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REVIEW ARTICLE

Does retina play a role in Parkinson's Disease?

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Abstract
Visual disorder is one of the non-motor symptoms found in Parkinson's disease (PD). It can be easily identified in the early stages even before the spread of pathological conditions to the brain parts. Studies have revealed that loss of dopamine (DA) cells in retinal layers is a prime cause for both retinal disturbance and pathological conditions of PD. This reduction of DA in retina is due to the aggregation of phosphorylated α-synuclein (aSyn) in the intra-retinal region, which eventually results in visual impairment in PD. Until now, very limited studies have been focused on the mechanism of aSyn influence and DA depletion as a cause for both retinal layer dysfunction and PD. Thus, more research is warranted to provide the missing connection between the exact role of DA and aSyn as a risk factor for visual problems in PD. Hence, the current review's focus is on the function and effects of DA degeneration in retinal cells of PD. Further, we suggest that iron plays a major role in regulating the aggregation of aSyn in the DA cells of retina and brain in PD. The study finds that the unidentified pathophysiological role of retinal degeneration in PD is an essential biomarker that needs further investigation to use it as a novel therapy in treating retinal dysfunctions in PD.

Keywords Parkinson's disease (PD) · Visual dysfunction · Retinal biomarker · α-Synuclein (aSyn) · Dopamine (DA)

Abbreviations

PD	Parkinson's disease
AD	Alzhiemer's disease
DA	Dopaminergic neurons
aSYN	α-Synuclein
OCT	Optical coherence tomography
mfERG	Multifocal ERG
ERG	Electroretinograms
VEP	Visual-evoked potentials
TH	Tyrosine hydroxylase
MPTP	1-Methyl, 4-phenyl, 1-2-3-6-tetrahydropyridine
PERG	Pattern electroretinogram
STF	Spatial tuning function
RNFL	Retinal nerve fiber layer
RPE	Retinal epithelial cells
IPL	Inner plexiform layer
INL	Inner nuclear layer
GCL	Ganglion cell layer
PL	Photoreceptor layer
GPCR	G-protein coupled receptor protein
cAMP	Cycline adenosine monophosphate
DAT	Dopamine transporter
LTS	Lewy-type α-synucleinopathy
DARC	Detection of apoptosing retinal cells
SD-OCT	Spectral-domain optical coherence tomography
VH	Visual hallucination

Introduction

Retina is popularly called the "window to the brain". Any abnormalities in the brain affects the normal functions of the retinal layers and its parts. Disorders in the brain and retina are associated with many conditions including Parkinson's disease (PD), Alzheimer's disease and glaucoma. PD is characterized by the degeneration of dopaminergic neurons (DA) in the substantia nigra region of the brain. Although motor impairment is the major drawback seen in PD, one of the non-motor manifestations observed in PD is

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the visual dysfunction. Many studies have observed that PD patients display various forms of visual impairments including colour discrimination, visual acuity, contrast sensitivity, blurred image, motion perception and loss of vision [1, 2]. This visual dysfunction is mainly caused due to the depletion of DA levels in amacrine and inner plexiform cells of the retina in PD patients [3].

DA is a very important biochemical molecule necessary for the regulation of the brain and to the retina for retinal development, visual signalling and refractive development [4]. It has been proved that abnormal changes in DA and depletion of amacrine cell of retina lead to alterations in the receptive properties of ganglion cells, which eventually results in dysfunctional visual processing in PD patients [5]. In a recent functional study, it was observed that aSyn was found to be aggregated in the inner nuclear, inner plexiform layer and ganglion cell layer of the intra-retinal region [6]. Thus, it could be assumed that irreversible loss of DA in both the brain and retina of the PD patients is merely due to the accumulation of the phosphorylated aSyn [7]. Moreover it was found that iron plays a pivotal role in the aggregation of aSyn and depletion of DA neurons in the retinal cells of PD patients [8]. These studies suggest that identification of specific retinal biomarkers in PD would be a stepping stone to detect this neurodegenerative disease in the early stages. Thus, in this review we highlight the normal and irregular functions of DA and aggregation of aSyn in the retinal layers as a causative agent for visual dysfunctions associated with PD. Further, we also suggest that retina is a potential early biomarker in PD and more research that would unravel its mechanism will fill the gap and emerge as a promising remedial route for retinal dysfunctions in PD.

Visual dysfunctions in Parkinson's disease

Among the non-motor symptoms of PD, visual abnormalities are frequently observed during the early stages of the disease. Some of the visual symptoms found in the PD are described below.

Visual contrast acuity

The ability of the eye to resolve even the small details of stimulus is known as visual acuity. According to a study, it was reported that dysfunction in visual acuity might be a prime factor in causing chronic hallucinations in PD patients [9]. It has been explored that loss of amacrine cells and aggregation of α synuclein in the retina could be the reason for visual contrast acuity in PD patients. In 2015, Lin et al. [10] reported the use of a new iPad application to measure low contrast acuity in PD patients; it could serve as a quick screening tool to complement more formal testing of patients with PD and other neurologic disorders.

Colour vision

Colour vision is cone medicated and is processed by two pathways such as parvocellular and koniocellular visual pathways. Further, the achromatic information is transmitted through the magnocellular pathway. Earlier it has been reported that in PD, there is occurrence of chromatic and achromatic sensitivity changes due to the parvocellular, koniocellular and magnocellular pathways [11]. It has been reported that in PD patients, the colour vision impairment correlates with the severity of clinical symptoms and PD disease progression [12]. Colour vision dysfunction in PD may be associated with significant loss of cells in the ganglion cell layer [13], but studies related to dopamine deficiency and severity of colour vision impairment still remain unanswered.

Eye movement

Eye movement problems are important aspects of PD conditions [9]. There are three kinds of eye movements, saccadic eye movements which directs us to gaze at a specific object or to read lines in prints; pursuit eye movement which allows us to follow moving objects; and vergence eye movement that allows us to move our eyes in different directions [14]. In a functional study, it has been reported that electrooculography (EOG) responses are normal for PD patients when the eyes are in a resting condition; however, 75% of PD patients reported abnormalities in saccadic and smooth pursuit eye movements [9]. Elmar et al. [15] reported that dopaminergic dysfunction might not be a prime reason for impairment of saccadic eye movement in PD, but basal ganglia dysfunction might be the reason for the difficulty to rapidly execute alternating voluntary gaze shift (AVGS).

Pupil reactivity

Larger pupil diameter and unequal pupil sizes after light adaptation have been observed in PD patients [16]. Longer light reflex latencies and constriction times have also been observed while contraction amplitudes may be reduced, suggesting early involvement of the parasympathetic system in PD [9]. In PD, the contraction ability of the iris muscle is maximum when compared to controls; this suggests that the muscle might have acquired adaptive sensitivity changes [17].

VEP and ERG

Retinal responses to visual stimuli generate electrical activity in the eye, as does the transmission of these response to the primary visual cortex [18]. Measurement of the amplitude and latency of such electrical responses provide information on the functional integrity of the visual pathway and both electroretinograms (ERG) and visual-evoked potentials (VEP) which has been extensively studied in Parkinson's disease [9]. In PD patients, the ERG amplitude is reduced in a variety of light conditions and this indicates the defect in visual processing involving dopamine neurons. VEP response to coloured stimuli, especially blue-yellow horizontal gratings, are affected in PD. VEP latency and ERG wave alterations are evident in PD patients when compared to control and delay visual processing at one or more stages of the visual system [9].

Mechanism of DA in normal and PD retina

The retina and brain are associated over a range of neurological disorders such as Alzheimer's disease (AD), Parkinson's disease (PD) and glaucoma. Many experimental evidences have suggested that PD patients exhibit various forms of visual dysfunctions such as visual acuity, contrast sensitivity, colour discrimination and motion perception [1, 2]. In PD patients, dopaminergic cell degeneration is not only limited inside the brain, but also in the retinal layer. Dopamine (DA) is an essential neurotransmitter found in the retina and is involved in various functions of the retina such as retinal development, visual signalling and refractive development [4]. Thus, the deficiency of DA, associated with loss of amacrine cells in retina, would result in altered visual processing by changing the input of ganglion cells [5].

In normal retina cells, the DA acts through the G-protein coupled receptor protein (GPCR) by regulating the cyclic adenosine monophosphate (cAMP). The activation of rod and cone photoreceptors are inhibited by D2—receptor family of DA, while bipolar, horizontal, RGCs and amacrine cells are excited by D1—receptors of DA. Thus in a normal cell, DA is released into retinal cells by using the gap junction permeability concept, where first the interaction between the rod and cone with horizontal cells are initiated followed by AII:AII and AII:cone bipolar communication. Finally, there is a reduction in the gap junction permeability with simultaneous rise in DA concentration (Fig. 1) [19–22]. Thus, DA acts both in the outer and inner retinal layer which results in alterations in flow of visual information in a complicated manner. In other words, dopamine is a chemical messenger for light adaptation, promoting the flow of information through cone circuits while diminishing that through rod circuits.

The neurological evidence for deficiency of DA in human retina was first reported with reduction of tyrosine hydroxylase (TH) in PD patients [23]. DA depletion can be found majorly in the three different layers of retina. Degeneration of retinal DA neurons and their postsynaptic AII amacrine cells was allied with loss of TH immune-reactivity in the inner plexiform layer of PD retina [24]. According to another study, reduction of DA levels in basal ganglia and frontal cortex decreased the superior colliculus region that has an essential role in producing saccadic eye movements in PD patients [25]. In PD, the inner retinal layer thinning is found especially in the GCL and IPL of the inferior sector with the loss of dopamine transporter (DAT), which proved the loss of retinal dopaminergic cell degeneration in PD. Thus, DA is involved in controlling the overall retinal visual system, and any impairment in DA and its metabolites would result in retinal degeneration associated with PD.

Some of the studies have presented the mechanism of dopaminergic neurons in the retina of PD subjects. MPTP (1-methyl, 4-phenyl, 1-2-3-6-tetrahydropyridine) in PD animal models causes visual impairment due to retinal DA morphological changes or absence of retinal DA along with loss of retinal amacrine cells [24]. In rotenone-treated rat model, inhibition of complex I was noted with a depletion of DA in the striatum and substantia nigra as well as in the retinal amacrine cells [26]. As a therapeutic approach, in a rat model of hemi-parkinsonism, dopaminergic neurons were replaced through direct differentiation of limbus-derived neural progenitors that act as a potential stem cell approach in PD [27]. Limited studies have been conducted in animal models and observed for retinal alterations as depicted in Table 1 [28–33].

Indistinct mechanism of aSyn and iron in normal and Parkinson's retinal cells

The relation of iron with aSyn and retina has a major role in PD-associated visual impairment. Iron is a cofactor for the synthesis of neurotransmitters and plays an important role in visual phototransduction cascade. In a previous study, it was shown that iron deposition alters the expression of aSyn and results in aSyn aggregation and toxicity in PD patients [34]. Post-translational modifications of aSyn affect iron and dopamine-dependent oxidative stress, thereby increasing the tendency of aSyn aggregation. In retina, the iron uptake is mediated by transferrin/transferrin receptor pathway and it is exported by ferroportin along with ceruloplasmin and hephaestin. Iron uptake occurs in the RPE through aSyn which has an effective role in iron levels due to its presence on the C-terminal end [35, 36]. During translation, it is alleged that iron modulates aSyn synthesis through an iron-responsive element

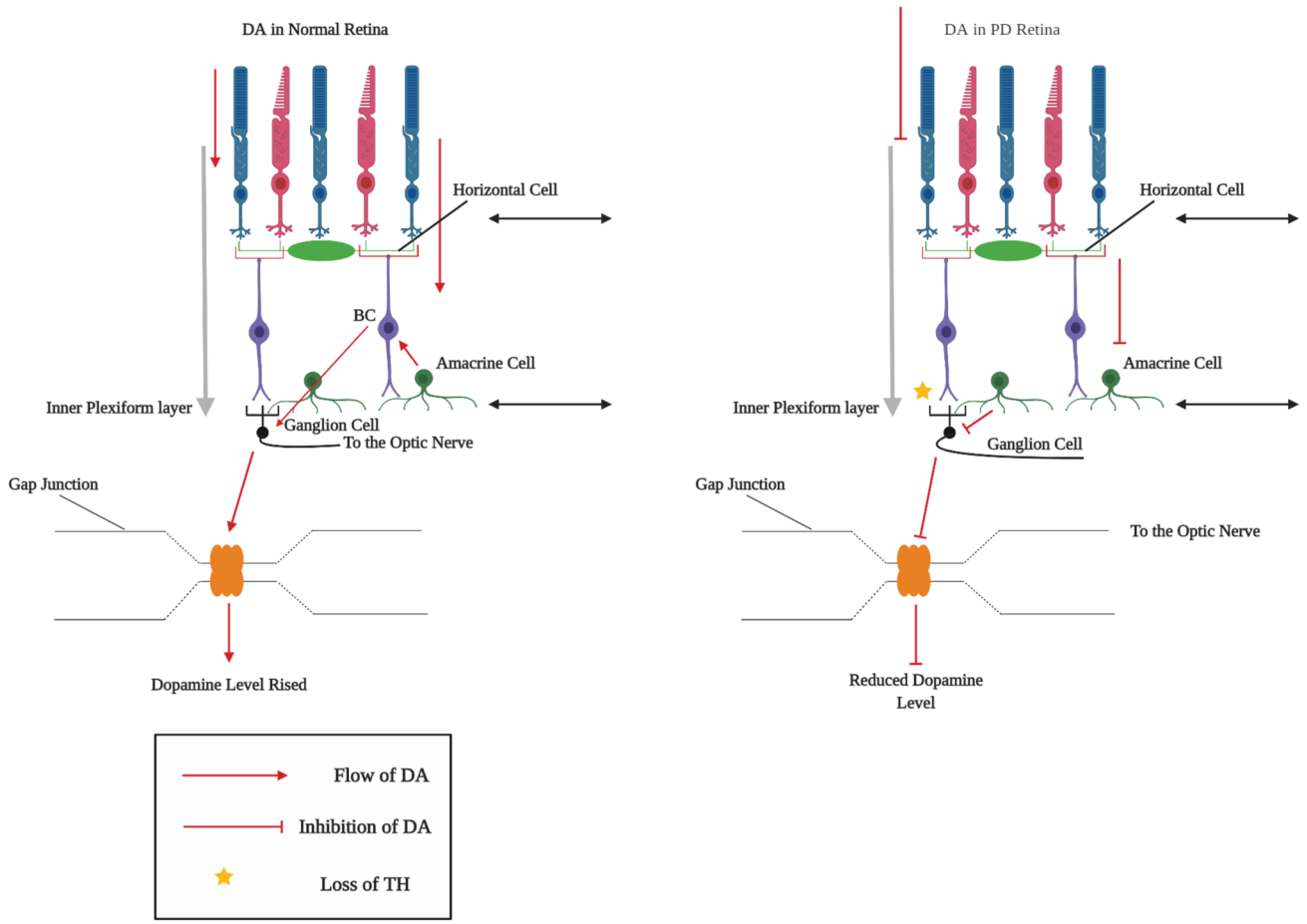

Fig. 1 Normal and abnormal flow of DA in retina: the figure depicts the normal and abnormal flow of dopamine (DA) inside and outside the retina. DA is a chemical messenger for light adaptation, promoting the flow of information through cone circuits while diminishing that through rod circuits. This abnormal flow could be a reason for the visual problems faced by Parkinson's disease patients. In the figure sign depicts the flow of DA, whereas the sign—resembles the inhibition of DA flow

Table 1 Animal model studies related with dopamine in the ophthalmology of Parkinson's disease

S. No	Animal model	Toxin/inhibitor	Ophthalmological alterations	Reference
1	Rat	Rotenone	Depletion of dopamine in the striatum, substantia nigra and retinal amacrine cells	[26]
2	Mouse	6-OHDA	Decreased rotational behaviour and restored motor functions	[28]
3	Rat	–	Reduction in amphetamine-induced rotation	[27]
4	Monkeys	MPTP	Reduced dopamine and dihydroxyphenylacetic acid levels in the retina	[29]
5	Monkey	MPTP	Reduction in dopamine level	[30]
6	Mice	MPTP	Reduced level of tyrosine hydroxylase Decreased concentration of dopamine	[31]
7	Monkey	MPTP	Decrease in γ-aminobutyric acidergic and glycinergic amacrine cells	[24]
8	Rats	–	Depletion of norepinephrine and dopamine	[32]
9	Rats	Alpha-methyl-para-tyrosine	Reduced visual-evoked potential amplitude	[33]

MPTP 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

on the 5′-UTR region. Also, more iron content aggregates aSyn and alters dopamine to a toxic compound that ends up in the poor activity of both aSyn and dopamine [8, 37]. This highlights the interconnection between aSyn, dopamine and iron in PD [38].

As reported earlier, aSyn is a highly conserved protein where its function remains unclear [39, 40]. The deposits of aSyn in Lewy bodies and Lewy neurites are connected with abnormal phosphorylated aSyn [41], whereas the unphosphorylated state is seen in retinal cell layers [42]. In contrast, a confirmative study on phosphorylated deposition of aSyn at serine-129 in retina was explained by [6, 43]. The pathophysiology of aSyn in retina has not been elucidated, though studies have stated its presence in the inner plexiform layer (IPL) of mouse and human retinas [44, 45]. The presence of aSyn in healthy retinas is found to be in four retinal layers such as inner nuclear layer (INL) and IPL, ganglion cell layer (GCL) and photoreceptor layer (PL) [46, 47]. In addition, colocalization of aSyn and synaptophysin constitute phagocytic structures which were observed in RPE [47]. For the first time, in PD, Bodis-Wollner et al. confirmed the presence of aSyn aggregates in INL, IPL and GCL. In PD retinal cells, phosphorylated aSyn, Lewy-like inclusions and neurites were found to be in INL and GCL [48]. Moreover, decreased dopamine and TH immunoreactivity were seen in IPL and INL [46]. Hence, the localization aSyn along with iron interaction in retinal layers might have a mechanistic behaviour on visual impairment in PD (Fig. 2).

Retina as a candidate biomarker in Parkinson's disease

Early diagnosis and disease-modifying therapies in PD would be beneficial in understanding the disease mechanism and identifying specific biomarkers [49]. Though numerous biomarkers have been explored, retina has shown optical properties and ease of access to non-invasive approaches for early detection of neurodegenerative diseases [50]. Imaging techniques are a useful diagnostic tool for identifying the close relationship between the eye and brain; hence, the retina is a candidate biomarker in neurodegenerative diseases [6]. Retinas can be potentially assessed for the presence of synucleinopathy using optical coherence tomography (OCT), eye fundus and angiography. These techniques will permit to visualize the retina and its changes [6].

Though varied standard measuring protocols have been analyzed for specific diseases, there is no particular method reliable for evaluating retina in PD. Lewy-type α-synucleinopathy (LTS) can be detected in retina using fluorescent dyes through intravitreal injection, where it results in minimal complications in clinical ophthalmology. Based on retinal LTS fluorescent ligands, intraocular injection and retinal imaging analysis are used to perceive PD progression [6]. Visual dysfunctions such as reduced electroretinogram (ERG) responses and visual-evoked potentials have been reported in PD patients and animal

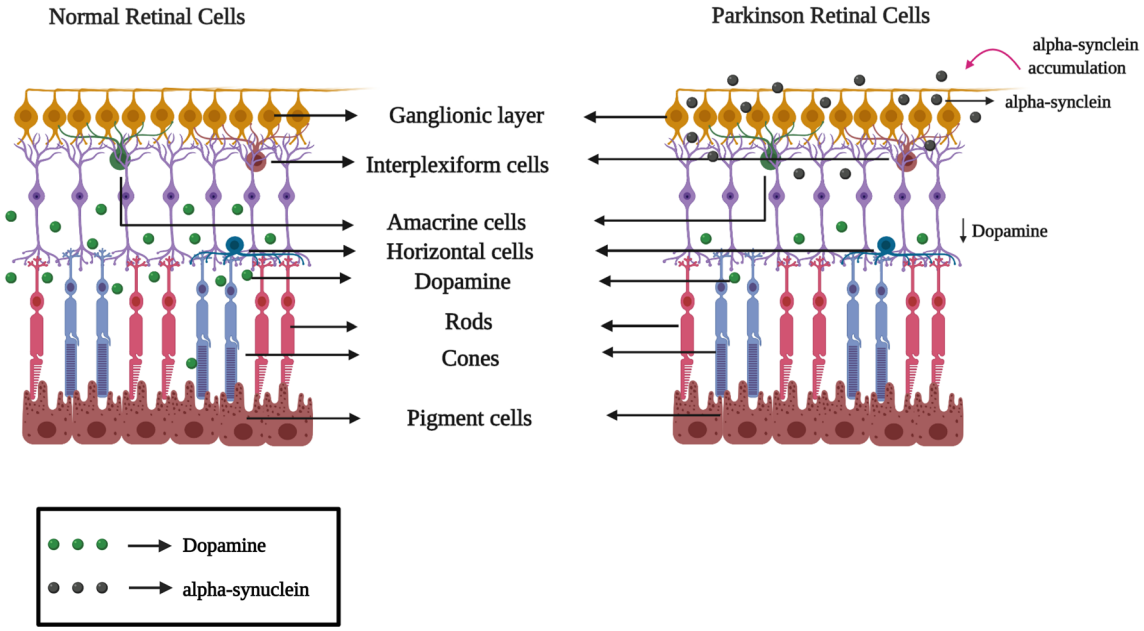

Fig. 2 Depicts the probable mechanism of α-synuclein in Parkinson's retinal cells: the probable mechanism explains when iron uptake occurs in retinal epithelial cells through α-synuclein and iron modulates α-synuclein synthesis, thereby increasing α-synuclein accumulation and aggregation in retinal cells and thus causing dopamine level to decrease and act as a toxic compound in retinal cells

models [51, 52]. ERG has been used for early detection in two untreated PD patients, where one study revealed no ERG changes with significant reduction in *b*-wave amplitude, whereas another study exhibited decreased *a*-wave and *b*-wave amplitude [53].

Significant differences in retinal nerve fibre layer (RNFL) thickness with varied OCT measurements have been detected in PD. Peripapillary nerve fibre layer thickness in PD has been detected in 17 studies, of which 12 studies correlated with thinning in RNFL as well as inferotemporal [54], temporal [55, 56], nasal [57], diffuse area [58], inferior nasal and temporal [59], both inferotemporal and superotemporal and inferior regions [60]. In contrast, five studies did not show RNFL thinning in PD [61, 62]. The discrepancy in these studies is due to sample size and different measurement protocol and devices. In addition, age and disease duration with severity is a significant factor in RNFL thickness in PD [41]. Fourier-domain devices are consistent in identifying axonal atrophy in RNFL of PD [63]. RNFL thickness correlated with PD and the pronounced retinal alterations were detected by OCT [64].

OCT imaging technique has been utilized in patients to identify the thinning of ganglion cell layer, inner plexiform layer, and inner nuclear layer [65, 66]. By OCT imaging,structural alterations in retinal layers such as retinal dopamine loss and foveal dysfunction in PD can be detected [41]. Several PD studies used automated OCT measures in which three studies were excluded, since the thickness of vertical retinal layers was identified manuallyfrom OCT images or with software [41, 67]. Another study showed the changes in the foveal region using advanced method [68]. The thickness of retinal vertical layers was determined in four studies, in which two studies detected the thinning in the inner layer [69, 70] and one in interocular differences [68], and the other study did not show any difference between PD and controls [71]. The inner layers in the foveal pit was identified with thinning in PD. Retinal imaging using OCT and DARC (detection of apoptosing retinal cells) was carried out in rotenone-induced PD rat model, where the study found an increased ganglion cell apoptosis and swelling of the retinal layers. In addition, a follow-up study showed neurodegenerative changes in the substantia nigra and striatum which concludes that retinal changes are early manifestations in PD [72]. DARC has been applied in various animal models of retinal neurodegeneration, where it has been shown to successfully detect ganglionic cell apoptosis [73]. While various studies have evaluated the retinal changes in PD, till date there have been incomplete clinical trial studies conducted using OCT in PD.

Immunohistological studies show the presence of aSyn and Lewy bodies in the inner plexiform layer and RNFL with retinal thinning using OCT, and ERG responses were altered effects with decreased dopamine levels observed in the retina [43, 48]. In a study, 49 eyes from PD patients were analyzed for retinal alterations using spectral-domain optical coherence tomography (SD-OCT) which showed decreased retinal microvascular density [74]. In one group, the presence of aSyn showed thickening of the outer plexiform layer in PD [75]; conversely, the other group showed thinning of the outer plexiform layer [76].

Visual hallucination (VH) is one of the features in PD, where decreased visual perception and decreased contrast sensitivity as well as colour vision are related to VH in PD [10, 41, 51]. RNFL has been associated with VH and PD severity [41]. Visualizing the retinal layers would be a beneficial biomarker and forecaster of VH in PD [41]. Low contrast sensitivity was detected in PD with larger acuity reduction [10]. The colour vision is used for disease staging [77], whereas visual field is used as an adjunct in PD [53, 78].

Thus, the mechanisms of retinal thinning and the defect in visual information processing in PD are yet to be identified. It is stated that the retina acts as a window that reflects the brain pathology and serves as a PD biomarker. Hence, from these findings, it is inferred that more research has to be conducted in creating a track for therapeutic strategies.

Future perspectives

In the research of ophthalmic condition associated with Parkinson's disease, conflicting results appear regarding the study of retinal thinning using OCT and the exact role of phosphorylated aSyn in the retina. There were no exact results correlating the severity and duration of disease with structural changes on OCT and accumulation of phosphorylated aSyn. Relatively low number of sample size and quality of post-mortem retinas and different study protocols for retinal studies on PD do not allow making a final conclusion about the specificity and importance of aSyn in PD. Future studies should include patients with different stages of disease and it should be age matched to assess the involvement of aSyn in PD progression. Most importantly in future, there is also a need to develop non-invasive, high-resolution, preferably label-free, αSYN-imaging techniques to visualize and quantify aSyn reactivity in the retina of PD patients.

Conclusion

PD results in progressive retinal degeneration and accumulation of phosphorylated aSyn in the retinal layers. Retinal layer thinning can be seen in the early stages of disease and it could be measured by non-invasive SD-OCT technique and DARC (Detection of Apoptotic Retinal Cells) for evaluating retinal cell apoptosis. The mechanism of dopamine regulation by phosphorylated aSyn in the retinal layers might

cause retinal neurodegeneration as in the brain. Neuropathological, structural and electrophysiological alterations in the PD retina and also phosphorylated aSyn aggregation in PD retina give some evidences for suggesting that the retina can be used as a biomarker for PD. However, we need some strong research proof to confirm this idea.

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Compliance with ethical standards

Conflict of interest SMD, IM, APN, DV and VB declare that they have no conflict of interest.

Research involving human participants and/or animals This is a review article; thus, it does not contain any studies with human participants performed by any of the authors.

Informed consent This is a review article; thus it does not need any consent form.

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