Original Article

Retinal Degeneration in Patients with Wilson's Disease: An OCT Study in Asian Indian Population

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Abstract

Background: Wilson's disease (WD) is an autosomal recessive disorder of copper metabolism. We aimed to study the abnormalities in the retinal layers in patients with WD using optical coherence tomography (OCT). **Methods:** The study is a chart review of 16 patients with WD (six females) who underwent OCT at our hospital during follow-up visits. Spectral-domain OCT was performed in all subjects to assess the thickness of macula and retinal nerve fiber layer (RNFL) and the data was compared with 14 healthy controls (three females). **Results:** The mean age of the patients was 20.81 ± 7.47 years and controls was 26.86 ± 9.95 years. The mean age at the onset of the illness was 16.25 ± 5.57 years (range 11–28 years) with the mean duration of illness being 4.81 ± 3.31 years at the final follow-up examination. The mean macular thickness was found to be significantly reduced in patients (232.13 ± 19.39) when compared to controls (271.30 ± 17.32 μm; $P = 0.01$). There was a significant difference in the ganglion cell and inner plexiform (GCIP) layer between the patients (86.83 ± 8.20 μm) and controls (97.72 ± 5.31 μm; $P = 0.01$). In addition, the outer nuclear layer with the photoreceptor layer (ONL + PRL) thickness was also reduced in WD (93.90 ± 10.23 μm vs. 108.43 ± 10.00 μm; $P = 0.01$) There was no change in the RNFL thickness, between the two groups ($P = 0.53$). **Conclusions:** Abnormalities of the retinal layers were observed in the patients with WD. OCT is a non-invasive tool to identify and quantify the abnormalities of the retinal layers.

Keywords: Ganglion cell layer, macular thickness, optical coherence tomography, retinal degeneration, retinal nerve fiber layer, Wilson's disease

Introduction

Wilson's disease (WD) is an autosomal recessive disorder caused by mutations in the ATP7B gene, which leads to the deposition of copper in the liver, brain, cornea, and other organs.[1–4] WD is a treatable disorder, however, if left untreated, it may lead to permanent disability and even death.[4] Hepatic, neurological, and neuropsychiatric variants are the common clinical presentations seen in WD.[5]

The ophthalmic manifestations of WD include the presence of the 'Kayser–Fleischer' (KF) ring in the cornea and the development of a premature cataract, typically described as the "sunflower cataract."[6,7] While the KF ring results from the abnormal accumulation of copper within the Descemet membrane of cornea, the sunflower cataract is caused by the deposition of copper under the lens capsule.[8,9] Recently, studies have identified copper deposits and their sequelae in the retina and optic nerve using electroretinography and anterior segment optical coherence tomography (OCT).[9,10] In a study on the Electroretinography (ERG) finding in newly diagnosed patients with WD, the authors identified that the Visual evoked potentials (VEP) latencies, photopic and scotopic A waves, and oscillatory potentials were prolonged in WD. These changes showed partial reversal when the patient was sufficiently chelated.[11] OCT is a technique used to obtain cross-sectional images of different ocular tissues with high resolution (1–15 μm). Using long-wavelength light beams, different layers of ocular tissues can be separated to perform three-dimensional volumetric measurements.[12–14] The axial resolution of OCT is defined by the properties of the light source and sampling of the interferometric signal (20–5 μm) while the lateral resolution of the OCT is defined by the objective and the focusing media in front of the sample.[15] The most important clinical measure, in terms of neurological disorders, is the retinal nerve fiber layer (RNFL) thickness. Recent studies have identified RNFL thickness as a potential candidate marker of neurodegeneration in diseases such as Alzheimer's, Parkinson's, Huntington's, multiple sclerosis, and other neurodegenerative retinopathies.[16–19]

Only sparse literature exists on the utility of OCT in the WD and these studies indicate the presence of RNFL thinning

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in the WD.[9,20] However, the clinical correlations of RNFL thinning are not well understood. In this study, we aimed to study the abnormalities in the retinal layers in patients with WD using OCT.

Materials and Methods

This study is a retrospective chart review and was performed in the Department of Neurology and was approved by the Institute's Ethics Committee.

Relevant demographic and clinical details of the patients were obtained from the case files for final analysis of WD patients who were evaluated with OCT at our institute. Sixteen patients with WD were included in the study All patients had neurological manifestations at presentation. All the participants were evaluated with OCT using the Spectral-domain OCT. The diagnosis of WD was made based on the clinical features, presence of the KF ring (confirmed by the slit-lamp examination), magnetic resonance imaging (MRI) changes, and biochemical reports. Only the subjects with normal visual acuity (6/6) in both eyes were included in the study. Furthermore, all the patients were evaluated by the ophthalmologist and refractive errors were ruled out. The patients with comorbid conditions such as glaucoma, cataract (WD related or otherwise), diabetes, hypertension, ocular trauma, prior intraocular surgery, laser treatment, or any other ocular pathology were not included in the OCT study [Figure 1]. All patients were already on zinc and chelation therapy with penicillamine at the time of recruitment. The disease severity was assessed by the Global Assessment Scale for Wilson's Disease: (GAS-WD) during the time of OCT.[21] The demographic and OCT data of healthy controls were obtained from the database of our laboratory.

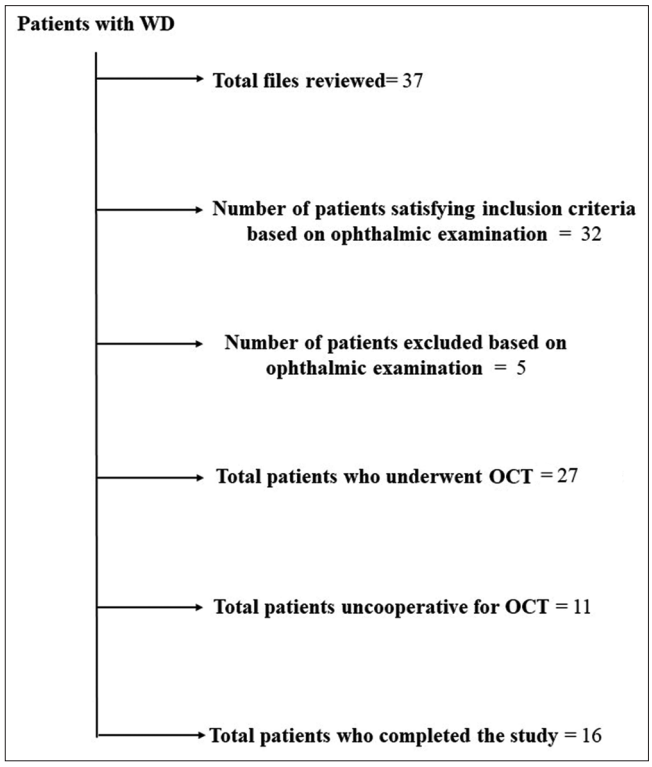

Figure 1: Flowchart showing final recruitment of patients in study guidelines used in the study

Optical coherence tomography

OCT was performed using the spectral-domain OCT (SD-OCT, Spectralis, Heidelberg Engineering, Heidelberg, Germany) in all the subjects under adequate light conditions. Both eyes were separately scanned for each subject. The scanning was performed using the in-built, automated eye-tracking system (TruTrack and Tracking laser tomography) to compensate for the effect of eye movement. The scanning of the macula was done on a 20° ×20° cube with 49 raster lines, each containing 1024 pixels separated by a distance of 120 mm. The artifacts were minimized using high-speed acquisition to improve the image definition. Images of signal strength more than 20 dB with well-centered images were used for analysis.

The RNFL segmentation and subsequent RNFL thickness assessment were performed by automated segmentation. The thickness of the RNFL was measured around a disk in a circle of 3.5 mm diameter by using 1536 A-scans. The mean RNFL thickness was measured and reported in micrometers.

The macular thickness (M^{th}) was measured in circles of 1, 2, and 3 mm diameters. The images of the macular region were then segmented to determine the thickness of the layers of the retina at the macula. The thickness was measured at the perifovea for all layers except the outer nuclear layer with the photoreceptor layer (ONL + PRL) which was measured at the center of the fovea. The measurements were made in the macula as a whole and also in the nasal, temporal, superior, and inferior quadrants separately. The thickness of the ganglion cell and inner plexiform layer complex (GCIP), the inner nuclear layer (INL), the outer plexiform layer (OPL), and the ONL + PRL were separately measured.

Statistical analysis

The statistical analysis was performed in R software (version 3.6.0). The internal correlations were avoided by analyzing the mean values of the measurements taken from both eyes for all subjects. The normality of data was confirmed using the Shapiro–Wilk test. For comparison of means among patients and controls, the Student's t-test was used. Pearson's correlations were performed to check the relationship between the clinical variables and OCT measures.

Results

Clinical characteristics

Sixteen patients (6 females and 10 males) were included in study and the data were compared with 14 healthy controls (3 females and 11 males). The mean age of patients at the time of performing OCT was (20.81 ± 7.47 years, range: 12–37 years) and for the controls was (26.86 ± 9.95 years,

range: 10–40 years), the difference being not statistically significant ($P = 0.07$). The mean age at the onset of illness was 16.25 ± 5.57 years (range 11–28 years) and the mean duration of illness was 4.81 ± 3.31 years (range 01–12 years). The mean GAS-WD score at the time of OCT was 10.06 ± 6.01 [Table 1].

Among the 16 patients, 11 had a shorter disease duration (<5 years) and 5 had a longer disease duration (≥5 years) based on the calculation of the mean. There was a significant difference in the age between the patients with shorter disease duration compared to those with longer disease duration (17.36 ± 5.18 years vs. 28.6 ± 5.37 years; $P = 0.005$). The mean duration of illness in patients with shorter disease duration was 2.82 ± 1.17 years and 9.2 ± 1.64 years in the patients with longer disease duration (P=<0.001). However, there was no difference in the age at onset or GAS-WD score.

All the patients had a neurological form of WD and had a variety of movement disorders. Tremor was the most common movement disorder observed in 62.5% followed by dystonia (56.3%), and parkinsonism (31%). Postural tremors were seen in 80%, wing beating, and rest tremors in 10% each. Among the dystonias, limb dystonia was the predominant phenomenology seen in 77.8%. Facial dystonia was seen in 22.2% and lingual, truncal, and cervical dystonia were seen in 11.1% each. Myoclonus and ataxia were seen in one patient each.

Table 1: Demographic and clinical features of the study participants

	WD	Controls	Significance
	(*n*=16)	(*n*=14)	
Gender (male:female)	10:6	11:3	
Age (years)	20.81±7.47	26.86±9.95	0.07
Age at onset (years)	16.25±5.57		
Duration of WD (years)	4.81±3.31		
GAS	10.06±6.01		

WD: Wilson's disease, GAS: Global assessment scale for Wilson's disease

Table 2: Retinal layer measurements in the patients with WD and healthy controls

Retinal layers	WD (*N*=16)	Controls (*N*=14)	Significance
RNFL (μm)	106.39±10.54	105.53±9.89	0.53
Retinal nerve fiber layer measurements			
Superior	132.90±16.22	130.57±13.83	0.43
Temporal	68.73±9.25	67.83±9.58	0.87
Inferior	140.35±17.76	137.43±14.88	0.25
Nasal	83.58±14.50	86.30±16.04	0.65
Macular thickness measurements			
M^{th} (μm)	232.13±19.39	271.30±17.32	0.01
GCIP (μm)	86.83±8.20	97.72±5.31	0.01
INL (μm)	38.10±4.11	40.32±2.31	0.16
OPL (μm)	30.78±4.12	30.23±2.46	0.49
ONL + PRL (μm)	93.90±10.23	108.43±10	0.01

GCIP: Ganglion cell and inner plexiform layer, I: Inferior part, INL: Inner nuclear layer, M^{th}: Total macular thickness, ONL+PRL: Outer nuclear layer and photoreceptor layer, OPL: Outer plexiform layer, RNFL: Retinal nerve fiber layer

OCT

The mean macular thickness (M^{th}) was significantly lower in patients (232.13 ± 19.39 μm) compared to the healthy controls (271.30 ± 17.32 μm; $P = 0.01$). On further segmentation of the retinal layers, the ganglion cell and inner plexiform layer (GCIP) were significantly reduced in patients (86.83 ± 8.20 μm) compared to the controls (97.72 ± 5.31 μm; $P = 0.01$). In addition, the ONL + PRL layers were also significantly reduced in the patients with WD (93.90 ± 10.23 μm) as compared to the controls (108.43 ± 10.00 μm; $P = 0.01$). There was no significant difference in the macular thickness in the individual quadrants between the patients and controls [Table 2].

The mean RNFL thickness in patients (106.39 ± 10.54 μm) was not significantly different when compared to the controls (105.53 ± 9.89 μm; $P = 0.53$) [Figure 2].

In addition, there was no significant difference in the RNFL thickness between the patients with shorter and longer disease duration in the right eye (111.73 ± 11.48 μm vs. 103.8 ± 9.5 μm; $P = 0.18$) and the left eye (110.27 ± 9.83 μm vs. 102.6 ± 9.69 μm; $P = 0.182$).

Correlations

Despite the absence of significant difference in the RNFL thickness among the patients and controls, there was a significant negative correlation between the duration of the illness and the RNFL thickness of the superior (r = -0.42, $P = 0.01$) and inferior quadrants (r = -0.61, $P = 0.01$). The GAS-WD scores negatively correlated with the RNFL's temporal quadrant (r =-0.55, $P = 0.01$) and inferior quadrant (r =-0.44, $P = 0.01$).

The duration of disease was found to correlate negatively with the macular layer thickness (r =-0.11, $P = 0.01$). The GAS-WD also correlated with the thickness of the macular layer (r =-0.41, $P = 0.01$), ganglion cell layer (GCL) (r =-0.43, $P = 0.01$) and GCIP layers (r =-0.42, $P = 0.01$).

Discussion

OCT is a non-invasive tool that is used to study the retinal layers and obtain cross-sectional images of the retinal layers, allowing quantitative analysis of ocular tissues.[17,22] OCT can assess the thickness of the macular layers and RNFL and is consistently helpful in assessing neurodegenerative diseases.[23] The brief and non-invasive nature of the OCT makes the device an ideal candidate to evaluate retinal degeneration.

Embryologically, the retina originates from the diencephalon and has a high density of neuronal cells and fibers, and may be structurally and functionally regarded as an extension of the brain.[24–26] Previous studies have consistently observed the nerve fiber layer thinning to be associated with reduced brain

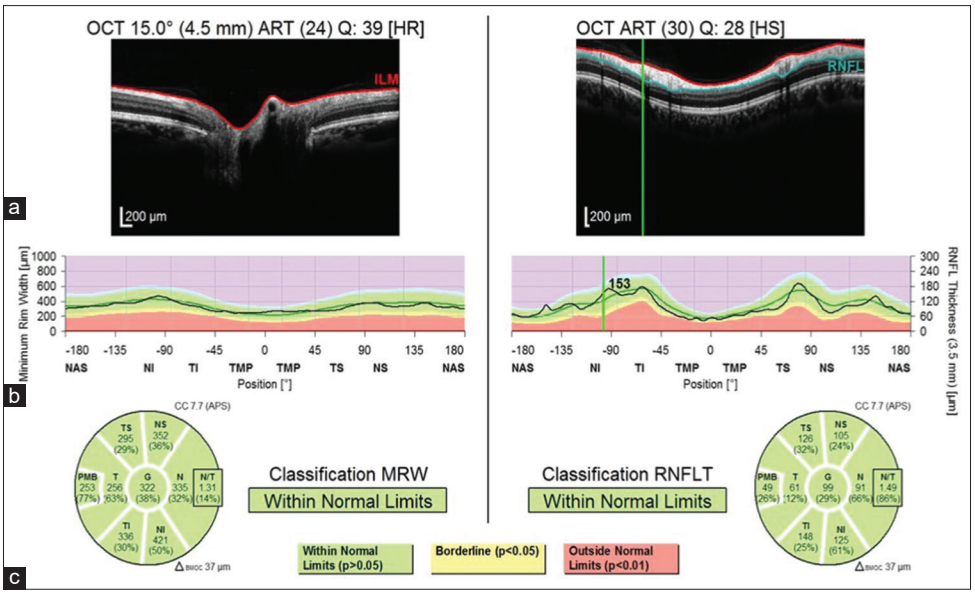

Figure 2: SD-OCT of the right eye of a patient showing normal RNFL values in all regions. (a) OCT image depicting the segmented RNFL (red line). (b) Plot showing the TSNIT (temporal, superior, nasal, inferior, temporal) graph (black line) within normal limits. (c) RNFL thickness measurement in each sector of the subject with the normative control values within brackets

volumes suggesting that these intraocular findings may be representative of the global pathology of the central nervous system.[27] Hence, the retina lends itself as a window to study the neurodegenerative changes in the brain.

In this study, we evaluated the RNFL and macular thickness as objective and surrogate indicators of retinal degeneration in patients with WD. We found significant differences in the macular thickness specifically in the GCIP and ONL + PRL layers between the patients and controls. Moreover, the correlation analysis revealed a significant association between the clinical variables (duration of disease, GAS-WD score) and OCT measurements (macular thickness and RNFL of the superior and inferior quadrants).

Previous studies have reported a decrease in the macular thickness and those of GCIP and INL layers in the WD.[20,28] The degeneration of the retinal ganglion cell axons account for the observed thinning of the retinal layers in the WD patients. In agreement, we also found a loss of overall macular thickness and thinning of the GCIP and ONL + PRL layers in our patients. The ganglion cells form a network of extensive overlapping of dendrites. The GCIP and PRL are important layers of the retina and have different compositions. While GCIP is composed of the GCL and the inner plexiform layer (IPL), ONL consists of the cell body of the rod and cone cells and the PRL consists of photoreceptor cells. These cells are the specialized neuroepithelial cells which are involved in visual phototransduction. The photoreceptor processes give rise to the fiber layer of Henle.[20] The absence of significant differences in the thickness of other macular layers probably suggests that copper-induced cytotoxic changes may specifically affect the GCIP layers.

The earlier studies have also found a thinning of RNFL in the patients with WD. A recent study by Langwińska-Wośko *et al*.[28] found that total RNFL and macular thickness are reduced in patients with WD. In addition, two other studies have found RNFL to be reduced significantly in patients with WD.[9,20] However, we did not observe any significant reduction of RNFL thickness between the groups. This disparity may be attributed to the lower mean age of our patients and shorter disease duration [Table 3]. These results imply that the loss of RNFL may be a later phenomenon in the natural history of WD compared to the loss of macular thickness.[28] Additionally, early and adequate chelation therapy may be neuroprotective and may rescue the retinal nerve fibers. These results are further supported by our correlation results which showed that the RNFL thickness reduces with increasing duration of the disease ($r = -0.49$) and the GAS scores ($r = -0.49$). Another recent study was conducted by Svetel *et al*. (2021)[29] in patients with WD to evaluate the relationship between the OCT parameters and the form of the disease, therapy, and symptoms, duration as well as the severity of neurological impairment. The results of the study demonstrated that patients with WD had significantly lower intraocular pressure in both eyes and lower RNFL thickness as compared to HC globally.

The degeneration of the ganglion cells and their axons is responsible for the reduced thickness of the GCIP complex in WD patients. Similar results were reported by other authors stating the thinning of RNFL, and the other internal layers point toward abnormalities in the ganglion cells and their axons.[20] Similar results, Langwińska-Wośko *et al*.[28] found that OCT parameters correlated negatively with the neurological impairment assessed by the Unified Wilson's Disease Rating Scale (UWDRS) score. We were able to reproduce similar results.

Table 3: Comparison of the present study with other studies of OCT in patients with Wilson's disease

Author	Sample size and Demographics	Methods	Results
Albrecht *et al*.[20]	42 WD, 76 HC. Mean age: 40.2±13.6 years, Duration of illness: 15.7±10.6 years	OCT was performed using the Spectralis OCT device (Heidelberg Engineering, Heidelberg, Germany). The peripapillary RNFL thickness, total macular thickness, and manually segmented all retinal layers in foveal scans were done. The results were compared with VEPs and clinical parameters	The mean thickness of the RNFL, paramacular region, the IPL, and the INL layer was reduced in WD. VEPs were altered with delayed N75 and P100 latencies, but the N140 latency and amplitude was unchanged
Langwińska-Wośko *et al*.[9]	58 WD, 30 HC Mean age: 38.7 years (31.1 to 42.1 years), Duration of illness: 10.7 to 11.1 years.	OCT was performed using a Spectralis OCT. Total thickness of the macula (M^{th}) and of the retinal nerve fiber layer (RNFL) was measured separately. Macular images were manually segmented to determine the thickness of specific layers of the retina at the macula: the ganglion cell and inner plexiform layer complex (GCIP), the inner nuclear layer (INL), the outer plexiform layer (OPL), and the outer nuclear layer plus the photoreceptor layer (ONL + PRL). VEPs were measured and electroretinography was performed	Macular and RNFL were thinner in WD patients who had changes on MRI than in patients without changes. N135 latency was prolonged in the MRI-negative group when compared to the controls. The electroretinogram latencies were prolonged in the MRI + group while the amplitudes were diminished when compared to the MRI-negative group
Langwińska-Wośko *et al*.[28]	58 WD. Mean age: 38.5±12.5 years, duration of illness: 9.0±10.8 years	Patients were divided into two groups based on the presence (UWDRS +) and absence (UWDRS-) of neurological symptoms. OCT was done using Spectralis OCT to assess the thickness of the macular thickness and total RNFL	Total RNFL as well as macular thickness were significantly decreased in the UWDRS+group vs. the UWDRS- group
Present study	16 WD, 14 HC Mean age: 20.81±7.47 years, duration of illness: 4.8±3.31 years	Spectral-domain OCT was performed in all subjects to assess the thickness of the RNFL as well as the macular thickness	The mean macular thickness was found to be significantly reduced in the WD patients. There was a significant difference in the ganglion cell and inner plexiform layer (GCIP) between patients and controls. The outer nuclear layer with the photoreceptor layer (ONL + PRL) thickness was also reduced in WD

WD: Wilson's disease, HC: Healthy controls, OCT: Optical coherence tomography, GCIP: Ganglion cell and inner plexiform layer, I: Inferior part, INL: Inner nuclear layer, M^{th}: Total macular thickness, IPL: Inner plexiform layer, ONL + PRL: Outer nuclear layer and photoreceptor layer, OPL: Outer plexiform layer, RNFL: Retinal nerve fiber layer

A limitation of this study is that we did not evaluate if there was an impact of biochemical variables, such as serum copper, ceruloplasmin levels, and urinary copper excretion, on the retina. However, all of our patients were on chelation treatment using varying doses, regimens, and compliance at the time OCT was done. Hence, the biochemical variables may not have been uniform in all the patients. Another limitation is the small sample size. Hence, these results are preliminary and require validation in cohorts with larger sample sizes and presymptomatic patients. In addition, sequential OCTs in longitudinal studies on the same cohort are warranted to evaluate the effect of chelation therapy on the reversal of retinal abnormalities.

The novelty of our study is that the macular thickness was reduced before RNFL thickness in the early disease which may suggest that RNFL thinning is a relatively late occurrence in the natural history of WD. Hence, the evaluation of macular thickness could be an earlier biomarker for WD.

Considering that there are only a handful of studies which performed OCT in WD, the limited knowledge on these issues and variability in the ethnicity of the previously reported cohorts, our data provide a different perspective and improve our understanding of the retinal abnormalities observed in the patients with WD. In addition, there are many mutations described in the ATP7B gene which may vary among different ethnicities and could explain the differential progression and involvement of the retinal tissues in the course of the illness.[29]

Conclusions

OCT is a non-invasive tool to study the retinal changes in patients with WD and is useful for the estimation of the degree of neurodegeneration, monitoring of therapy, and prognostication. The thinning of the GCL and OPL may serve as markers for the progression of the disease or efficacy of the therapy in WD. However, follow-up studies are required to determine the clear association between neuronal and retinal degenerations. Finally, the role of OCT in detecting early neurological involvement in the presymptomatic stages of WD, asymptomatic carriers, and in patients with non-neurologic forms of WD, needs to be explored further.

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Conflicts of interest

There are no conflicts of interest.

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