Retinal Imaging

Age-related retinal thickness in Down's syndrome: A high-risk population for dementia

Madeleine J. Walpert[a,*], Eduardo M. Normando[b,c], Tiina Annus[a], Sally R. Jennings[a], Liam R. Wilson[a], Peter Watson[d], Shahid H. Zaman[a], M. Francesca Cordeiro[b,c], Anthony J. Holland[a]

[a]*Cambridge Intellectual and Developmental Disabilities Research Group, Department of Psychiatry, University of Cambridge, Cambridge, Cambridgeshire, UK*
[b]*The Imperial College Ophthalmic Research Group (ICORG), Imperial College London, South Kensington Campus, London, UK*
[c]*The Western Eye Hospital, Imperial College Healthcare NHS Trust, Marylebone, London, UK*
[d]*MRC Cognition and Brain Sciences Unit, University of Cambridge, Cambridge, UK*

Abstract

Introduction: People with Down's syndrome (DS) have a high prevalence of early-onset Alzheimer's disease. Early markers of Alzheimer's disease pathology identifiable before clinical change are needed for the evaluation of preventative treatments. The retina, an extension of the brain, may provide a noninvasive imaging site.

Methods: Forty-nine adults with DS and 36 age-matched controls completed retinal nerve fibre layer (RNFL) assessments using optical coherence tomography. RNFL thickness was analyzed in relation to cognitive status and age and previously acquired cortical thickness and cerebral amyloid β binding data in a subgroup.

Results: RNFL thickness was greater in the DS group and did not show age-related thinning. RNFL correlated positively with cognitive scores and cortical thickness and was reduced in participants with positive cerebral amyloid β binding.

Discussion: Increased RNFL in adults with DS may represent early Alzheimer's disease–related changes. Thinning was present in those with cerebral amyloid β binding, independent of age.
© 2019 Published by Elsevier Inc. on behalf of the Alzheimer's Association. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords: Down's syndrome; Alzheimer's disease; Dementia; Retina; Optical coherence tomography

1. Background

People with Down's syndrome (DS) have a predisposition for developing early-onset Alzheimer's disease (AD) pathology and dementia. Development of senile plaques composed of β-amyloid (Aβ) peptide is observed in virtually 100% of DS individuals over the age of 40 years [1]. Approximately 50% of individuals progress to a clinical diagnosis of dementia by their 50s [2], a figure that continues to rise with increasing age. In addition to increased burden of Aβ, people with DS develop neurofibrillary tangles and have evidence of brain cell death.

The retina and optic nerve form part of the central nervous system and are derived from the diencephalon during early foetal development [3]. In many diseases, including diabetes mellitus, hypertension, and arthritis, characteristic signs develop in the retina [4]. This study investigated whether changes reported in the retinas of typically developing patients with mild cognitive impairment (MCI) or dementia are also observed in the retinas of adults with DS, before clinical evidence of dementia.

The retinal nerve fibre layer (RNFL) typically follows a "double-hump" pattern, with the thickest areas being the inferior and superior quadrants, due to the primary blood vessels crossing the optic nerve head [5]. Degeneration of the RNFL, shown as decreased thickness, is a normal part of ageing [6]; however, studies have shown that in patients with AD and MCI, there is significantly thinner RNFL when compared with age-matched healthy controls. The largest RNFL decrease in dementia is seen in the superior quadrant [7–9], followed by the inferior quadrant, with the temporal quadrant being "resistant to fibre loss" [10]. Several studies have investigated the correlation between cognitive ability (measured using the Mini–Mental State Examination [MMSE] [11]) and RNFL thickness to test the hypothesis that lower scores would correlate with thinner RNFL. Results have been inconclusive, and a recent meta-analysis concluded that there was no consistent evidence of a correlation [12].

Optical coherence tomography (OCT) is a noninvasive imaging technology that provides high-resolution cross-sectional images of the retina allowing for micron precision segmentation of the intraretinal layers [13]. OCT is a promising technology particularly in populations with low compliance, there are relatively few exclusion criteria, assessments are easy to undertake, and it is fast and cost-effective. Few studies have used OCT in people with DS. Three studies were identified from current literature, two in children with DS [14,15], and one in a small number of adults [16]. All studies showed increased thickness in the macular compared with controls but did not report on RNFL thickness.

People with DS have an overproduction of Aβ that is driven by the additional copy of the Aβ precursor protein (APP) gene inherited in triplicate in DS. For this reason, they provide an unparalleled opportunity to study the impact of excessive Aβ before and during the onset of clinical dementia. In this study, the impact of increased Aβ burden on the structure of the retina is examined and its relationship to well-documented brain changes explored. Retinal changes associated with AD may be valuable as proxy outcome measures in future clinical trials.

2. Methods

2.1. Study design and participants

Forty-nine participants with DS and 36 healthy controls completed OCT imaging and neuropsychological assessments. Participants with DS were identified from a preexisting cohort and with assistance from the DS Association. Control participants were recruited through the University and were age-matched to the DS group. Ethical approval was given by the East of England Cambridge Central Research Ethics Committee (study ref. 18/EE/1118), and the study was conducted according to the principles of the Declaration of Helsinki. Exclusion criteria included recent eye surgery, diabetes mellitus, nystagmus, history of retinal disease, retinal detachment or previous vitreoretinal procedures, severe cataracts, and presence of psychiatric illness other than dementia for the DS group and including dementia in the control group. Written informed consent was obtained and for individuals with DS without capacity to consent a consultee was identified, in accordance with the Mental Capacity Act, 2005. Previously collected magnetic resonance and positron emission tomography (MRI and PET) neuroimaging data on cortical thickness and cortical Aβ binding were available for a subset of the DS group. Neuroimaging data were acquired between 2012 and 2014, and OCT imaging was undertaken between 2015 and 2016.

2.2. Procedures

Retinal imaging: Spectral-domain OCT (Heidelberg Engineering, Heidelberg, Germany) was used to measure RNFL thickness using the glaucoma application with automatic retinal tracking enabled. Macular and posterior pole measures were conducted using the EDTRS (Early Treatment Diabetic Retinopathy Study) grid. Averages were computed for the fovea, inner macular and outer macular rings, and for each retinal layer over a $30° \times 25°$ retinal area. Image preprocessing was undertaken using the Spectralis Viewing Module (6.3.4.0; Heyex). Automatic segmentation was completed for all images and those with a quality index <15 were discarded in accordance with OCT guidelines [17]. All measurements for retinal data are given in micrometers (μm). Corresponding retinal measures from both eyes of each participant were averaged to give a single value. Before this, paired comparison t-tests were undertaken to ensure no significant differences between the left and right eye measurements.

The Cambridge Cognition Examination (CAMCOG-DS) [18] was used to assess cognitive ability in the DS group. The CAMCOG-DS, based on the CAMCOG, was specifically designed for people with intellectual disabilities, assessing areas of cognition known to decline with the onset of dementia. The Cambridge Examination for Mental Disorders in the Elderly for people with DS (CAMDEX-DS) informant interview [19] was conducted with family members and carers of the DS participants. The CAMDEX is a structured interview of known validity and reliability used to retrospectively assess changes in an individual's personality, behaviour, and functional abilities to determine the presence or not of dementia and to exclude the possibility of other disorders that mimic dementia, such as depression and hypothyroidism.

MRI and PET neuroimaging was completed in a subset of the DS cohort as part of a previous study. PET scans were acquired in 3D mode on a General Electric Medical Systems Advanced PET Scanner using Pittsburgh compound [11C] (PIB). Mean cortical Aβ load was calculated in all cortical regions using the nondisplaceable binding potential (BPND). Positive PIB binding (PIB +ve) status was

determined based on the binding value of a given region being at least two standard deviations above that of the mean PIB Aβ load in the striatum. Participants that did not meet this criteria were given a PIB negative (PIB −ve) status. MRI scans were completed on a 3-Tesla Siemens Magnetom Verio Scanner (Siemens, AG, Germany). Cortical thickness was assessed with FreeSurfer (version 5.3) using the protocol devised by Fischl and Dale [20]. Full details on the imaging data acquisition and the methodology for PIB group division are published in Annus et al. (2016) [21].

2.3. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 23. Data were tested for normal distribution and outliers. The Bonferroni correction was applied to control for multiple comparison effects, and the adjusted P value of 0.012 was considered significant throughout unless otherwise stated. Sample size calculations were determined from previous research studies in MCI and dementia.

2.4. Role of the funding source

The funders of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the paper and submission for publication.

3. Results

Sixty participants with DS and 37 typically developing controls were recruited to this study. Four DS participants withdrew from the study. Eight participants' (seven DS and one control) data were below the acceptable OCT image quality threshold and removed from analyses. Previously collected neuroimaging data from an earlier study were available for 17 DS participants, and these participants formed a subgroup for analyses relating brain and retinal changes. Demographics of all groups can be seen in Table 1.

Table 1
Demographic information of the DS and control groups

Group	N	Sex females: males	Mean age and standard deviation	Age range
DS	49	26:23	35.80 ± 9.48	18–55
Controls	36	13:23	37.68 ± 12.01	21–56
PIB subgroup	17	8:4	42.06 ± 7.08	34–55
PIB +ve group	5	2:3	50 ± 5	42–55
PIB −ve group	12	8:4	38.75 ± 4.82	34–47
PIB +ve matched control group	8	2:6	53.5 ± 2.07	50–55
PIB −ve matched control group	12	4:8	38.2 ± 5.03	31–46

NOTE. Subgroups include participants with DS who underwent prior neuroimaging and amyloid binding group based on PIB binding potential identified. Control participant subgroups are age matched to DS PIB groups.

Abbreviations: DS, Down's syndrome; PIB, Pittsburgh compound [11C].

There were no significant age or sex differences between DS and healthy control groups (age: $t_{(64.530)} = -.815$, $P = .435$; sex: $\chi_{(1)} = 2.401$, $P = .121$). Within the DS subgroup, participants with PIB +ve binding status were significantly older than those in the PIB −ve group ($t_{(15)} = -4.337$, $P = .001$). For subgroup analyses, typically developing participants were matched to each of the binding status groups for comparison. There were no significant differences in age between these groups (PIB +ve and matched controls: $t_{(11)} = .120$, $P = .228$; PIB −ve and matched controls: $t_{(22)} = .248$, $P = .806$).

3.1. Comparisons between RNFL thickness in DS and age-matched controls

Contrary to the hypothesis, results showed increased thickness in global RNFL ($P < .001$), and RNFL quadrants ($P < .001$), in the DS group when compared with age-matched controls with the exception of the nasal quadrant ($P = .378$). The largest difference between groups was seen in the inferior quadrant with the DS group having an average of 27.6 μm thicker than the control group. Superior and temporal quadrants also had average differences of >20 μm thicker in the DS group.

Other than increased thickness, the structure of the retina was not strikingly different in the DS group. In both groups, thinnest RNFL was observed in the nasal and temporal quadrants, and the thickest RNFL was seen in the inferior and superior quadrants. In the control group, there were no significant differences between nasal and temporal quadrants, or between inferior and superior quadrants; however, in the DS group, there were significant differences between all quadrants ($P < .001$). Average thickness values of both groups are shown in Fig. 1. Examples of the RNFL images and differences between age- and sex-matched DS and control participants are shown in Supplementary Material.

3.2. Additional OCT parameters

The primary focus of this article is to discuss thickness and structural differences in the RNFL with respect to age and onset of AD. Owing to unexpected findings of thicker RNFL in adults with DS, we also explored the parameters of the macular and posterior pole, to support the findings in the RNFL and to further explore retinal differences.

The macular was significantly thicker in the DS group (n = 39) compared with the matched controls (n = 36) in both the fovea $t_{(73)} = 4.379$, $P < .001$, and the outer macular $t_{(73)} = 5.137$, $P < .001$. The inner macular was thicker by an average of 9 μm in the DS group, but this was not significantly different ($P = .020$).

Furthermore, comparisons of the posterior pole were conducted between the groups, DS participants had significantly thicker inner retinal layers, $t_{(73)} = 4.480$, $P < .001$; however,
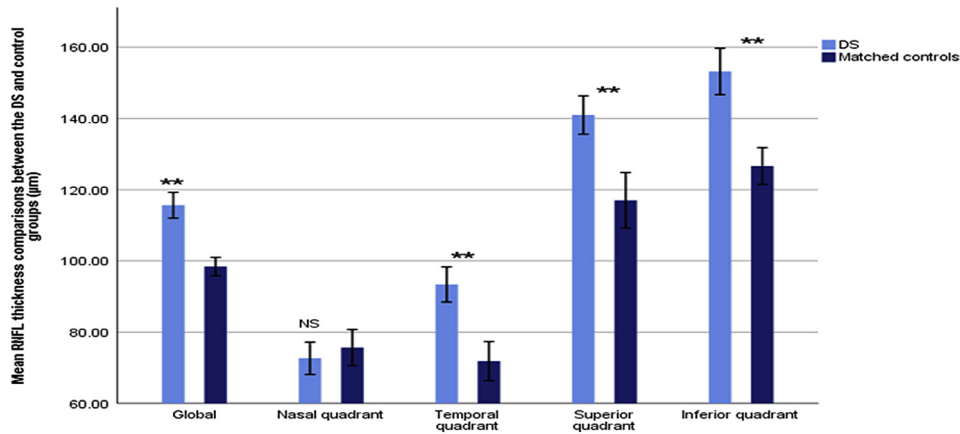
Fig. 1. Grouped bar chart showing the mean RNFL thickness (µm) across the DS and age-matched healthy control groups. Global RNFLT and RNFLT of all quadrants except the nasal were significantly thicker in the DS group. **$P < .001$. Abbreviations: DS, Down's syndrome; NS, not significant; RNFL, retinal nerve fiber layer.

the outer layers were significantly thinner in DS, $t_{(73)} = -2.889$, $P = .005$.

Further exploration of the retinal layers was undertaken, finding no significant differences between the RNFL and the retinal pigment epithelium layers and, additionally, the outer nuclear layer was significantly thinner in the DS group. This layer appears to be driving the significant difference in the outer layers between groups, as the outer plexiform layer was significantly thicker in the DS group along with the majority of other layers. Thinner outer nuclear layer is an intriguing finding that is not supported by previous DS studies in children, and the outer nuclear layer has been shown to decrease in thickness in those with AD compared with controls [22], though relatively few studies have considered the posterior pole layers in retinal analysis. Table 2 shows

Table 2
Macular and posterior pole measures between DS and age-matched controls

Retinal area	DS (n = 39)	Controls (n = 36)	P
Fovea	299.65 + 28.80	274.18.80	<.001
Inner macular	355.56 + 19.17	346.42 + 13.80	.021
Outer macular	320.83 + 14.75	303.93 + 13.64	<.001
Inner layers average	236.64 − 13.47	221.80 + 12.00	<.001
RNFL	41.27 + 6.26	41.32 + 4.22	.963
Ganglion cell layer	41.13 + 3.42	33.35 + 2.27	<.001
Inner plexiform layer	34.67 + 2.52	27.62 + 1.98	<.001
Inner nuclear layer	40.70 + 32.07	32.07 + 2.42	<.001
Outer layers average	77.26 + 1.42	78.41 + 1.98	.005
Outer plexiform layer	28.18 + 3.04	26.10 + 1.90	<.001
Outer nuclear layer	50.77 + 5.82	60.28 + 7.64	<.001
Retinal pigment epithelium	13.24 + .99	12.92 + .87	.142

NOTE. DS sample is lower due to reduced compliance with the retinal box scan, and there were no significant differences in age between the reduced DS group and controls ($t_{(65.64)} = -.609$, $P = .545$). The majority of retinal areas show significantly increased thickness in the DS group. Significant P value of $P < .012$.
Abbreviations: DS, Down's syndrome; RNFL, retinal nerve fiber layer.

additional macular and posterior pole differences between groups.

3.3. Age-related changes in RNFL thickness

In line with evidence from control populations and patients with AD, it was hypothesized that there would be increased retinal thinning with age in DS, compared with controls. Findings showed that there were no correlations between RNFL and age in adults with DS and that typical patterns of age-related decline were not observed. RNFL correlations with age ranged between $r = -.048$ and $r = .102$, none of which were significant. For the controls, medium negative correlations of $r = -.322$ and $r = -.305$ were observed in the global and inferior quadrants, respectively. These correlations were not significant but were supportive of expected age-related thinning particularly in this population where the maximum age was 56 years. Scatterplots for both groups are shown in Fig. 2.

Further analysis was undertaken to assess RNFL differences across age decades. A scatterplot of the temporal quadrant values (Fig. 3) shows that there were nonsignificantly higher RNFL values in DS participants in their 40s ($f_{(3)} = 3.064$, $P = .221$). The average thickness of the temporal quadrant in DS in their 40s was 13 µm higher than in the 30s and 8 µm higher than in the 20s and 50s. This was contrary to our predictions that highest RNFL would be seen in younger participants and would decrease gradually with age and more dramatically than in control participants.

3.4. Relationship between CAMCOG scores and RNFL thickness

There was a positive nonsignificant correlation between CAMCOG scores and superior ($r = .269$, $P = .071$) and nasal quadrant thickness ($r = .244$, $P = .135$) in the DS group. In the
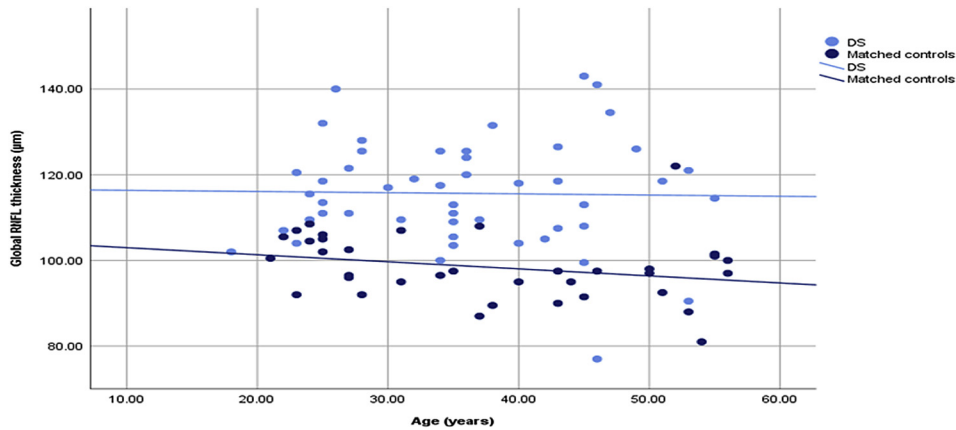
Fig. 2. Cross-sectional age profile of global RNFL in DS and age-matched controls. A nonsignificant age-related decline was seen in the control group as expected; however, the DS group showed no correlation between RNFL and age. Thickest RNFL measures are seen in the DS group in their 40s. Abbreviations: DS, Down's syndrome; RNFL, retinal nerve fiber layer.

temporal quadrant, there was a negative correlation (r = −.168, P = .264) and no correlation in the inferior quadrant.

3.5. Exploratory investigations of retinal and cortical thickness in the presence of cerebral Aβ

The link between the brain and the retina and how AD processes affect both was investigated in the subgroup of people with DS who had completed both neuroimaging and retinal studies. Exploratory analyses were undertaken to explore the relationship between RNFL and cortical thicknesses and whether retinal structure differs in those who had previously been identified as having positive cerebral Aβ binding.

The small number of participants in this subgroup had undergone MRI and PET neuroimaging between one and four years before retinal imaging. It was predicted that those with a historic status of positive Aβ binding would have thinner retina than those with a negative binding status at that time. It was hypothesized that there would be a strong positive correlation between retinal thickness and cortical

thickness and that both retina and cortex would be thinner in those with positive Aβ cerebral binding.

Comparisons between the PIB +ve and PIB −ve groups showed that there were no significant differences in RNFL thickness. It was noted, however, that the PIB +ve group displayed lower thickness in all but the temporal quadrant. Further investigations compared the retinal thicknesses of each PIB group with an age-matched control group. As with the full DS group, the PIB −ve group had significantly thicker RNFL in every quadrant except nasal; however, in the PIB +ve group, the superior and inferior quadrants were statistically similar to the control group. This result suggests that there is reduced RNFL thickness in DS who are PIB +ve positive, lowering the values to those seen in typically developing controls. Temporal quadrant thickness in both PIB groups and their matched control groups are shown in Fig. 3.

Cortical thickness was compared to retinal thickness in this subgroup of participants. Significant positive correlations were identified in the temporal cortex, both with the global RNFL thickness (r = .592, P = .012) and the superior
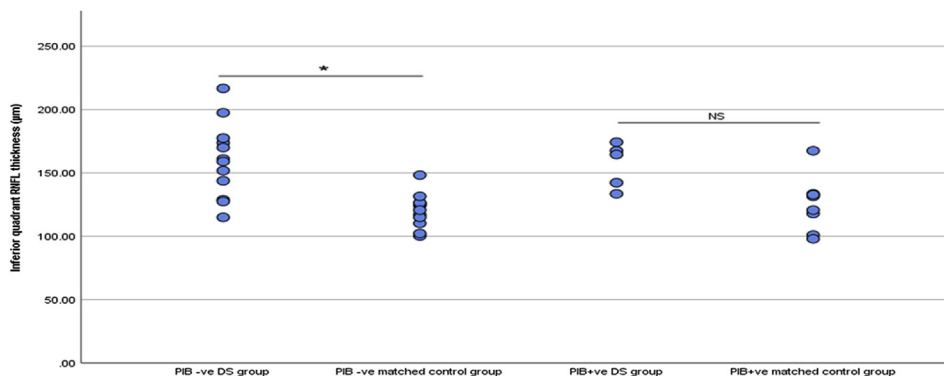

Fig. 3. Grouped plot showing inferior quadrant RNFL of PIB groups and matched control groups. PIB groups were not significantly different. Significant differences were only seen between the PIB −ve and matched groups. No significant differences were found between the PIB +ve group and age-matched control group. *P < .012. Abbreviations: DS, Down's syndrome; NS, not significant; RNFL, retinal nerve fiber layer; PIB, Pittsburgh compound [11C].
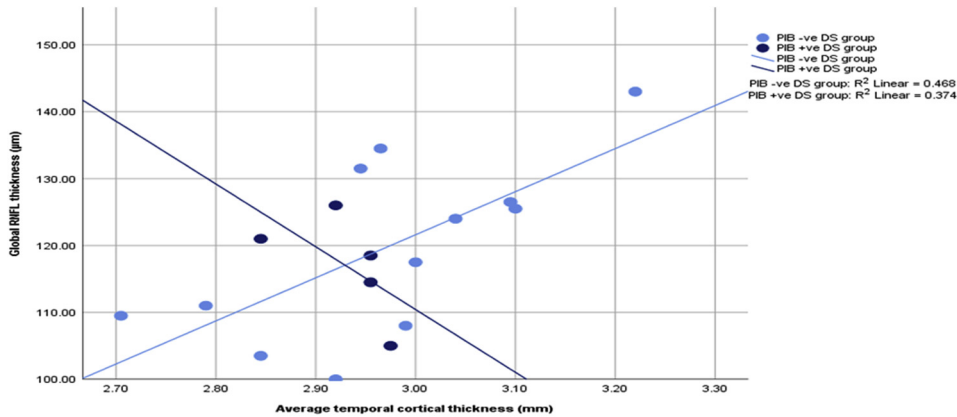
Fig. 4. Correlations of the PIB +ve and PIB −ve groups RNFL and cortical thickness. There were strong positive correlations in the PIB +ve group; however, in the PIB −ve group, correlations were strongly negative. Abbreviations: DS, Down's syndrome; NS, not significant; RNFL, retinal nerve fiber layer; PIB, Pittsburgh compound [11C].

quadrant thickness (r = .590, *P* = .013). There were several other examples of positive correlations across the RNFL quadrants and cortical regions that were not significant. Comparisons were also made between the PIB +ve and PIB −ve groups, and results showed that as with the full subgroup, PIB −ve participants had strong positive correlations between the thickness of the temporal cortex and the global RNFL (r = .684, *P* = .014) and the superior quadrant (r = .604, *P* = .037). In contrast, the PIB +ve group had mostly negative associations between cortical and retinal thicknesses. Correlations were not significant but were strikingly different to those of the PIB −ve group, particularly for the temporal cortex and global RNFL (r = −.612) and superior quadrant (r = −.336). Correlations between temporal cortex and global RNFL for both PIB groups are shown in Fig. 4.

4. Discussion

People with DS are the most at risk group for developing AD at a young age, an age similar to that in families with specific single gene mutations [23]. As with these families, people with DS are most likely to benefit from the trial of treatments aimed at preventing the onset and progression of AD pathology, as the use of such treatments well before dementia becomes apparent would be justified in this population. The challenge for any such trial is to identify an early biomarker that could be a proxy outcome measure. It is therefore important to note that the participants with DS were able to tolerate and cooperate with the OCT assessments. However, the results of this study were not as anticipated and further research is needed before the value of retinal imaging in this older population of people with DS can be fully determined.

The hypotheses for this study arose from previous research in the typically developing population at risk of or with evidence of dementia. In these previous studies, patients with MCI and AD have shown thinning of the RNFL with age beyond the rate expected during normal ageing.

In people with DS, it was therefore predicted that retinal structure may reflect these patterns would be emphasized in a younger age group due to accelerated ageing and high prevalence of AD and that increased retinal thinning would be present well before the clinical features of dementia were apparent.

Contrary to our expectations, we found significantly thicker RNFL in adults with DS when compared with age-matched controls and that age-related thinning observed in the typically developing population was not evident in the DS group.

Owing to the limited age range of the control group in this study (18–56 years), we did not anticipate significant age-related thinning as seen in previous research. This age range was matched to our DS group and is reflective of the average life span in DS; therefore, we did except age-related changes in the DS group. Further investigations into the relationship between RNFL thickness and age indicated that there was a nonsignificant increase in thickness in the fourth decade. It is around the age of 40 that people with DS invariably have evidence of Aβ plaques in the brain [24], and this may be the age that retinal Aβ plaques also occur. One study has shown Aβ deposition in the retinas of participants with DS without dementia. All participants in that study, aged between of 30 and 60 years, had evidence of retinal Aβ positivity [25]. Furthermore, three of these participants did not show Aβ positivity in the brain, indicating that retinal Aβ may precede, or be more readily detectable than, cerebral Aβ. Studies in typically developing patients with MCI have shown increased thickness in the macular region [26,27] when compared with both age-matched controls and patients with dementia. Increased RNFL thickness may therefore be a temporary state linked with early and evolving AD pathologies. Our data support this theory, as DS participants in their 50s did not show further increased RNFL thickness above those in their 40s. However, in this older age group, there were only a small number of participants. In MCI patient studies, increased thickness has been attributed to inflammation caused by gliosis, neuronal death, and Müller

cell swelling. Inflammation is a protective response to the toxic peptide $A\beta_{42}$ but may also trigger increased apoptosis and microglial activity, that both cause cell swelling as a temporary state.

Correlations between cortical and retinal thicknesses were as expected in the PIB −ve group; however, correlations seen in the PIB +ve group were reversed. Previous research has shown that people with DS have thicker cortex than age-matched controls and that cortical thickness is significantly less in those with DS who are PIB +ve [28]. The results of this study suggested that the PIB +ve group cortical thinning changes exceeded the thinning seen in the retinal measures.

Retinal changes may be more significant at particular stages of AD pathology and may be shown as increased thickness in those at the age when cerebral $A\beta$ binding becomes apparent. Longitudinal studies assessing change over time, particularly over the critical time point of the 30–40 seconds, when brain changes become apparent will be necessary to fully understand retinal structure changes in DS. A limiting factor of this study is that the PIB +ve group consisted of only five participants, age ranging from 42 to 55 years. All participants had confirmed positive $A\beta$ binding between one and four years before retinal imaging; therefore, we can be reasonably confident of their $A\beta$ status at the time of this study. Studies with larger groups that had had both retinal and neuroimaging would be needed to validate the findings seen in this study.

In conclusion, retinal and cerebral changes relating to the development of AD pathology evolve over time and a cross-sectional study such as this is limited in the conclusions that can be drawn. The retina is clearly abnormal in people with DS, but whether this is primarily due to developmental reasons or because of age-related AD pathology remains uncertain. However, our data suggest that RNFL is thicker in the 40s and thinner when cerebral $A\beta$ binding becomes apparent. Taken together with reports of $A\beta$ deposition in the retina in people with DS [25], our findings suggest that the retina is undergoing AD-related changes that later lead to retinal thinning. A longitudinal study combining RNFL and retinal $A\beta$ imaging is required to study such evolving changes and to determine their potential as a biomarker for AD.

Acknowledgements

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.dadm.2019.08.007.

RESEARCH IN CONTEXT

1. Systematic review: A literature review using traditional (e.g. PubMed) sources was undertaken. Although there were many examples of optical coherence tomography research in Alzheimer's disease (AD), only three studies were identified in people with Down's syndrome (DS). These relevant citations are appropriately cited.

2. Interpretation: Our hypotheses were based primarily on research in the AD community, as people with DS have high prevalence for AD and accelerated ageing. Our findings indicated that there may be retinal changes linked to early processes in AD, but that retinal nerve fiber layer thickness was not correlated with age in DS.

3. Future directions: This is the first time that the retinal nerve fiber layer has been measured over a large age range in people with DS. Furthermore, this is the only study that has investigated the retinal nerve fiber layer alongside brain changes and cognition. Further studies are needed in larger groups, particularly in those with dementia or early signs of dementia.

References

[1] Haier RJ, Head K, Head E, Lott IT. Neuroimaging of individuals with Down's syndrome at-risk for dementia: Evidence for possible compensatory events. NeuroImage 2008;39:1324–32.

[2] Holland AJ, Hon J, Huppert FA, Stevens F, Watson P. Population-based study of the prevalence and presentation of dementia in adults with Down's syndrome. Br J Psychiatry 1998;172:493–8.

[3] Purves D, Augustine G, Fitzpatrick D, Katz L, LaMantia A-S, O McNamara J, et al., eds. The Retina. 2nd ed. Sunderland (MA): Sinauer Associates; 2001.

[4] Pinazo-Duran MD, Zanon-Moreno V, Garcia-Medina JJ, Arvalo JF, Gallego-Pinazo R, Nucci C. Eclectic ocular comorbidities and systemic diseases with eye involvement: a review. Biomed Res Int 2016;2016:10.

[5] Varma R, Skaf M, Barron E. Retinal nerve fiber layer thickness in normal human eyes. Ophthalmology 1996;103:2114–9.

[6] Parikh RS, Parikh SR, Sekhar GC, Prabakaran S, Babu JG, Thomas R. Normal age-related decay of retinal nerve fiber layer thickness. Ophthalmology 2007;114:921–6.

[7] Berisha F, Feke GT, Trempe CL, McMeel JW, Schepens CL. Retinal abnormalities in early Alzheimer's disease. Invest Ophthalmol Vis Sci 2007;48:2285–9.

[8] Kirbas S, Turkyilmaz K, Anlar O, Tufekci A, Durmus M. Retinal nerve fiber layer thickness in patients with Alzheimer disease. J Neuro Ophthalmol 2013;33:58–61.

[9] La Morgia C, Ross-Cisneros FN, Koronyo Y, Hannibal J, Gallassi R, Cantalupo G, et al. Melanopsin retinal ganglion cell loss in Alzheimer disease. Ann Neurol 2015;79:90–109.

[10] Bambo MP, Garcia-Martin E, Gutierrez-Ruiz F, Pinilla J, Perez-Olivan S, Larrosa JM, et al. Analysis of optic disk color changes in Alzheimer's disease: A potential new biomarker. Clin Neurol Neurosurg 2015;132:68–73.

[11] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.

[12] 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, Assessment & Disease Monitoring 2017;6:162–70.

[13] Huang D, Swanson EA, Lin CP, Schuman JS, Stinson WG, Chang W, et al. Optical Coherence Tomography. Science 1991;254:1178–81.

[14] O'Brien S, Wang J, Smith HA, Donaldson DL, Haider KM, Roberts GJ, et al. Macular structural characteristics in children with Down syndrome. Graefes Arch Clin Exp Ophthalmol 2015; 253:2317–23.

[15] Weiss AH, Kelly JP, Phillips JO. Infantile nystagmus and abnormalities of conjugate eye movements in down syndrome. Invest Ophthalmol Vis Sci 2016;57:1301–9.

[16] Laguna A, Barallobre M-J, Marchena M-Á, Mateus C, Ramírez E, Martínez-Cue C, et al. Triplication of DYRK1A causes retinal structural and functional alterations in Down syndrome. Hum Mol Genet 2013;22:2775–84.

[17] Huang Y, Gangaputra S, Lee KE, Narkar AR, Klein R, Klein BEK, et al. Signal quality assessment of retinal optical coherence tomography images. Invest Ophthalmol Vis Sci 2012;53:2133–41.

[18] Hon J, Huppert FA, Holland AJ, Watson P. Neuropsychological assessment of older adults with Down's Syndrome: An epidemiological study using the Cambridge Cognitive Examination (CAMCOG). Br J Clin Psychol 1999;38:155–65.

[19] Ball SL, Holland AJ, Huppert FA, Treppner P, Watson P, Hon J. The modified CAMDEX informant interview is a valid and reliable tool for use in the diagnosis of dementia in adults with Down's syndrome. J Intellect Disabil Res 2004;48:611–20.

[20] Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci U S A 2000;97:11050–5.

[21] Annus T, Wilson LR, Hong YT, Acosta J, Fryer TD, Cardenas A, et al. The pattern of amyloid accumulation in the brains of adults with Down syndrome. Alzheimers Demen 2016;12:538–45.

[22] Garcia-Martin E, Bambo MP, Marques ML, Satue M, Otin S, Larrosa JM, et al. Ganglion cell layer measurements correlate with disease severity in patients with Alzheimer's disease. Acta Ophthalmol 2016;94:e454–9.

[23] Bateman RJ, Xiong C, Benzinger TLS, Fagan AM, Goate A, Fox NC, et al. Clinical and biomarker changes seen in dominantly inherited Alzheimer's disease. N Engl J Med 2012;367:795–804.

[24] Head E, Lott IT, Patterson D, Doran E, Haier RJ. Possible compensatory events in adult down syndrome brain prior to the development of Alzheimer disease neuropathology: targets for nonpharmacological intervention. J Alzheimers Dis 2007;11:61–76.

[25] Rafii MS, Wishnek H, Brewer JB, Donohue MC, Ness S, Mobley WC, et al. The Down syndrome biomarker initiative (DSBI) pilot: proof of concept for deep phenotyping of Alzheimer's disease biomarkers in Down syndrome. Front Behav Neurosci 2015;9:1–11.

[26] Ascaso FJ, Cruz N, Modrego PJ, Lopez-Anton R, Santabárbara J, Pascual LF, et al. Retinal alterations in mild cognitive impairment and Alzheimer's disease: an optical coherence tomography study. J Neurol 2014;261:1522–30.

[27] Salobrar-Garcia E, Hoyas I, Leal M, de Hoz R, Rojas B, Ramirez AI, et al. Analysis of retinal peripapillary segmentation in early Alzheimer's disease patients. Biomed Res Int 2015; 2015:636548.

[28] Annus T, Wilson LR, Acosta-Cabronero J, Cardenas-Blanco A, Hong YT, Fryer TD, et al. The Down syndrome brain in the presence and absence of fibrillar β-amyloidosis. Neurobiol Aging 2017; 53:11–9.