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Research Article

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Retinal Nerve Fiber Layer Thickness Analysis with Optical Coherence Tomography in Wolfram Syndrome

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Abstract

Purpose: To evaluate the peripapillary retinal nerve fiber layer (RNFL) in Wolfram's Syndrome (WS) using optical coherence tomography (OCT).

Methods: The peripapillary RNFL of eighteen eyes of nine patients with the clinical diagnosis of WS were measured using Stratus OCT. The RNFL was determined consecutively three times.

Results: The mean RNFL thickness is inferior to the 99% normal limit given by the instrument´s normative database in all patients. The superior and inferior quadrants were beneath the 99% normal limit in every patient. The nasal quadrant was at the level 1-5% in 37.0% of the measurements and at the level 5-95% in 3.7%. The temporal quadrant was at the level 1-5% in 13.0% of the measurements and at the level 5-95% in 5.5%.

Conclusion: In our series, there is an overall decrease of the RNFL thickness. The nasal and temporal quadrants were the least affected. This is the first time that this characteristic of the disease is described. Understanding the pattern of RNFL damage can be important clinically to differentiate WS from other causes of hereditary optic atrophy that have distinct patterns of RNFL loss. This provides further insight in the lesion pattern and pathophysiology of the disease.

Keywords

Wolfram syndrome; DIDMOAD; Retinal nerve fiber layer; Stratus OCT; Optic nerve atrophy

Background

Wolfram Syndrome (WS) is typically associated with diabetes insipidus, diabetes mellitus, optic atrophy (OA) and deafness [1,2], that's why this is also referred to as DIDMOAD. The best available criteria for diagnosis are early onset diabetes mellitus and progressive optic atrophy, which gives a positive predictive value for WS of 83% and a negative predictive value of 1% [3], but positive genetic testing may have a role. Other frequent features are neurological and genitourinary disorders [4-6]. These patients have a less severe and slower progression of diabetic complications than in classic type 1 diabetes [7]. The prevalence of this rare progressive neurodegenerative disorder was estimated at 1 of 770 000 in the United Kingdom in 1995 [3], 1 of 100 000 in the United States in 1977 [8] and 1 of 500000 in Germany in 2011 [9].

The majority of patients with WS carry loss-of-function mutations in the WFS1 gene, mapped to chromosome 4p16.1 [10]. There is a second autosomal recessive form of WS (WFS2), mapped to 4q22-q24 [11]. Defects in mitochondrial DNA were reported in sporadic cases [12]. Molecular analysis is an evolving field, with constant discovery of novel mutations, the possibility of use in the refinement of clinical diagnostic criteria and correlations with phenotype [9,13].

WS produces severe optic atrophy and retinal nerve fiber layer thickness (RNFL) abnormalities. The aim of this study was to evaluate the RNFL by OCT in 9 cases of Wolfram Syndrome. OCT evaluation can be useful in the differential diagnosis of other causes of hereditary optic atrophy. WS, despite being rare, is a well known disease but the RNFL damage pattern assessed by OCT has not been described so far in WS.

Methods

Nine consecutive patients of six different pedigrees, diagnosed with WS were recruited from the Ophthalmology Department of São João Hospital, in Oporto, Portugal. The diagnosis of WS was based on the presence of insulin-dependent diabetes mellitus and progressive OA, not explained by any other reason. A positive family history contributed to the diagnosis. OA was confirmed by the presence of an optic disc pallor with regular and well-demarcated borders after other causes were excluded, particularly Leber´s hereditary optic atrophy, thiamine-responsive anemia and compressive brain lesions. To exclude other causes of optic atrophy every patient performed analytical studies and brain Magnetic Resonance Imaging (MRI). WFS1 mutation was investigated in 5 of the pedigrees. Genetic study was performed in one patient of each pedigree.

Informed consent was obtained from each patient, according to Declaration of Helsinki. All patients performed a complete ophthalmologic examination (best corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure measurement, indirect ophthalmoscopy and optic nerve head photography) and the OCT protocol.

Optical coherence tomography protocol

The OCT measurements were obtained with the Optical Coherence Tomographer (Stratus OCT, Version 4.0.2, Carl Zeiss Meditec, Dublin, CA) after pharmacologic pupillary dilation. The fast RNFL (3.4-mm circle protocol) scan acquisition protocol was used for RNFL analysis. This protocol consists of 256 individual A-scans in a circular path with a 3.46 mm diameter centered on the optic disc. The machine scans the area 3 consecutive times and gives the average thickness value of the 3 scans for each clock-hour, for 4 quadrants (superior, temporal, inferior and nasal) as well as an overall average thickness value for the entire circumference. An expert operator repeated the measurements, until 3 measurements judged to be of good quality were achieved for each eye. To increase reliability, all

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measurements were analyzed, because despite the good quality of the scans considered, there was some intratest variability.

We evaluated the mean RNFL thickness, the 12 clock-hour thickness and the 4-quadrant thickness. These values were compared against the instrument´s normative database of age-matched controls to derive percentile values. The 4 percentile values provided by the machine's software are color-coded and correspond to the following values: 95-100% (white), 5-95% (green), 1-5% (yellow) and <1% (red). We analyzed the results of the 3 measurements of 18 eyes. The mean values of global average thickness, quadrant and hour thickness were calculated.

The OCT does not provide a normative database for subjects less than 18 years, so for the four patients under this age we applied the database for the age of 18 years.

Results

Patients

We studied 9 Caucasian patients with WS belonging to 6 families, with 2 couples of brother and sister and one couple of sisters. In the remaining 3 families only one child was affected with WS. Our sample comprised 2 male and 7 female patients. Their ages ranged from 11 to 38 years. Mean duration of known disease was 11.3 years (± 8.7) ranging from 1 to 29 years.

Genetic confirmation of the disease was obtained in five families for a total of seven patients. There was parental consanguinity history in two families. Four families were homozygous for mutation of exon 8 of WFS1 gene. One patient was heterozygous for the mutation, although clinically affected.

Diabetes mellitus was the first manifestation in all except one patient. Mean age of diagnosis was 8.7 years (range 3-22 years). The mean age of diagnosis of OA was 11.1 years (range 8-20 years). The best-corrected visual acuity ranged from counting fingers to 20/50. There was worse visual acuity in patients with longer time of disease. Intraocular pressure was normal in every patient. None had diabetic retinopathy.

Five patients had hearing loss. Diabetes insipidus was present in two patients. Some urological and neurological abnormalities were detected (recurrent urinary tract infections, hydronephrosis, hydroureter, depression, seizures and cognitive deficit).

RNFL thickness

The mean global RNFL thickness was abnormal in every patient, with 100% of measurements being below the 1% level of normal distribution percentile. The mean RNFL thickness was 50.18 ± 8.21 μm (range from 33.52 to 68.01 μm).

In the analysis by quadrants, inferior and superior quadrants were always abnormal, with all measurements below the 1% percentile. The measurements of the temporal quadrant were below the 1% percentile in 81.5% (n=44) and the measurements of the nasal quadrant were below the 1% percentile in 59.3% (n=32) (Table 1).

The most affected clock-hours corresponded to the superior (hours 12, 1 and 2) and inferior quadrants (hours 6, 7 and 8), plus hour 11, in the temporal superior sector (Figure 1). The single most affected hours are 11 and 12 hours, with 96.3% and 98.1% of measurements below the 1% percentile, respectively, and none in the 5-95%. There was some intratest variability in the scans, but OCT RNFL thickness profile was symmetrical between both eyes in all patients (Table 2).

The relation of thickness profile with genotype, age and gender of the subjects is listed in Table 3.

Conclusions

OCT is a noncontact, noninvasive imaging technique and is reproducible in the measurement of peripapillary RNFL thickness [14]. It is used in patients with glaucoma and was also useful to study patients with hereditary optic atrophies [14,15]. In patients with dominant optic atrophy, the thickness at the temporal-most clock hour and the temporal quadrant were abnormal, while in glaucoma this quadrant is usually spared until latter stages of the disease [15]. In male patients with Leber´s hereditary optic neuropathy, the RNFL is thickened in the early stages of the disease and severely thinned in atrophic phase. The temporal fibers (papillomacular bundle) are the first and most severely affected; the nasal fibers seem to be partially spared in the late stage of disease [16].

Our results of RNFL thickness analysis reflect the severity of the optic atrophy in WS. The mean average thickness was highly affected in every patient and all quadrants were affected, specially the inferior and superior quadrants. This great decrease of RNFL thickness can demonstrate the severity of the disease. Interestingly, in our series, the nasal quadrant seemed to be the least affected, followed by the temporal quadrant.

Table 1: Average RNFL thickness and quadrant RNFL thickness analysis. SD – Standard deviation.

	Average thickness	Quadrant analysis			
		Superior	Nasal	Inferior	Temporal
Mean ± SD (μm)	50.18 (± 8.21)	57.39 (± 16.68)	45.02 (± 7.89)	59.69 (± 11.54)	38.31 (± 7.31)
Percentiles Distribution					
<1%	54 (100%)	54 (100%)	32 (59.3%)	54 (100%)	44 (81.5%)
1-5%	0	0	20 (37.0%)	0	7 (13.0%)
5-95%	0	0	2 (3.7%)	0	3 (5.5%)
Intratest variability Mean ± SD (μm)	4.61 (± 2.44)	7.22 (± 4.31)	7.61 (± 4.91)	8.44 (± 4.20)	10.22 (± 6.58)
Difference between eyes Mean ± SD (μm)	2.54 (± 1.66)	5.00 (± 2.41)	5.67 (± 2.92)	6.19 (± 3.45)	4.48 (± 2.86)

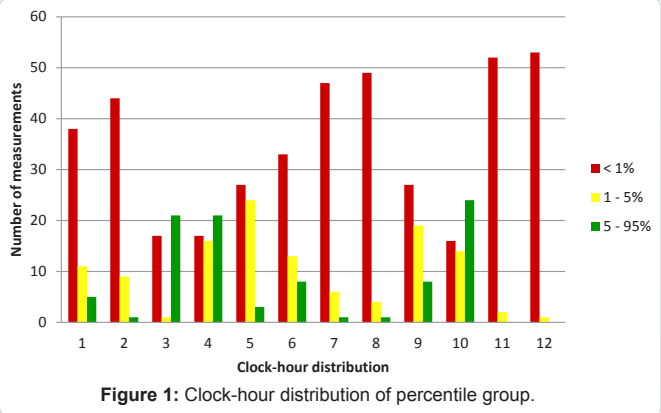

Figure 1: Clock-hour distribution of percentile group.

The papillomacular bundle fibers are the first group of ganglion cells affected in dominant optic atrophy and Leber's hereditary neuropathy [16,17]. Correspondingly, the temporal quadrant is the one that appears earlier and more severely affected in the RNFL analysis with OCT in these two neuropathies [15,16]. In patients with multiple sclerosis a RNFL reduction across all 4 quadrants has been described with the superimposed inflammatory attacks to the optic nerve causing additional axonal damage with a temporal preponderance [18]. To our knowledge, the optic nerve fiber destruction pattern has not been described in WS. Unlike Leber's hereditary neuropathy and dominant optic atrophy, our results indicate that the nasal and temporal quadrants are more preserved, suggesting a different injury pattern and distinct pathophysiological mechanisms. Note that some of the measurements listed in nasal and temporal quadrants fit in normal range but it correspond to disparate values over the remaining two measurements of the same eye.

This study showed that the WS lesions are symmetrical in location and severity. These findings differentiate this neuropathy from glaucoma, which is the most common optic neuropathy [19,20]. However, the symmetrical optic atrophy can also be found in other hereditary optic neuropathies, particularly in dominant optic atrophy and atrophic Leber's hereditary optic neuropathy [15,16].

One limitation of our study is that we used the normative database of 18 years old for children under this age. However, El-Dairi and colleagues described that measurements of RNFL thickness were not dependent on age in population of children younger than 18 years old [21]. Published studies of RNFL thickness in adults do not demonstrate much reduction of the average RNFL thickness until 40 to 60 years of age [22,23]. But as RNFL thickness normally decreases with age, when we compare children under 18 to patients with 18 years old, we could eventually introduce an underestimation of the

Table 2: Clock-hour distribution and corresponding quadrant.

	Clock-hour analysis											
Corresponding quadrant	**Superior**			**Nasal**			**Inferior**			**Temporal**		
	12	1	2	3	4	5	6	7	8	9	10	11
Mean ± SD (µm)	53.37 ± 16.67	60.93 ± 22.18	57.96 ± 16.30	52.26 ± 12.31	40.76 ± 9.49	42.33 ± 7.47	57.67 ± 12.75	63.50 ± 15.83	58.33 ± 14.66	41.46 ± 9.22	38.31 ± 9.84	35.35 ± 7.84
Percentiles Distribution (%)												
<1%	53 (98.2)	38 (70.4)	44 (81.5)	31 (57.4)	17 (31.5)	27 (50.0)	33 (61.1)	47 (87.0)	49 (90.7)	27 (50.0)	16 (29.7)	52 (96.3)
1-5%	1 (1.8)	11 (20.4)	9 (16. 7)	20 (37.0)	16 (29.6)	24 (44.4)	13 (24.1)	6 (11.1)	4 (7.4)	19 (35.2)	14 (25.9)	2 (3.7)
5-95%	0 (0.0)	5 (9.2)	1 (1.8)	3 (5.6)	21 (38.9)	3 (5.6)	8 (14.8)	1 (1.9)	1 (1.9)	8 (14.8)	24 (44.4)	0 (0.0)
Intratest variability Mean ± SD (µm)	10.19 ± 5.43	9.89 ± 5.47	11.67 ± 6.41	10.56 ± 5.84	8.28 ± 4.65	10.89 ± 5.36	13.44 ± 7.11	9.39 ± 6.50	9.56 ± 6.13	13.39 ± 8.52	13.94 ± 9.50	8.89 ± 4.71

Table 3: RNFL thickness, gender, age and genotype by subject. Patient 1 and 2, 3 and 4, 7 and 8 are couples of brothers and sisters. Patient 5 is heterozygous for the mutation, all other homozygous. Molecular analysis for patients 7 and 8 was not performed.

Patient	Average thickness (Mean µm)	Superior Quadrant (Mean µm)	Nasal Quadrant (Mean µm)	Inferior Quadrant (Mean µm)	Temporal Quadrant (Mean µm)	Gender	Age (years)	Genotype
1	44.26	45.50	39.33	52.17	40.33	♀	11	c. 2141_2164dup
2	39.08	33.67	41.83	46.17	34.67	♂	18	c. 2141_2164dup
3	65.74	87	56.33	77.50	42.00	♀	14	c. 2146G>A
4	59.09	71.67	55.83	69.50	39.00	♂	10	c. 2146G>A
5	45.79	49.17	41	59.83	33.17	♀	31	c. 94C>A
6	46.59	42.33	42.00	52.17	47.50	♀	12	c. 2164_2165dup24
7	50.10	58.67	42.83	66.33	32.50	♀	32	-
8	47.35	57.17	44.17	48.00	39.83	♀	19	-
9	53.56	71.33	41.83	65.50	35.83	♀	38	c. 2206G>A

disease, probably not affecting the pattern of the lesion, which was our main outcome.

Another limitation may be the difficulty in capturing images with Stratus OCT in visually impaired people, which is reflected in intratest variability, so we used the three good quality scans obtained for each eye.

We presented a small case series, making it difficult to draw definitive conclusions. Future research in the field should seek to establish correlations between the pattern of injury, visual acuity, disease progression and genotype-phenotype. These findings can have clinical importance, as they may help in the differential diagnosis of optic atrophy and also in diabetics in pediatric age with vision loss of unexplained origin.

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