DOI: 10.4274/tjo.19327

Original Article / Özgün Araştırma

Optical Coherence Tomography Findings in Patients with Wolfram Syndrome

Wolfram Sendromlu Hastalarda Optik Koherans Tomografi Bulguları

Bengü Ekinci Köktekir*, Berker Bakbak*, Şaban Gönül*, Şansal Gedik*
*Selçuk University Faculty of Medicine, Department of Ophthalmology, Konya, Turkey

Summary

Objectives: To report the optical coherence tomography (OCT) findings in patients with Wolfram syndrome.

Materials and Methods: Four patients who fulfilled the criteria for Wolfram syndrome were recruited to the study. In all patients, OCT was performed with Stratus OCT (OCT-3, Carl Zeiss Meditec, Inc. Germany). The fast retinal nerve fiber layer (RNFL) and fast macular thickness protocols were used to measure the RNFL and macular thickness, respectively. The fast optic disc protocol was used to determine the cup-to-disc ratios of the optic disc. All patients were examined with VEP (Retimax, CSO Strumenti Oftalmici, Florence, Italy).

Results: In eight eyes of four patients (3 male and 1 female) with a mean age of 18.5±2.08 years (range 16-21 years), RNFL, macular thickness, and cup-to-disc ratios were determined. The mean RNFL was 42.2±5.6 µm (range 34.1-49.5 µm), while the mean macular thickness and cup-to-disc ratios were 145±15 µm (range 125-160 µm) and 0.79±0.07 (range 0.7-0.92), respectively. There was a moderate negative correlation between VEP latencies and macular and RNFL thicknesses (Spearman correlation coefficient was -0.23 and -0.34, respectively).

Conclusions: RNFL loss and secondary optical atrophy are severe complications that may affect the visual acuity in patients with Wolfram syndrome. Retinal changes in these patients may be quantified and can be observed using OCT. (Turk J Ophthalmol 2014; 44: 212-5)

Key Words: Diabetes mellitus, macular thickness, optic atrophy, Wolfram syndrome, visual loss

Özet

Amaç: Wolfram sendromlu hastaların optik koherans tomografi bulgularını bildirmek.

Gereç ve Yöntem: Çalışmaya Wolfram sendromu kriterlerinin tamamını taşıyan dört hastamız dahil edildi. Optik koherans tomografi (OKT), tüm hastalarda Stratus OCT (OCT-3, Carl Zeiss Meditec, Inc. Almanya) ile yapıldı. Retina sinir lifi tabakası (RSLT) ve maküla kalınlıklarını ölçmek için sırasıyla hızlı RSLT ve hızlı maküla kalınlığı protokolleri kullanıldı. Cup-disk oranını belirlemek için hızlı optik disk protokolü kullanıldı. Tüm hastalara VEP yapıldı (Retimax, CSO Strumenti Oftalmici, Floransa, İtalya).

Bulgular: Ortalama yaşları 18,5±2,08 (16-21 yaş aralığında) olan dört hastanın (3 erkek ve 1 kadın) sekiz gözünde RSLT kalınlığı, maküla kalınlığı ve cup-disk oranları belirlendi. Ortalama RSLT kalınlığı 42,2±5,6 µm (34,1-49,5 µm aralığında) iken, ortalama maküla kalınlığı ve cup-disk oranları sırasıyla 145±15 µm (125-160 µm aralığında) ve 0,79±0,07 (0,7-0,92 aralığında) olarak bulundu. VEP latansları ile maküla kalınlığı ve RSLT kalınlığının orta derecede negatif korelasyon gösterdiği görüldü (Spearman korelasyon katsayısı sırasıyla -0,23 ve -0,34 idi).

Sonuç: Retina sinir lifi tabakası kaybı ve ikincil optik atrofi, Wolfram sendromlu hastalarda görme keskinliğini etkileyebilecek ciddi komplikasyonlardır. Bu hastalardaki retinal değişiklikler OKT kullanılarak ölçülebilir ve gözlenebilir. (Turk J Ophthalmol 2014; 44: 212-5)

Anahtar Kelimeler: Diyabet mellitus, maküla kalınlığı, optik atrofi, Wolfram sendromu, görme kaybı

Address for Correspondence/Yazışma Adresi: Bengü Ekinci Köktekir MD, Selçuk University Faculty of Medicine, Department of Ophthalmology, Konya, Turkey
Gsm: +90 532 353 27 16 E-mail: benguekinci@hotmail.com **Received/Geliş Tarihi:** 12.06.2013 **Accepted/Kabul Tarihi:** 02.12.2013
This study has been presented as an e-poster in 16th Afro-Asian Congress of Ophthalmology, Istanbul, Turkey, 2012

Introduction

Wolfram syndrome (WS), also known as DIDMOAD syndrome, is a neurodegenerative disorder with associations to diabetes insipidus (DI), diabetes mellitus (DM), optic atrophy (OA), and sensorineural deafness.[1,2] Among these associations, patients usually present with early-onset DM (insulin-dependent type) followed by OA in the first decade, while DI and sensorineural deafness are usually presented in the second decade.[3] Von Graffe first described the association of DM and OA in 1858, while in 1938, Wolfram suggested that this association is part of the syndrome.[4,5] WS has been revealed as a rare autosomal recessive disease that usually presents in consanguineous families.[6] A gene for WS (WFS1) was mapped on chromosome 4p.[7]

Although OA is an important diagnostic feature of WS, the knowledge about the features of OA in this syndrome is limited. Optical coherence tomography (OCT) findings have not been discussed previously in the literature. The aim of this study was to document the OCT findings in patients with WS, which might be taken into account in the follow-up of these patients.

Materials and Methods

This study adhered to the tenets of the Declaration of Helsinki, and the study protocol was approved by the local ethics committee. All patients gave their informed consent to participate in the study.

The study recruited eight eyes of four patients who were diagnosed with WS. All patients underwent complete ophthalmic examination in addition to retinal nerve fiber thickness measurement, macular thickness measurement, and measurement of cup-to-disc ratios optic disc by OCT (Stratus OCT-3, Carl Zeiss Meditec, Inc. Germany).

Retinal nerve fiber layer (RNFL) thickness was measured by the fast RNFL protocol and macular thickness was measured by the fast macular thickness protocol. The cup-to-disc ratios of the optic nerve were obtained by the fast optic disc protocol through optical coherence tomography (OCT).

All patients underwent electrophysiological evaluation with visual evoked potentials (VEP) (Retimax, CSO Strumenti Oftalmici, Florence, Italy).

The correlation of the RNFL thickness to macular thickness and correlation of RNFL or macular thickness to VEP latency were evaluated for Spearman rank correlation using SPSS 16.0.

Results

The mean age of the four patients (3 female and 1 male) was 18.5±2.08 years (range 16-21 years). Three of the four patients were siblings (2 sisters and 1 brother). All patients had all the components of DIDMOAD disease.

The mean visual acuity was 0.60±0.60 logMAR (range 1.00 to 0.18 logMAR). The mean intraocular pressure, which was measured by the Goldmann applanation tonometer, was 15±2.3 mmHg (range 11 to 18 mmHg). Anterior segment evaluation of the patients revealed no pathology.

All patients had OA without diabetic retinopathy, which was documented by fundus photography (Figure 1a). RNFL and macular thicknesses and cup-to-disc ratios were evaluated by Stratus OCT, as shown in Figure 1b, 1c and 1d.

The mean RNFL thickness was measured as 42.2±5.6 µm (range 34.1-49.5 µm), while mean the macular thickness and cup-to-disc ratios were 145±15 µm (range 125-160 µm) and 0.79±0.07 (range 0.7-0.92), respectively (Table 1).

Macular thickness was found to be reduced, but decreases in the RNFL thickness and macular thickness of the patients did not correlate well (Spearman correlation coefficient = -0.400), while decrease in RNFL thickness and cup-to-disc ratios were moderately correlated (Spearman correlation coefficient=0.632).

The mean VEP latency (P-100) was measured as 63.9±17.2 (range 50.9 to 87.3) ms. Both the macular thicknesses and RNFL thicknesses were moderately negatively correlated with P-100 latencies (Spearman correlation coefficient= -0.23 and -0.34).

Discussion

Wolfram syndrome is a neurodegenerative disease that is usually manifested by DM and OA in the first decade of life.[1,2] Defined as an autosomal recessive disease, this disorder is more frequently observed in consanguineous families.

Table 1. Features of the patients with DIDMOAD syndrome

Patients	Mean±SD	Range
Age (years)	18.5±2.08	16-21
RNFL (µm)	42.2±5.6	34.1- 49.5
Macular thickness (µm)	145±15	125-160
C/d ratio	0.79±0.07	0.7-0.92

RNFL: Retinal nerve fiber thickness, C/d ratio: cup-to-disc ratio

Figure 1a. Bilateral optic atrophy as a feature of DIDMOAD syndrome in a patient

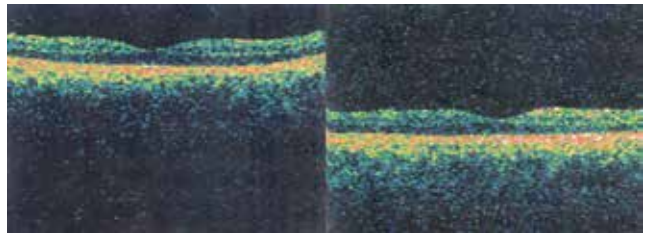


Figure 1b. Bilateral macular thickness in the same patient

DI and sensorineural deafness, which usually present in the second decade, are the other associations of the syndrome. The prevalence, severity, and the age of onset of these manifestations are variable in some studies.[8]

Diagnosis of the OA in WS was based on the morphological findings of the optic disc through fundus photography, which were supported by electrophysiological testing reported in the literature. Regarding electrophysiological testing, Barret et al. and Simsek et al.[1,9] reported abnormality in the VEP of WS patients, whereas electroretinography (ERG) or electrooculography revealed normal values in most studies.

No quantified data was reported regarding the RNFL thickness in WS patients. Langwinska et al.[10] performed OCT; however, no information about the thickness of RNFL or macula was given. Moreover, the patients in the latter study showed no evidence of diabetic retinopathy with healthy maculas.

The macular region has already been evaluated, but the focus of most previous studies has been on whether diabetic retinopathy was present or not.[10] Macular thickness was not previously discussed in patients with WS. In our study, we give quantified data revealing decreases in both RNFL thickness and macular thickness.

Furthermore, optic disc sizes were not included in previous studies on WS. Although OA was emphasized as a diagnostic criterion, no study has reported cup-to-disc ratios or the correlation of cup-to-disc ratios to the RNFL thickness in these patients.

In our study, the ages of the patients were 16,18,19, and 21 years. All patients had fulfilled the criteria for the disease. OA and DM were the presenting features in our cases.

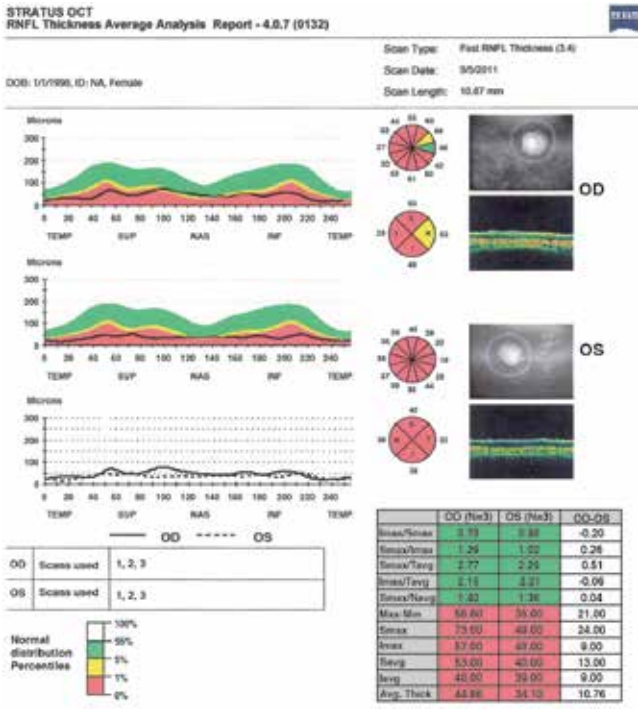
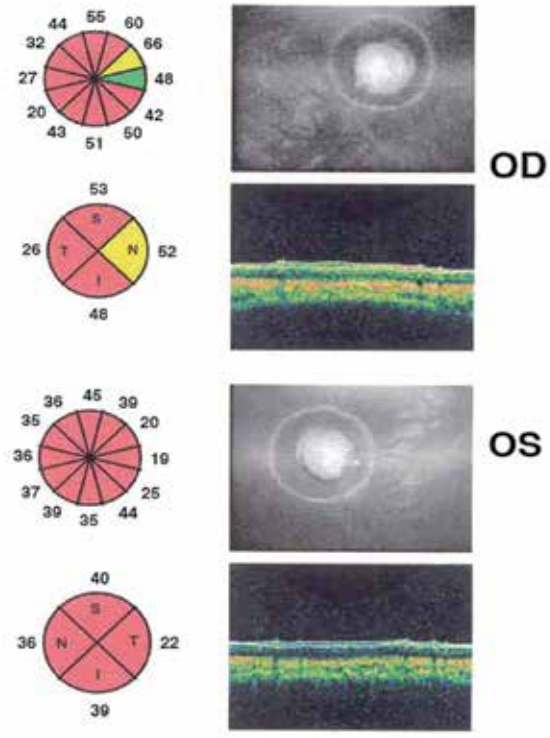


Figure 1c. Retinal nerve fiber measurement of the same patient

Average RNFL thickness in Caucasians was reported as 98.1±10.9 μm.[10] We evaluated the thickness of RNFL and macula by OCT in our patients. All had decreased RNFL thickness with a mean value of 42.2±5.6 μm. Moreover, because of neurodegeneration, mean macular thickness was also low with a mean value of 145±15 μm. The decrease in the RNFL did not correlate well to the decrease in macula thickness. This finding showed that the OA is the main symptom of the disease, and it is usually detected in early decades. However, with the decrease of the RNFL, macular thickness may also decrease and should be evaluated and followed up quantitatively in later decades of the disease.

The neurodegeneration process in WS is progressive.[11] With fundoscopic evaluation, early findings might be observed with



	OD (N=3)	OS (N=3)	OD-OS
Imax/Smax	0.78	0.98	-0.20
Smax/Imax	1.29	1.02	0.26
Smax/Tavg	2.77	2.26	0.51
Imax/Tavg	2.15	2.21	-0.06
Smax/Navg	1.40	1.36	0.04
Max-Min	56.00	35.00	21.00
Smax	73.00	49.00	24.00
Imax	57.00	48.00	9.00
Savg	53.00	40.00	13.00
Iavg	48.00	39.00	9.00
Avg. Thick	44.86	34.10	10.76

Figure 1d. Optic disc morphology of the same patient

pigmentary maculopathy.[12] Optic atrophy usually appears after the diagnosis of DM. In the second decade, most cases result in OA. Evaluation of the OCT of the nerve fiber layer might be helpful in the follow-up of these patients. Macular thickness also decreases with retinal nerve fiber atrophy. However, the decrease of the former may not correlate with the severity of OA. Nevertheless, we believe that macular thickness is an important follow-up parameter as both macular thickness and RNFL thickness show negative correlation with VEP latency.

This is the first study reporting OCT findings in WS. Macular thickness reduction and retinal nerve fiber atrophy are observed. However, the decrease in the former may not correlate with the severity of OA. Retinal changes may be quantified and observed using OCT. Future studies should investigate the decrease in the macular thickness in these patients, using a larger number of patients and a longer duration of follow-up.

References

1. Barret TG, Bunday SF. Wolfram (DIDMOAD) syndrome. J Med Genet. 1997;34:838-41.
2. Batıoğlu F, Şimşek T, Şimşek E, Atmaca L. Wolfram sendromu. MN-Oftalmoloji Dergisi. 1998;5:205-8.
3. Bekir NA, Gungor K, Guran S. A DIDMOAD syndrome family with juvenile glaucoma and myopia findings. Acta Ophthalmol Scand. 2000;78:480-2.
4. Von Graffe A. Uber die mit diabetes vorkommenden shstorunger. Arch Ophthalmol. 1858;4:230-4.
5. Wolfram DJ. Diabetes mellitus and simple optic atrophy among siblings. A report of four cases. Proc Mayo Clin. 1938;13:715-8.
6. Nagi A. Diabetes insipitus, diabetes mellitus, optic atrophy and deafness. A clinical and genetic study. Postgrad Med J. 1978;54:815-7.
7. Inoue H, Tanizawa Y, Wasson J, et al. A gene encoding a transmembrane protein is mutated in patients with diabetes mellitus and optic atrophy (Wolfram syndrome). Nat Genet. 1998;20:143-8.
8. Najjar SS, Saikaly MG, Zaytoun GM, Abdelnoor A. Association of diabetes insipidus, diabetes mellitus, optic atrophy and deafness. The Wolfram or DIDMOAD syndrome. Arch Dis Child. 1985;60:823-8.
9. Simsek E, Simsek T, Tekgul S, Hosal S, Seyrantepe V, Aktan G. Wolfram syndrome: a multi-disciplinary clinical study in nine Turkish patients and review of the literature. Acta Paediatr. 2003;92:55-61.
10. Budenz DL, Anderson DR, Varma R, et al. Determinants of normal retinal nerve fiber layer thickness measured by Stratus OCT. Ophthalmology. 2007;114:1046-52.
11. Langwinska-Wosko E, Broniek-Kowalik K, Szulborski K. A clinical case study of a Wolfram syndrome-affected family: pattern visual evoked potentials and electroretinography analysis. Doc Ophthalmol. 2012;124:133-41.
12. Bucca BC, Klingensmith G, Bennett JL. Wolfram syndrome: a rare optic neuropathy in youth with type 1 diabetes. Optom Vis Sci. 2011;88:1383-90.