTER 2

Retinal thickness correlates with parietal cortical atrophy in early-onset Alzheimer's disease and controls

Jurre den Haan, Sarah F. Janssen, Jacoba A. van de Kreeke,
Philip Scheltens, Frank D. Verbraak, Femke H. Bouwman

Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring,
November 2018, Volume 10, 49-55.

Abstract

The retina may reflect Alzheimer's disease (AD) neuropathological changes and is easily visualized with optical coherence tomography (OCT). Retinal thickness decrease has been correlated to AD, however without information on amyloid status. We correlated retinal (layer) thickness to AD biomarkers in amyloid positive early onset AD (EOAD) patients and amyloid negative controls. We measured macular thickness and peripapillary retinal nerve fiber layer (pRNFL) thickness with OCT in 15 EOAD patients and 15 controls and correlated retinal thickness to visual rating scores for atrophy on MRI. Total macular thickness correlated to parietal cortical atrophy in both groups (Spearman Rho -.603, p=0.001). Macular and pRNFL thickness were not significantly decreased in EOAD compared to controls. Retinal thickness does not discriminate EOAD from controls, but is correlated to parietal cortical atrophy in both groups. These findings may suggest reflection of cerebral cortical changes in the retina, independent of amyloid.

Background

With the currently increasing amount of clinical trials for Alzheimer's disease (AD) and its prodromal stage, a patient friendly and sensitive diagnostic method for an early diagnosis is urgently needed. The retina is embryologically derived from the neural tube and as a protrusion from the brain, it shares many similarities with brain tissue. Through the pupil, the retina and its neurons are easily examined with optical coherence tomography (OCT) thus serving as a potential non-invasive diagnostic target in neurodegenerative diseases such as AD, Parkinson's disease (PD) and dementia with Lewy bodies (DLB)[1-4].

Currently cortical atrophy on MRI, as a biomarker for neurodegeneration, can be assessed with visual rating scores for global cortical atrophy, medial temporal lobe atrophy and parietal cortical atrophy[5-7]. Typically, late onset Alzheimer's disease (LOAD) shows medial temporal lobe atrophy, while early onset Alzheimer's disease (EOAD) shows a diffuse pattern including parietal cortical atrophy[8]. Retinal thickness decrease measured with OCT might serve as a non-invasive proxy of cortical atrophy on MRI. Previous research showed both total macular and peripapillary retinal nerve fiber layer (RNFL) thinning in AD measured with OCT, however this was not consistent in all studies. In a recent meta-analysis we found an absolute decrease of peripapillary RNFL of 10 μm and of total macular thickness of 16 μm in AD compared to controls[9].

Like AD, glaucoma is a complex neurodegenerative disease and shows considerable overlap of neuro-retinal changes with AD[10-14]. Previous studies did not account for the possible confounding effect of glaucoma on OCT measurements in AD patients, nor did they include established AD-biomarkers as part of AD clinical diagnosis (NIA-AA)[10,11,15].

The objective of this study was to assess retinal layer thickness in amyloid positive early onset AD patients compared to amyloid negative healthy controls, with the exclusion of glaucoma. In addition correlation of retinal measures with established biomarkers in AD, such as cortical atrophy on MRI, was assessed.

Methods

Subjects

Fifteen subjects with EOAD and 17 controls(age < 70 years, MMSE ≥17, thus capable of giving informed consent), were included from the screening program of the Alzheimer Center of the VU University Medical Center embodying the basis of the Alzheimer Dementia Cohort (ADC)[16]. Controls comprised subjects with subjective cognitive decline (SCD), defined as subjective cognitive complaints without objective cognitive impairment on neuropsychological assessment, no signs of neurodegeneration on neuroimaging and absence of amyloid pathology based on CSF and/or amyloid-PET. Patients and controls underwent a standardized ADC screening program including: MMSE, magnetic resonance imaging (MRI), and lumbar puncture for amyloid-$\beta_{1\text{-}42}$, tau_{181} and phosphorylated tau (pTau)-levels. MRI visual rating scores for cortical atrophy were used for medial temporal lobe atrophy (MTA), global cortical atrophy (GCA) and parietal cortical atrophy (PCA)[6,7]. MRI-scans were scored by a blinded rater prior to a multidisciplinary consensus meeting where a clinical diagnosis was made by consensus. All AD patients fulfilled NIA-AA criteria and had evidence of amyloid pathology in cerebrospinal fluid (CSF) and/or amyloid-Positron Emission Tomography (PET) (Florbetaben n=13, Florbetapir n=9)[15]. CSF tau_{181}/ Amyloid-$\beta_{1\text{-}42}$ ratio >0.52 was considered indicative for AD[17]. Parametric images of amyloid-PET scans were assessed by experienced raters and visually interpreted as amyloid positive or amyloid negative following FDA guidelines for Florbetaben and Florbetapir. Exclusion criteria were (ophthalmological) conditions interfering with OCT quality/retinal thickness: severe cataract, age related macular degeneration and glaucoma and neurological or systemic chronic conditions known to interfere with retinal thickness (e.g. multiple sclerosis (MS), Parkinson's disease (PD), diabetes mellitus (DM), rheumatoid arthritis (RA), sarcoidosis, Crohn's disease, and colitis ulcerosa). In addition we excluded subjects with ischemic stroke and/or mild to severe white matter hyperintensities on MRI, operationalized as a Fazekas score>1[18].

Eye examinations

Subjects were included within a year after the ADC screening program and underwent the following eye examinations: best corrected visual acuity (BCVA), intra ocular eye pressure (IOP) using non-contact tonometry (if IOP>20mmHg we used contact applanation tonometry), slit lamp examination of the anterior and posterior segment and fundus photography (Topcon TRC 50DX type IA), Heidelberg Retinal Tomography (HRT) optic nerve head (ONH) analysis and Frequency Doubling Technology (FDT) for visual fields. Tropicamide 0.5% was administrated for pupil dilation to facilitate optimal ophthalmic examination.

We followed the 4th European Glaucoma Guideline criteria: glaucoma was diagnosed when 2 of the 3 following measurements were abnormal: ocular pressure (>21 mmHg), structural glaucomatous changes (examined with HRT using the Moorfields Regression Analysis) and functional changes (examined with FDT technique)[19]. All examinations were interpreted by an ophthalmologist and resident in ophthalmology (FV and SJ). This study was designed and conducted according to the Declaration of Helsinki and the study protocol was approved by the Ethical Committee of the VU University Medical Center. All patients gave their written informed consent in the presence of their caregiver.

Optical Coherence Tomography

Two protocols for both eyes were performed in each subject with Heidelberg Spectralis Spectral Domain (SD) OCT: 1) central retina(macula) dense horizontal scanning; central 20°x20° area; 49 b-scans (averaging 16 frames per b-scan); 512 a-scans per b-scan, and 2) axonal ring scan around the optic nerve head for RNFL.
Peripapillary RNFL was measured in six sectors provided by Heidelberg software. Macular thickness was measured in the Early Treatment of Diabetic Retinopathy Study (ETDRS)-map (fovea (**Ø** 1mm), and the mean of four quadrants of both the inner ring (**Ø** 3mm), area 2 to 5, and the outer ring(**Ø** 6mm), area 6 to 9, ring) (figure 1). In the fovea, the inner and the outer ring segmentation analysis was performed with Heidelberg segmentation software (version 1.9.204.0) to calculate thickness of the following retinal layers: 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) and retinal pigment epithelium (RPE) (figure 1).

Statistical analysis

Sample size calculation

In our previous meta-analysis with 887 AD patients and 864 controls we found a mean RNFL difference of 10µm with a standard deviation of 9µm[9]. If the true effect is 10µm with a standard deviation of 9µm, 13 subjects in each group are needed to reject the null hypothesis of no difference between the AD and control group with a power of 0.80. We therefore included 15 subjects in each group.

Data analysis

Means of retinal layer thickness in both eyes and visual cortical atrophy scores in both hemispheres were calculated. Data were (visually) tested for a normal distribution using histograms and Q-Q plots. We tested measures that were normally distributed with an independent samples t-test, non-normally distributed measures with a Mann Whitney-U test and binary variables with a Fisher's exact test. We used Pearson to correlate retinal layer thickness with CSF and MMSE and Spearman's Rho to correlate with MRI visual

rating scores. We considered, but did not choose to correct with a post hoc Bonferroni correction for multiple testing, because of the explorative nature of the study. Data analysis was performed with IBM SPSS Statistics (version 22.0) and GraphPad Prism (version 6.0) was used for graphs.

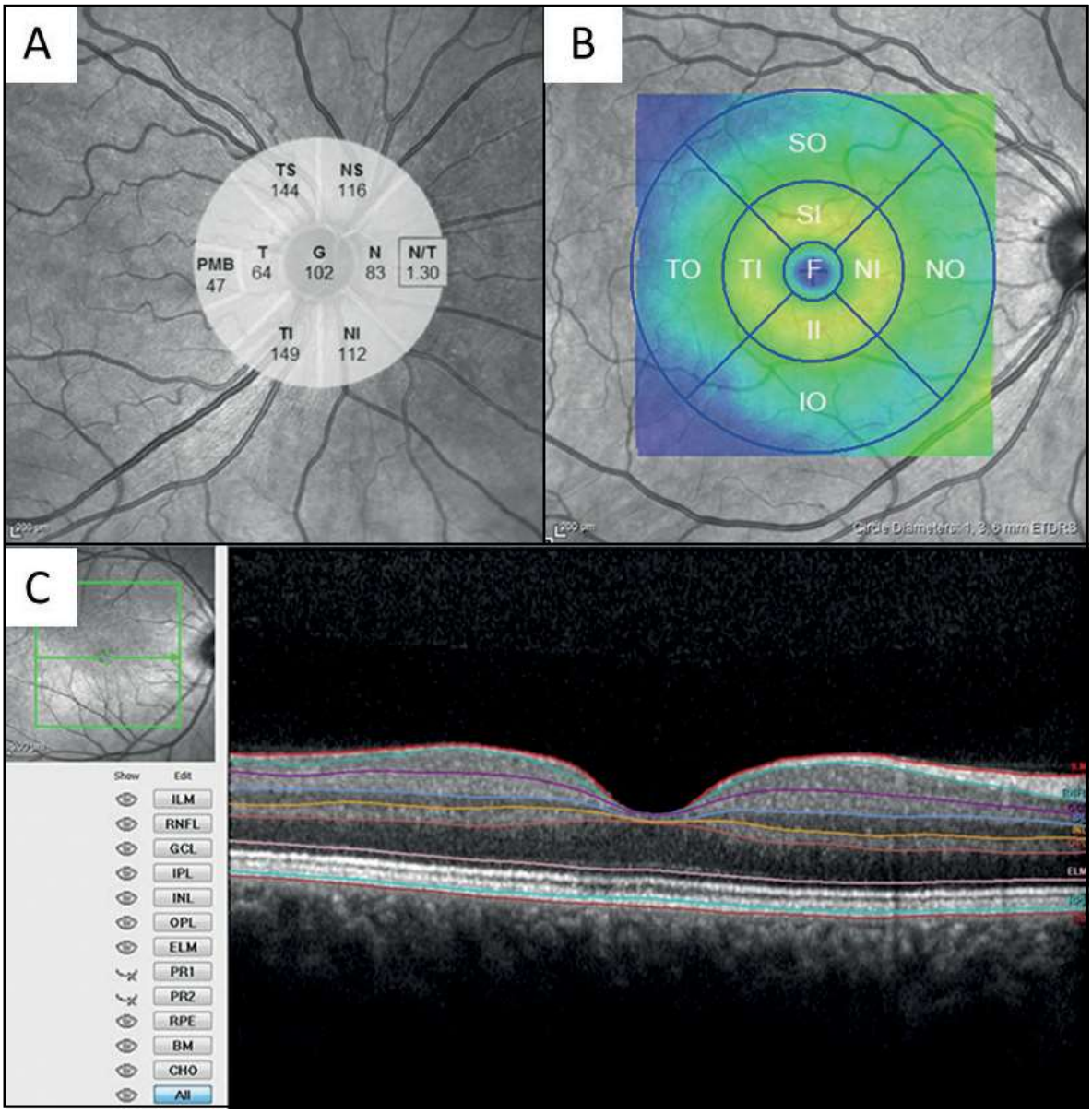

Figure 1 Optical Coherence Tomography (OCT)

OCT images. A) Around the optic nerve head (Peripapillary): retinal nerve fiber layer (RNFL) thickness is measured in the following sectors: temporal superior (TS), nasal superior (NS), nasal (N), nasal inferior (NI), temporal inferior (TI), temporal (T). Mean RNFL thickness (G), nasal/temporal ratio (N/T) and papillo-macular bundle(PMB) are also calculated. B) In the macula, retinal thickness is measured in the fovea(F)(Ø 1mm), inner ring(Ø 3mm) and outer ring(Ø 6mm) following the ETDRS-grid. The inner ring and outer ring are subdivided in four sectors (superior, nasal, inferior, temporal). C) OCT-scan (horizontal B-scan) through the macula shows segmentation of individual retinal layers: RNFL= retinal nerve fiber layer, GCL= ganglion cell layer, IPL= inner plexiform layer, INL= inner nuclear layer, OPL= outer plexiform layer and RPE= retinal pigment epithelium. Displayed are also ILM= inner limiting membrane; ELM, external limiting membrane, and BM, basal membrane.

Results

Baseline characteristics

Characteristics of patients and controls are listed in table 1. We found no differences for sex, age BCVA and IOP. MMSE, atrophy scores on MRI, CSF levels for amyloid-beta$_{1-42}$, Tau$_{181}$ and pTau and amyloid PET were indicative for an AD diagnosis in patients and were normal in controls. Two controls were excluded because of epiretinal membrane in one and glaucoma in the other. None of the other participants fulfilled criteria for glaucoma. Two patients and two controls however could be considered glaucoma suspect due to suspicious but not abnormal ONH topography and subtle visual fields defects. Excluding these participants did not alter the results.

		AD	Controls	p-value
Demographics	Number	15	15	
	Sex (m/f)	8/7	8/7	1.000[a]
	Age	62.20(±3.67)	62.00(±6.27)	.916[b]
	MMSE	21.10(±3.49)	28.53(±1.68)	**.000[b]**
CSF[1]	Amyloid$_{1-42}$	527.21(±110.18)	1095.27(±143.17)	**.000[b]**
	Tau$_{181}$	739.21(±397.64)	220.27(±81.35)	**.000[b]**
	pTau	104.57(±72.78)	37.45(±10.92)	**.006[b]**
PET[2]	Amyloid-PET (n positive/n total)	7/7	0/13	**.000[a]**
MRI	MTA	1.5(0-2.5)	0(0-2.0)	**.003[c]**
	GCA	1.0(0-2.0)	0(0)	**.001[c]**
	PCA	1.5(0-2.0)	0(0-1.0)	**.002[c]**
Ophthalmologic	IOP (mmHg)	15.97(±2.65)	15.83(±2.79)	.894[b]
	Visual Acuity (logmar)	-0.04(±.06)	-0.04(±.11)	.919[b]
	HRT: Moorfield	1.43(0.95-2.13)	1.51(1.14-1.89)	.106[c]
	FDT: MD	-1.86(-20.99-4.39)	0.15(-3.82-5.74)	**.021[c]**
	FDT: PSD	5.05(2.12-14.64)	3.99(2.74-6.09)	.202[c]

Table 1 Cohort characteristics

For normal distributed measures means and standard deviations are shown. For non-normal distributed measures, median, minimum and maximum are shown. [1] CSF was missing in one AD patient and 4 controls. [2] Amyloid-PET was performed in 7 AD patients and 13 SCD subjects. [a] Fisher exact, [b] independent sample t-test, [c] Mann Whitney-U test. Abbreviations: AD= Alzheimer's Disease, m=male, f=female, MMSE= mini mental state Examination, CSF= cerebrospinal fluid, pTau = phosphorylated Tau, MTA= medial temporal lobe atrophy, GCA= global cortical atrophy, PCA=parietal cortical atrophy, IOP= intra ocular pressure. HRT=Heidelberg Retinal Tomography, FDT=frequency doubling technology, MD= mean defect, PSD= pattern standard deviation.

Retinal (layer) thickness

Peripapillary RNFL (AD 95.9 µm(±9.0), HC 97.5 µm(±6.96), p=.479) and total retinal layer thickness in the ETDRS defined areas (AD 316.1µm(±11.0), HC 320.5µm(±7.5), p=.136) were not significantly different between groups (figure 2, table 2). Segmentation of the ETDRS defined foveal, inner and outer ring areas showed no significant decrease of the individual retinal layers: 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) and retinal pigment epithelium (RPE) in AD patients (table 2).

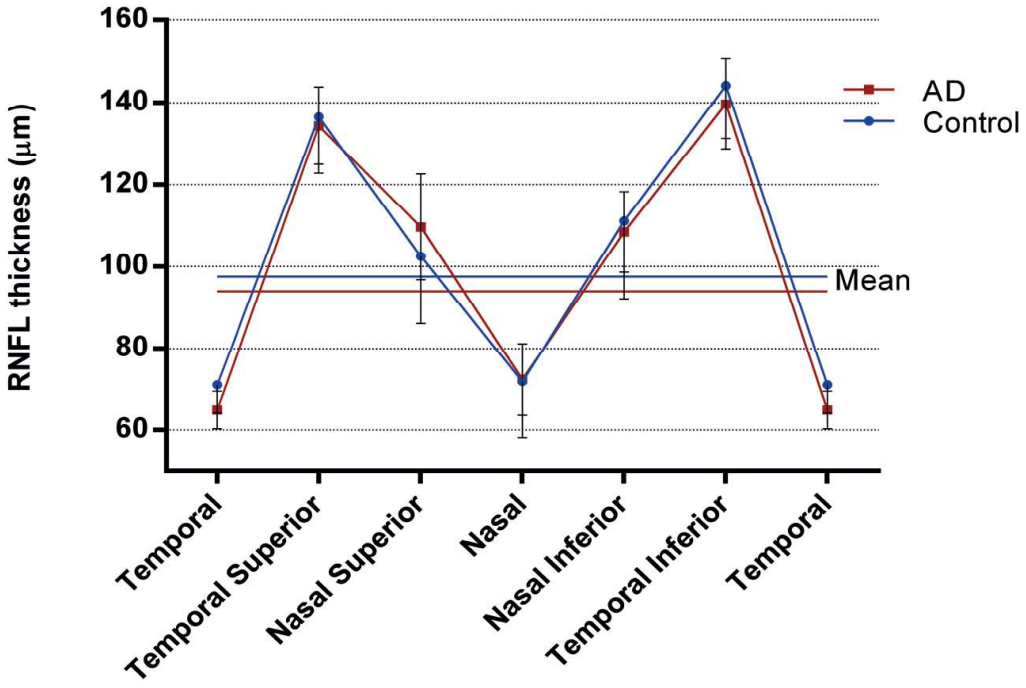

Figure 2 Peripapillary RNFL (in µm)

Peripapillary retinal nerve fiber layer thickness (RNFL) presented as mean and in 6 sectors do not significantly differ between AD and controls.

		AD	Controls	p-value[a]
Retinal thickness	Fovea	280.47(18.00)	281.867(17.19)	.853
	Inner Ring	339.63(11.33)	343.69(9.00)	.286
	Outer Ring	292.67(11.46)	297.30(8.34)	.216
RNFL	Fovea	12.70(2.07)	13.17(1.68)	.503
	Inner Ring	21.92(1.91)	21.81(1.73)	.872
	Outer Ring	34.17(3.33)	35.57(3.92)	.303
GCL	Fovea	15.47(3.90)	15.67(3.36)	.881
	Inner Ring	50.73(2.99)	51.26(2.83)	.620
	Outer Ring	34.47(2.16)	35.05(2.02)	.456
IPL	Fovea	21.67(3.72)	22.00(3.39)	.799
	Inner Ring	41.55(1.90)	41.88(2.05)	.648
	Outer Ring	28.57(1.62)	28.94(1.47)	.512
INL	Fovea	22.33(5.74)	21.57(3.57)	.664
	Inner Ring	41.18(2.87)	40.91(2.63)	.786
	Outer Ring	32.47(1.62)	32.54(1.56)	.902
OPL	Fovea	26.93(4.66)	25.87(3.40)	.480
	Inner Ring	32.39(4.30)	33.49(3.30)	.439
	Outer Ring	27.28(1.97)	27.78(2.23)	.515
ONL	Fovea	94.97(11.05)	97.13(8.48)	.552
	Inner Ring	70.21(8.66)	72.71(6.78)	.386
	Outer Ring	56.54(6.81)	58.68(5.92)	.367
RPE	Fovea	16.50(1.31)	16.30(1.10)	.654
	Inner Ring	15.18(0.60)	15.58(1.39)	.323
	Outer Ring	13.50(0.70)	13.78(1.30)	.476
Macular volume (mm^3)		8.51(0.40)	8.69(0.21)	.146

Table 2 Macular thickness: segmentation analysis

Retinal thickness in μm(sd) in the macula of all individual layers and macular volume do not significantly differ between AD and controls. [a]independent sample t-test.
RNFL= retinal nerve fiber layer, GCL=ganglion cell layer, IPL=inner plexiform layer, INL=inner nuclear layer, OPL=outer plexiform layer, ONL=outer nuclear layer, RPE=retinal pigment epithelium.

Correlation with AD-biomarkers

We found a correlation between mean total macular thickness in the inner and outer ring with PCA (Spearman's Rho= -.603, p=0.001) and GCA (Spearman's Rho= -.443, p=0.018) on MRI in the total group, but not with MTA (figure 3). Correlations with PCA in separate diagnostic groups were comparable (AD: Spearman Rho= -.561, p=0.029, Controls: Spearman rho= -.587 p=0.035). The correlation with GCA in the AD subgroup was significant (Spearman rho=.-592 p=0.020). All controls were scored GCA 0, and as a result no correlation could be calculated. Total macular thickness in the fovea, the inner ring and the outer ring were not correlated with CSF amyloid-$\beta_{1\text{-}42}$, tau_{181}, and p-tau levels. Mean RNFL was not correlated with CSF amyloid-$\beta_{1\text{-}42}$, tau_{181}, and p-tau levels or any of the cortical atrophy scores on MRI. No correlation with MMSE as measure for disease severity was found.

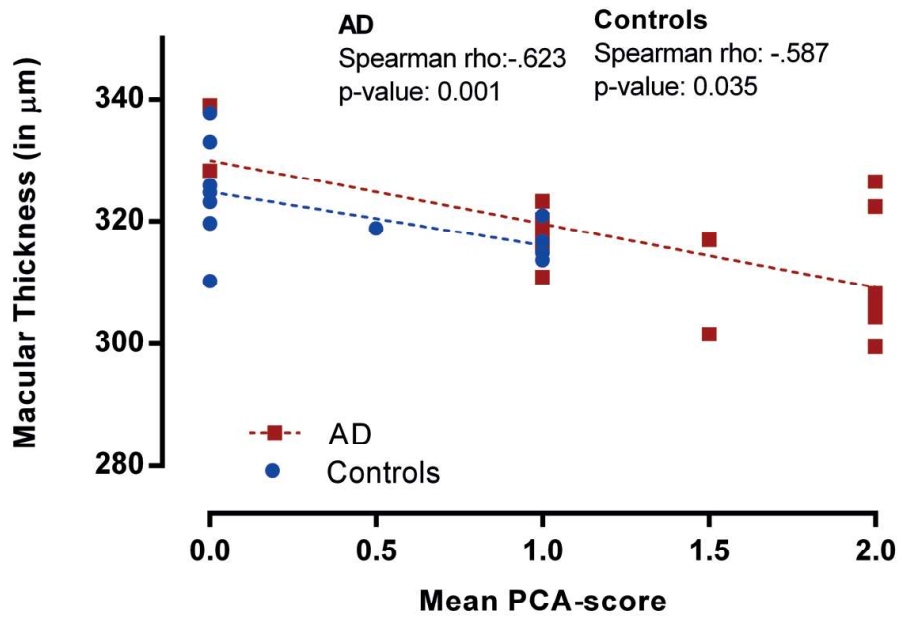

Figure 3 Correlation between macular thickness and parietal cortical atrophy (PCA)

Scatterplot visualizing the inverse correlation between macular thickness (mean of inner and outer ring of ETDRS grid) and mean visual rating score for parietal cortical atrophy on MRI.

Discussion

We showed that total macular thickness does not differ between AD and controls, but does correlate with posterior cortical atrophy in both EOAD and controls, suggesting a relationship between eye and brain that is independent of amyloid. The PCA visual rating score incorporates atrophy of the posterior cingulate, parietal-occipital sulcus (including the cuneus) and parietal lobe, covering cortices involved in optical processing[7]. Our findings suggest a direct correlation between macular thinning and focal neuronal loss of these cortical areas.

Only few studies described the relation between retinal layers and MRI features in cognitive impairment and/or controls. One study found an association between decreased brain grey matter volume (GMV) and disrupted white matter (WM) microstructure and retinal layer thickness that was present only in controls and not in cognitively impaired patients[20]. Others described a relation between medial temporal lobe volume with RNFL thickness and total macular thickness in cognitively healthy[21]. This confirms the relation we found between retinal thinning and cortical atrophy. Remarkably no study assessed this relationship specifically in a group of AD patients. We added to this literature in relating cortical atrophy measurements of AD patients to retinal thickness, also taking parietal cortical atrophy in account.

In contrast to previous studies, we did not find retinal thickness to be decreased in AD in this clearly defined and biomarker proven cohort[3,9,22]. The absence of retinal thickness thinning in the current EOAD cohort, compared to previous studies with OCT in predominantly LOAD, may be a reflection of differences between EOAD and LOAD. Neuro-radiologically, for example, medial temporal lobe atrophy (MTA) is often more prominent in LOAD compared to EOAD[8]. MTA is however also affected by age and should therefore be taken into account when assessing atrophy[8,23]. Like MTA, retinal thickness decreases with age, and therefore retinal thinning may be more prominent in LOAD compared to EOAD[24,25] explaining the lack of RFNL thinning in this study.

On the other hand, EOAD often shows a diffuse pattern of posterior atrophy on MRI (posterior cingulate cortex, temporo-parietal areas, and precuneus), while hippocampal atrophy may be absent[26,27]. As these regions contain cortices involved in visual processing, retrograde atrophy of the retina might be expected[28,29]. Despite the presence of posterior atrophy in our EOAD cohort no decrease in retinal thickness was observed. Thus, contra-intuitively, our data showed no support for retrograde atrophy resulting from atrophy in cortices involved in visual processing in EOAD.

One of the key strengths of this study is the use of amyloid biomarkers. In order to assess the retinal changes as a result of AD, without the contribution of age related (neurodegenerative) factors, we deliberately designed this study in an EOAD cohort with confirmed amyloid pathology in CSF and/or amyloid-PET. Previous studies with OCT in AD lacking amyloid biomarker conformation might have included a heterogeneous patient cohort with different dementia types. Clinical amyloid PET studies show that a clinical diagnosis of AD is not confirmed by amyloid-PET in 5-38% of the cases[30-33] and neuropathological research reported a mismatch of clinical and neuropathological diagnosis of at least 17%[34]. Other studies in neurodegenerative diseases, showed that retinal thinning is also present in PD and DLB[1,4,35]. This stresses the need to use disease specific biomarkers as part of inclusion criteria in order to assess cohorts based on their underlying neuropathology.

Another strength is the assessment of glaucoma. Since both AD and glaucoma are neurodegenerative diseases with progressive loss of neuronal tissue and overlapping pathological molecular pathways, glaucoma should be considered as a possible confounder in the relationship between AD and retinal thickness[10-14]. We therefore strictly assessed glaucoma with both structural and functional tests and found that visual fields defects were more often present in AD. This may be explained by the fact that visual field testing is not only a retinal but also a cognitive task and might thus be challenging for AD patients to perform. Nevertheless, none of the patients fulfilled clinical criteria for glaucoma, ruling it out as a cause of retinal thinning in both the EOAD and control group.

Limitations of this study are its small number of patients and its cross sectional design. The presented cohort is powered to detect a true effect of ≥10μm of mean RNFL thickness as reported in previous studies[9]. To detect a smaller true effect, a larger cohort is needed. Second, comparing retinal thickness decrease over time may be more sensitive for a neurodegenerative disease process, independent of amyloid load, and thus may be suitable as an alternative to MRI for showing progression over time.

Future studies should include more subjects including a LOAD group, longitudinal measurements, and disease specific imaging aiming to detect retinal amyloid. Correlation with volumetric MRI data (e.g. hippocampus, optical tract, cortical thickness) may add to the understanding of the relation between retinal and cerebral neuronal loss.

Conclusion

In this amyloid proven cohort without glaucoma, retinal layer thickness is correlated to parietal cortical atrophy in both EOAD and controls. This suggests reflections of cortical thickness in the retina. Longitudinal studies including a larger number of EOAD and LOAD patients correlating retinal thickness with biomarkers for amyloid/neuronal injury as well as disease specific biomarkers (e.g. retinal amyloid) are needed to elucidate the possible role of the retina as a source of diagnostic and/or prognostic biomarkers in AD.

References

1. Yu JG, Feng YF, Xiang Y, et al. Retinal nerve fiber layer thickness changes in Parkinson disease: a meta-analysis. *PLoS One.* 2014;9(1):e85718.
2. Wang M, Zhu Y, Shi Z, Li C, Shen Y. Meta-analysis of the relationship of peripheral retinal nerve fiber layer thickness to Alzheimer's disease and mild cognitive impairment. *Shanghai Arch Psychiatry.* 2015;27(5):263-279.
3. Thomson KL, Yeo JM, Waddell B, Cameron JR, Pal S. A systematic review and meta-analysis of retinal nerve fiber layer change in dementia, using optical coherence tomography. *Alzheimer's & dementia (Amsterdam, Netherlands).* 2015;1(2):136-143.
4. Moreno-Ramos T, Benito-Leon J, Villarejo A, Bermejo-Pareja F. Retinal nerve fiber layer thinning in dementia associated with Parkinson's disease, dementia with Lewy bodies, and Alzheimer's disease. *Journal of Alzheimer's disease : JAD.* 2013;34(3):659-664.
5. Frisoni GB, Fox NC, Jack CR, Jr., Scheltens P, Thompson PM. The clinical use of structural MRI in Alzheimer disease. *Nature reviews Neurology.* 2010;6(2):67-77.
6. Frisoni GB, Scheltens P, Galluzzi S, et al. Neuroimaging tools to rate regional atrophy, subcortical cerebrovascular disease, and regional cerebral blood flow and metabolism: consensus paper of the EADC. *Journal of neurology, neurosurgery, and psychiatry.* 2003;74(10):1371-1381.
7. Koedam EL, Lehmann M, van der Flier WM, et al. Visual assessment of posterior atrophy development of a MRI rating scale. *Eur Radiol.* 2011;21(12):2618-2625.
8. van der Flier WM, Pijnenburg YAL, Fox NC, Scheltens P. Early-onset versus late-onset Alzheimer's disease: the case of the missing APOE ε4 allele. *The Lancet Neurology.* 2011;10(3):280-288.
9. den Haan J, Verbraak FD, Visser PJ, Bouwman FH. Retinal thickness in Alzheimer's Disease: a systematic review and meta-analysis. *Alzheimer's & Dementia: Diagnosis, Assesment & Disease Monitoring.* 2017;6 (2017):162-170.
10. Gupta V, Gupta VB, Chitranshi N, et al. One protein, multiple pathologies: multifaceted involvement of amyloid beta in neurodegenerative disorders of the brain and retina. *Cell Mol Life Sci.* 2016.
11. Wostyn P, De Groot V, Van Dam D, Audenaert K, Killer HE, De Deyn PP. Age-related macular degeneration, glaucoma and Alzheimer's disease: amyloidogenic diseases with the same glymphatic background? *Cell Mol Life Sci.* 2016.
12. Cordeiro MF. Eyeing the brain. *Acta neuropathologica.* 2016;132(6):765-766.
13. Davis BM, Crawley L, Pahlitzsch M, Javaid F, Cordeiro MF. Glaucoma: the retina and beyond. *Acta neuropathologica.* 2016;132(6):807-826.
14. Janssen SF, Gorgels TG, Ramdas WD, et al. The vast complexity of primary open angle glaucoma: disease genes, risks, molecular mechanisms and pathobiology. *Prog Retin Eye Res.* 2013;37:31-67.
15. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's and Dementia.* 2011;7(3):263-269.
16. van der Flier WM, Pijnenburg YA, Prins N, et al. Optimizing patient care and research: the Amsterdam Dementia Cohort. *Journal of Alzheimer's disease : JAD.* 2014;41(1):313-327.

17. Duits FH, Teunissen CE, Bouwman FH, et al. The cerebrospinal fluid "Alzheimer profile": easily said, but what does it mean? *Alzheimers Dement.* 2014;10(6):713-723 e712.
18. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol.* 1987;149(2):351-356.
19. European Glaucoma Society Terminology and Guidelines for Glaucoma, 4th Edition - Chapter 2: Classification and terminologySupported by the EGS Foundation: Part 1: Foreword; Introduction; Glossary; Chapter 2 Classification and Terminology. *The British Journal of Ophthalmology.* 2017;101(5):73-127.
20. Liu S, Ong YT, Hilal S, et al. The Association Between Retinal Neuronal Layer and Brain Structure is Disrupted in Patients with Cognitive Impairment and Alzheimer's Disease. *Journal of Alzheimer's disease : JAD.* 2016;54(2):585-595.
21. Casaletto KB, Ward ME, Baker NS, et al. Retinal thinning is uniquely associated with medial temporal lobe atrophy in neurologically normal older adults. *Neurobiol Aging.* 2016;51:141-147.
22. Coppola G, Di Renzo A, Ziccardi L, et al. Optical Coherence Tomography in Alzheimer's Disease: A Meta-Analysis. *Eye (Lond).* 2015;10(8):e0134750-e0134750.
23. Rhodius-Meester HFM, Benedictus MR, Wattjes MP, et al. MRI Visual Ratings of Brain Atrophy and White Matter Hyperintensities across the Spectrum of Cognitive Decline Are Differently Affected by Age and Diagnosis. *Front Aging Neurosci.* 2017;9:117.
24. Alasil T, Wang K, Keane PA, et al. Analysis of normal retinal nerve fiber layer thickness by age, sex, and race using spectral domain optical coherence tomography. *J Glaucoma.* 2013;22(7):532-541.
25. Demirkaya N, van Dijk HW, van Schuppen SM, et al. Effect of age on individual retinal layer thickness in normal eyes as measured with spectral-domain optical coherence tomography. *Investigative ophthalmology & visual science.* 2013;54(7):4934-4940.
26. Karas G, Scheltens P, Rombouts S, et al. Precuneus atrophy in early-onset Alzheimer's disease: a morphometric structural MRI study. *Neuroradiology.* 2007;49(12):967-976.
27. Frisoni GB, Testa C, Sabattoli F, Beltramello A, Soininen H, Laakso MP. Structural correlates of early and late onset Alzheimer's disease: voxel based morphometric study. *Journal of Neurology, Neurosurgery & Psychiatry.* 2004;76:112-114.
28. Prins D, Hanekamp S, Cornelissen FW. Structural brain MRI studies in eye diseases: are they clinically relevant? A review of current findings.
29. Cowan WM. Anterograde and Retrograde Transneuronal Degeneration in the Central and Peripheral Nervous System. In: Nauta WJH, Ebbesson SOE, eds. *Contemporary Research Methods in Neuroanatomy*. Berlin, Heidelberg: Springer Berlin Heidelberg; 1970:217-251.
30. Ossenkoppele R, Jansen WJ, Rabinovici GD, et al. Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. *JAMA.* 2015;313(19):1939-1949.
31. Zwan MD, Bouwman FH, Konijnenburg E, et al. Diagnostic impact of [18F]flutemetamol amyloid imaging in young-onset dementia. *Alzheimer & Dementia Research&Therapy.* 2017;In Press.
32. Schipke CG, Peters O, Heuser I, et al. Impact of beta-amyloid-specific florbetaben PET imaging on confidence in early diagnosis of Alzheimer's disease. *Dement Geriatr Cogn Disord.* 2012;33(6):416-422.

33. Grundman M, Pontecorvo MJ, Salloway SP, et al. Potential impact of amyloid imaging on diagnosis and intended management in patients with progressive cognitive decline. *Alzheimer Dis Assoc Disord.* 2013;27(1):4-15.
34. Beach TG, Monsell SE, Phillips LE, Kukull W. Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005-2010. *Journal of neuropathology and experimental neurology.* 2012;71(4):266-273.
35. Pillai JA, Bermel R, Bonner-Jackson A, et al. Retinal Nerve Fiber Layer Thinning in Alzheimer's Disease: A Case-Control Study in Comparison to Normal Aging, Parkinson's Disease, and Non-Alzheimer's Dementia. *American journal of Alzheimer's disease and other dementias.* 2016.