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RETINAL MANIFESTATIONS OF WALKER–WARBURG SYNDROME IN TWO SIBLINGS WITH *RXYLT1* MUTATIONS

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Abstract

Purpose: We report two siblings with genetically confirmed Walker–Warburg syndrome (WWS), studied with multimodal imaging, who presented with different retinal manifestations.

Methods: This is a retrospective report of two WWS cases with ultra-widefield fundus photography, fluorescein angiography, and ultrasound. Molecular diagnosis was achieved using panel testing and targeted variant testing.

Results: Two siblings, one male and one female, born 17 months apart with a diagnosis of WWS underwent retinal examination with imaging. The 3-month-old female infant exhibited microphthalmia, persistent hyaloidal arteries, and retrolental membranes with total tractional retinal detachments on ultrasound in both eyes. The 22-day-old male newborn exhibited persistent hyaloidal arteries and extensive peripheral avascular retina on angiography in both eyes. Both were found to be positive for the same two pathogenic variants in the *RXYLT1/TMEM5* gene, which accounts for approximately 9% of cases of genetically confirmed WWS.

Conclusion: Siblings with genetically confirmed WWS can have variable presentations despite identical genotype. This highlights the phenotypic disease spectrum of WWS, which may be similar to that seen in familial exudative vitreoretinopathy.

Keywords

familial exudative vitreoretinopathy; Walker–Warburg syndrome; retinal dysgenesis; *RXYLT1* ; *TMEM5*

Walker–Warburg syndrome (WWS) is a rare disease associated with lissencephaly Type 2 (lack of brain gyri) caused by a disorder of neuronal migration. It is one of three known congenital muscular dystrophies—the other two being Fukuyama congenital muscular dystrophy (primarily seen in Japan) and muscle–eye–brain disease (primarily seen in Finland). In contrast to these, WWS is characterized by more severe neurologic and

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ocular manifestations and a typically fatal outcome.[1] Patients with WWS exhibit Type II lissencephaly, cerebellar malformations, retinal abnormalities, and congenital muscle dystrophy. Few case reports exist in the literature describing the specific retinal findings seen in this syndrome (Table 1), but these include retinal detachments, persistent hyaloidal arteries, and retinal folds.

WWS is a result of a defective glycosylation of a-dystroglycan, which plays a key role in neuronal migration. Mutations of *POMT1*, *POMT2*, *POMGnT1*, *FKRP*, *FKTN*, *LARGE*, *RXYLT1*/*TMEM5*, and *ISPT* genes have been found to be associated with WWS, although in nearly half of cases, a genetic association is not found.[9] To the best of our knowledge, no previous reports of WWS have included genetic testing and provided detailed retinal descriptions including angiography. In this study, we present two siblings (male and female), both diagnosed with WWS through genetic testing.

Case Descriptions

Two siblings were seen at Children's Hospital Los Angeles 17 months apart after referral from their local pediatric ophthalmologists. The parents have no ocular history and no other children. Explicit verbal consent and IRB approval were obtained before publication.

Case 1

This is a 3-month-old female infant born at 37 weeks' gestation to a mother with poorly controlled gestational diabetes mellitus. Shortly after birth, the child developed seizures and was hospitalized at an outside hospital where a brain MRI revealed diffuse cerebral cortical malformations with pachygyria and polymicrogyria, diffuse cerebellar dysplasia, hypoplasia of the brain stem, and hydrocephalus. She was noted to have microphthalmia and other eye abnormalities and referred to our ophthalmology clinic for evaluation.

Examination revealed visual acuity of at least light perception in both eyes. Pupils were unreactive in the left eye and unable to be assessed in the right eye. Penlight examination was significant for microphthalmia with a large retrolental plaque visible in both eyes. Examination under anesthesia the following day revealed an intraocular pressure of 15 in the right eye and 9 in the left eye. Horizontal corneal diameters were 10 mm in both eyes with apparent microphthalmia. Anterior segment examination was notable for persistent tunica vasculosa lentis on the anterior and posterior surfaces. There was no view to the retina because of a yellow plaque containing vessels behind each lens (Figure 1, A and B). This plaque appeared more consistent with persistent fetal vasculature than retinal tissue. Fluorescein angiography demonstrated retrolental vessels, some of which leaked in the late frames (Figure 1, C and D). B-scan ultrasonography revealed a thick membrane emanating from the optic nerve to the posterior lens in both eyes, consistent with a closed funnel retinal detachment (Figure 1, E and F). In the right eye, there was also a subretinal hemorrhage.

Panel genetic testing revealed two heterozygous pathogenic frameshift mutations in the *RXYLT1*/*TMEM5* gene in exon 1 (c.147delC [p.Ala50Argfs*39]) and exon 6 (c.947delA [p.Lys316Argfs*19]), confirming a diagnosis of autosomal recessive Walker–Warburg

syndrome. Given the poor visual potential and prognosis, the decision was made to forgo surgical management of the retinal detachments.

Case 2

Case 2 is a 22-day-old male newborn, born at 36 weeks' gestation, to the same parents 17 months later. He was transferred to our hospital on the second day of life because of concerns for congenital hydrocephalus. Brain MRI showed severe enlargement of the lateral and third ventricles, severe thinning of the cerebral parenchyma with volume loss of the frontal and parietal lobes, thin and abnormal cortical mantles, signs of an old basal ganglia hemorrhage, flattened and hypoplastic bilateral cerebellar hemispheres and vermis, and kinking of the brain stem secondary to mass effect from severe hydrocephalus. Head sonography did not reveal any evidence of acute intracranial hemorrhage, and neurosurgery subsequently placed a ventriculoperitoneal shunt. Creatine phosphokinase levels were significantly elevated, raising suspicion for a congenital muscular dystrophy especially in the context of the sibling's diagnosis of WWS.

Bedside examination revealed visual acuity of at least light perception in both eyes. Pupils and intraocular pressure were unremarkable. Anterior segment examination showed no evidence of cataract or iris abnormalities, but the hyaloid artery was inserted into the central lens in both eyes. Posterior examination revealed optic nerve hypoplasia, with the left nerve appearing more severely affected than the right (Figure 2, A and B). Diffuse fundus hypopigmentation, foveal hypoplasia, and peripheral retinal avascularity with retinal pigment epithelium mottling were also seen. In both eyes, persistent hyaloidal arteries were seen extending from the optic nerve to the lens (Figure 2, C and D). Fluorescein angiography demonstrated premature termination of the retinal vessels in midzone 2 with peripheral nonperfusion (Figure 2, E and F). There was mild leakage of the vessels nasally but no evidence of neovascularization in either eye. The patient received peripheral laser photocoagulation to the avascular retina of both eyes. On follow-up examination 1 week later, no significant changes were noted other than peripheral laser scars. Targeted variant testing confirmed the presence of the same two heterozygous mutations in *RXYLT1*/*TMEM5* (c.147delC [p.Ala50Argfs*39] and c.947delA [p.Lys316Argfs*19]), confirming the diagnosis of WWS.

Discussion

WWS has an autosomal recessive inheritance and a typical life expectancy of less than 12 months.[10] Mutations in the *RXYLT1*/*TMEM5* gene account for approximately nine percent of cases of genetically confirmed WWS.[9] The clinical diagnostic criteria were established by an early study of patients with WWS by Dobyns et al[10] and included Type II lissencephaly, cerebellar malformations, retinal abnormalities, and congenital muscle dystrophy. The spectrum of retinal involvement observed included severe microphthalmia, retrolental masses caused by persistent hyperplastic primary vitreous, colobomatous malformations, retinal detachment secondary to retinal dysplasia, and some less severe abnormalities such as "leopard-spot" peripheral retinopathy.

Owing to typical patient age, severity of medical comorbidities, and the presence of coexisting anterior segment pathology, posterior segment findings are difficult to identify on clinical examination. While histopathologic reports exist, clinical descriptions of the retinal findings are lacking. Since the establishment of the diagnostic criteria for WWS by Dobyns et al, seven case reports were found by literature search describing specific retinal findings seen in Walker–Warburg syndrome—a summary of each has been included in Table 1. Although Mano et al[6] included optical coherence tomography findings, no previously published report has included genetic testing along with fluorescein angiography.

Our series of two siblings is a unique example of identical genetic mutations of WWS leading to significantly different ophthalmologic phenotypes. Both siblings suffered from severe brain abnormalities including hydrocephalus and cerebellar dysplasia/hypoplasia, as well as ocular abnormalities that resembled a familial exudative vitreoretinopathy–like phenotype. However, the younger sibling's retinal disease (Case 2) was much less severe when compared with his older sister (Case 1), who exhibited profound retinal pathology including bilateral microphthalmia and total tractional retinal detachments. A diagnosis of WWS may be considered in anyone meeting Dobyns' criteria, even with less severe retinal findings.

Familial exudative vitreoretinopathy is a separate group of hereditary vitreoretinopathies associated with a number of known causative genes, most involving the Wnt signaling pathway.[11,12] Family members of patients with familial exudative vitreoretinopathy bearing the same genotype may have varying phenotypic penetrance—some can even appear normal—and patients with familial exudative vitreoretinopathy may even exhibit variable degrees of severity between eyes.[13–15] The siblings presented here had WWS driven by identical mutations but exhibited contrasting familial exudative vitreoretinopathy–like retinal phenotypes despite similar brain and systemic findings. It remains unclear why early steps in retinal development related to α-dystroglycan or Wnt signaling can manifest differently within families and even within the same patient.

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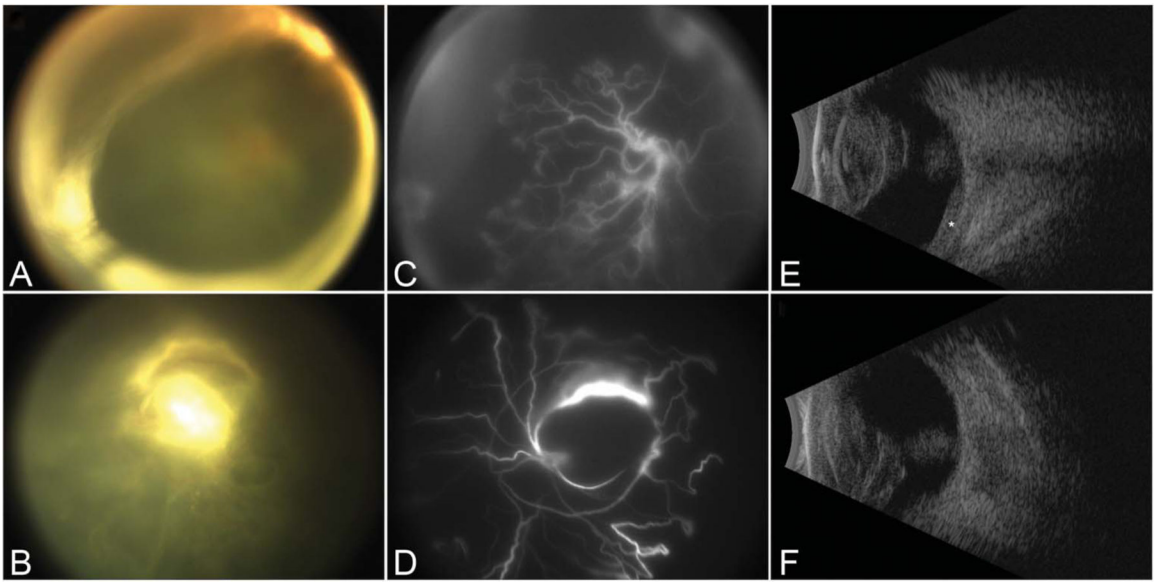

Fig. 1.

Retinal findings in the 3-month-old female infant with WWS (Case 1). Color fundus image (RetCam3, Clarity Medical Systems, Pleasanton, California) of the right (**A**) and left (**B**) eyes demonstrate yellow plaques containing vessels behind each lens. RetCam fluorescein angiography of the right (**C**) and left (**D**) eyes shows only the retrolental persistent hyaloidal vessels with no view to the retinal vasculature. B-scan ocular ultrasonography of the right (**E**) and left (**F**) eyes demonstrates thick membranes emanating from the optic nerve to the posterior lens consistent with closed funnel retinal detachment in both eyes. There is layered subretinal hemorrhage in the right eye (white asterisk, **E**). There are no masses or calcifications, and both globes appear small in size.

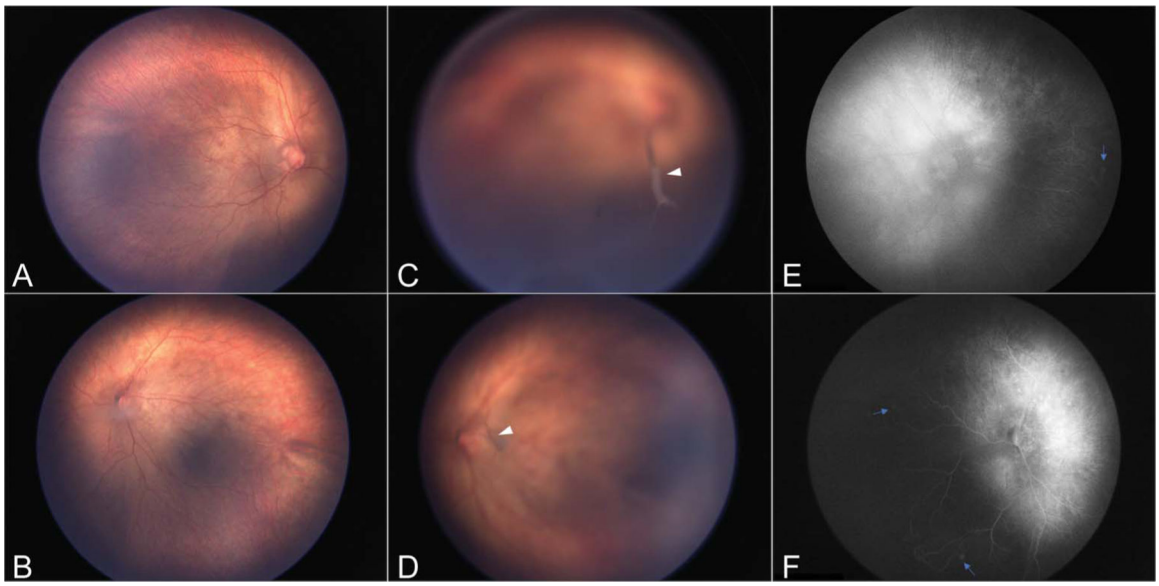

Fig. 2.

Retinal findings in the 22-day-old male newborn sibling (Case 2). RetCam color fundus images of the right (**A**) and left (**B**) eyes demonstrated an avascular retinal periphery in midzone 2 with a mottled appearance, along with persistent hyaloid arteries emanating from the optic nerves. Additional color fundus images, taken with the camera focus adjusted anteriorly, highlight the persistent hyaloidal artery stalks (white arrowheads) seen in the right (**C**) and left (**D**) eyes. RetCam fluorescein angiography demonstrates premature truncation of vessels in midzone 2 with peripheral nonperfusion in the right (**E**) and left (**F**) eyes. Trace leakage of the vessels is realized nasally in both eyes (blue arrows) at the avascular border with no evidence of neovascularization in either eye.

Table 1.

Case Reports of Walker–Warburg Syndrome With Retinal Findings

Case	Year	Age/Sex	Ophthalmic Findings	Retinal Imaging	FA Imaging	Genetic Testing	Ophthalmic Treatment and Outcome
Rhodes et al[2]	1992	5 days/male	Macrophthalmia, persistent hyaloid artery, retinal dysplasia, retinal folds in the right eye on autopsy. Retinal dysplasia, total RD accompanied by vitreous hemorrhage in the left eye.	None	No	None	None. Death at 5 days.
Gerding et al[3]	1993	9 months/ female	Severe iridocorneal malformation, a membrane-like structure of the lens, and funnel-shaped retinal dysplasia on autopsy.	None	No	None	None. Death at 9 months.
Berrocal et al[4]	2004	2 months/girl	Prominent retinal folds, macula-involving, and touching the posterior and inferior temporal lens capsule in each eye and bilateral cataracts.	None—photograph of external eye only	No	None	None. Progressive cataracts, ambulatory visual acuity in the left eye during 5 years of follow-up.
Khalaf et al[5]	2006	52 days/male	Bilateral cataracts, microphthalmic right eye with secluded pupil, buphthalmic left eye with enlarged hazy cornea and shallow anterior chamber, persistent fetal vasculature in the right eye, and total RD in the left eye.	Ultrasound	No	None	None. Death at 7 months.
Mano et al[6]	2015	14 days/male	Persistent hyaloidal artery, widespread loss of fundus pigmentation, transparent choroidal vessels, absence of a distinct macular reflex, and elevated IOP bilaterally. OCT findings: no foveal pit and an indistinct laminar structure of the retina.	Fundus photographs, OCT	No	*POMT1* variant	Topical IOP pressure-lowering medication. Death at 8 months.
Hakim et al[7]	2018	2 days*	Bilateral funnel RD. Normal anterior segment examination.	Ultrasound	No	None†	None. Death at age 39 days.
Farsi et al[8]	2020	1 day/male	Unilateral microphthalmia, bilateral anterior segment dysgenesis, and bilateral funnel retinal dysplasia.	Ultrasound	No	Homozygous for *ISPD* variant (c.832A.T)	None.
This report: Case 1	2022	3 months/ female	Microphthalmia, persistent hyaloidal arteries, retrolental membranes with closed funnel RD in both eyes. Subretinal hemorrhage in the right eye.	Fundus photographs, ultrasound, FA	Yes	*RXYLT1*/*TMEM5* variants	None.
This report: Case 2	2022	22 day/male	Optic nerve hypoplasia, persistent hyaloidal artery, and peripheral avascular retina in both eyes. Minimal angiographic leakage of vessels in both eyes.	Fundus photographs, FA	Yes	*RXYLT1*/*TMEM5* variants	Panretinal photocoagulation.

*Gender unspecified.

†No chromosomal imbalance found by comparative genomic hybridization.

FA, fluorescein angiography; IOP, intraocular pressure; OCT, optical coherence tomography; RD, retinal detachment.