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Characterization of retinal architecture in Parkinson's disease

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ABSTRACT

Background: Parkinson's disease (PD) is a neurodegenerative disorder associated with dopaminergic cell loss and α-synuclein aggregation in Lewy bodies, which has been demonstrated in the retina.
Methods: We performed a spectral-domain optical coherence tomography (OCT) study in patients with PD and healthy controls to measure the peripapillary retinal nerve fiber layer thickness and macular volume. Intra-retinal segmentation was performed to measure the volume of the retinal nerve fiber (RNFL), ganglion cell (GCL), inner plexiform (IPL), inner nuclear (INL), outer plexiform (OPL), and outer nuclear (ONL) layers. Analysis was carried out blinded to the clinical status of study participants.
Results: 101 PD and 46 healthy control eyes were included in the study. In PD patients, peripapillary retinal nerve fiber layer was not significantly thinner (96.95 μm vs 94.42 μm, $p = 0.08$) but macular volume was (8.58 mm3 vs 8.33 mm3, $p = 0.0002$). Intra-retinal segmentation showed that PD subjects have reduced GCL, IPL, INL and ONL volumes. In contrast, the OPL volume was significantly increased (0.81 mm3 vs 0.78 mm3 $p = 0.0214$).
Conclusions: Thickening of the OPL is a novel finding which may correspond to the localization of α-synuclein in the OPL of PD patients. We hypothesize that the enlargement of the OPL may represent a potential biomarker of α-synuclein aggregation in PD. This may have significant clinical implications.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder affecting dopaminergic substantia nigra neurons within the brainstem. Changes in motor functions are cardinal manifestations of PD. These include resting tremor, bradykinesia, postural instability, and cogwheel rigidity [1]. Furthermore, visual symptoms including decreased visual acuity, reduced color vision, deficits in visuo-spatial orientation, and visual hallucinations are commonly reported in patients with PD [2]. Dopamine serves a critical role for visual processing in the retina and has been shown to be deficient in the PD retina [3]. Retinal dopamine deficiency may lead to visual symptoms in PD and treatment with levodopa has been shown to improve contrast sensitivity [4].

Improvements in retinal imaging have allowed for correlations between histopathology in post-mortem anatomy with in-vivo images [5]. In particular, optical coherence tomography (OCT) provides a unique opportunity to investigate retinal morphology relevant to neuronal function and synaptic transmission. It allows the in-vivo examination of the retinal nerve fiber layer (RNFL), and retinal segmentation allows automated volumetric quantification of the ganglion cell layer (GCL), the inner plexiform layer (IPL), the inner nuclear layer (INL), the outer plexiform layer (OPL) and the outer nuclear layer (ONL). Although several OCT studies have shown macular thinning in patients with PD when compared to healthy controls (HC), the relative contribution of individual retinal layers leading to the observed macular thinning in PD remains controversial [6,7].

Advances in intra-retinal segmentation have created opportunities for investigating neurodegenerative disorders including PD with the potential to develop biomarkers [6]. The 140 amino-acid human α-synuclein (AS) protein plays a central role in the etiology of PD and forms fibrillar aggregates in Lewy bodies and Lewy neurites in the brain [8]. α-Synuclein is involved in lipid binding, mitochondrial function, and synaptic transmission [9]. Several point mutations, whole gene multiplication, and abnormal phosphorylation of AS are pathogenic for PD [9]. Tissue protein and mRNA investigations across vertebrate species have shown AS gene expression in the OPL of the normal retina [10]. Autopsy studies have shown increased intra-cytoplasmic aggregation of AS, typical of PD, localized to the inner retinal layers [2]. Furthermore, the presence of AS, a hallmark of α-synucleinopathies, has also been localized to the inner retina in patients with PD [10].

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Against this background, we performed an OCT study to investigate structural changes in different retinal layers by applying intra-retinal segmentation in patients with PD compared to HC.

2. Patients and methods

2.1. Patient population

Patients were recruited from the Wayne State University Movement Disorders Center. All patients had definite PD according to the established UK Brain Bank diagnostic criteria for idiopathic PD [11]. Clinical data including Hoehn and Yahr [12] scores were obtained from the medical record charts. The Unified Parkinson's Disease Rating Scale (UPDRS) [13] scores were not available for all patients. All patients were evaluated by a single Movement Disorders expert and received various treatments for PD. Age and sex-matched HC subjects were also included in the study. The study was approved by the local Institutional Review Board and informed consent was obtained from all subjects.

2.2. OCT protocol

Images were obtained on a single Heidelberg SPECTRALIS SD (Spectral Domain)-OCT with N-Site Analytics platform (Heidelberg Engineering Inc., Heidelberg, Germany). To evaluate the macular volume and thickness, a 30 × 20 area consisting of 61 high resolution B-scans with an average Automated Real Time (ART) of 9, centered on the fovea was obtained. To evaluate the peripapillary retinal nerve fiber layer (pRNFL) thickness, a high resolution single line circular B-scan measuring with a radius of 3.4 mm, with an average ART of 80, centered on the papilla was used. The pRNFL thickness and total macular volume (TMV) were calculated by the Heidelberg 5.4 imaging software. The TMV was defined as the volume between the inner limiting membrane and the inner boundary of the retinal pigment epithelium within a 6-mm diameter circle centered on the fovea. However, we segmented only six layers within the macula as described below. Images used met the quality control requirements outlined in the OSCAR-IB criteria [14]. Images from any participant with pathology that could potentially interfere with retinal structure, including but not limited to glaucoma, diabetes, and previous intraocular surgery, were excluded.

2.3. Intra-retinal segmentation

Macular scans were analyzed using fully automated segmentation software (Heidelberg Engineering Inc., Heidelberg, Germany). Poor quality scans, per OSCAR-1B criteria [14] or misalignments were rejected prior to segmentation. Both HC and the PD images were reviewed to account for any misalignment of the beam as it enters the pupil. This was addressed by assessing the uniformity of contrast saturation of all six layers on a single B-line scan through the fovea. The beam misalignment was determined to be 20% in both HC and PD patients. All patient information was removed from the images, which were given a unique identifier and analyzed blinded to the clinical status of the study participants. Volume layer thickness was individually measured using the standard 1 mm, 3 mm, and 6 mm ETDRS grid. The following layers were automatically segmented, retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL) and outer nuclear layer (ONL) as shown in the figure. The retinal layers were not combined (Fig. 1).

2.4. Statistical analysis

Statistical analyses were performed using the STATA v. 13.1 (StataCorp, College Station, Texas, USA). Multivariate analysis was performed using MANOVA as an omnibus significance test of the retinal layers aggregate contribution to the difference between PD and HC. A multivariate regression analysis was then used to assess the contribution of independent variables: diagnosis (PD v. HC), age, gender and eye (OS vs OD) to the dependent variable of retinal layers. Only the layers with a significant difference ($p < 0.05$) between PD and HC were subsequently used in univariate analysis. Comparison of individual retinal layers, as well as the TMV and pRNFL, between PD patients and HC was performed using generalized estimating equation (GEE) with normal distribution and an identity link function and exchangeable correlation. This is an established method of analyzing paired biological data (e.g., OCT data from a pair of eyes), which guards against conflation of statistical significance that can result from use of paired biological data from the same subject (i.e., pair of eyes) [15]. We also re-analyzed the data using two-way, inter-ocular correlation coefficient adjusted t-statistics, i.e., a more conservative test of significance, and did not see any change in our results. Multivariate regression analysis was also used to explore the age corrected relation between retinal layer volumes and measures of disease severity (i.e., Hoehn and Yahr scores and disease duration).

3. Results

The medical records and OCT images of 66 patients with PD were reviewed. Seven patients were excluded from the study based on medical history due to ocular pathology that could interfere with retinal

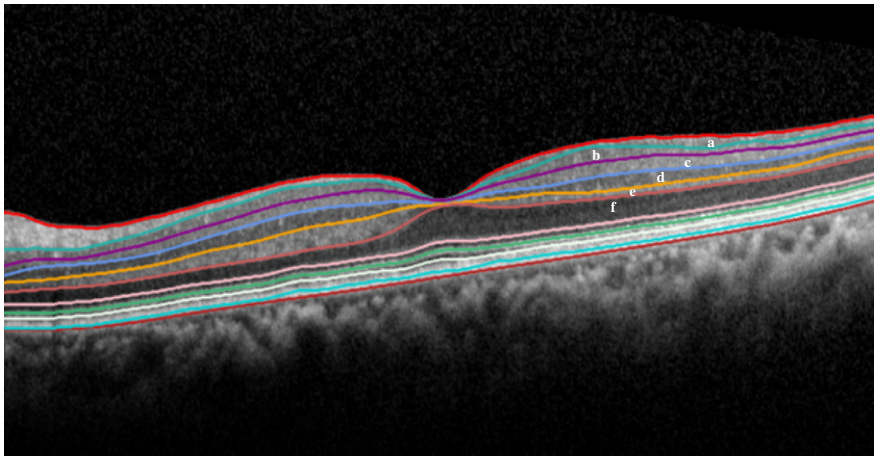

Fig. 1. Intra-retinal segmentation. Intra-retinal segmentation as performed by the software for the SPECTRALIS SD-OCT in the eye of a patient with Parkinson's disease. Layers are labeled: a—retinal never fiber layer (RNFL), b—ganglion cell layer (GCL), c—inner plexiform layer (IPL), d—inner nuclear layer (INL), e—outer plexiform layer (OPL), and f—outer nuclear layer (ONL).