



Changes In The Retinal Nerve Fiber Layer In Patients With Parkinson's Disease, Progressive Supranuclear Palsy, And Multiple System Atrophy With And Without Dementia

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Received: 31 Jan 2025

Published: 3 Mar 2025

Abstract

Background: Several studies have evaluated RNFL thickness in PD, with only a few on other Parkinsonian syndromes. There is insufficient information on the pattern of changes in these patients who have dementia. Therefore, the present study examined the RNFL thickness in Parkinsonism patients with and without dementia.

Methods: In this cross-sectional study, all patients diagnosed with PD, MSA, and PSP from March 2017 to February 2019 were evaluated. The severity of the disease and the presence of dementia were determined using the UPDRS and MMSE tests, respectively. The thickness of the RNFL was measured in the superior, inferior, nasal, and temporal quadrants using the 3D-OCT 1000 Mark II. Statistical methods, including the independent t-test, one-way analysis of variance (ANOVA), and the Pearson correlation coefficient, were used to analyze the data at a significance level of 0.05 using SPSS statistical software.

Results: Fifty-three patients were examined. The mean age and mean UPDRS showed a significant difference between the groups, while gender and disease duration did not show. The mean RNFL thickness in the nasal sector had a significant difference among the three groups, with a thinner thickness in patients with MSA ($P<0.05$). Patients with PD, PSP, and MSA with dementia showed a significantly greater reduction in RNFL thickness in the upper and temporal quadrants, nasal quadrant, and upper and temporal quadrants compared to PD, PSP, and MSA without dementia, respectively ($P<0.05$).

Conclusion: Evaluating RNFL can be useful in predicting ocular involvement. Once validated in further studies, OCT may serve as a biomarker for predicting the presence or progression of movement disorders. OCT may also assist in predicting the presence of dementia in these patients by reflecting a more significant reduction in RNFL thickness compared to patients without dementia.

Keywords: Parkinson's disease, Progressive supranuclear palsy, Multiple system atrophy, Dementia, Retinal nerve fiber layer, Optical coherence tomography

Conflicts of Interest: None declared

Funding: None

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Cite this article as: Daraei P, Taheri M. Changes In The Retinal Nerve Fiber Layer In Patients With Parkinson's Disease, Progressive Supranuclear Palsy, And Multiple System Atrophy With And Without Dementia. *Med J Islam Repub Iran.* 2025 (3 Mar);39:33. <https://doi.org/10.47176/mjiri.39.33>

Introduction

Parkinson's disease (PD), Progressive Supranuclear Palsy (PSP), Multiple System Atrophy (MSA), and Corticobasal Degeneration (CBD) are movement disorders characterized by the degeneration of dopaminergic neurons in the central nervous system (CNS).

PD is a progressive movement disorder associated with the degeneration of dopaminergic neurons within the basal ganglia, substantia nigra, and pars compacta of the mid-brain. The characteristic features include movement dysfunctions such as resting tremor, rigidity, and bradykinesia.

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↑What is "already known" in this topic:

Although some studies have shown no changes in PD, most reports have shown thinning of the RNFL, whether segmental or global. However, only a few studies have compared RNFL thickness changes between PD and other atypical Parkinsonian diseases. Furthermore, fewer studies have assessed RNFL changes in these patients with dementia.

→What this article adds:

RNFL examination can be a useful tool for predicting ocular involvement in Parkinsonism. Once this is confirmed, a threshold for RNFL thickness to prevent disease progression can be explored, and it may also help predict the presence of dementia by reflecting a more significant reduction in RNFL thickness.

The incidence of the disease increases with advancing age. It also affects other organs that are not directly related to the movement centers, such as the involvement of the visual system (1, 2).

PSP is characterized by pseudobulbar palsy, supranuclear ocular palsy, axial rigidity, dystonia, dementia, and early loss of postural reflexes. PSP in the early stages is similar to PD (1, 2).

MSA includes a group of disorders characterized by neurodegeneration, especially in the substantia nigra, striatum, autonomic nervous system, and cerebellum. It consists of three types. Type 1 (Striato-Nigral Degeneration (SND)) presents with progressive parkinsonism without tremors and a poor response to levodopa due to the loss of dopamine-containing neurons in the striatum. A dystonic reaction following a low dose of levodopa is common. In Type 2 (Shy-Drager Syndrome (SDS)), orthostatic hypotension is typical. Nocturnal stridor is often significantly suggestive of SDS diagnosis. Type 3 (Olivopontocerebellar Atrophy (OPCA)) presents as a parkinsonism syndrome combined with cerebellar syndrome and supranuclear gaze disturbance (1, 2).

There are some visual abnormalities in these diseases, including sensitivity to contrast, color vision defects, and dysfunction of retinal ganglion cells in PD; Pallor of the optic disc in MSA; Blurred vision, eye movement disturbances (diplopia), and retinal changes in PSP; And visuospatial deficits in PSP. To evaluate these retinal changes and their patterns, assessing the retinal nerve fiber layer (RNFL) is essential (3).

Optical coherence tomography (OCT) can detect retinal changes in various diseases of CNS. OCT is an imaging technique that uses light to capture high-resolution cross-sectional images of the eye and reveals subtle and delicate changes that have occurred in the retina and optic nerve (4, 5). It has been considered a biomarker because it is a fast, accessible, reproducible, non-invasive, and relatively inexpensive imaging technique. It can also provide an in-vivo histopathological image of the RNFL (5). Multiple studies have evaluated the RNFL involvement in movement disorders. Most studies have been conducted on PD, and only a few studies have assessed this involvement in other Parkinsonian syndromes (6). Although some studies showed no changes in PD, most reports indicated thinning of the RNFL, whether segmental or global, with different patterns based on the dominant type of parkinsonism being tremor or akinetic-rigid (6, 7).

In several studies conducted on patients with PSP, CBD, and MSA, Albrecht and colleagues showed various changes in the retina in these diseases as well as in PD, with the most severe changes observed in PSP and MSA. They demonstrated that the ratio of the outer nuclear layer (ONL) to the outer plexiform layer (OPL) can differentiate PSP from other Parkinsonian syndromes (4). Furthermore, Fischer and colleagues reported a significant thinning of the RNFL in patients with MSA (8).

However, only a few studies compare RNFL thickness changes between PD and other atypical Parkinsonian diseases. Additionally, few studies have assessed RNFL changes in patients with dementia, mainly in Alzheimer's

disease (AD) (9), and one study evaluated RNFL involvement in patients with various causes of dementia, including dementia associated with PD (5). This study showed a significant reduction in RNFL thickness in all types of dementia compared to the control group, with more notable thinning in patients with dementia associated with Lewy bodies compared to those with Alzheimer's disease and dementia associated with PD (5).

However, a review of the literature shows a lack of information regarding the pattern of changes in patients with Parkinsonian syndrome who also have dementia. Therefore, the present study evaluates RNFL changes in patients with PD and other Parkinsonian syndromes (PSP, CBD, and MSA) with and without dementia.

Methods

This cross-sectional study examined all patients diagnosed with PD, PSP, and MSA who visited the movement disorders clinic of Rasoul Akram Hospital from March 2017 to February 2019.

All patients were examined by a neurologist and an ophthalmologist. The severity of the disease was determined using the Unified Parkinson's Disease Rating Scale (UPDRS). With the aim of conducting the Mini-Mental Examination (MMSE), patients were divided into two groups: with and without dementia.

Since RNFL is a suitable measure for assessing neurodegenerative changes in the eye, the thickness of RNFL in patients with PD, PSP, and MSA with and without dementia was measured and compared.

RNFL measurement

Tropicamide was used to induce pupil dilation. The thickness of the RNFL was measured using three-dimensional Optical Coherence Tomography (3D-OCT) 1000 Mark II. RNFL was divided into four quadrants: superior, inferior, nasal, and temporal. All four quadrants of the retina were measured separately to measure RNFL thickness.

Using an in-person interview, physical examination, and OCT, the necessary data were collected and recorded in pre-prepared questionnaires. Variables included demographic information, duration of illness, history of neurodegenerative disease, history of ocular disease, MMSE score, UPDRS, and OCT results.

Statistical methods, including the independent t-test, one-way analysis of variance (ANOVA), and the Pearson correlation coefficient, were used to analyze the data using SPSS statistical software. The statistical significance level was set at 0.05.

Inclusion and exclusion criteria

Inclusion criteria:

- All patients were diagnosed with PD, PSP, and MSA based on clinical and radiological criteria.

Exclusion criteria:

- All patients exhibit symptoms and signs of other neurological diseases, such as pure Alzheimer's disease and multiple sclerosis (MS).

- All patients are suspected of having a demyelinating disease.

- All patients with diabetes mellitus (DM).
 - All patients are suspected of having eye diseases such as glaucoma, optic neuropathy, and ischemic optic neuropathy.
 - All patients who did not consent to the OCT test.
 - All patients with eye diseases that interfered with imaging.
- Ethical considerations:
- The Helsinki Declaration was taken into account.
 - All study procedures were explained thoroughly to all patients included in the study.
 - Informed written consent was obtained from all patients or their first-degree relatives.
 - No additional costs were imposed on the patients.
 - The study was approved by the Ethics Committee of Iran University of Medical Sciences.
 - Data were collected and analyzed using codes instead of identifying data.

Results

Fifty-three patients / one hundred and six eyes (twenty-eight patients with PD, fifteen patients with PSP, and ten patients with MSA) were examined.

In patients with PD, the mean age was 63.28 ± 10.22 years. Seventeen patients (60.7%) were male and eleven (39.3%) were female. The mean duration of the disease was 4 years, and the mean UPDRS score was 15.7.

In patients with PSP, the mean age was 61.93 ± 12.81 years. Ten patients (66.7%) were male and five (33.3%) were female. The mean duration of the disease was 3.2 years, and the mean UPDRS score was 28.1.

In patients with MSA, the mean age was 67.30 ± 8.26 years. Eight patients (80%) were male, and two (20%) were female. The mean duration of the disease was 3 years, and the mean UPDRS score was 20.

The mean age and mean UPDRS score showed a significant difference between groups, but there was no significant difference in gender and duration of the disease.

Among a total of 28 patients with PD, 26 were diagnosed with PD and 2 with PD and dementia. Both PD patients with dementia were female ($P=0.024$). The mean age of patients with PD was significantly lower than that of patients

with PD with dementia (62.3 vs. 76 years, P -value = 0.001). The mean UPDRS score for PD patients and PD patients with dementia was 15.7 and 15.5, respectively (non-significant).

Among the patients with PSP, 8 had PSP, and 7 had PSP with dementia. All eight patients with PSP were male, and among the seven patients with PSP with dementia, two were male, and five were female ($P=0.001$). The mean age of PSP patients was 61.3 years, and that of PSP patients with dementia was 62.5 years (non-significant). The mean UPDRS score for PSP patients and PSP patients with dementia was 21.2 and 36, respectively ($P=0.002$).

Considering the patients with MSA, 7 had MSA, and 3 had MSA with dementia (not significant between genders). The mean age of MSA patients was significantly lower than that of MSA patients with dementia (68.7 vs. 64 years, $P=0.011$). The mean UPDRS score for MSA patients and MSA patients with dementia was 14.8 and 32, respectively ($P=0.070$).

The MMSE score showed a significant difference between the groups (Table 1).

The mean thickness of RNFL in the nasal section showed a significant difference between the three groups with thinner thickness in patients with MSA (Table 2).

Patients with PD suffering from dementia showed a significantly greater reduction in RNFL thickness in the superior and temporal quadrants compared to patients with PD without dementia (Table 3).

Patients with PSP suffering from dementia showed a significantly greater reduction in RNFL thickness in the nasal quadrant compared to patients with PSP without dementia (Table 4).

Patients with MSA suffering from dementia showed a significantly greater reduction in RNFL thickness in the superior, inferior, and temporal quadrants compared to patients with MSA without dementia (Table 5).

Considering the relationship between RNFL thickness and disease severity (UPDRS), statistical analysis revealed a significant change in the temporal quadrant in patients with PD and PSP (negative correlation), but no correlation was found in patients with MSA (Table 6).

Table 1. Compares the MMSE scores among three groups of patients

| Variable | | PD | PSP | MSA | P-value |
|----------|-------|------------------|------------------|-----------------|---------|
| MMSE | Mean | 27.87 ± 2.40 | 24.06 ± 5.88 | 25.6 ± 2.94 | 0.001 |
| | Lower | 20 | 13 | 21 | |
| | Upper | 30 | 30 | 29 | |

Table 2. Compares the OCT results in different sectors among three groups of patients

| Variable | Quadrant | PD | PSP | MSA | P-value |
|-------------|----------|--------------------|--------------------|--------------------|---------|
| OCT results | Superior | 127.51 ± 12.76 | 120.5 ± 17.34 | 119.65 ± 22.46 | 0.282 |
| | Inferior | 130.19 ± 15.46 | 127.53 ± 16.44 | 124.85 ± 11.13 | 0.430 |
| | Nasal | 77.75 ± 12.12 | 78.23 ± 11.30 | 69.85 ± 10.12 | 0.027 |
| | Temporal | 71 ± 12.94 | 66.69 ± 8.61 | 69.25 ± 9.07 | 0.537 |

Table 3. Compares the OCT results in different sectors among patients with PD and PD patients with dementia

| Variable | Quadrant | PD | PD With Dementia | P-value |
|-------------|----------|--------------------|------------------|---------|
| OCT results | Superior | 128.40 ± 12.77 | 116 ± 4.61 | 0.030 |
| | Inferior | 130.40 ± 16.02 | 127.5 ± 2.88 | 0.631 |
| | Nasal | 77.26 ± 12.44 | 84 ± 2.30 | 0.140 |
| | Temporal | 72 ± 12.89 | 58 ± 3.46 | 0.011 |

Table 4. Compares the OCT results in different sectors among patients with PSP and PSP patients with dementia

| Variable | Quadrant | PSP | PSP With Dementia | P-value |
|-------------|----------|--------------|-------------------|---------|
| OCT results | Superior | 125.14±17.23 | 115.08±16.52 | 0.205 |
| | Inferior | 129.85±20.63 | 124.83±9.82 | 0.114 |
| | Nasal | 82.42±8.06 | 73.33±12.85 | 0.031 |
| | Temporal | 68.78±8.16 | 64.25±8.82 | 0.171 |

Table 5. Compares the OCT results in different sectors among patients with MSA and MSA patients with dementia

| Variable | Quadrant | MSA | MSA with dementia | P-value |
|-------------|----------|-------------|-------------------|---------|
| OCT results | Superior | 137.16±6.99 | 112.14±22.73 | 0.001 |
| | Inferior | 133±5.36 | 121.35±11.23 | 0.022 |
| | Nasal | 74±4.97 | 68.07±11.35 | 0.502 |
| | Temporal | 78.66±2.87 | 65.21±7.65 | 0.003 |

Table 6. Shows the correlation between OCT results and disease severity (UPDRS)

| Variable | Quadrant | Disease | Correlation | P-value |
|-------------|----------|---------|-------------|---------|
| OCT results | Superior | PD | -0.251 | 0.062 |
| | | PSP | -0.274 | 0.172 |
| | | MSA | 0.099 | 0.677 |
| | Inferior | PD | -0.103 | 0.449 |
| | | PSP | -0.374 | 0.061 |
| | | MSA | 0.273 | 0.243 |
| | Nasal | PD | -0.015 | 0.913 |
| | | PSP | -0.290 | 0.152 |
| | | MSA | 0.195 | 0.41 |
| | Temporal | PD | -0.268 | 0.04 |
| | | PSP | -0.384 | 0.05 |
| | | MSA | 0.006 | 0.98 |

Table 7. Shows the Pearson Correlation Coefficient between OCT results and disease duration

| Variable | Quadrant | Disease | Correlation | P-value |
|-------------|----------|---------|-------------|---------|
| OCT results | Superior | PD | -0.551 | 0.001 |
| | | PSP | 0.204 | 0.312 |
| | | MSA | 0.470 | 0.031 |
| | Inferior | PD | -0.381 | 0.004 |
| | | PSP | -0.122 | 0.554 |
| | | MSA | 0.518 | 0.011 |
| | Nasal | PD | -0.406 | 0.002 |
| | | PSP | 0.356 | 0.073 |
| | | MSA | 0.394 | 0.087 |
| | Temporal | PD | -0.367 | 0.005 |
| | | PSP | -0.022 | 0.910 |
| | | MSA | 0.598 | 0.005 |

Furthermore, regarding the relationship between RNFL thickness and disease duration, statistical analysis showed a significant change in all four quadrants in patients with PD (negative correlation), no correlation in patients with PSP, and significant changes in the superior, inferior, and temporal quadrants in patients with MSA (positive relationship) (Table 7).

Discussion

From a developmental perspective, the retina originates from the diencephalon and is part of the central nervous system. They are affected by diseases such as PD, which can lead to deficiencies in visual acuity and color vision, consequently resulting in color and contrast disruptions and double vision (3).

The retina contains dopaminergic cells. In animal models, the dependence of higher visual areas on dopamine has been demonstrated. This suggests that in patients with dopamine deficiency (such as PS and PSP), the visual process is affected. Furthermore, the accumulation of tau protein plays a role in retinal degeneration in PSP, and tau protein

deposition in the retina has been demonstrated in adult humans, along with significant retinal degeneration in AD (3).

The retina processes visual information, and the retinal ganglion cells (RGC) convey it through the optic nerve. RGCs are classified into four subgroups. (a) The parvocellular pathway or P cells reach the parvocellular layers of the lateral geniculate body. (b) The magnocellular pathway or M cells project to the magnocellular layers of the lateral geniculate body. (c) The K pathway or bistratified ganglion cells connect to the koniocellular layers of the lateral geniculate body. And (d) intrinsically photosensitive ganglion cells that project to the suprachiasmatic nucleus (10).

There is preferential damage to P cells compared to M cells (5). P cells are mainly located in the central region of the macula and are associated with color differentiation, visual acuity, sensitivity of the central visual field, and contrast sensitivity for high spatial frequencies. M cells are primarily located in the peripheral regions of the macula and in the retina (in the upper, nasal, and lower areas around the optic nerve). They play roles in processing achromatic vision data, sensitivity of the peripheral visual field, motion

detection, and contrast sensitivity for low spatial frequencies (10). The fact that patients with MSA have normal visual acuity and color vision with atrophy of the lower section of the RNFL indicates that M cells are more involved than P cells, contrary to PD, which has more temporal and macular central atrophy and consequently leads to greater visual symptoms such as reduced VA, disruption in color differentiation, deficits in motion perception, and visual hallucinations (10).

Stemplewitz and colleagues assessed morphological changes in the retina in 22 patients with PSP using OCT. The mean age was 66.2 ± 6.5 years. The mean duration of disease was 4.3 (0.5-8) years. The mean PSP rating scale was 41.6 ± 15 (4). Although a decrease in RNFL thickness was observed in all eight macular segments, they showed a greater reduction in the inferior nasal and inferior temporal segments. No correlation was found between the decrease in RNFL thickness and disease severity or duration. The authors demonstrated significant retinal changes in PSP compared to control and PD patients and concluded that these findings support third nerve palsy, visual impairment, and brain atrophy, distinguishing them from the PD and control groups (3).

Albrecht and his colleagues assessed the RNFL thickness around the papilla in 84 patients (40 patients with PD, 19 with MSA, 10 with CBS, and 15 with PSP) and in 35 normal control subjects. The mean follow-up period was 25 ± 2 months. Considering age and sex, the patients were matched between the MSA and CBS groups except for gender. There was no significant difference in the retinal layer between male and female control groups. The severity of the disease did not differ among patients. The duration of the disease was longer in PD, but no significant difference was observed between the other groups. The mean RNFL thickness around the papilla did not show a significant difference between the groups. However, the mean total macular thickness and macular volume in PSP patients were significantly reduced compared to the PD and control groups, while the reduction in MSA and CBS did not reach a significant level. The reduction in macular thickness in PSP occurred in both the central and peripheral regions of the retina, and in MSA, a significant reduction in the peripheral paramacular retinal thickness (compared to the control group) was observed. There were no correlations between visual acuity, disease duration, and PDRS-3 with the mean peripapillary RNFL thickness, macular thickness, macular volume, and segmental retinal layers. In this study, MSA showed a non-significant tendency toward thinner paramacular layers. The mean RNFL was $97/79 \mu\text{m}$ (4).

In a study by Sevim and colleagues, 72 patients were examined. The mean disease duration for PD was 5.3 years, and for PSP was 3.5 years. Considering the disease duration, age, and sex, no significant difference was observed between the groups. In patients with PSP, the peripapillary retinal nerve fiber layer (PRNFL) was thinner in all sectors compared to the PD and control groups, but it was only significant in the superior sector. Additionally, all retinal layers were thinner compared to the PD and control groups except for the retinal pigment epithelium (RPE). In PD, disease duration was significantly associated with thinner

PRNFL thickness, and in PSP, this correlation was with thinner mean macular RNFL (mRNFL) (11).

Schneider and colleagues assessed RNFL thickness in 16 patients with PSP, 12 with MSA, 65 with PD, and 41 control patients. The duration of disease for PD was 8.9 years, for MSA 4.9 years, and for PSP 3.9 years. Considering age, there was no significant difference between patients and the control group. The mean duration of disease was longer in PD compared to MSA and PSP. The mean UPDRS-3 in PD (29) was lower than in MSA (45) and PSP (44). RNFL thickness decreased in all patients compared to the control group. In patients with PD and MSA but not PSP, retinal thickness was significantly correlated with age. The mean RNFL thickness in PSP was 17.4 ± 2 , in MSA 18 ± 1.8 , in PD 18.3 ± 1.8 , and in the control group 18.8 ± 1.4 (6).

In a meta-analysis, Mendoza-Santesteban and colleagues examined the results of OCT in patients with MSA. They showed that there is a significant thinning in all quadrants of the RNFL in patients with MSA, except for temporal, which was not significant (10).

Moreno-Ramos and colleagues assessed the thinning of RNFL in patients with dementia related to PD, Lewy Body dementia, and AD. Ten patients from each group and ten age-matched cognitively healthy individuals were enrolled in this study. OCT was performed to measure RNFL thickness. The results indicated a significant reduction in RNFL thickness in all patient groups compared to the control group. In the patient groups, those with dementia with Lewy bodies had a non-significantly greater thinning of RNFL compared to patients with AD and PD. They showed that greater cognitive decline is associated with a greater reduction in RNFL thickness (5).

Although the present study shows the effects of neuronal degeneration on retinal nerve fibers in patients with PD, PSP, and MSA, the more important finding is that these effects are more severe in these diseases when accompanied by dementia. Additionally, it indicates that the loss of the retinal nerve layer depends on the severity and duration of the disease.

Limitations

The main limitation of this study was the lack of cooperation from patients undergoing OCT due to movement issues and tremors.

Conclusion

In patients with movement disorders, visual abnormalities may not have obvious signs during a regular eye examination. Thus, an RNFL examination can be useful for predicting ocular involvement. Once confirmed in future studies, a threshold for RNFL thickness to prevent disease progression can be explored. On the other hand, with further studies, OCT can also be used as a biomarker to predict the progression of movement disorders. Given the potential relationship between RNFL thickness and disease severity—a negative correlation in patients with PD and PSP shown in this study—OCT may also help predict the existence of dementia in these patients by reflecting a more significant reduction in RNFL thickness compared to patients without

dementia. It is recommended that a larger study with a greater sample size be designed and conducted to provide more details about retinal involvement.

Authors' Contributions

The authors contributed equally to this work.

Ethical Considerations

The study was approved by the Ethics Committee of Iran University of Medical Sciences with the number 1396/03/31/3220.

Acknowledgment

This study is extracted from a neurology thesis, and we thank the Iran University of Medical Sciences and Rasool Akram Hospital for supporting this work.

Conflict of Interests

The authors declare that they have no competing interests.

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