testing with single muscle nerve fiber electromyography was not required in this particular case because of subsequent testing. Additionally, thyroid eye disease would not provide a unifying diagnosis for the patient's other ocular or systemic findings. When the thyroid workup was negative and results from genetic testing were obtained, the patient's exophthalmos was determined to be an atypical manifestation of KSS.

Ophthalmic involvement in mitochondrial disease is well described,[2] yet chronic progressive external ophthalmoplegia (CPEO) with exophthalmos has only been described in one other report.[3] Differential diagnosis for proptosis includes inflammatory, vascular, infectious, cystic, neoplastic, and traumatic factors, all of which were excluded in our patient. CPEO usually presents with ptosis, progressing to weakness and eventual complete paralysis of extraocular muscles. Maeda and Idehara[3] presented an unusual case of exophthalmos in CPEO, although this patient did not have a pigmentary retinopathy. As in our patient, thyroid disease was ruled out, and imaging showed atrophic extraocular muscles. The authors suggested that exophthalmos might be secondary to advanced loss of support by extraocular muscles. Per our patient's history, ophthalmoplegia began at least 4 years before she sought care, and thus, such an explanation is plausible in her case.[3]

Although muscle biopsy typically confirms the diagnosis of KSS, noninvasive genetic testing was pursued in our patient because of the increased risk of adverse reaction to anesthesia associated with mitochondrial disorders.[4] 96% of mitochondrial DNA deletions in KSS are sporadic. Maternal transmission, however, has been reported, and it is therefore important to examine an affected individual's mother for clinical or genetic manifestations of disease.[5]

To our knowledge, this is the first patient with KSS to present with bilateral exophthalmos with the classic findings of CPEO, pigmentary retinopathy, sensory ataxia, and heart block. We hypothesize that exophthalmos may be a finding in late presentations of KSS because of decreased globe support by atrophic extraocular muscles. Our findings contradict the commonly accepted notion that significant pain, proptosis, or pupil involvement are not associated with CPEO, although such findings should still prompt evaluation for alternative etiologies. Because of the systemic nature of this genetic condition, it is imperative to involve a multidisciplinary team of providers in KSS patients' care. If an ophthalmologist suspects such a diagnosis, an EKG and thorough cardiac examination must be prioritized, because cardiac involvement may be life threatening. Although there is currently no cure, early diagnosis can facilitate optimal management of systemic disease manifestations and may reduce patient morbidity and mortality.

Literature Search

PubMed was searched on December 13, 2018, without date or language restriction, using the following terms singly or in combination: *Kearns-Sayre syndrome*, *exophthalmos*, *proptosis*, *chronic progressive external ophthalmoplegia*.

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Congenital glycosylation disorder: a novel presentation of coexisting anterior and posterior segment pathology and its implications in pediatric cataract management

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We report a case exhibiting the coexistence of anterior and posterior segment pathology in the same eye secondary to a congenital disorder of glycosylation resulting from a *DPAGT1* gene mutation. This case details a novel gene mutation in a male infant found to have bilateral congenital cataracts, removed at 6 and 7 weeks of life, only to uncover bilateral retinal and optic atrophy. Our report highlights issues of surgical timing for syndrome-related pediatric cataracts, given the risks related to secondary glaucoma versus deprivation amblyopia, in an infant born with both cataracts and vision-limiting posterior segment pathology.

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Table 1. Summary of systemic clinical findings in our patient with a compound heterozygous mutation in the *DPAGT1* gene

Organ system	Clinical findings
Craniofacial	Shortened palpebral fissures
	Double tracks on fleshy earlobes
Neurologic	Neonatal hypotonia[a]
	Lack of Moro reflex
	Myoclonic jerks
	Intractable epilepsy
Musculoskeletal	Joint stiffness
	Joint contractures (digits and knees)
	Wide spacing between 1st and 2nd toes
	Rocker bottom feet
	Bell-shaped chest
Cardiovascular	QT prolongation
	Sinus bradycardia pauses[b]
	Patent foramen ovale
	Severe mitral regurgitation
	Dilated cardiomyopathy
	Pulmonary hypertension
Pulmonary	Weak respiratory effort[c]
Gastrointestinal	Protein-losing enteropathy
Genitourinary	Bilateral undescended testicles
Renal	Hydronephrosis
Hematologic	Hypoglycemia
	Hypoalbuminemia
	Thrombocytopenia
	Prolonged PT and PTT[d]

PT, prothrombin time; *PTT*, partial thromboplastin time.
[a]Gatrointestinal hypotonia ultimately required placement of a gastrostomy tube.
[b]Severity of sinus bradycardia ultimately required placement of a pacemaker.
[c]Continued poor respiratory effort after birth ultimately required tracheostomy placement.
[d]Severe coagulopathy ultimately resulted in a gastrointestinal bleed and bilateral subgaleal hematomas.

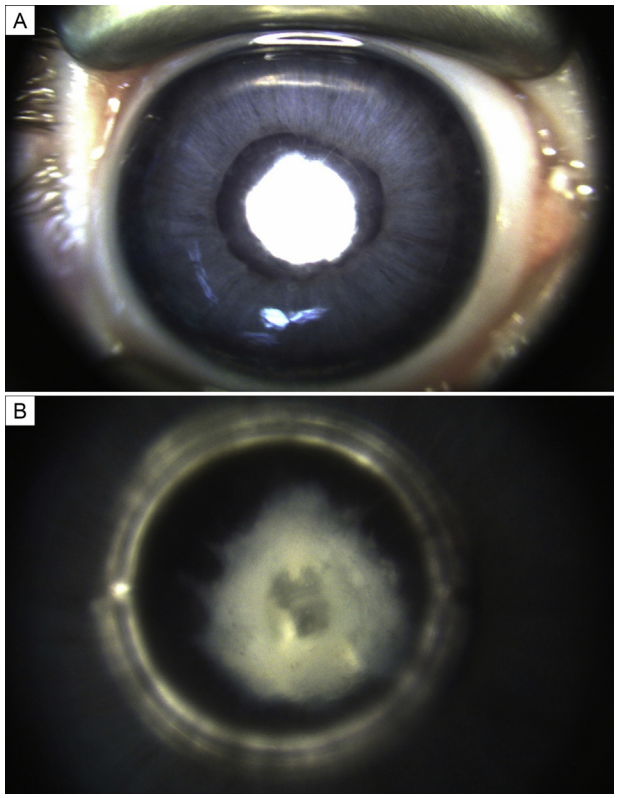

FIG 1. RetCam (Phoenix Technology Group, CA) photographs of the right eye. A, Anterior segment view showing the iris stromal hypoplasia. B, Anterior segment view showing the congenital nuclear cataract.

DPAGT1 (dolichyl-phosphate GlcNAc phospho transferase-1), a gene located on chromosome 11q23.3, encodes a catalyst for protein glycosylation. Mutations in *DPAGT1* are linked to two clinically distinguishable and rare disorders: congenital myasthenia syndrome (*DPAGT1*-CMS) and congenital disorder of glycosylation (*DPAGT1*-CDG). Over 100 subtypes of CDG have been described. The exact incidence is unknown, because many patients go unrecognized or misdiagnosed due to the rare and complex nature of these disorders. Severity and prognosis vary greatly, depending on the genetic abnormality. Clinical presentation of CDG typically begins in early infancy and most often includes hypotonia, developmental delay, failure to thrive, neurologic abnormalities, hypoglycemia, and variable hepatic, ocular, gastrointestinal, skeletal, immunologic, and coagulopathic disorders. Ocular abnormalities have been described in at least 53 CDG subtypes and are the predominant feature in Peters-plus syndrome (*B3GALTL*-CDG) and retinitis pigmentosa (*DHDDS*-CDG, *POMGNT1*-CDG, *SRD5A3*-CDG).[1,2] We describe a patient with a compound heterozygous mutation in the *DPAGT1* gene and discuss his unique ophthalmologic presentation.

Case Report

A 5-day-old boy was transferred to Penn State Health Milton S. Hershey Medical Center with a suspected genetic condition. He was born to healthy, nonconsanguineous white parents by cesarean section at 37 weeks' estimated gestational age. The pregnancy was complicated by gestational diabetes, polyhydramnios, and decreased fetal movement. The mother had experienced 3 prior spontaneous abortions and had delivered another male infant with bilateral microphthalmia and cataracts who expired at 8 weeks of multisystem failure.

The infant was cyanotic, exhibiting minimal respiratory effort, and ultimately required intubation. Initial evaluation revealed multiple systemic abnormalities (Table 1). Ophthalmologic examination at 6 days of life revealed a strong wince to light bilaterally. He had bilateral microcornea with anterior segment dysgenesis, including dense pupillary membranes, peripheral iris stromal hypoplasia, and congenital nuclear cataracts, with no view to the posterior segment due to limited pharmacologic dilation (Figure 1). B-scan ultrasonography revealed attached retinas, with no

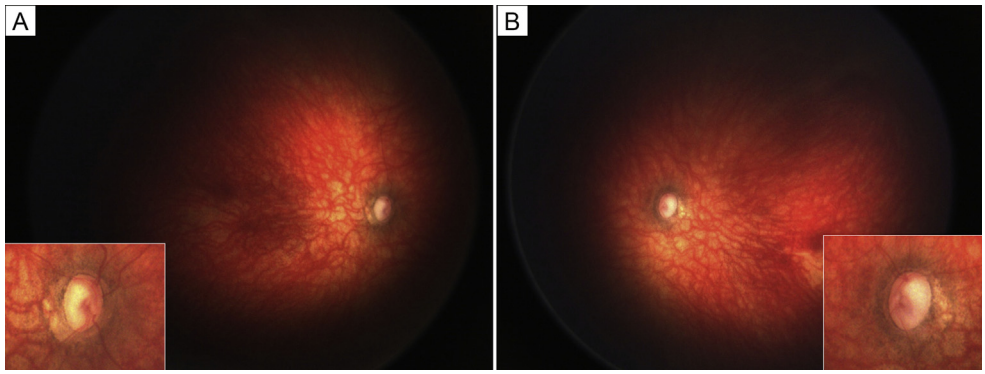

FIG 2. RetCam photographs of bilateral retinas showing bilateral foveal hypoplasia, blonde fundi with highly visible choroidal vasculature, macular retinal pigment epithelial atrophy, and retinal vascular attenuation with inlayed, magnified photographs of the optic nerves showing bilateral optic nerve atrophy and hypoplasia in the right eye (A) and left eye (B).

evidence of mass or posterior staphyloma. Moderate microphthalmia was confirmed, with axial lengths of 15.4 mm (right eye) and 13.88 mm (left eye) by immersion A-scan.

Cataract surgery was performed at age 6 weeks (right eye) and 7 weeks (left eye). Examination under anesthesia after cataract removal revealed bilateral optic nerve atrophy/hypoplasia, foveal hypoplasia, blonde fundi with highly visible choroidal vasculature, macular retinal pigment epithelial atrophy, and retinal vascular attenuation (Figure 2).

Final genetic analysis became available at 12 weeks of life. Whole-exome sequencing from the patient was compared to parents and his deceased brother for rapid diagnosis. Analysis revealed compound heterozygous pathogenic variants in the *DPAGT1* gene. The first is a known pathogenic variant (c. 324G>C; p. Met108Ile), for which the father was a heterozygous carrier. The second is a likely pathogenic variant (c. 692T>G; p. Phe231Cys), for which the mother was a heterozygous carrier: this mutation has not been previously reported.

Our patient manifested phenotypes from both CMS and CDG syndromes. He died at 17 months of age because of multiorgan failure. A postmortem examination was declined.

Discussion

Defining a genetic disorder in newborns requires time for disease manifestations to develop and also for availability of genetic testing results. The complex presentation of both *DPAGT1*-CMS and *DPAGT1*-CDG phenotypes in our patient made the ultimate diagnosis difficult.

DPAGT1-CMS is an autosomal recessive condition characterized by fatigable limb girdle muscle weakness, accumulation of tubular aggregates on muscle biopsy, and variable response to pyridostigmine.[3] Presenting features at birth or soon after include hypotonia and signs of neuromuscular dysfunction including ptosis, dysphagia, facial paresis, and muscle fatigability.[3,4] No associated intraocular abnormalities have been reported. Mutations in *DPAGT1* affect glycosylation of the muscle acetylcholine receptor, altering its assembly and insertion into postsynaptic membranes, causing defects in neuromuscular junction signaling.[3]

DPAGT1-CDG is a severe autosomal recessive condition affecting multiple organ systems with a high mortality rate in infancy.[3] Manifestations include psychomotor retardation, hypotonia, hyporeflexia, cerebellar ataxia, epilepsy, cataracts, glaucoma, retinopathy, myopathy, joint contractures, hypertrichosis, liver fibrosis, coagulopathy, and failure to thrive.[5,6] These *DPAGT1* mutations lead to defects in production and transfer of an intermediate oligosaccharide within the endoplasmic reticulum, thus inhibiting protein and lipid synthesis in various organs.[7] *DPAGT1*'s role within the eye is currently unknown.

Over 40 *DPAGT1*-CGD cases are described in the literature: 16 are from a single consanguineous family.[3,5] Of the 24 individual cases, 15 had ocular manifestations, including astigmatism and ocular melanosis (1), strabismus (5), cataracts (6), and retinitis pigmentosa–like findings or optic nerve hypoplasia (3).[4] None of the 15 cases reported the coexistence of anterior and posterior segment pathology in the same eye.

To our knowledge, this is the first reported case of both anterior and posterior segment pathologies present in the same eye of a patient with *DPAGT1*-CDG.[8] This case highlights the complexity of pediatric syndromic cataract management: knowledge of vision-limiting posterior segment pathology would have influenced the decision for cataract surgery, particularly given the infant's systemic prognosis.

Two major ocular risks to consider managing newborns with congenital cataracts include glaucoma versus

deprivation amblyopia. With bilateral idiopathic congenital cataracts, the posterior segment is often spared, and early cataract removal is recommended for the best visual outcome with timeline to initial surgery between 4-6 weeks for unilateral cataracts and 4-10 weeks for bilateral cases.[9] A 50% glaucoma risk reduction has been reported if cataract surgery is delayed from 4 to 8 weeks of age as opposed to a threefold higher risk in those eyes undergoing early removal between 4-6 weeks of age (compared to delay in surgery from 7 weeks to 6 months).[10] In light of reported cases of childhood glaucoma in CDG patients, if limited visual potential secondary to irreversible causes, such as retinal or optic nerve pathology, were known prior to cataract surgery, both parents and physician may have weighed the risks/benefits of early versus late surgery differently given the risk of lifelong glaucoma.[9]

The risks of anesthesia, especially in syndromic patients with multisystem dysfunction, should also be weighed carefully. We were able to combine cataract surgery with other medically necessary procedures to limit the overall anesthetic burden to our patient.

Our experience may help parents and physicians to make informed decisions regarding treatment of CDG and timing of cataract surgery, given the potential for retina and/or optic nerve abnormalities that may limit the final visual outcome. Unilateral cataract surgery to limit both anesthetic and bilateral glaucoma risks, once such posterior segment pathology is discovered, may also be considered in these cases.

Literature Search

PubMed MEDLINE, OVID MEDLINE, and Clinical Key were searched in December 2018, without date restriction, using the following search terms: DPAGT1, *congenital glycosylation disorder*, *CDG*, *congenital disorders of glycosylation*, *congenital myasthenia syndrome*, *CMS*, *ocular findings in CDG*, *ocular findings in CMS*, *retina* AND *CDG* or *retina* OR *CMS*, *eye* AND *CDG* OR *CMS*, *congenital cataract* AND *glaucoma* OR *amblyopia*. Articles cited in reference lists of retrieved articles were also researched. Foreign-language literature was considered when applicable.

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Pigment dispersion syndrome and response to laser peripheral iridotomies in a child with Marfan syndrome

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Pigment dispersion syndrome (PDS) and pigmentary glaucoma have rarely been reported in Marfan syndrome and have never been reported in a child with Marfan syndrome. We report the clinical and ultrasound biomicroscopic findings of PDS in a 14-year-old girl with Marfan syndrome and its favorable response to bilateral laser peripheral iridotomy.

Marfan syndrome is a systemic connective tissue disorder that results from mutations in the *FBN1* gene that encodes fibrillin-1.[1] Ocular

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