Retinal Nerve Fiber Layer Thinning in Genetic FTD

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Background

Retinal abnormalities have been found in a number of different neurodegenerative diseases. A recent study highlighted the presence of retinal neurodegeneration in subjects with progranulin (GRN) mutations, both during the symptomatic and presymptomatic phase (Ward et al, Early retinal neurodegeneration and impaired Ran-mediated nuclear import of TDP-43 in progranulin-deficient FTLD, *Journal of Experimental Medicine*, 2014). GRN is one of three major genes that cause genetic Frontotemporal Dementia (FTD), as well as mutations in microtubule-associated protein tau (MAPT) and C9orf72 hexanucleotide repeat expansions. Although not well established, the continuing development of retinal imaging techniques shows potential to identify early presymptomatic change and could also be a measure of disease progression. This pilot study therefore, investigates retinal changes in both presymptomatic and symptomatic subjects across all three genetic mutations (GRN, MAPT, C9orf72).

Methods

We have recruited a genetic FTD cohort consisting of 20 participants so far. Here we present preliminary results from 7 symptomatic participants: 4 C9orf72 mutations and 3 MAPT mutations, and 13 presymptomatic participants: 7 mutation positive carriers and 6 mutation negative controls.

We performed spectral domain optical coherence tomography (Optos OCT SLO) on all subjects. Peripapillary retinal nerve fiber thickness (RNFL) and macular volume were measured using the inbuilt OCT software (Fig.1), whilst thickness of the other layers of the retina were measured using a software programme called OCTseg (Fig.2 [www5.cs.fau.de/research/software/octseg/]). All images are anonymised and sent to Moorfields Eye Hospital Reading Centre for reading. The images are reviewed and any unexpected findings are reported in a timely manner. Images were rated for their gradeability, and RNFL images are additionally rated for accuracy of placement of the image relative to the optic disc. Ungradeable and poor quality images were excluded from analysis.

Although none of the participants had any ocular symptoms we found incidental findings in five patients. These include: Small Choroidal Nevus, Retinal Hole and Tear which underwent prophylactic laser surgery, Left Epiretinal Membrane with Traction, Peripheral Retinal Tear, and Asteroid Hyalosis.

Results

Average thickness of retinal layers and the macular volume in each of the groups are summarised in Table 1. There were no significant differences between groups. However there was a trend for a lower RNFL thickness in affected cases compared with mutation negative controls (p=0.12): average RNFL thickness for affected cases was 96.3 (standard deviation (sd) = 10.1) µm. For the presymptomatic cases average RNFL thickness was 103.4 (11.5) µm for mutation positive carriers and 106.4 (7.5) µm for mutation negative controls.

Conclusions

Consistent with a previous study in patients with GRN mutations preliminary findings in this pilot study are suggestive that RNFL may be decreased in genetic FTD. We aim to investigate this cross-sectionally in a larger group of symptomatic and presymptomatic participants as well as follow the cohort longitudinally.

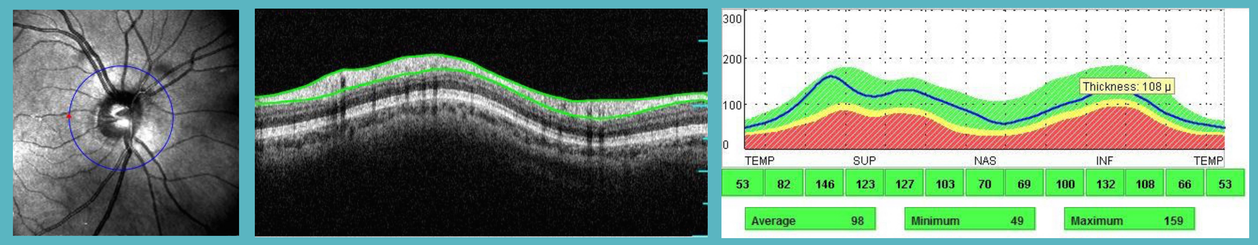

Figure 1. Automated peripapillary retinal nerve fiber layer thickness measured using OPTOS OCT-SLO

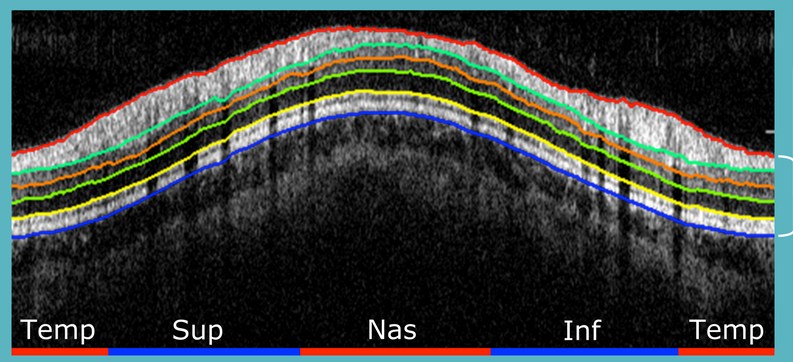

Figure 2. Further segmentation of the whole retina achieved using OCTseg software

Retinal Layer [shown in Figure 3]	Participant Group	Average Retinal Thickness (Mean, Standard Deviation)
ONL [4] (Outer Nuclear Layer)	Mutation Negative Controls	11.4 (1.9) pixels (px)
	Mutation Positive Carriers	11.1 (1.2) px
	Affected Cases	10.3 (0.8) px
OPL INL [5,6] (Outer Plexiform Layer, Inner Nuclear Layer)	Mutation Negative Controls	8.0 (1.2) px
	Mutation Positive Carriers	8.9 (1.2) px
	Affected Cases	8.3 (0.6) px
RPE PR [1,2] (Retinal Pigment Epithelium, Photoreceptor Layer)	Mutation Negative Controls	12.9 (0.8) px
	Mutation Positive Carriers	13.3 (0.7) px
	Affected Cases	12.9 (0.6) px
Overall Retina [1-9]	Mutation Negative Controls	57.8 (2.8) px
	Mutation Positive Carriers	57.2 (4.8) px
	Affected Cases	54.8 (3.2) px
RNFL [9] (Retinal Nerve Fiber Layer)	Mutation Negative Controls	106.4 (7.5) µm
	Mutation Positive Carriers	103.4 (11.5) µm
	Affected Cases	96.3 (10.1) mm^3
Macular Volume	Mutation Negative Controls	3.8 (0.2) mm^3
	Mutation Positive Carriers	3.9 (0.2) mm^3
	Affected Cases	3.8 (0.2) mm^3

Table 1. Average retinal thickness across layers of the retina

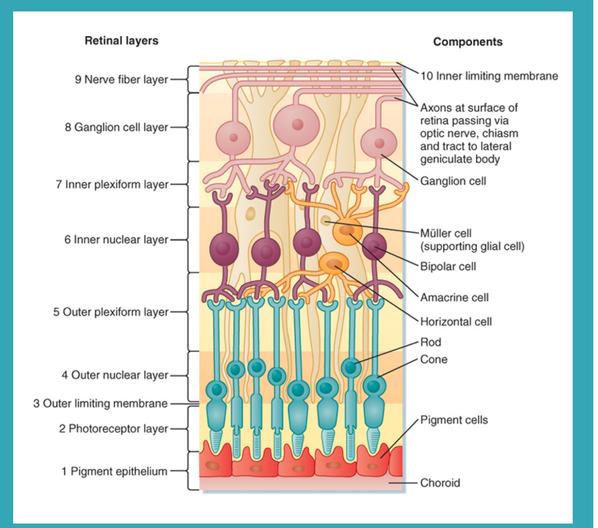

Figure 3. Retinal Layers

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