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REVIEW

Early ophthalmologic features of Parkinson's disease: a review of preceding clinical and diagnostic markers

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Abstract

Non-motor symptoms in Parkinson's disease are an important cause of morbidity and may even precede the onset of the motor features of the disease. Visual abnormalities are among the most frequent non-motor symptoms observed during the early stages of the disease. Some of the visual symptoms of Parkinson's disease can likely be explained by the presence of dopaminergic neurons within the retina, where the progressive loss of dopamine and the accumulation of α-synuclein within the retinal layers leads to visual dysfunction, while some are caused by abnormalities in cortical visual processing. Many of these visual symptoms can be overlooked or go unrecognized. We review the visual symptoms in Parkinson's disease, including visual-processing and ocular motility abnormalities, stereopsis deficits, and visual hallucinations, focusing on the early stages of the disease. We focus on the reciprocal influence between the visual symptoms and the progression of the disease, analyzing the influence of dopaminergic therapy on the visual abnormalities. Finally, we discuss the possible role of some of these visual symptoms as possible markers or early diagnostic signs of the disease.

Keywords Parkinson's disease · Visual hallucinations · Visual-processing abnormalities · Oculomotor dysfunctions · Stereopsis impairment

Introduction

Parkinson's disease (PD) is a neurodegenerative disease that has been described to primarily affect the basal ganglia and the motor system [1, 2]; however, non-motor symptoms play an important role in the quality of life of patients and may predict disease progression and possible outcomes. Rapid eye movement sleep behavior disorder (RBD) [3, 4], constipation [5], hyposmia [6], and depression [7] may precede the onset of motor symptoms in PD and are considered prodromal signs of the disease. According to the Braak neuropathology staging system for PD, the involvement of the substantia nigra, which is thought to trigger the onset of the motor symptoms in PD patients, occurs relatively late in the disease course (stage 3), whereas the initial involvement of the medulla and pontine tegmentum may account for some early non-motor manifestations [8]. This may explain the presence of early non-motor symptoms preceding the motor phase of the disease. Other findings, including dermatologic manifestations [9], bladder dysfunction [10] and speech disorders [11], might also appear in the early phases of the disease. The presence of non-motor symptoms may correlate with more severe motor disabilities and with a poorer quality of life [10].

Ocular symptoms are frequently seen early in the disease and could be considered as prodromal symptoms of PD as well; indeed, some authors suggested using the presence of visual impairments as a possible marker for the early diagnosis of PD [12]. Visual symptoms and ocular motor abnormalities are seen in other parkinsonian syndromes such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and multiple system atrophy (MSA); their presence is critical to the differential diagnosis of atypical Parkinsonism.

Our report seeks to review some of the least-recognized visual symptoms in the early stages of PD and analyze, when

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possible, the reciprocal influence between visual abnormalities and disease progression and the influence of dopaminergic therapy on those symptoms. We highlight the clinical importance of these symptoms as early markers of disease and possible predictors of outcome, with an emphasis on visual-processing abnormalities and oculomotor dysfunction.

Background

Visual symptoms are common in PD. A recent study showed that ~78% of patients with a clinical diagnosis of PD reported at least one problem related to vision or visuospatial functioning including visual hallucinations, double vision and freezing of gait (which seemed to be associated with impaired contrast sensitivity) [13, 14]. Although dry eyes and reduced blink rate are the most common ocular abnormalities seen in PD [15], many other problems with vision, visual processing, and ocular motility may also occur; these will be discussed in this review with a focus on the early stages of the disease.

Visual symptoms might be partly related to the well-established presence of two types of dopaminergic neurons in the human retina: the amacrine cells (within the inner layer) and the inner plexiform cells [16]. The first neurochemical evidence of dopamine depletion in the human retina correlated with the observed reduction of tyrosine hydroxylase immunoreactivity in the dopaminergic cells within the retina of a small group of patients with PD [17]. Postmortem analysis of untreated PD patients showed decreased retinal dopamine concentration, whereas concentrations were normal in PD patients treated with a dopamine-replenishing drug [18]. Moreover, further investigations showed the presence of misfolded [19] and phosphorylated [20] α-synuclein deposits in the retina of PD patients, indicating that at least some visual dysfunction observed in these patients might correspond to the failure of the retinal circuitry. Other visual symptoms seen in PD, such as visual hallucinations and abnormalities in stereopsis, are caused by alterations in cortical visual processing [21, 22]. Interestingly, a recent MRI study showed significant alterations in optic radiation connectivity distribution in patients with early PD [23].

In addition to problems in visual processing, which are due to alterations of the dopaminergic circuitry at the retinal level or cortical visual processing areas, patients with PD can have ocular motility manifestations of the disease, such as abnormalities in saccades and smooth pursuit. Specific cortical and subcortical areas involved during disease progression may play a pivotal role in generating some of the ocular motor dysfunction seen in PD [24–26].

Direct morphological evidence of retinal involvement in PD can be assessed in a non-invasive way via the optical coherence tomography (OCT) [27]. Recent use of this technique showed thinning of the inner retinal nerve-fiber layer (RNFL) [28, 29]. Interestingly, the retinal thinning appears to be more prominent contralateral to the side of motor symptoms, on the same side of the affected substantia nigra [30]. Further, a few studies failed to find RNFL thinning in PD patients [31, 32], although one study showed that the outer nuclear and photoreceptor layers was thinner compared to unaffected controls [31].

In addition, thinning of the ganglion cell layer within the inner retina correlates with the duration and severity of the disease [33, 34]. Macular retinal thickness and total macular volume are also reduced in PD including the inner and outer plexiform layers [33, 35]. The degree of macular thinning in patients with PD may correlate with disease progression and severity of the disease as measured by the Hoehn and Yahr scale and the Unified Parkinson's Disease Rating Scale part III (UPDRS III) [33, 36]. Therefore, macular measurements via OCT might be a marker for PD disease progression [35]. Recent investigations note an increased thickness of the choroid in PD patients compared to unaffected controls [37].

Findings

Color vision

Color vision impairments have been well reported in de novo (untreated) PD patients [38]. The classic "gold standard" method to assess color deficiency is the Farnsworth–Munsell 100 Hue Test. This test requires the patient to arrange a series of 100 colored discs in a chromatic sequence. The test is time consuming and influenced by poor cognition [39]. Motor deficits related to disease progression might not reflect true color deficiencies [40, 41]. Some authors, in fact, suggested that color vision impairments observed in PD patients are partly due to overall motor slowing in these patients [41]. However, other tests, such as chromatic discrimination ellipses, which are less susceptible to these confounders, have also revealed color vision and contrast abnormalities in PD patients [42]. When measuring the contrast thresholds along the three main color axes that isolate cone function in patients with PD (protan and deutan for the red-green axis, tritan for the blue-yellow axis), color vision loss mostly affected the latter axis [43, 44].

In addition, color vision can be impaired in patients with RBD (an early manifestation of alpha-synucleinopathies [4]) who have not yet developed PD [45]. Moreover, the presence of color vision impairments in RBD patients is a risk factor for disease conversion [46]. A recent study reported that PD patients with RBD and color impairments may have a more rapid disease progression [47]. Color discrimination deficits in PD have also been studied in patients with the LRRK2

gene mutation [48]; interestingly, these patients had more color impairment than idiopathic PD patients [49].

Disease progression and therapeutic impact Color vision deficits strongly correlate with disease duration [50], and in some cases, levodopa therapy may improve color vision in PD patients [51]. These findings have led some authors to suggest color vision impairments as a possible early diagnostic sign for PD [38, 45].

Contrast sensitivity

Visual-contrast sensitivity is the ability to distinguish a visual object from its background. There are two types of contrast sensitivity: spatial, useful to distinguish static visual stimuli, and spatiotemporal, for moving stimuli tracked with smooth pursuit movement of the eyes [52]. Patients with PD have impaired visual-contrast sensitivity [53, 54], most commonly seen in spatiotemporal contrast sensitivity [55], although some authors have reported impairment in spatial-contrast sensitivity to be more evident [52]. Some studies have shown impairments across the entire spatial-frequency range [56], whereas others show diminished contrast sensitivity only in the medium-to-high range [57, 58].

Disease progression and therapeutic impact Worsening contrast sensitivity is related to the progression of the disease [56] and is partly reversible with levodopa therapy [54, 58, 59]. In fact, when PD patients with marked "on–off" fluctuations are tested during their "on" condition, their contrast sensitivity resembles that of age-matched controls [57].

Saccades

Alterations of saccadic movements are prominent in PD patients, even in the early stages of disease; thus, some authors suggested them as a possible marker for the clinical diagnosis [60]. Electrooculography recordings in PD patients show impairments in saccadic and smooth pursuit eye movements [61]. Saccades can be classified into two main types: reflexive external (or visually guided) saccades and voluntary internal (including volitional, predictive, antisaccades and memory-guided) saccades, both of which are impaired in PD but to different degrees.

Hypometric-reflexive and voluntary saccades are primary oculomotor disturbances associated with PD [62]. They lead to a characteristic multistep sequence of eye movements, where PD patients typically reach the target through a series of discrete small saccades [63, 64]. The hypometria seen in PD patients is more pronounced in the memory-guided voluntary saccades than in the visually guided reflexive saccades [60]. Moreover, PD patients show difficulties in initiating memory-guided saccades [65], whereas this pattern is relatively spared in visually guided saccades [66].

Modulation of the neuronal activity at the level of the superior colliculus (sc) by cortical areas such as the dorsolateral prefrontal cortex (which is thought to be involved in the regulation of memory guided voluntary saccades) and the parietal eye field (which is thought to regulate reflexive visually guided saccades) and the basal ganglia, have a significant impact on the regulation of saccadic eye movements [67]; an excessive inhibition of the sc by the substantia nigra in PD patients seems to lead to some of the saccadic abnormalities observed in these patients [68].The prominent impairment of voluntary saccades might be explained by the fact that basal ganglia are more involved in the control of these saccades; however, this model cannot explain all the ocular motor abnormalities seen in PD patients since, for example, the neuronal pathway involved in generating visually guided reflexive saccades may bypass the basal ganglia circuit [68, 69].

Contradictory results have been reported when studying antisaccades in PD patients. Lueck et al. [70] failed to show a worse performance in this specific task compared to age-matched controls, whereas other studies demonstrated PD patients with slower antisaccades, more directional errors [71], and longer reaction times in the antisaccade tasks [72].

Disease progression and therapeutic impact The amplitude of both voluntary and reflexive saccades reduces in relation to disease progression (the former to a greater extent than the latter) [62], and the latency of the visually guided saccades worsens in the early stages of the disease; however, it seems to stabilize after Hoehn and Yahr stage II [62]. Although these effects are relatively small, levodopa and dopamine agonists have dichotomous effects on saccades; indeed, while they shorten the latency of the voluntary saccades, they prolong the latency of the reflexive ones. No large changes in saccadic amplitude have been reported for both visually and memory-guided saccades after levodopa therapy [62].

Smooth pursuit eye movements

Smooth pursuit eye movements (SPEM) are defined as tracking eye movements designed to follow a moving object and keep the image on the fovea. SPEM abnormalities may be present in the healthy elderly population [73]; however, they are a well-recognized finding in PD [61, 66]. Several cortical and subcortical areas, as well as specific regions in the brainstem and cerebellum, are involved in their generation and control; briefly, the junction of occipital, parietal and temporal cortices at area V5 and its connections with the basal ganglia, parietal and frontal eye fields and cerebellar areas, play a pivotal role in generating and controlling SPEM [24]. Early untreated PD patients showed reduced pursuit gain [74]. A subset of neurons in the substantia nigra pars reticularis (SNpr) shows an arrest of its tonic discharge

during the initiation and maintenance of SPEM [75]; its malfunction may therefore theoretically explain to some extent the presence of SPEM deficits in PD patients.

Disease progression and therapeutic impact The use of dopaminergic drugs (either bromocriptine or levodopa) has been associated with an improvement in pursuit gain in PD patients [74]. This was confirmed by another study that showed a significant improvement after subcutaneous administration of Apomorphine in 21 early drug-naïve PD patients [76]. However, it should be noted that some authors failed to observe a major improvement in SPEM after levodopa administration [77].

Square-wave jerks

Square-wave jerks (SWJ), are defined as saccadic intrusions driving the eyes away from the fixation point, followed by a corrective saccade back to the target [78]. Although they are present even in the general population [78, 79], SWJ are often more prominent in several neurological conditions, especially in parkinsonian disorders [78]. SWJ have been observed early in the course of PD with mean amplitude of 2° [80]. This finding challenged the common idea that SWJ > 1° appeared more frequently in other parkinsonian disorders such as PSP and MSA compared to PD [78]. Interestingly, increased frequency and amplitude of SWJ in PD patients has been reported after unilateral pallidotomy [81]. The underlying mechanism for pathological SWJ is poorly known; pathological SWJ might be related to the disinhibition of the sc or the fastigial oculomotor region in the cerebellum, or they might result from increased activity of the frontal eye fields in PD patients [80].

Convergence insufficiency

Convergence insufficiency is a binocular-alignment dysfunction characterized by failure of eye convergence when fixating on near objects resulting in a remote near point of convergence and exotropia [82]. Several studies showed reduced convergence amplitude in PD patients compared to unaffected controls [15, 83, 84]. Convergence amplitude and the near point of convergence have been shown to be better in PD patients in the treated "on" state compared to PD patients in their "off" state, suggesting that levodopa may improve this deficit [85].

Ocular tremor

Gitchel and colleagues [86] demonstrated the presence of ocular oscillations in a large cohort of patients with PD (including untreated de novo PD patients). These patients showed abnormal eye movements with an oscillatory pattern while fixating on a target and a mean measured frequency of 5.7 Hz, which is approximately within the range of PD tremor (4–8 Hz) [87]. They failed to observe a similar ocular tremor in patients with a clinical diagnosis of essential tremor [88]. These findings have been debated and interpreted by others as an oscillatory vestibulo-ocular reflex induced by head tremor (either subclinical head tremor or transmitted limb tremor) because it was noted that these ocular oscillations were in antiphase to the direction of head tremor [89]. Further studies may show how these findings correlate to the progression of the disease and how dopaminergic therapy can impact these signs.

Stereopsis

Stereopsis, also known as depth perception, is the visual ability to perceive the world in three dimensions. To achieve that the brain uses two distinct inputs: the monocular cue, which includes the relative size of the objects, texture gradients and shades, and a binocular cue, which requires both eyes and gives a precise tridimensional perception analyzing the disparities perceived by each eye. A neuronal pathway connecting the retina to the occipital cortex is necessary for a normal depth perception. The cortical area mostly involved in stereopsis has been proven to be the extrastriate cortex [21]; more specifically, recent studies suggest that abnormal stereopsis might be associated with non-dominant extrastriate cortical atrophy [21]. De novo drug-naïve PD patients may have stereopsis impairments [90]. When drug-naïve PD patients with normal stereopsis were compared to PD patients with abnormal stereopsis, the latter group showed a significant volume reduction in the gray matter of the right extrastriate visual cortex [21].

PD patients with abnormal stereopsis show worse motor functions and higher unified Parkinson's disease-rating scale (UPDRS) motor scores when compared to PD patients without stereopsis impairments. Moreover, depth perception deficits in PD patients can also correlate with decreased color perception [91].

Disease progression and therapeutic impact The presence of stereopsis abnormalities in PD has been associated with a more rapid cognitive decline and was found as a predictor for dementia in PD patients at 24 months [92]. These data suggest an association between stereopsis impairments and the progression of the disease [91].

Visual hallucinations

Visual hallucinations are frequent in PD and related disorders; however, there are no exact data on prevalence because of the diagnostic challenges. Some studies reported a 22–38% prevalence of visual hallucinations in PD patients [93], which was shown to rise to 74% in a 20-year follow-up period [94]. Epidemiological studies have pointed out

the existing association between dopaminergic therapy and the development of visual hallucinations in PD [95], which complicates the assessment of PD-induced hallucinations. In addition, the prevalence of visual hallucinations is higher in patients with PD dementia compared to patients without dementia [32], and therefore, hallucinations may be a reflection of dementia in some cases. Visual hallucinations have also been associated with contrast sensitivity and visual-color abnormalities [96]. Nevertheless, minor hallucinatory phenomena, such as the presence or passage hallucinations and visual illusions, have been reported also in drug-naïve de novo PD patients, even in the premotor phase of the disease [97]: these findings reinforce the hypothesis that the presence of hallucinations in PD patients is part of the disease itself and not only due to a iatrogenic phenomenon or a manifestation of late stage disease. Interestingly, the patients of this study with minor hallucinatory phenomena were more likely to have RBD at baseline compared to the patients without hallucinations. Probable RBD at baseline in PD was found to be a predictor of psychosis, including hallucinations, later on during the disease course in PD [98]. One may therefore argue that minor hallucinatory phenomena in RBD patients and in PD patients during the early phases of the disease, may be used to screen and identify those who are more likely to develop psychosis during the disease progression.

Disease progression and therapeutic impact Different considerations should be done for the association between levodopa and visual hallucinations. In the past, the presence of visual hallucinations in PD patients has been correlated with dose and duration of treatment with levodopa and therefore was thought to be primarily due to levodopa therapy [99]. However, there is now increasing evidence that challenges this hypothesis [100] since minor visual hallucinatory phenomena can be seen in drug-naïve de novo PD patients [97]. The overall results of these studies suggest that levodopa may contribute to some visual hallucinations, but these usually occur separate from levodopa therapy in patients with PD.

The underlying mechanism to the passage hallucinations phenomenon might be explained by the Braak progression model of Lewy bodies pathology; the early involvement during the disease course of the brainstem, as opposed to the relatively late involvement of the cortical structures, is thought to explain the presence of minor hallucinatory phenomena in the early stages of disease [101].

Discussion

Non-motor symptoms play an important role in the early diagnosis of PD, especially when classic motor symptoms, such as resting tremor, bradykinesia, rigidity and postural instability, might still be subclinical and difficult to appreciate. Our review supports using visual impairments as possible early markers of disease as previously suggested [12]. When visual deficits have been tested with specific tests to assess color discrimination and contrast sensitivity among other non-motor domains such as sleep abnormalities, hyposmia, dysautonomia and depression, they showed a high discriminatory power in differentiating early PD patients from unaffected controls [12]. Some of these visual abnormalities may occur not only in the early phases of the disease but may even precede the onset of the disease itself.

The presence of visual abnormalities at baseline may help to predict disease progression: color vision impairments have been associated with an increased risk of dementia in PD patients [102], whereas stereopsis abnormalities correlate with a more rapid cognitive decline [92]. Therefore, the presence of visual abnormalities might not only serve as an early marker of PD but might also predict disease complications and outcomes.

Visual deficits in PD can influence overall motor function [103], leading to postural instability, more frequent falls, and worsening quality of life; decreased contrast sensitivity was associated with increased risk of freezing gait [13]. On the other hand, patients with the tremor-predominant phenotype showed fewer color vision deficits and a more benign course [47]. The underlying mechanisms for these phenotypical differences are unclear. The presence of comorbid brain pathology or different brain localization of α-synuclein deposits in these patients might explain the differences in phenotype [47].

Visual disturbances evolve as the disease progresses. Color vision impairments, loss of contrast sensitivity and stereopsis deficits correlate with the progression of the disease [50, 56, 91]. Specific data about the influence of the dopaminergic therapy on visual symptoms are also reported; levodopa improves color vision and contrast sensitivity in PD patients [58] and can influence saccades [62]. These findings support the hypothesis that visual disturbances are related to the well-established loss of dopaminergic neurons in the retina, indicating that at least some symptoms might be explained by an acquired alteration of the flow of visual information at the retinal level.

Different considerations should apply to the association between levodopa and visual hallucinations. In the past, the presence of visual hallucinations in PD patients correlated with dose and duration of treatment with levodopa and therefore was attributed primarily to levodopa therapy [99]. However, new evidence challenges this hypothesis [100] because minor visual hallucinatory phenomena can also be seen in drug-naïve de novo PD patients [97]. The overall results of these studies suggest that levodopa may contribute to some visual hallucinations, but these usually occur separate from levodopa therapy in patients with PD.

Impaired color vision has been demonstrated in RBD patients who have not yet developed PD [104]. Moreover, the presence of color vision impairments in RBD patients has been identified as a risk of disease conversion [47]. Therefore, color vision impairments may be an early diagnostic sign of PD [105].

The search for a biomarker of early-stage PD has been ongoing and quite unsuccessful. The use of OCT provides in vivo cross-sectional images of the retina and of the optic disc. This technique is useful in studying several neurodegenerative diseases such as Alzheimer's disease, multiple sclerosis, and even PD [33]. An inverse correlation between macular thickness and severity of PD has been observed [36]. In the near future, diagnostic use of OCT is plausible in the early stages of PD, helping physicians to achieve an early diagnosis, improve disease management, and, possibly, predict a better outcome [33]. Several authors have proposed visual symptoms as early markers of disease, and in some cases, visual symptoms may also predict disease progression. More studies are required to assess the definitive predictive value of visual abnormalities as early PD markers; however, as previously suggested by others, a combination of symptoms rather than isolated symptoms might be the best predictor of the probability of developing PD.

In conclusion, our review shows that visual and ocular motor abnormalities are common in PD, even in the early phase of the disease. Some of these symptoms may progress during the course of the disease, and levodopa therapy can influence the severity of many of them. Some ocular disturbances might even constitute prodromal signs and symptoms of PD or even early markers of disease. Early identification of these symptoms might therefore permit an earlier clinical diagnosis of PD and might also predict disease outcome, leading to a better quality of life for the patient.

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Compliance with ethical standards

Ethical approval for research involving human participants This manuscript is a review of past clinical studies, all of which were performed in accordance with ethical standards in effect on their respective publication dates.

Conflicts of interest All authors declare that they have no conflict of interest.

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