Published in final edited form as:

J AAPOS. 2014 October ; 18(5): 461–465.e1. doi:10.1016/j.jaapos.2014.07.162.

Ophthalmologic correlates of disease severity in children and adolescents with Wolfram syndrome

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Abstract

Purpose—To describe an ophthalmic phenotype in children at relatively early stages of Wolfram syndrome.

Methods—Quantitative ophthalmic testing of visual acuity, color vision, automated visual field sensitivity, optic nerve pallor and cupping, and retinal nerve fiber layer (RNFL) thickness assessed by optical coherence tomography (OCT) was performed in 18 subjects 5–25 years of age. Subjects were also examined for presence or absence of afferent pupillary defects, cataracts, nystagmus, and strabismus.

Results—Subnormal visual acuity was detected in 89% of subjects, color vision deficits in 94%, visual field defects in 100%, optic disk pallor in 94%, abnormally large optic nerve cup:disk ratio in 33%, thinned RNFL in 100%, afferent pupillary defects in 61%, cataracts in 22%, nystagmus in 39%, and strabismus in 39% of subjects. RNFL thinning ($P < 0.001$), afferent pupillary defects (P

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= 0.01), strabismus ($P = 0.04$), and nystagmus ($P = 0.04$) were associated with more severe disease using the Wolfram United Rating Scale.

Conclusions—Children and adolescents with Wolfram syndrome have multiple ophthalmic markers that correlate with overall disease severity. RNFL thickness measured by OCT may be the most reliable early marker.

Wolfram syndrome, also known as DIDMOAD, was first described in 1938 by Wolfram and Wagener.¹ It is a rare, autosomal recessive syndrome that consists of diabetes insipidus (DI), diabetes mellitus (DM), optic nerve atrophy (OA), and sensorineural deafness (D).^{2–5} Other reported manifestations include hydronephrosis, dilated urinary bladder, anosmia, vertigo, color blindness, cerebellar dysfunction, and delayed puberty.^{3,4,6} Wolfram syndrome results in early mortality in the third or fourth decade of life and is caused by mutations the *WFS1* or *WFS2* genes (OMIM 222300).^{7–9} *WFS1* encodes a transmembrane protein localized to the endoplasmic reticulum (ER) named wolframin, which plays a crucial role in maintaining ER homeostasis, including calcium regulation, redox regulation, ER stress signaling, and cell death. *WFS2* (aka *CISD2*) encodes endoplasmic reticulum intermembrane small protein (ERIS), which plays a role in ER calcium homeostasis. *WFS1* or *WFS2* expression preferentially damages retinal ganglion cells and hypothalamic and brainstem neurons, but it is not clear how or why.^{7–10}

Ophthalmologic manifestations in Wolfram syndrome include optic nerve atrophy, color vision defects, cataracts (congenital and acquired), abnormal pupillary light reflexes, nystagmus, and visual fields defects.^{2,5} Optical coherence tomography (OCT) of the retina has been reported in only a small number of studies.^{5,11} Quantitative ophthalmologic phenotyping of subjects with Wolfram syndrome, particularly at early stages of the disease, is lacking. The purpose of this study was to report the quantitative testing of 18 subjects with Wolfram syndrome varying in severity of disease and as young as 5 years of age to determine which ophthalmic findings were altered in the early stages of Wolfram syndrome and which correlate with overall disease severity for use as biomarkers in future clinical trials.

Subjects and Methods

The study was approved by the Institutional Review Board of Washington University in St. Louis. A total of 18 participants were recruited through the Washington University Wolfram Syndrome Registry website (<http://wolframsyndrome.dom.wustl.edu/medical-research/Wolfram-Syndrome-Home.aspx>) to participate in standardized evaluations across domains known to be associated with Wolfram syndrome at the annual Washington University Wolfram Syndrome Research Clinic. Minimal diagnostic criteria to enroll in the registry were the diagnosis of insulin-dependent diabetes mellitus and optic atrophy by a physician before 18 years of age or genetic confirmation of a *WFS1* mutation. Informed consent from parents for minor participants or from adult participants was obtained prior to study enrollment.

Ophthalmic Measures

A comprehensive ophthalmic examination was performed by one of the authors (JH or LT). Examination included the following tests: best-corrected visual acuity by Snellen optotype, automated visual fields (Zeiss Humphrey Visual Field Analyzer II; Carl Zeiss Meditec Inc, Dublin, CA), cycloplegic refraction, ocular motility, binocular vision, color vision (Hardy-Rand-Rittler, performed under a MacBeth Easel Lamp), pupillary light reflexes, slit-lamp biomicroscopic evaluation, fundus examination, and OCT (Zeiss Cirrus HD-OCT, 4000-5444 version 4.5.1.11; Carl Zeiss Meditec Inc, Dublin, CA) of the optic nerves and retina.

Visual field defects were quantified as mean deviation (MD) and pattern standard deviation (PSD).¹² Automated threshold visual fields are used for the detection of small stationary spots of light displayed for 200 msec at unpredictable locations throughout the central 30° of vision. MD is a measure of global visual threshold. Subjects who can see dimmer spots of light than others of similar age have higher MD, whereas subjects who require brighter spots have lower MD. Normal MD values range typically from 0 decibel (dB) to -2 dB. PSD measures the uniformity (or irregularity) of sensitivity across the visual field, that is, the absence of focal “blind spots.” PSD is the difference between the threshold value for each point and the average visual field sensitivity (MD). Subjects who have age-normal sensitivity at each point—no blind regions—have a PSD of 0, whereas those who have blind regions will have high PSDs.

Optic nerve cup:disk ratio was measured from clinical examination, fundus photographic images, and OCT. Optic nerve pallor was graded on a scale of 0–4, with grade 0 indicating no pallor and 4 indicating stark pallor.

Retinal nerve fiber layer (RNFL) thickness was measured using OCT images. Measurements were obtained for each eye but are reported for clarity in the results as averages between the two eyes.

Onset of visual impairment or diagnosis of optic neuropathy was established through review of outside medical records and parent history.

Wolfram Rating Scale

Overall severity of disease was measured using the Wolfram United Rating Scale (WURS), a psychometrically sound and validated rating scale that captures all major symptoms involved in Wolfram syndrome.⁷ Each major feature of Wolfram syndrome is rated for severity, and the scores are summed. This rating scale generates two main subscales: physical symptoms (possible range, 0–100) and behavioral symptoms (possible range, 0–55) as well as a total symptoms score (possible range, 0–155). The WURS has been shown to have high inter-rater reliability (ICCs > 0.93), moderate to high internal consistency reliability (Cronbach’s $\alpha = 0.78$ – 0.91), and good concurrent and predictive validity.¹³ A pediatric neurologist specializing in genetic neurodevelopmental conditions performed the WURS on all subjects. Subjects were examined also by a pediatric endocrinologist, an audiologist, and an otolaryngologist in addition to undergoing cognitive testing and brain MRI. These assessments have been reported in part in other publications.^{6,13–16}

Statistical Analyses

Descriptive statistics were performed to determine the baseline ophthalmic function of the study participants. Spearman correlations were performed to determine whether any of the ophthalmic findings that used continuous scales correlated with WURS severity. A repeated measures general linear model was used to examine differences across optic nerve quadrants of RNFL thickness. An independent samples *t* test was used to assess categorical ophthalmic measures and WURS severity. A *P* value of <0.05 was considered significant.

Results

Clinical findings for the 18 patients are listed in Table 1. Mean patient age was 14.2 years (range, 5–25 years); half of the patients were 12 years of age. Average age of detection of visual impairment by an outside examiner before enrollment in the study was 9.2 years. Impaired vision was diagnosed when children were examined by an eye care provider after experiencing difficulty with visual tasks in elementary school.

Visual Acuity and Refractive Error

Best-corrected visual acuity was 20/40 or worse in 16 subjects (89%). Mean best-corrected visual acuity was 20/60 (logMAR, 0.33), with a range of 20/20 to 20/2000 (logMAR, 1.0–0.01). Refractive error ranged from -8.75 D to $+3.5$ D spherical equivalent, with a mean of -0.9 D.

Color Vision

Color vision deficits were detected in 17 subjects (94%); severe dyschromatopsia was detected in 10 (56%). These subjects were unable to identify any of the color plates (a score of 0/52 plates; 26 each eye tested monocularly). Of the remaining patients, 4 (22%) had moderate dyschromatopsia (score, 8–16 correct of 52); 3 (17%), mild dyschromatopsia (score, 32–39 correct of 52). Red-green perception deficits tended to be worse than blue-yellow. One patient (6%) demonstrated normal color vision sensitivity (51 correct of 52).

Visual Field

Visual field examination by automated perimetry (HFA II 30-2) was performed in 12 subjects who were capable of performing the test. Of the 6 subjects who were untestable, 2 were too young to perform the test reliably and 4 had vision too poor to complete the task. All of the 12 testable subjects demonstrated visual field defects (Table 1). The defects were overall elevated thresholds, measured as negative MD values, and focal defects, measured as nonzero PSD scores (Table 1). Five subjects (42%) had severe field loss, evident as inferior altitudinal, double arcuate, or ring scotomas; 2 (16%) had moderate depression with superior arcuate defects; and 5 (42%) had mild overall field depression.

Optic Nerve Pallor and Cupping

Optic nerve pallor (atrophy) was detected in 17 subjects (94%) by indirect, direct, and slit-lamp biomicroscopic ophthalmoscopy (using a 90 D loupe). Of the 18 subjects, 17 had substantial pallor ($\geq 2+$ pallor), and 1 had 1+ optic disk pallor. An abnormally large optic

nerve cup was detected in 6 subjects (33%), defined as >0.3 cup:disk diameter ratio (Table 1). No signs of vascular narrowing and/or diabetic retinopathy were detected.

Retinal Nerve Fiber Layer

All subjects (100%) had thinned retinal nerve fiber layers (RNFL) on OCT of the retina. RNFL thinning differed across quadrants, ranging from 1.5 to 4.5 standard deviations below normal (difference across quadrants $P < 0.001$). The topography of thinning (Figure 1), from most severe to least was: superior, inferior, temporal, and nasal quadrant. As shown in the scatterplot of Figure 2, average RNFL thickness correlated with the WURS Physical Scale, such that thinner RNFL was associated with worse physical symptoms ($r = -0.71$; $P = 0.001$).

Afferent Pupillary Defect

Eleven subjects (61%) had afferent pupillary defects, equivalent in both eyes, assessed as subnormal velocity and amplitude of direct light stimulation response (“sluggish”). Near target (convergence) pupillary responses were normal amplitude and velocity in each subject, verifying absence of an efferent (pupillomotor third cranial nerve or iridologic musculature) abnormality as a cause of the deficient response.

Lenticular Opacity (Cataract)

Cataracts were detected on slit-lamp biomicroscopic examination in 4 subjects (22%). The opacity subtype varied: posterior subcapsular, peripheral spokes, snowflake, cortical, and lamellar.

Ocular Motor

Nystagmus was observed in 7 subjects (39%), 6 of whom had horizontal conjugate jerk nystagmus when gaze was directed more than 15° from primary gaze (gaze-evoked nystagmus). One patient (6%) had rotary/torsional/see-saw nystagmus.

Strabismus was detected in 7 subjects (39%). Constant exotropia 12 was measured in 6; 1 subject had accommodative/refractive esotropia.

Wolfram Severity and Visual Pathology

Wolfram disease as measured by the Wolfram United Rating Scale (WURS) was more severe in patients who had an afferent pupillary defect ($P = 0.01$), strabismus ($P = 0.04$), or nystagmus ($P = 0.04$ [2-tailed independent samples t test]). The severity of RNFL thinning correlated with the overall severity of the patient’s disease (Spearman rank correlation $P < 0.001$; Figure 2). Table 2 shows the correlation and nonsignificance values for each of the other ophthalmic markers measured by a continuous scale, that is, logMAR visual acuity, color vision score, optic nerve pallor grade, cup:disk ratio, visual field MD, and visual field PSD. Increase in age was not correlated significantly with either decrease of visual acuity or decrease of RNFL thickness (Pearson correlation, $P = 0.45$ and 0.57 , resp.).

Discussion

Optic nerve atrophy and reduced visual acuity are key features of Wolfram syndrome in its early stages, with progressive deterioration and worsening quality of life.^{2,5,11,17–21} Comprehensive ophthalmologic phenotyping of patients across a range of Wolfram disease severity and ages has heretofore been lacking. In our Wolfram syndrome group we found a range of visual dysfunction, including reduced acuity, dyschromatopsia, afferent pupillary defects, visual field deficits, optic nerve pallor and cupping, thinned RNFL, cataracts, nystagmus, and strabismus. All of our patients had substantially thinned RNFLs, even those with no or mild visual symptoms. This indicates that either optic nerve degeneration occurs earlier than clinically noteworthy visual changes or that the retinal ganglion cell layer never develops fully in Wolfram syndrome. It is possible that both processes occur. Analogously, MRI in young, minimally affected patients in our study group revealed substantially subnormal brainstem volumes.^{14,22} Assessment of children who test positive for the *WFS* gene mutation combined with longitudinal follow-up will be critical for sorting out these possibilities.

Our results suggest that RNFL thickness measurements will be highly useful in gauging the progression of Wolfram syndrome. Patients with higher physical disease severity ratings on the WURS also had the thinnest RNFLs. RNFL thickness is a quantitative and objective measure unrelated to the patients' individual psychophysical performance capability. A limited number of previous studies have measured RNFL thickness in Wolfram syndrome, but they have utilized the Stratus OCT rather than the Cirrus HD-OCT,^{5,11} which employs a scanning beam, like the Stratus, but has the advantages of enhanced axial resolution and higher scanning speed.^{23,24} The Cirrus HD-OCT has an axial resolution of 2 μm and a scan speed of 27,000 scans per second, whereas the Stratus OCT has a minimal axial resolution of 10 μm and a scan speed of 400 scans per second. Though both machines capture a large number of scans, they may yield different RNFL results for the same subject.^{23,24}

Our results are in general agreement with the report of Mota and colleagues¹¹; the RNFL thinning in Wolfram patients appears to be most severe for the superior and inferior quadrants of the peripapillary nerve fiber layer. OCT measures in children with suspected Wolfram syndrome should therefore place special emphasis on thinning of the superior and inferior quadrants. It is possible, however, that thinning of the vertical RNFL quadrants, exceeding the thinning of the horizontal quadrants, is common to hereditary optic neuropathies rather than a signature peculiar to Wolfram syndrome. In adults with dominant optic atrophy (*OPA1* mutation), RNFL thinning is most severe vertically also (see Ito and colleagues,²⁵ Figure 4). OCT measurement has become common in pediatric ophthalmic practices and may be more useful than other visual function tests, particularly for multisite longitudinal and clinical trials of children with Wolfram syndrome.

Color vision and visual field sensitivity, although impaired in patients with Wolfram syndrome, can only be measured by psychophysical means that may not be as reproducible as OCT. Automated visual field testing requires significant cooperation and entails a relatively long testing time.²⁶ This is especially challenging in children with impaired vision, making it less useful for pediatric longitudinal studies. Of our 18 patients, 6 could

not complete the visual field testing. We were unable to establish a convincing relationship between color vision or visual field sensitivity and overall disease severity.

Wolfram syndrome is a rare disorder, with multiple ocular and systemic manifestations including low vision to legal blindness.^{2–4,6,17,21} Our study provides a detailed ophthalmic phenotype in patients at relatively early stages of the disease. We were able to identify abnormalities at the youngest age tested (5 years). No intervention is known currently to alter the progression or life expectancy in Wolfram syndrome patients. Careful mapping of the natural history of Wolfram syndrome across many domains will be useful for any future therapeutic intervention trials. Ophthalmologic measures such as the RNFL have promising biomarker characteristics in our cross-sectional analyses. We are conducting longitudinal assessment of our cohort in hopes of defining the natural history of the disease while identifying promising biomarkers for clinical trials.

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FIG 1.

Mean number of standard deviations below normal (compared to a normal pediatric population; z score) on retinal nerve fiber layer thickness measures for each retinal quadrant in Wolfram Syndrome participants.

FIG 2.

Correlation between estimated physical disease severity (WURS Physical Scale) and average retinal nerve fiber layer thickness measured using optical coherence tomography ($r_s = 0.71$; $P = 0.001$). Average retinal thickness in the pediatric population is 107.¹⁴

Table 1

Prevalence of ophthalmic findings and mean $\pm$ SD scores (for continuous measures) in the 18 patients with Wolfram syndrome

Study parameter	Mean $\pm$ SD	Range	Percentage patients affected
Age study examination, years	14.2 $\pm$ 5.5	(5.9 to 25.8)	—
Age detection impaired vision, years	9.2 $\pm$ 3.9	5.0 to 17.0	—
Visual Acuity, Snellen (normal, 20/20)	20/60	20/2000 to 20/20	89
Visual acuity, logMAR (normal, 1.00)	0.33 $\pm$ 0.25	0.01 to 1.00	94
Average RNFL thickness, μ m (normal, 107 $\pm$ 11.1 μ m)	56.2 $\pm$ 6.9	45 to 71	100
RNFL thickness z score (normal, 0)	-4.9 $\pm$ 0.7	-3.5 to -6.0	100
Visual field MD, dB (normal, 0 to -2)	-12.9 $\pm$ 6.2	-5.2 to 22.4	100
Visual Field PSD, dB (normal, 0)	7.2 $\pm$ 3.6	2.0 to 12.7	100
Color vision score (normal, 50-52)	13.2 $\pm$ 17.3	0 to 51.0	94
Optic nerve pallor (normal, 0)	2.4 $\pm$ 0.9	0 to 4	94
Optic nerve cup:disk ratio (normal, 0.4)	0.4 $\pm$ 0.2	0.2 to 0.8	33
Afferent pupillary defect	—	—	61
Nystagmus	—	—	39
Strabismus	—	—	39
Cataract	—	—	22

MD, mean deviation; PSD, pattern standard deviation; SD, standard deviation.

Table 2

Spearman correlations (r_s) or independent samples test (t) for WURS scores and ophthalmologic measures, both eyes combined^a

Parameters		WURS physical	WURS behavior	WURS total
RNFL thickness (n = 18)	r_s	-0.71	-0.00	-0.34
	P value	0.001	0.98	0.18
Cup:disk ratio (n = 18)	r_s	0.20	0.44	0.27
	P value	0.43	0.07	0.27
Optic nerve pallor (n = 18)	r_s	0.43	0.39	0.40
	P value	0.07	0.10	0.09
Visual acuity, log MAR (n = 18)	r_s	0.21	0.30	0.32
	P value	0.40	0.22	0.20
Color vision score (n = 18)	r_s	-0.27	-0.28	-0.28
	P value	0.29	0.27	0.23
Humphrey VF, MD (n = 12)	r_s	-0.24	-0.34	-0.33
	P value	0.50	0.34	0.35
Humphrey VF, PSD (n = 12)	r_s	0.35	0.24	0.34
	P value	0.33	0.50	0.33
Afferent pupillary defect (n = 18)	t	-2.33	-2.58	-2.95
	P value	0.04	0.02	0.01
Strabismus (n = 18)	t	-1.46	-2.34	-2.18
	P value	0.16	0.03	0.04
Nystagmus (n = 18)	t	-1.66	-2.22	-2.25
	P value	0.11	0.04	0.03

MD, mean deviation; *PSD*, pattern standard deviation; *VF*, visual fields.

^a $P < 0.05$ considered statistically significant.