for Zika virus in the third trimester. Microcephaly was confirmed via intrauterine ultrasonography at 7 months' gestation. Serology for syphilis, toxoplasmosis, HIV, and hepatitis B was negative throughout the gestational period. Serology for rubella and cytomegalovirus was IgG positive and IgM negative at 9 weeks' gestation.

On examination at our clinic, uncorrected visual acuity was 20/470 in the right eye and 20/1900 in the left eye using Teller Acuity Cards. Intraocular pressure was 10.5 mm Hg in both eyes (Tono-Pen; Reichert, Buffalo, NY). Biomicroscopy showed clear corneas, lenses with no opacities, normal irides, and a normal anterior chamber (Figure 1). The horizontal corneal diameter was approximately 10 mm in the right eye and 11 mm in the left eye. An indirect binocular fundus examination revealed attached retinas, normal maculae, well-delimited optic nerves with normal nerve cupping and normal axial length, mild vascular tortuosity, and no choroidal lesions. Assessment of alignment revealed an esotropia of 30$^{\Delta}$ by Hirschberg testing (Figure 1) with a preference for the right eye and normal versions.

Results of dynamic retinoscopy were $-6.00 + 6.00 \times 90^{\circ}$ in the right eye and $-5.50 + 6.50 \times 90^{\circ}$ in the left eye. Cycloplegic retinoscopy examination showed $-4.50 + 7.00 \times 90^{\circ}$ in the right eye and $-5.00 + 7.00 \times 90^{\circ}$ in the left eye. The Lea Screen Hiding Heidi test revealed binocularly reduced contrast sensitivity.

Corneal keratometry was measured using the Pentacam HR (Oculus, Wetzlar, Germany). See Figure 2. The boy had irregular and asymmetrical astigmatism with increased sagittal curvature in both eyes associated with a corresponding decrease in the corneal thickness. The rather symmetric refractive error might suggest lower asymmetry of the left cornea, but the patient's inability to fix the deviated eye as well as his impaired cognition affected the quality of the examination.

The optic nerve appeared normal. Brain magnetic resonance imaging revealed structural changes related to malformations induced by the Zika virus (Figure 1).

Optical lenses for ametropia correction were prescribed. The patient continues to be followed for early visual intervention.

Discussion

Ocular embryology and the neurotropism of the Zika virus could account for the possible corneal involvement in our patient by as-yet-unknown mechanisms.[4] Studies in mice have revealed Zika RNA in the cornea, neurosensory retina, and optic nerve.[5] These findings are consistent with the origin of the present ectasia. The strong right eye preference might not be associated with the current ectasia but could be associated with the esotropia. Because of examination limitations, it was not possible to determine which eye was most affected.

For patient rehabilitation, it is important to emphasize ametropia identification and correction, considering the hypoaccommodation already described in this group of patients.[6] Because identified cases of intrauterine infection by Zika virus with ocular involvement are still very recent, and this is, to our knowledge, the first report of corneal ectasia associated with CZS, the evolution of the ectasia remains unknown.

Literature Search

PubMed was searched on July 17, 2019, without language restriction, using the following terms: *CZS*, *Zika*, *cornea*, *children*, *visual deficiency*, and *strabismus*.

References

1. Jaenisch T, Rosenberger KD, Brito C, Brady O, Brasil P, Marques ET. Risk of microcephaly after Zika virus infection in Brazil, 2015 to 2016. Bull World Health Organ 2017;95:191-8.
2. de Paula Freitas B, de Oliveira Dias JR, Prazeres J, et al. Ocular findings in infants with microcephaly associated with presumed Zika virus congenital infection in Salvador, Brazil. JAMA Ophthalmol 2016;134:529-35.
3. Yepez JB, Murati FA, Pettito M, et al. Ophthalmic manifestations of congenital Zika syndrome in Colombia and Venezuela. JAMA Ophthalmol 2017;135:440-45.
4. Fernandez MP, Parra Saad E, Ospina Martinez M, et al. Ocular histopathologic features of congenital Zika syndrome. JAMA Ophthalmol 2017;135:1163-9.
5. Miner JJ, Diamond MS. Zika virus pathogenesis and tissue tropism. Cell Host Microbe 2017;21:134-42.
6. Ventura LO, Lawrence L, Ventura CV, et al. Response to correction of refractive error and hypoaccommodation in children with congenital Zika syndrome. J AAPOS 2017;21:480-484.e1.

Extraocular muscle biopsy during surgery for strabismus of unknown etiology

Jed H. Assam, MD,[a] Aaron M. Miller, MD,[b,c,d] Patricia Chevez-Barrios, MD,[a,e,f] and Andrew G. Lee, MD[a,b,c,g,h,i,j,k,l]

Author affiliations: [a]Department of Ophthalmology and Visual Sciences, University of Texas Medical Branch, Galveston; [b]Ophthalmology, Institute for Academic Medicine Houston Methodist, Houston, Texas; [c]Ophthalmology, Weill Cornell Medical College, New York, New York; [d]Houston Eye Associates, The Woodlands, Texas; [e]Departments of Pathology and Genomic Medicine and Ophthalmology, Houston Methodist, Houston, Texas; [f]Departments of Pathology and Laboratory Medicine and Ophthalmology, Weill Cornell Medical College, New York, New York; [g]Ophthalmology, Neurology, and Neurosurgery, Weill Cornell Medicine, New York, New York; [h]Ophthalmology UT MD Anderson Cancer Center, Houston, Texas; [i]Texas A&M College of Medicine, Houston; [j]Ophthalmology, Baylor College of Medicine and the Center for Space Medicine, Houston, Texas; [k]Ophthalmology, University of Iowa Hospitals, Iowa City; [l]Ophthalmology, University of Buffalo, Buffalo, New York

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Correspondence: Andrew G. Lee, MD, Chair, Blanton Eye Institute, Houston Methodist Hospital, 6560 Fannin St #450, Houston, TX 77030 (email: AGLee@houstonmethodist.org).

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Most cases of strabismus have a chronic and stable or known etiologic diagnosis prior to surgery. In some cases, however, surgery is undertaken to correct a stable ocular misalignment without a definitive etiology. We present 2 cases, one with euthyroid Graves' orbitopathy and the other with amyloid light-chain amyloidosis, in which extraocular muscle biopsy performed intraoperatively allowed histopathologic confirmation of a clinical diagnosis.

Case Presentations

Case 1

A 50-year-old white man presented at the Blanton Eye Institute for chronic (>2 years), recurrent, binocular, horizontal diplopia and intermittent eye pain in both eyes. Past medical history was significant for mild type 1 Chiari malformation (5.1 mm) and a remote diagnosis of pseudotumor cerebri, with transient treatment on acetazolamide, which was not tolerated and self-discontinued prior to presentation. On neuro-ophthalmological examination, visual acuity was 20/20 in each eye, and pupils were normal. There was bilateral injection over the medial and lateral rectus insertions, mild proptosis in both eyes, and a comitant esotropia of 20$^{\Delta}$. The remainder of the eye examination, including dilated fundus examination, was normal in both eyes. Magnetic resonance (MR) imaging of the head showed a stable Chiari malformation, with a normal MR venogram and cerebral angiogram. Serial lumbar punctures showed normal opening pressures of 12 and 15 cm H_2O, with normal cerebrospinal fluid contents. On serologic testing, thyroid function testing was normal, and anti-acetylcholine receptor antibodies testing for myasthenia gravis was negative. The patient was treated with empiric acetazolamide without improvement, but no papilledema or visual field defect was noted. Because the esotropia was stable, the patient was referred to adult strabismus services for surgery. Two 6 mm bilateral muscle biopsy specimens were excised at 5–6 mm posterior to the muscle insertion at the time of bilateral medial rectus recessions and sent as fresh specimens directly to ocular pathology. Histology showed extraocular skeletal muscle atrophy infiltrated by mucopolysaccharides (Figure 1). Repeat thyroid function testing again showed normal thyroid-stimulating hormone (TSH) and free T4 levels; however, additional testing for thyroid-specific immunoglobulin (TSI) was found to be elevated, consistent with a diagnosis of euthyroid Graves' orbitopathy. The patient achieved complete resolution in diplopia symptoms after strabismus surgery, and pain symptoms were well controlled with oral nonsteroidal anti-inflammatory medications. Smoking cessation counseling was also reinforced.

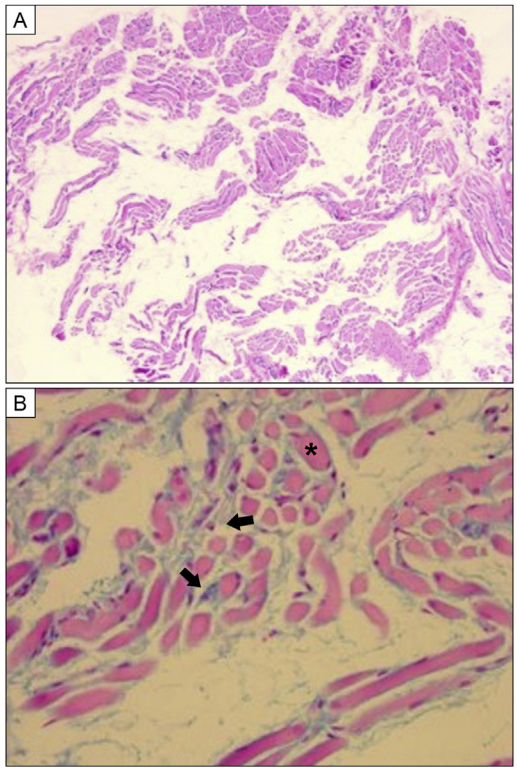

FIG 1. Medial rectus biopsy with periodic acid-Schiff (PAS) stain (A) and Alcian blue stain (B), demonstrating light blue glycosaminoglycan deposits (black arrows) and pink fibers indicating skeletal muscle atrophy (asterisk), consistent with Graves' orbitopathy.

Case 2

A 38-year-old white man was referred to the Blanton Eye Institute by oncology for binocular horizontal diplopia, newly observed anisocoria, and gradually worsening proptosis. Past medical history was significant for smoldering multiple myeloma (SMM), childhood pancreatitis, hepatomegaly, mild renal dysfunction, peripheral neuropathy, hyperlipidemia, and hypertension. Fat and serial bone marrow biopsy performed in the year prior to presentation showed no evidence of amyloid deposits with normal karyotyping. A bone scan was negative for lytic lesions. In the absence of identified amyloid deposition the diagnosis of SMM was maintained with the patient followed clinically. Ocular history was significant for previous strabismus surgery for a childhood A-pattern esotropia at age 2 with subsequent consecutive exotropia, which was determined to be chronic by the time he presented at our clinic.

On examination the patient was found to have anisocoria, worse in the light, with a decreased reaction to light in the right eye and proptosis measuring 26 mm in the right eye and 27 mm in the left eye by Hertel

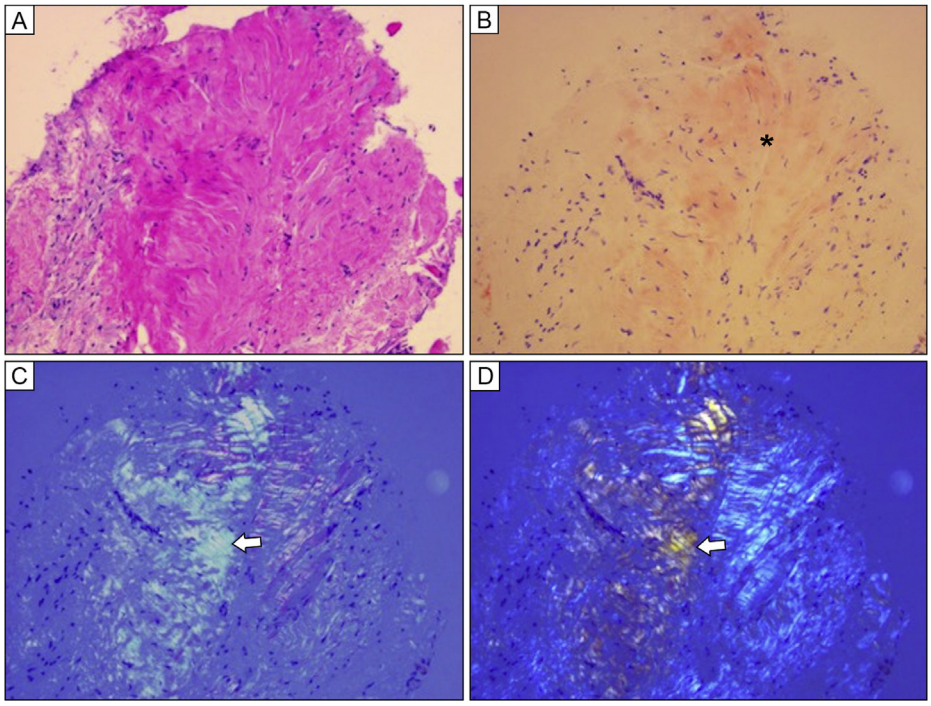

FIG 2. Medial rectus biopsy with PAS stain (A) and Congo red stain (B) demonstrating skeletal muscle replaced by dense fibrous tissue with focal amyloid deposition in orange-red (asterisk). Dichroism from apple-green (C) to orange (D) of amyloid deposits as seen under polarization (white arrows).

exophthalmometry. Motility examination revealed bilateral moderate global ophthalmoplegia (−2) and an exotropia of 20^{Δ} in primary gaze. An extensive laboratory work-up, including myasthenia gravis and thyroid eye disease autoimmune panels, was negative, and testing of serum vascular endothelial growth factor, IgG4, catecholamines (epinephrine, norepinephrine, dopamine), renin activity, and aldosterone was within normal limits. Both MR imaging and computed tomography (CT) studies of the brain and orbits were notable only for bilateral proptosis. Orbital ultrasound showed bilateral enlargement of all rectus muscles.

Given his constant exotropia, the patient was referred to adult strabismus clinic for surgical evaluation. During anesthesia for bilateral medial rectus resections, passive forced ductions were negative for restriction, and a bilateral extraocular muscle biopsy was performed, which revealed skeletal muscles with eosinophilic deposits and thickened vessel walls by amyloid deposition, confirmed by Congo red positivity, with diachroism under polarization (Figure 2), consistent with amyloidosis. The patient was subsequently referred back to his oncologist, given the ocular amyloidosis, and subsequently underwent additional bilateral bone marrow biopsy and a renal biopsy, which were also amyloid positive. Treatment with daratumumab, ixazomib, and dexamethasone was initiated for multiple myeloma. In follow-up evaluation the patient showed good improvement in diplopia symptoms after strabismus correction and is currently tolerating chemotherapy.

Discussion

Although the most common cause of either unilateral or bilateral proptosis in adults is thyroid eye disease (TED), other etiologies should be considered in the differential diagnosis, including infiltration, metastatic disease, lymphoma, inflammation (orbital inflammatory pseudotumor, IgG4 disease), and amyloid. Although the majority of TED occurs in the hyperthyroid (80%) state (ie, Graves disease), it can occur as well in hypothyroid (5%-10%) and euthyroid (5%-10%) individuals.[1] TED is the most common extrathyroidal manifestation of Graves disease, presenting clinically in as many as 30%-50% of cases.[1,2] A complete laboratory work-up for TED includes TSH, thyroxine, triiodothyronine, and autoantibody testing for thyroid peroxidase and TSI.[3] Imaging modalities (CT, MR imaging, and orbital ultrasound) may augment clinical and laboratory evaluation as well as help to interrogate for alternative pathology in the differential of TED. The diagnosis of TED typically can be made on the basis of clinical (eyelid retraction, exophthalmos, optic nerve dysfunction, extraocular muscle restriction) and laboratory markers. Patients with atypical features for TED,

including lack of thyroid disease (euthyroid function) or a history of malignancy (eg, lymphoma, metastatic disease), strictly unilateral cases, or cases with atypical pattern of extraocular muscles (eg, lateral rectus muscle) or involvement of the tendon may be candidates for orbital biopsy. Characteristics histopathologic features of TED include extensive glycosaminoglycan deposition between muscle fibers and inflammatory infiltrate with resulting interstitial edema.[4,5]

Orbital amyloidosis has been reported with multiple myeloma.[6,7] Amyloidosis typically occurs in middle-aged adults (54-57 years) and can produce unilateral or bilateral proptosis, ophthamoplegia, or ptosis. Amyloid light-chain amyloidosis is more often associated with multiple myeloma and has been found to arise symptomatically in up to 15% of cases and has been found incidentally in up to 30% of multiple myeloma patients.[7] Orbital imaging may show distinctive radiographic signs of orbital infiltration or extraocular muscle involvement; however, imaging alone is not diagnostic, and previous reports have shown extraocular muscle measurement variability between modalities.[8,9] Orbital amyloidosis diagnosis typically requires a tissue biopsy, and surgical excision may be a primary treatment for localized orbital amyloidosis.[6] Our case 2 had smoldering myeloma and multiple prior fat pad and bone marrow biopsies, which were negative.

In both cases presented here extraocular muscle biopsy performed at the time of strabismus surgery allowed a histopathologic confirmation of a clinical diagnosis. Clinicians should consider the possibility that strabismus surgery with an extraocular muscle biopsy may be both therapeutic and diagnostic in strabismus of unknown etiology.[10]

References

1. Kashkouli MB, Pakdel F, Kiavash V. Hyperthyroid vs hypothyroid eye disease: the same severity and activity. Eye (Lond) 2011;25:1442-6.
2. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association guidelines for the diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid 2016;26:1343-421.
3. Fukushima H, Matsuo H, Imamura K, et al. Diagnosis and discrimination of autoimmune Graves' disease and Hashimoto's disease using thyroid-stimulating hormone receptor containing recombinant proteoliposomes. J Biosci Bioeng 2009;108:551-6.
4. Shan SJ, Doughlas RS. The pathophysiology of thyroid eye disease. J Neuoroophthalmol 2014;34:177-85.
5. Longo CM, Higgins PJ. Molecular biomarkers of Graves' ophthalmopathy. Exp Mol Pathol 2019;106:1-6.
6. Mora-Horna ER, Rojas-Padilla R, López VG, Guzmán MJ3, Ceriotto A3, Salcedo G. Ocular adnexal and orbital amyloidosis: a case series and literature review. Int Ophthalmol 2016;36:281-98.
7. Goshe JM, Schoenfield LS, Emch T, Singh AD. Myeloma-associated orbital amyloidosis. Orbit 2010;29:274-7.
8. Lennerstrand G, Tian S, Isberg B, et al. Magnetic resonance imaging and ultrasound measurements of extraocular muscles in thyroid-associated ophthalmopathy at different stages of the disease. Acta Ophthalmol Scand 2007;85:192-201.
9. Nagy EV, Toth J, Kaldi I, et al. Graves' ophthalmopathy: eye muscle involvement in patients with diplopia. Eur J of Endocrinol 2000;142:591-7.
10. Eade EL, Hardy TG, McKelvie PA, McNabe AA. Review of extraocular muscle biopsies and utility of biopsy in extraocular muscle enlargement. Br J Ophthalmol 2018;102:1586-90.

Pharmacologic mydriasis in an infant following parental use of topical glycopyrronium tosylate

Steven Seto, BS,[a] Alison A. Teo, MD, Meng,[a] and Ryan D. Walsh, MD[a,b]

We report the case of a 2-month-old boy with unilateral pharmacologic mydriasis from inadvertent exposure to glycopyrronium after parental use of glycopyrronium wipes. Clinician familiarity with the potential effects of glycopyrronium exposure may aid in the recognition, diagnosis, and prevention of pharmacologic mydriasis as well as the reduction of costly and unnecessary evaluations.

Anisocoria is a common condition, with etiologies ranging from benign to potentially life-threatening. Pharmacologic mydriasis is a frequently encountered cause. Glycopyrronium is a topical anticholinergic approved in the United States in 2018 for the treatment of primary axillary hyperhidrosis in patients at least 9 years of age. Mydriasis is a potential side effect of this medication. With its recent approval, ophthalmologists are likely to encounter increasing numbers of patients presenting with pharmacologic mydriasis secondary to exposure to topical glycopyrronium.

Case Report

A 2-month-old boy presented at the Neuro-ophthalmology Clinic at the Medical College of Wisconsin Eye Institute for evaluation of anisocoria. Six days prior, the patient's mother noted unequal pupils after retrieving him from daycare, with the left pupil being larger than the right. The anisocoria was greater in bright than dim

Author affiliations: [a]*Department of Ophthalmology & Visual Sciences, Medical College of Wisconsin, Milwaukee, Wisconsin;* [b]*Department of Neurology, Medical College of Wisconsin, Milwaukee, Wisconsin*

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Correspondence: Ryan D. Walsh, MD, Froedtert & the Medical College of Wisconsin Eye Institute, 925 North 87th Street, Milwaukee, WI 53226 (email: rdwalsh@mcw.edu).

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