Invited Commentary

Seeing Parkinson Disease in the Retina

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Parkinson disease (PD) is a debilitating neurodegenerative disease caused by progressive death of dopaminergic neurons in the substantia nigra. This neurodegeneration classically causes a triad of bradykinesia, rigidity, and rest tremor. Patients with PD also develop nonmotor symptoms, such as olfactory loss, sleep dysfunction, autonomic dysfunction, neuropsychiatric disturbances, and cognitive impairment. Currently, PD is diagnosed clinically using the Movement Disorder Society clinical diagnostic criteria for Parkinson disease. However, some patients present with atypical features, complicating the diagnostic process. Therefore, there remains an unmet clinical need for noninvasive biomarkers that may improve our ability not only to diagnose PD, but also perhaps to identify individuals with presymptomatic or preclinical disease to enable earlier therapeutic interventions. Recently, there has been interest in the idea that the neurosensory retina may provide a window into pathology of the central nervous system.[1,2] One potential advantage of retinal biomarkers is that they can be assessed rapidly and noninvasively.

Related article

In this issue of *JAMA Ophthalmology*, Robbins and colleagues[3] report their findings from a single-center, cross-sectional, case-control study, designed to characterize alterations in the structure and microvasculature of the retina and choroid in eyes from patients with PD vs age- and sex-matched cognitively normal, healthy controls. They analyzed 124 eyes from 69 participants with PD and 248 eyes from 139 controls. Fourteen PD eyes (11%) and 30 control eyes (12%) were omitted because of motion/segmentation artifact, poor scan quality, or focal signal loss. Parkinson disease eyes had lower superficial capillary plexus vessel density and perfusion density in both the 6-mm Early Treatment Diabetic Retinopathy Study circle (2.0% and 2.1% lower, respectively) as well as in the inner ring of the 6-mm Early Treatment Diabetic Retinopathy Study circle (3.3% and 3.3% lower, respectively) but had the same sized foveal avascular zone. Although there were no anatomic differences in the central subfield thickness, ganglion cell-inner plexiform layer thickness, retinal nerve fiber layer thickness, or subfoveal choroidal thickness, PD eyes had larger total choroidal area (9.7% larger) and larger choroidal luminal area (8.9% larger) but lower choroidal vascularity index (0.8% lower) compared with control eyes.

Taken together, these findings support the overarching idea that structural and microvascular changes in the retina and choroid may reflect or be associated with the underlying pathology in PD. These interesting findings suggest that retinal biomarkers may have utility in improving our diagnostic algorithms for PD. Future studies should investigate whether these retinal and choroidal biomarkers differ in various subtypes of PD, as they demonstrate heterogeneity in disease presentation, response of motor symptoms to dopaminergic agents, and rate of disease progression.[4] If there is indeed a difference based on PD subtype, these findings would have important implications for improving our ability to counsel patients regarding prognosis. As the authors acknowledge, given the relatively low discriminative capacity of each of these optical coherence tomography (OCT)/OCT angiography (OCTA) parameters individually (area under the receiver operating characteristic curve, 0.50-0.63), these biomarkers will likely have to be used in conjunction with existing or other new biomarkers. Future large studies are also necessary to help clarify discrepancies between the present findings vs those of other recent studies[5,6] to overcome limitations of study heterogeneity and possible confounders. Novel developments in machine learning and artificial intelligence may facilitate the development of improved algorithms to maximize reliability and reproducibility in the analysis of OCT/OCTA findings.

Despite the excitement surrounding the use of retinal biomarkers, an issue to consider is how the structure and microvasculature of the retina is affected by concomitant ophthalmic pathology, such as diabetic retinopathy, glaucoma, or age-related macular degeneration. Given the substantial prevalence of these disorders in the age group that PD typically affects, it will be important to disentangle changes attributable to PD vs those attributable to underlying ophthalmic disease. Another important avenue for longitudinal studies would be to examine whether the retinal and choroidal changes in PD are progressive and may identify subgroups of patients with more aggressive disease vs those with slower progression. There may also be other neurological or systemic diseases beyond PD that also have retinal manifestations on OCT and OCTA findings. For example, a 2018 study reported OCTA changes in preclinical biomarker-positive Alzheimer disease.[7] One potential difference was that in the preclinical Alzheimer disease cohort, the foveal avascular zone was enlarged compared with the biomarker-negative cohort, while in this study, there was no difference in foveal avascular zone between patients with PD compared with controls. Large multicenter studies that account for possible confounding factors, stratify participants based on disease severity, and include imaging parameters that can be compared across different imaging devices are essential before retinal biomarkers can be used in clinical practice.

In summary, in this study, Robbins and colleagues[3] report 2% to 3% lower superficial capillary plexus vessel density and perfusion density, 9% to 10% higher total choroidal and choroidal luminal area, and 1% lower choroidal vascularity index in eyes from patients with PD compared with eyes from age- and sex-matched cognitively normal controls. Regardless of whether these changes reflect a retinal manifestation of the pathophysiology of PD vs underlying cerebral vasculopathy (or both), these findings suggest

that OCT and OCTA may be a valuable addition to our armamentarium for PD diagnosis. Although these biomarkers are not yet ready for clinical practice given the likely need to use them in conjunction with other diagnostic tools, they provide a foundation for future studies to investigate the possibility.

ARTICLE INFORMATION

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