Potential role of retina as a biomarker for progression of Parkinson’s disease

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Abstract

- Optical coherence tomography (OCT) noninvasively quantifies the thickness of the retinal nerve fiber layer (RNFL). OCT has been studied in several neuro-ophthalmic conditions, including Parkinson's disease (PD). Recent studies suggest that the quantitative analysis of RNFL can be precisely and noninvasively done by OCT scans and the results suggest that the thickness of RNFL is significantly decreased in patients with PD compared with age-matched controls and the foveal retinal thickness correlates with disease severity in PD. In this article, the application of OCT imaging of the retina in PD was reviewed. Literature survey of PubMed was carried out using the search terms of "Optical Coherence Tomography" combined with "Parkinson's Disease" and "retinal nerve fiber layer" (without restriction to the year of publication). Some related articles were also included. The search was completed in Jul. 2011 and revised and updated as necessary. The aim of this article is to review the current literatures on the use of optical coherence tomography in patients affected by PD and to enhance its use in clinical practice in neuro-ophthalmology.

- KEYWORDS: Parkinson disease; optical coherence tomography; retinal nerve fiber layer thickness

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INTRODUCTION

Parkinson's disease (PD) is a most common neurodegenerative disorder characterized pathologically by a loss of dopaminergic neurons mainly in substantia nigra pars compacta as well as the presence of cytoplasmic inclusions (Lewy bodies) containing α-synuclein and ubiquitin [1]. At present, the development of therapy in PD is hampered by the lack of well-established biomarkers that can assist with diagnosis and/or tracking the progress of the disease. Reliable biomarkers that are based on the underlying disease process and meaningfully predict the clinical course are a major unmet need in PD. The emergence of biomarkers linking disease and therapeutic effects in a clear manner provides an opportunity to change the current drug development mode, which could lead to more cost-efficient and higher-quality clinical trials. This has raised the hopes to find a way out of the current funding crisis for novel, nonvalidated drugs and their clinical development.

Although SPECT [2], PET [3] and MRI [4] techniques have substantially advanced our ability to link imaging data with clinical measures of disease severity, however, until recently the progression coupling specific clinical syndromes in PD with pathological changes within discrete tract systems was limited. Optical coherence tomography (OCT) is a recently developed technology that enables investigators to rapidly and reproducibly evaluate morphology of the retina and to provide unique insights into this structure. While already being applied in the longitudinal assessment of glaucoma [5,6] and macular degeneration [7], OCT is currently being investigated for its utility in tracking the progresses of neurodegeneration within the retina in PD. Eventually, OCT could substantially increase the understanding of retinal injury mechanisms in PD, could provide a potential therapy-independent marker of PD progression. Therefore, the aim of this review is to provide insights into the changes of retinal nerve fiber obtained by OCT in PD and to evaluate whether retina can be used as a valuable marker to monitor the disease course in patients affected by PD.

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Intrinsic dopaminergic neurons have been identified in the retinas of different animal species, including humans \[^9\]. In PD patients' retina, dopamine extent is less than control adults. Results of neurochemical studies show that postmortem PD eyes have low dopamine content \[^9\], which gives the direct evidence of decreased DA concentration in the retinas of patients with PD. This is confirmed by another study showing reduced DA innervation in the central retina in 5 patients with Parkinsonian \[^10\]. In addition, there is a decrease in the number of dopaminergic amacrine cells in the retinas of the MPTP (1-methyl, 4-phenyl, 1-2-3-6-tetrahydropyridine) -treated monkeys \((P<0.001)^{11}\). Patients with PD commonly complain of impaired visual function and difficulty reading \[^12\]. At least part of the visual functions, such as absolute sensitivity, spatial contrast sensitivity, temporal sensitivity and color vision, is controlled by dopamine \[^8,13,14\]. Dopamine deficiency and dopaminergic neuronal degeneration in retina could give rise to many of the visual abnormalities observed in PD \[^8,15\]. In particular, the involvement of dopamine in controlling the coupling of horizontal and amacrine cell lateral systems appears to be central to the visual defects seen in PD patients \[^8\]. Impaired vision in PD was first shown by psychophysical and visual evoked potential (VEP) measurements in both rats\[^16,17\] and human\[^18\]. Resulting from the retinal alterations, PD subjects have reduced contrast sensitivity and reduced color vision which is progressive over time but can be improved with L-DOPA\[^19,20\]. Changes in the VEP and contrast sensitivity occur in PD patients and are identical to those observed in animal models whose dopaminergic retinal system has been destroyed, thus suggesting a degenerative process of this system in Parkinson's disease. This assumption is further confirmed by recent experimental evidence which links dopaminergic, preganglionic amacrine cells deficiency and visual processing by showing reduced ganglion cell activity\[^21-23\].

The visual dysfunction may be the result of pre-ganglionic dopaminergic deficiency in PD as retinal ganglion cells are not dopaminergic in either the human or the monkey. The retina in the animal model of PD using MPTP showed dopaminergic deficiency with loss of a subset of retinal amacrine cells, which provide input to ganglion cells \[^11,24\]. Retinal dopamine deficiency is believed to alter visual processing by modifying receptive field properties of ganglion cells \[^9\], whose axons form the RNFL. Dopamine modulates the receptive fields of ganglion cells through D1 and D2 receptors via feedback by establishing the gain of ganglion cells in the monkey and human retina\[^25\].

THE RETINA AS A MODEL OF NEURODEGENERATION IN PD

Dopamine has fully been established as a retinal major neurotransmitter or modulator present at many levels of the visual system, mainly in the amacrine cells and interplexiform cells \[^21-27\]. The retina is a highly discrete and eloquent CNS structure. The most accessible dopaminergic neurons of the vertebrate CNS are the dopaminergic amacrine cells of the retina. The relationship between brain and retina is complex in that the structural composition of the disease process may be similar in both locations. Besides the dopaminergic neuron loss in midbrain, retinal dopaminergic neurons also undergo degeneration, which leads to the visual dysfunction commonly complained by patients with PD. The retinal nerve fiber layer (RNFL) is unique as a model of neurodegeneration in that it is devoid of myelin, application of myelin to the optic nerve begins behind the eye, at the level of the lamina cribrosa. This organization is advantageous because the changes in the RNFL structure principally represent axonal damage. Hence, the retina can be used to focus on the neuronal and axonal components of PD pathological changes.

The inner retina layer (IRL) includes the nerve fiber layer, the ganglion cell layer, and the innerplexiform layer while the outer retina layer (ORL) consists of other layers starting from inner nuclear layer up to and including the retinal pigment epithelium. Amacrine cells, including dopamine amacrine cells are located in the inner layer close to ganglion cells. The RNFL represents axons of the ganglion cells. It is possible that impoverished dopaminergic input to the ganglion cells leads to atrophy of these selected fibers, which can be detected by OCT. The retina as a window on the brain may reveal the state of dopaminergic neurodegeneration in PD.

THE PHYSICS OF OCT

Optical coherence tomography (OCT) is emerging as a new medical imaging technology quantifying the RNFL thickness \(in vivo\)^\[^28\]. It functions as a type of optical biopsy, providing information on retinal pathology in situ and in real time, with resolutions approaching that of excisional biopsy and histopathology. The OCT instrument works by measuring the echo time delay of back-scattered infrared light and intensity of back refraction of light from different structures in the eye \[^28\]. The process uses an interferometer in combination with a low-coherence light source. An interferometer is used to measure the light reflected from a reference arm and from structures within the eye, and when back reflected light from these structures has traveled...
exactly the same distance, interference is produced and this is measured by the interferometer. The layers in the retina can be differentiated by the signal intensity of the back reflected light \[^{[29]}\]. With OCT, noninvasive high-resolution cross-sectional or three-dimensional images of the internal retinal structure are generated. The resulting images allow spectacular differentiation of the major retinal layers, which can then be analyzed for tissue thickness and volume in situ and in real time, to a resolution of less than 10μm, and to about 3μm with high-resolution OCT \[^{[30]}\]. Retinal thickness measured by OCT correlate very well with histological analysis \[^{[31-33]}\]. The OCT data-analysis program generates values for average RNFL thickness can be further divided into quadrant and clockface (12 zones) sectors for more detailed analyses. The sensitivity \[^{[28]}\] stability \[^{[34]}\] and good reproducibility \[^{[35,36]}\] of these measures makes OCT an ideal tool for the longitudinal assessment of degenerative change in retina.

OCT is somewhat analogous to ultrasound B-mode imaging, except that light is used instead of sound. In contrast to ultrasonography, it is impossible to detect light echoes with OCT directly with the reason that the speed of light is much faster than the speed of sound; therefore, correlation techniques must be used. Ultrasound is an associated method producing greater tissue penetration with lower resolution, whereas OCT is contingent upon tissue-density-dependent reflections of infrared light, resulting in better anatomical resolution.

**APPLICATION OF OCT IN PD**

The first use of OCT in PD was reported in 2004 by Inzelberg and colleagues \[^{[37]}\]. This group assessed 10 patients with PD. The researchers reported a significant inferior quadrant RNFL thinning in PD (147±20 microns) compared with controls (173±12 microns; 191±21 microns; \(P=0.0003\)). They also performed visual fields (VF) examination reliably in five patients. Reduction in sensitivity in the visual fields observed in these series, matched topographically the localized RNFL thickness loss, as previously discussed in other diseases where RNFL damage occurs \[^{[38]}\]. However, no correlation between the RNFL thinning and disease duration was detected.

In Altintas and colleagues’ study \[^{[39]}\], the patients were assessed with OCT, visual evoked potentials and Unified Parkinson’s disease rating scale (UPDRS) scores. When compared with healthy people, both the mean retinal nerve fiber layer average thickness (98.76±10.90μm \(r=114.54±5.72μm\) ) (\(P<0.05\)) and the mean total macular volume (6.82 ±0.32mm\(^3\) \(r=7.09 ±0.23\text{mm}^3\) ) were significantly reduced in Parkinson’s disease patients. Different from significant reduction in the inferotemporal parapapillary RNFL reported by Inzelberg et al.\[^{[37]}\], RNFL was found to be significantly decreased in the superior, nasal and inferior quadrants in this study.

The researchers also confirmed a highly significant inverse correlation between foveal retinal thickness and total and motor subscores of UPDRS in these patients, respectively (\(r=-0.660; P=0.004\)), (\(r=-0.625, P=0.007\)), which led to the conclusion that reduced foveal thickness is correlated to the severity of disease.

In 2009, Hajee and colleagues \[^{[40]}\] provided a more detailed and systematic characterization of OCT changes by evaluating the inner and outer retinal layers with high resolution Fourier-domain OCT \[^{[41]}\]. The thinning affects the inner nuclear layer (INL) (the site of amacrine cells and the ganglion cells). The results showed that the mean inner retinal layers (IRL) significantly thinner in relatively early PD than that in healthy controls, and the loss of RNFL is not caused by increased intraocular pressure. The inferior and superior IRLs are similarly affected in a group of PD eyes. The mean (SD) inferior IRL thickness of healthy eyes \(r=9.36\)PD eyes was 104.0 (23.5)μm \(r=89.83\) (11.1)μm (\(P=0.01\)). The mean superior IRL thickness of healthy eyes \(r=9.58\)PD eyes was 103.5 (24.3)μm \(r=88.79\) (11.3)μm (\(P=0.01\)). They also revealed 15% to 20% thinning of the macular region of the inner retina in PD. In addition, they assessed the reproducibility of data obtained with Fourier-domain OCT by comparing two consecutive OCT measurements in seven healthy controls \(r=13\) eyes in 1-week intervals. The mean inner retinal layer change was only 1.25μm. Most of the patients in this study were in the early stages of the disease. This lead to the hypothesis that retinal thinning may be relevant to the early diagnosis and neuroprotective treatment of PD. Fourier-domain OCT may contribute a quantitative imaging approach to the early diagnosis, treatment, and follow-up of progression of PD.

Recently, Aaker et al.\[^{[42]}\] detected the retinal changes in Parkinson’s disease with spectral-domain optical coherence tomography (SD-OCT). Eighteen eyes from nine subjects with PD and 19 eyes of 16 age-matched control subjects were imaged with the SD-OCT. RNFL, IRL, and macular thickness were measured for each eye using Heidelberg software. In contrast to the studies mentioned above, SD-OCT did not detect significant reductions in peripapillary RNFL and IRL thickness between PD patients and age-matched controls in this pilot study. Overall average RNFL thickness was 97μm for PD patients, which exactly
matched the normative database value. However, significant differences in macular thickness were detected in three of nine subfields between PD subjects and published normal values. In PD subjects, the outer superior subfield was 2.8% thinner ($P=0.026$), while the outer nasal and inner inferior subfields were 2.8% ($P=0.016$) and 2.7% ($P=0.001$) thicker than published normal values. This suggests that macular thickness measurements by SD-OCT may potentially be used as an objective, noninvasive, and easily quantifiable in vivo biomarker in PD. Even in PD patients with normal vision, there is a decrease in the electrical activity of the fovea as well as in the thickness of the RNFL. OCT scan can detect early subclinical PD-associated visual functional impairment objectively. The similar retinal changes were found in animal model. In mice with rotenone injected eyes, both the thickness and cell numbers of the retinal ganglion cell layer were significantly reduced. It is possible that impoverished dopaminergic input to a subset of ganglion cells, contributes to abnormal production of glutamate and atrophy of these selected fibers. Moreover, Altintas et al demonstrated that RNFL thickness correlates with disease severity. They reported in 17 PD eyes an inverse highly significant correlation between neurologic impairment (UPDRS both total and motor subscores) and inner foveal retinal thickness but not total macular or peripapillary thickness. However, a very recent study showed that no difference was detected between patients with PD and normal controls, despite a reduction in both visual acuity and contrast sensitivity in the residual evaluable PD cohort. Longitudinal studies employing newer techniques will be required to define the role of OCT as a potential diagnostic biomarker, in addition to technical problems inherent in the evaluation.

**THE FUTURE OF RETINAL IMAGING IN PD**

Neurodegeneration in PD is a complex and multifaceted process, affects a specific population of neurons. Use of objective biomarkers in tracking disease progression is the foundation of research into disease-modifying treatments for PD. Retinal imaging techniques have added greatly to our knowledge of this area, revealing further changes in retinal architecture that can be associated with relevant and easily measured clinical assessments.

With the dramatic advances in technology, its imaging performance has been significantly improved. The development of 'Fourier domain' (or 'spectral domain') detection which was first proposed in 1995, has significantly enhanced ophthalmic OCT technology. Fourier-domain OCT detects all light echoes simultaneously, leading to a dramatic increase in sensitivity that enables high-speed imaging. Much finer resolution of Fourier-domain OCT results in a more accurate representation of retinal topography. The overall image quality of Fourier domain OCT is also superior due to correction for eye movements, this is particularly relevant in PD patients with tremor. The high image-acquisition speeds of the Fourier-domain instruments generates the high-definition OCT images as well as the acquisition of three-dimensional OCT (3D-OCT) data sets which is especially promising. 3D-OCT data also provide information about the RNFL-thickness maps or topographic maps for greater retinal depth (three-dimensional) analysis. Together, these features provide promising improvement in RNFL thickness measurements and other morphometric measurements. The improved visualization and performance of new OCT technology suggests that this technique will have an increasingly important role in the assessment of processes of axonal and neuronal degeneration in neurological disease in general. Despite the advantages in the development in OCT, some important issues need be addressed. Different OCT instruments have different measurement protocols and different data analysis systems, so quantitative studies should be conducted to compare morphometry results and to establish consistent normative baselines.

In addition, questions remain about which protocols or visualization methods are best suited in a given situation, depending upon the disease stages and the resultant impact upon axons, neurons, or both. Whether OCT measures contribute a quantitative measure to the early diagnosis of PD other than a constellation of early signs also needs to be established.

It is revealed that the underlying neuropathological process (formation of Lewy bodies) in PD advances from peripheral to central neurons in a caudo-cranial direction. It is not known whether Lewy bodies exist in the retina of PD patients. In this situation, combinatory analysis of RNFL with other PD biomarkers might be effective. Alternatively, developing methods to detect specific molecules underlying PD pathogenesis taken from blood and CSF combined with genetic screenings of PD linked genes and imaging techniques would increase the possibility of detecting disease.

**CONCLUSIONS**

OCT is a valuable tool in evaluating the peripapillary RNFL in both optic neuropathies and diseases that affect the central nervous system. The successful use of OCT in clinical trials indicates that OCT may provide a valid and reliable
biomarker to tracing neurodegeneration within the retina and a primary outcome measure to detect the effects of new therapeutic strategies and follow-up of disease progression of PD. Also, this biomarker may be useful in identifying the disease early in the course so that early treatment can be started. This would be particularly valuable in settings where sophisticated neuroimaging is not available. The wide use of OCT in evaluating the optic nerve and the visual system has revolutionized our understanding and research of neuro-ophthalmic diseases. However, retinal nerve fiber thinning has been found in PD in relatively small numbers of patients, and how the structural damage of the retina changes with disease process is not well understood. Further studies in larger series are needed to ensure reproducibility and to evaluate the possibility to define cut-offs that could serve clinical purposes. Combinatory evaluation of the non-invasive techniques and post-mortem retinal work may help to clarify the exact relationship between RNFL thickness reduction and severity of the disease.

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