EDITORIAL

Visual Dysfunction and Parkinson's Disease

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Visual dysfunction is increasingly recognized as a common nonmotor aspect of Parkinson's disease (PD), with loss of visual acuity and color vision as well as higher order visual deficits.[1] A related observation is that patients with PD with visual dysfunction may have a more aggressive cognitive phenotype with faster conversion to dementia.[2,3] However, there are discrepancies between studies, with some showing no difference in visual acuity[4] and higher order visual measures between patients with PD and age-matched controls.[5] Differences are likely to arise due to heterogeneity in patients with PD, with sampling differences between small studies, many of which are cross sectional.

For this reason, large longitudinal prospective studies of visual changes in PD are valuable resources. In this issue of *Movement Disorders*, 2 large epidemiological studies examine the link between visual dysfunction and PD. Both take advantage of established clinical databases with secure PD diagnoses and accurate measures of visual function captured in their relative populations.[6,7] These studies highlight 2 distinct and clinically relevant aspects of visual dysfunction in PD: (1) that loss of visual function may be found at the very earliest stages of PD, a kind of early nonmotor sign, and (2) that visual dysfunction in established PD is a marker of poor prognostic outcomes.

In the first study, Han and colleagues[6] present a very large sample of more than 6 million people in South Korea with demographic and clinical measures as well as visual acuity, covering a study period of almost 9 years. This allowed them to identify measures associated with higher risk of developing PD. In addition to established risk factors such as nonsmoking, higher age, and diabetes, they observed that visual acuity was poorer in those patients diagnosed with PD during the observational period compared with those who did not develop PD (logMAR 0.41 ± 0.56 in patients with new PD vs. logMAR 0.13 ± 0.48 in those who did not develop PD; note that on a logMAR scale, higher values represent poorer vision). They also found that patients with poorer visual acuity showed significantly higher incidences of developing PD than those with good or normal acuities, with a hazard ratio (HR) of 1.36 and 1.27, respectively, for the 2 groups with poorest visual acuity (using best visual acuity patients as the reference and adjusting for age and sex).

Interestingly, they did not find a dose effect. Although poorer visual acuity was linked with higher risk of PD, when they stratified by severity of visual acuity, the very poorest levels of visual acuity (with visual acuities poorer than 10/100) did not show the highest hazard ratios for developing PD, especially after adjusting for age, sex, and other covariates. The authors suggest that this may represent lower diagnosis rates in the group with poorest vision as a result of lower health-seeking behavior in this group. However, an alternative explanation is that there is a genuine inverted U-shaped curve here, with PD-related visual dysfunction producing a mild phenotype, and where severe visual loss is seen, causes other than PD are responsible. Indeed, where visual deficits are seen in studies, differences between PD and controls are not profound.[8-10] It is our experience that visual dysfunction associated with PD is often asymptomatic and that patients with deficits on formal testing frequently are not aware of them in everyday life.

An important potential confounding factor here is age, as increasing age is linked with both higher risk of PD and poorer visual acuity. This does not seem to be adjusted for in all analyses. Where HRs are adjusted for age, effects do lessen. For example, in the Cox regression analysis, when adjusted for age (and other demographic factors), effects are reduced from 6 times higher in groups with poorest visual acuity to 1.3 times

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higher in these groups compared with the reference group with normal acuity. Nevertheless, the relationship between poorer vision and higher risk of PD does hold when adjusted for age and was especially marked in the group aged younger than 65 years.

No information was given for the causes of low visual acuity, and this is potentially biologically interesting. For example, diabetes is more common in PD,[11] so higher levels of diabetic retinopathy could be a potential cause for some loss of visual acuity in this subgroup and indeed higher levels of ocular disease such as cataracts are also seen in PD.[12]

In the second study, Hamedani and colleagues[7] examine the relationship between eye health and poor outcomes in PD, also using a population sample, this time taken from Medicare beneficiaries in the United States during a 4-year period. The sample is also impressively large, with 26 million people, including 287,000 with PD and 188,000 with vision loss. They compared the prevalence of visual impairment with various poor outcomes in PD, including hip fracture, depression, anxiety, dementia, and death.

Similar to Han and colleagues,[6] they found that visual dysfunction was more common in PD than non-PD, even when adjusted for confounders such as age, with an odds ratio of 1.60 (95% confidence interval [CI], 1.56–1.65). They go on to show that moderate to severe visual impairment in PD is associated with an increased rate of depression (HR, 1.23; 95% CI, 1.14–1.32), dementia (HR, 1.28; 95% CI, 1.21–1.36), and death (HR, 1.49; 95% CI, 1.44–1.55), even after adjusting for confounders such as age. Of note, visual impairment was higher in patients from racial and ethnic minority backgrounds. Given the link with visual impairment and poor outcomes in PD, this group should be given additional clinical support during neurological follow-up to prevent poor outcomes in PD.

The authors also found that higher rates of hip fracture were found in patients with poor vision, although this did not adjust for confounding factors. This relationship, albeit possibly a weaker one, merits consideration of bone protection for this patient group when assessed clinically.

The authors focused on patients with moderate to severe visual impairment. Given the observations from Han and colleagues[6] and others that visual dysfunction in PD is often more mild,[10,13] it is likely that even stronger associations would be seen between visual impairment and poor outcomes in PD if they included milder forms of visual impairment.

Hamedani and colleagues[7] consider why visual dysfunction is linked with poorer outcomes in PD. They suggest the relationship might be explained by differences in health-seeking behavior, with less health-seeking behavior in patients with PD with depression and dementia, leading to poor eye outcomes. An alternative possibility is that worsening PD leads to visual dysfunction, which is a risk factor in itself for dementia and poor outcomes.

The presence of visual dysfunction is recognized as a nonmotor feature of PD, with visual deficits noted along the visual processing hierarchy, from visual acuity[13] and contrast sensitivity deficits[14] to loss of color vision,[9] eye movement abnormalities,[15] and higher order visual deficits such as attention and neglect.[10] Some of these deficits are caused by retinal changes. Dopamine is a modulatory neurotransmitter in the retina,[16] and patients with PD have lower levels of dopamine around the fovea,[17] with reduced dopamine concentrations in the retina at postmortem.[18] Retinal thinning is found in PD, especially in the ganglion cell layer and inner plexiform layer, both dopamine-containing layers.[8] Postmortem studies show that alpha synuclein accumulates within these layers in PD and correlates with levels of brain α-synuclein in Lewy body dementia.[19]

Recently, visual deficits have emerged as prognostic markers of poor outcomes in PD. Higher order visual deficits such as errors copying pentagons are linked with double the rate of dementia after a 10-year follow-up[2]; color vision deficits also predict poorer outcomes,[3] and contrast sensitivity may correlate with disease severity.[20] We recently showed that dysfunction across all aspects of vision, including retinal thinning, in ganglion cell layer and inner plexiform layers, as well as color vision, visual acuity, contrast sensitivity, and higher order vision are linked with higher risk of dementia in PD.[8]

Visual dysfunction can be easily measured but is not always reported or tested in routine PD follow-up. These 2 studies show that it can be a useful nonmotor aspect of PD to track severity and predict outcomes. We need longitudinal studies in prodromal PD groups to identify whether visual testing could be useful at the very earliest stages. In the meantime, evidence is mounting that in established PD, visual dysfunction is a useful metric to identify those patients at higher risk of poor outcomes, to stratify clinical trials, and to intervene early in these groups so that we can start to improve outcomes and ultimately prevent dementia in PD. ■

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