Spectral-Domain Optical Coherence Tomography in Wagner Syndrome: Characterization of Vitreoretinal Interface and Foveal Changes

PIERRE-RAPHAEL ROTHSCHILD, CYRIL BURIN-DES-ROZIERS, ISABELLE AUDO, BRIGITTE NEDELEC, SOPHIE VALLEIX, AND ANTOINE P. BRÉZIN

• PURPOSE: To evaluate the spectrum of morphologic abnormalities in patients with Wagner syndrome by spectral-domain optical coherence tomography (SD OCT).
• DESIGN: Retrospective comparative case study.
• METHODS: Institutional study of patients entered into the French Vitreoretinopathy Study Group database. Twelve eyes of 9 patients from 3 unrelated families with genetically confirmed Wagner syndrome and 28 eyes from 15 age- and sex-matched healthy family controls were scanned by SD OCT. Morphology and layer thickness of the total retina, inner retinal layers, outer retinal layers, and photoreceptor layer at different degrees of eccentricity from the fovea were compared between the 2 groups.
• RESULTS: A thick multilayered membrane adherent to the perifovea but completely detached from the fovea, thus forming a bridge over the foveal pit, was observed in 84% of eyes from patients with Wagner syndrome. At the equatorial area, SD OCT imaging allowed visualization of the architecture of an avascular vitreous veil with localized retinal traction. Most retinal layers were significantly thinner in patients with Wagner syndrome compared to the control group, except at the foveal center where abnormal persistence of 1 or more inner retinal layers could be observed.
• CONCLUSION: SD OCT provides better structural insight into the range of retinal defects at the vitreoretinal interface and fovea, which is not only useful for improving diagnosis and management, but also for understanding the pathogenesis of Wagner syndrome. (Am J Ophthalmol 2015;160(5):1065–1072. © 2015 by Elsevier Inc. All rights reserved.)

Accepted for publication Aug 8, 2015.

From Assistance Publique–Hôpitaux de Paris, Groupe Hospitalier Cochin-Hôtel-Dieu, Service d'ophtalmologie, Université Paris Descartes, Sorbonne Paris Cité, Paris, France (P.R.R., A.P.B.); Institut National de la Santé et de la Recherche Médicale, Centre de Recherche des Cordeliers, Unité Mixte de Recherche 1138, équipe 17, Paris, France (P.R.R., S.V.); Institut National de la Santé et de la Recherche Médicale, Unité Mixte de Recherche 1163, Institut Imagine, Laboratoire de Génétique Ophtalmologique, Université Paris Descartes, Sorbonne Paris Cité, Paris, France (C.B., B.N.); Institut National de la Santé et de la Recherche Médicale, Unité Mixte de Recherche _S968, Paris, France (I.A.); Centre National de la Recherche Scientifique, Unité Mixte de Recherche 7210, Paris, France (I.A.); Université Pierre et Marie Curie Paris 6, Institut de la Vision, Paris, France (I.A.); Centre Maladies Rares/Centre d'Investigations Cliniques 503 Institut National de la Santé et de la Recherche Médicale, Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts, Paris, France (I.A.); Department of Molecular Genetics, Institute of Ophthalmology, London, United Kingdom (I.A.); and Université Paris-Descartes, Sorbonne Paris Cité, Assistance Publique–Hôpitaux de Paris, Laboratoire de Biologie et Génétique Moléculaire, Hôpital Cochin, Paris, France (S.V.).

Inquiries to Pierre-Raphael Rothschild, Service d'ophtalmologie, Hôpital Hôtel Dieu, 1 Place du Parvis de Notre-Dame, 75004 Paris, France; e-mail: rothschild.pr@gmail.com

WAGNER SYNDROME (OMIM#143200) IS A VERY rare vitreoretinal degenerative disorder with no systemic features, inherited as an autosomal dominant trait, and only 14 families have been reported worldwide with a molecularly confirmed diagnosis. This genetic disorder is caused by splice mutations in the *versican* (*VCAN*) gene, coding for a chondroitin sulfate proteoglycan named versican whose exact role in ocular tissues is largely unknown. The pattern of expression of versican during retinal development and in the adult retina supports a role in vitreous architecture and vitreoretinal interface, as well as in the maintenance of photoreceptor cells, and in the regulation of neurite formation and growth of the nerve fiber layer and inner plexiform layer where neural networks of ganglion cells are being formed.[1–3] The clinical spectrum of the disease is very large and age-dependent, with a highly variable expressivity even among affected members within a same family, making diagnosis of this disease very challenging.[4–6] The disease usually manifests in childhood, and affected patients show an optically empty vitreous with a characteristic fibrillary aspect of the vitreous core and an abnormal vitreous cortex with avascular peripheral veils.[7,8] Other features variably include moderate congenital myopia,[7,9–13] early-onset cataract,[7,10–14] glaucoma,[7,10–13] uveitis,[4,8,15] and foveal ectopia responsible for pseudostrabismus.[14,16,17] The severity of the disease is related to the progressive chorioretinal degeneration with atrophy and the occurrence of retinal detachments, both of these complications being the leading causes of visual loss in patients with Wagner syndrome.[7] Although retinal detachment has long been an unrecognized manifestation and is not

0002-9394/$36.00
http://dx.doi.org/10.1016/j.ajo.2015.08.012

TABLE 1. Summary of Clinical, Spectral-Domain Optical Coherence Tomography, and Molecular Findings in Patients With Wagner Syndrome

Family ID	*VCAN* Mutation	References	Patient ID	Sex	Age (y)	Eye	BCVA (LogMAR)	AL (mm)	SE (Diopters)	IOP	ExRM	Grade 1 FH	Grade 2 FH
A	c.4004-2A>T	Brézin et al[4]	A.IV.7	M	61.9	OD	0.4	25.05		17	Yes	Yes	Yes
			A.IV.8	M	51	OS	0.1	24.77	−7.75	11	Yes	Yes	No
			A.V.5	F	35.9	OD	0.1	23.84	−3.375	16	Yes	No	No
						OS	0.1	24.1	−5.5	16	Yes	No	No
			A.V.6	F	40.7	OD	0.2	27.05	−5.625	16	Yes	No	No
B	c.4004-6A>T	Rothschild et al[8]	B.I.2	F	72.6	OS	0.2			17	Yes	No	No
			B.II.1	F	44.7	OD	0.2	21.97	1	17	Yes	No	No
			B.II.4	F	47.4	OD	0.1		−0.875	16	Yes	No	No
						OS	0.1		−0.75	17	Yes	Yes	No
C	c.9265+1G>A	Rothschild et al[9]	C.II.1	M	30.5	OS	0	26.7	−3.125	17	Yes	Yes	Yes
			C.III.1	F	3	OD	0.5		−3		No	Yes	No
						OS	0.5		−6.375		No	Yes	No

AL= axial length; BCVA = best-corrected visual acuity; ExRM = extraretinal membrane; FH = foveal hypoplasia; IOP = intraocular pressure; SE = spherical equivalent; *VCAN* = versican gene.

as frequent in Wagner syndrome as in Stickler, all recent studies have reported retinal detachment in affected patients.[4,14] Visual acuity is reported to be normal or subnormal in young patients with Wagner syndrome but is constantly severely affected in older patients.

To gain insight into the qualitative and quantitative defects in the retina and at the vitreoretinal interface in Wagner syndrome, a retrospective intrafamilial comparative case study was conducted using the in vivo spectral-domain optical coherence tomography (SD OCT) imaging method.[18] The retinal structural information provided by SD OCT may help in clarifying the underlying pathologic mechanisms at play in Wagner syndrome, which remain poorly understood thus far.

METHODS

INSTITUTIONAL REVIEW BOARD APPROVALS FOR RETROspective chart reviews were obtained commensurate with the respective institutional requirements prior to the beginning of the study. Described research was approved by the Ethics Committee of the French Society of Ophthalmology and adhered to the tenets of the Declaration of Helsinki. Fully written informed consent was obtained for all patients.

This intrafamilial case-control study included patients followed for hereditary vitreoretinal diseases at a single institution, a university teaching hospital at Groupe Hospitalier Cochin Hôtel-Dieu, Paris, France. Patients enrolled in our cohort (The French Vitreoretinopathy Study Group) were offered standardized ophthalmic examination and genetic testing.

Patients with a clinical picture of Wagner syndrome and positive for a pathogenic mutation in the *VCAN* gene were enrolled in this study (cases). The control population included clinically unaffected family members who were non-carriers of *VCAN* mutations (controls). ETDRS best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, intraocular pressure measurements, dilated fundus examination, and spherical equivalent and axial length measurement (IOLMaster; Carl Zeiss Meditec AG, Jena, Germany) was performed for all studied patients (cases and controls) and findings have been partly reported elsewhere (Table 1).[4,8,9] SD OCT was performed using the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany). Patients with no SD OCT data; with a history of retinal detachment, macular edema, or premature birth; or with low-quality SD OCT images were excluded from the analysis (see Figure 1 for inclusion flow chart details).

• **SPECTRAL-DOMAIN OPTICAL COHERENCE TOMOGRAPHY ANALYSIS:** The SD OCT acquisition protocol included a horizontal and vertical 9-mm central linear scan (passing through the fovea). At least 30 scans were averaged to reduce the signal-to-noise ratio and low-quality images (signal-to-noise ratio below 25 dB) were discarded. Qualitative OCT image analysis included the quoting of the presence or absence of a membrane-like structure forming a bridge over the foveal pit according to our previous description in time-domain OCT of Wagner syndrome patients.[4] We also graded foveal abnormalities as previously described by others.[19] In brief, we noted the absence of extrusion of the plexiform layers (grade 1) from the central fovea, the absence of foveal pit (grade 2), the absence of outer segment lengthening (grade 3), and finally the absence of widening of the outer nuclear layer (grade 4). Quantitative analysis included manual segmentation of several retinal layers using the built-in caliper of the viewing software (HRA Spectralis viewing software version 5.6.4.0).