Parkinsonism and Related Disorders 17 (2011) 431–436

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Retinal thickness in Parkinson's disease☆

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ARTICLE INFO

Article history:
Received 2 November 2010
Received in revised form
7 March 2011
Accepted 8 March 2011

Keywords:
Parkinson's disease
Optical coherence tomography
Retina
Retinal nerve fibre layer
Macula

ABSTRACT

Background: Visual symptoms are common in Parkinson's disease with studies consistently demonstrating reductions in visual acuity, contrast sensitivity, colour and motion perception as well as alterations in electroretinogram latencies and amplitudes. Optical coherence tomography can examine retinal structure non-invasively and retinal thinning has been suggested as a potential biomarker for neurodegeneration in Parkinson's disease. Our aim was to examine the retinal thickness of a cohort of Parkinson's disease subjects (and age-matched controls) to establish the practical utility of optical coherence tomography in a representative older Parkinson's disease group.

Methods: Fifty-one established Parkinson's disease subjects and 25 healthy controls were subjected to ophthalmological assessment and optical coherence tomography (Zeiss Stratus 3000™) of macular thickness and volume and retinal nerve fibre thickness around the optic nerve head. Twenty four percent of control and 20% of Parkinson's disease subjects were excluded from final analysis due to co-morbid ocular pathology. Further data was excluded either due to poor tolerability of optical coherence tomography or poor quality scans.

Results: Despite a reduction in both visual acuity and contrast sensitivity in the residual evaluable Parkinson's disease cohort, we did not detect any differences between the two study groups for any measures of retinal thickness, in contrast to previously published work.

Conclusions: In addition to technical problems inherent in the evaluation, the lack of difference between Parkinson's disease and healthy control subjects suggests longitudinal studies, employing newer techniques, will be required to define the role of optical coherence tomography as a potential diagnostic biomarker.

1. Introduction

Visual symptoms are common in Parkinson's disease (PD) and include difficulty reading and double vision [1,2], feelings of presence and passage in the visual periphery and complex visual hallucinations [3]. Whilst some of these symptoms are likely to stem from "central" visual processing deficits, others may be related to lower level disturbances of visual function. Visual acuity (VA) [4], contrast sensitivity (CS) [5,6], colour perception [7,8], motion perception [9] and the pattern electroretinogram (PERG) response [10,11] are all impaired in PD, with retinal dysfunction advanced as one possible explanation for these findings. However, with the exception of PERG data, sub-cortical or cortical disturbances in visual processing could explain at least some of the visual deficits in PD, and tools to probe the retina in isolation are therefore important to address the retinal contribution to visual dysfunction in PD.

Optical Coherence Tomography (OCT) is a non-invasive technique for obtaining cross-sectional images of the retina, with an axial resolution of 10 microns. OCT is capable of assessing the thickness of retinal nerve fibre layers (RNFL) around the optic nerve head, thus providing a measure of the integrity of the retinal ganglion cell axons as they exit the retina, as well as providing

Abbreviations: PD, Parkinson's disease; HC, healthy control; OCT, optical coherence tomography; RNFL, retinal nerve fibre layer; REM, rapid eye movement; VA, visual acuity; UCVA, uncorrected VA; BAPVA, "best at presentation" VA; CS, contrast sensitivity; PERG, pattern electroretinogram; IOP, intraocular pressure; UPDRS, unified Parkinson's disease rating scale.

☆ The review of this paper was entirely handled by an Associate Editor, V. Bonifati.

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doi:10.1016/j.parkreldis.2011.03.004

information on macular morphology. Previous OCT studies have demonstrated morphological changes in retinal structure in multiple sclerosis, Alzheimer's disease and glaucoma [12–14]. RNFL thinning has been found in PD, albeit in relatively small numbers of patients [15–17] and macular thickness has also been reported to be reduced [15,18,19]. One possible explanation for these findings is that dopaminergic deficiency deprives the retina of key trophic factors vital to maintaining structural integrity [20]. To date, the functional implications of these reported morphological changes are unclear.

The Biomarkers Definitions Working Group define a biomarker as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention [21]. OCT might prove a useful potential biomarker for assessing disease progression in PD and fulfils the "objectivity" criterion of this definition. However, to be considered as a viable potential biomarker, altered retinal morphology in PD would need to be a robust and repeatable finding in larger cohorts, preferably with longitudinal follow-up, and be applicable to a typical cohort of elderly PD patients with a variety of co-morbidities (*i.e.* good external validity).

We therefore compared retinal structure in a PD and healthy age-matched control cohort for evidence of RNFL or macular thinning and assessed the utility of OCT as a potential biomarker for disease progression in PD. We hypothesised that PD patients would demonstrate thinning of the peri-papillary RNFL and the macula compared to HC, but that the use of OCT as a biomarker may be limited by the co-occurrence of retinal disease (macular degeneration, glaucoma) and tolerability in a representative PD sample.

2. Methods

2.1. Subjects

The study was approved by the NHS Local Research Ethics Committee and all participants gave written informed consent prior to study inclusion. The study design was cross-sectional with PD participants over the age of 49 years consecutively recruited from the Newcastle upon Tyne NHS Trust Movement Disorder service. The healthy, age-matched control (HC) cohort comprised spouses/partners of study participants and was supplemented from an existing research database held at the Institute for Ageing and Health, Newcastle University, UK. These HC participants had expressed an interest in taking part in clinical research projects if they fulfilled inclusion criteria and were approached consecutively. PD participants were part of a larger cohort taking part in a study of visual symptoms in PD (PD $n = 90$; HC $n = 32$) and were consecutively approached for entry into the OCT arm of the study.

Inclusion criteria for the study were:

- an established diagnosis of PD
- ability to give informed consent
- suitable caregiver to provide additional information

Exclusion criteria were:

- severe dementia (MMSE <10)
- poor sitting stability – making clinical evaluations difficult for the patient
- absence of a regular caregiver to provide support
- active medical psychiatric illness which could interfere with assessment
- alcohol abuse, head injury, stroke, epilepsy or other major physical illness
- history of severe visual loss

All participants fulfilled UK Brain Bank Criteria for a diagnosis of PD [22]. All PD subjects were tested taking their normal medications and disease severity was assessed using parts II and III of the Unified Parkinson's Disease Rating Scale (UPDRS) [23].

2.2. Ophthalmological assessment

Ophthalmological assessment included measurement of uncorrected (UCVA) and "best at presentation" (BAPVA) LogMAR visual acuity (VA) (tested at 4 m). Contrast sensitivity (CS) was assessed at 40 cm with the head stabilized and normal near refractive correction utilized (Mars letter CS chart, Mars Perceptrix™). Intraocular pressure (IOP) was recorded with an Icare™ automated tonometer. Cataract severity was graded by two independent assessors (NKA, MPC) on a pragmatic scale for cortical, nuclear and posterior capsular lens opacity (0 = absent; 1^+ = mild; 2^+ = moderate; 3^+ = marked; 4^+ = severe) with consensus sought between both assessors in the event of discrepancy. Slit lamp examination was used to document structural corneal, retinal or optic nerve pathology.

2.3. OCT

Measures of peri-papillary RNFL, macular thickness and volume were made using a commercially available Optical Coherence Tomography (OCT) device (Zeiss Stratus 3000™) following pupillary dilation. Scan quality was assessed by examining the signal strength and confidence limits generated by the automated software analysis. "Best fit" automated contour lines were reviewed for OCT scans with a signal strength < 5/10 or with a macular protocol confidence limit >20 microns. Scans with poor fit contour lines or missing data were excluded from analysis. An illustration of the automated OCT output is provided in Supplementary Fig. 1.

The fast RNFL scan protocol consisted of a single 360° circular scan with a diameter of 3.4 mm centered on the optic disc, containing 256 A-scans taken in a single session of 1.92 s. Peri-papillary RNFL thickness parameters were automatically calculated by OCT 3000 unit software and included: average thickness (360° measurement), temporal quadrant thickness (226–315°), superior quadrant thickness (316–45°), nasal quadrant thickness (46–135°), and inferior quadrant thickness (136–225°) (Supplementary Fig. 1). The fast macula scan protocol consisted of 6 mm radial line scans centered on the macula, each containing 128 A-scans taken in a single session of 1.92 s. Six sets of intersecting and equally spaced scans were obtained each crossing the central fovea. The automated analysis program presents both mean foveal thickness and total macular volume in a 6.00 mm macular map.

2.4. Statistics

Data were analyzed using the JMP 8 statistical package (SAS Institute Inc). The distribution of data was examined for normality (Shapiro–Wilk test). Means and standard deviations (SD) were calculated. Normally distributed data were analyzed with parametric tests (Independent sample *t*-tests) and non-normally distributed data with non-parametric tests (Wilcoxon Rank Sums). Pearson chi-square test was employed for comparison of frequencies and Fisher's exact test utilized when

Table 1
Basic group demographics.

	HC	PD	*p*
	$n = 25$	$n = 51$	
Age (years)	71.6 ± 7.8	71.3 ± 7.7	†0.864
Gender (% male)	56	65	**0.616
PD duration (years)		9.1 ± 6.0	
L-dopa dose (mg/day)		460.8 ± 388.8	
Agonist use (%)		37	
UPDRS II		14.9 ± 7.1	
UPDRS III		25.7 ± 12.5	
% Glaucoma (n)	0 (0)	4 (2)	**1.000
% Previous cataract surgery (n)	12 (3)	8 (4)	**0.678
% Diabetes mellitus (n)	8 (2)	6 (3)	**1.000
% Hypertension (n)	32 (8)	20 (10)	**0.260
% Right cataract (n)	64 (16)	73 (37)	**0.596
% Left cataract (n)	60 (15)	73 (37)	**0.302
% AMD (n)	8 (2)	10 (5)	**1.000
% Optic atrophy (n)	12 (3)	10 (5)	**1.000
RIOP (mmHg)	14.5 ± 3.4	13.8 ± 2.7	§0.466
LIOP (mmHg)	14.6 ± 2.7	14.1 ± 2.8	§0.465
Right UCVA	0.42 ± 0.37	0.47 ± 0.29	§0.407
Left UCVA	0.32 ± 0.26	0.47 ± 0.29	§0.051
Binocular UCVA	0.24 ± 0.27	0.32 ± 0.26	§0.279
Right BAPVA	0.10 ± 0.24	0.20 ± 0.24	§0.048
Left BAPVA	0.10 ± 0.19	0.20 ± 0.23	§0.054
Binocular BAPVA	−0.01 ± 0.12	0.08 ± 0.15	§0.016
Right CS	1.56 ± 0.19	1.48 ± 0.17	§0.019
Left CS	1.58 ± 0.14	1.50 ± 0.17	§0.062
Binocular CS	1.68 ± 0.09	1.60 ± 0.13	§0.009

Values expressed as means ± SD (unless otherwise stated).
Statistical tests: †*t* Test; §Wilcoxon rank sum; **Pearson χ^2 ± Fisher's exact test where groups frequency <5.
UPDRS = Unified Parkinson's disease rating scale; AMD = Age-related macular degeneration; RIOP = Right intraocular pressure; LIOP = Left intraocular pressure; UCVA = Uncorrected visual acuity; BAPVA = "Best at presentation" visual acuity; CS = Contrast sensitivity.