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]

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

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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

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environments. There was no known injury. The patient was asymptomatic, with otherwise normal-appearing eyes, behavior, activity level, and oral intake. Past medical, surgical, and family history were unremarkable. He was not taking any medications (including topical or inhaled agents), and there were no known potential exposures (including no familial use of scopolamine patches). He had been brought to the Children's Hospital of Wisconsin Emergency Department the same day, where, on examination, he had a 4 mm reactive right pupil and a 6 mm unreactive left pupil in light. In darkness, the right pupil dilated appropriately (no measurements were noted), whereas the left pupil remained at 6 mm. There was no ocular dysmotility or ptosis. The remainder of his physical examination was normal. Computed tomography (without contrast) of the head was negative. The patient was discharged with Neuro-ophthalmology follow-up within 1 week.

On presenting to our clinic, the patient's anisocoria was reported to have significantly improved 2 days after onset. A photograph from the day following initial presentation showed the pupils measuring roughly 1.5 mm on the right and 4 mm on the left in room light. On examination, the patient was able to fix but not follow, as expected for age. His pupils were equal, measuring 3.5 mm in the light and 6 mm in darkness bilaterally, and they were reactive to light, with no relative afferent pupillary defect. The remainder of the examination was normal. Further review of history revealed that the patient's father had been using topical glycopyrronium wipes for primary axillary hyperhidrosis. On the morning of anisocoria onset, the patient's father had used glycopyrronium and, shortly after, wiped the patient's left eye with his finger. He had not washed his hands after glycopyrronium use. The patient was diagnosed with pharmacologic mydriasis following inadvertent glycopyrronium exposure. Reexamination 8 weeks later was again normal.

Discussion

Anticholinergics induce mydriasis via blockade of acetylcholine at the muscarinic receptors of the pupillary constrictor muscle. Glycopyrronium is a topical anticholinergic approved in June 2018 for the treatment of primary axillary hyperhidrosis in patients at least 9 years of age. The medication is delivered via a premoistened towelette to the axillae. Glycopyrronium, a derivative of glycopyrrolate, is a competitive muscarinic acetylcholine receptor antagonist; similar to glycopyrrolate, it is a permanently charged quaternary amine that minimizes blood-brain barrier permeability.[1] Thus, systemic and central nervous system adverse effects are reduced with glycopyrrolate and its derivatives.[1] Peak plasma concentration in children after once daily application of a 2.4% glycopyrronium cloth to the axilla for 5 days was 0.07 ng/mL, without evidence for drug accumulation.[1]

Topical glycopyrronium for primary axillary hyperhidrosis was studied in the replicate double-blind vehicle-controlled ATMOS-1 and ATMOS-2 phase III clinical trials in males and nonpregnant females at least 9 years of age for 4 weeks of treatment[2,3] and in a 44-week open label extension study.[4] Although results were positive overall, a variety of anticholinergic treatment-emergent adverse effects (TEAE) were noted in a small subset of patients. The most common anticholinergic adverse effects were dry mouth (24.2%), mydriasis (6.8%), urinary hesitation (3.5%), blurred vision (3.5%), nasal dryness (2.6%), dry eyes (2.4%), constipation (2.0%), and urinary retention (1.5%).[2] Longer-term usage of topical glycopyrronium in the 44-week extension study showed variations in incidence of anticholinergic TEAEs but a high prevalence of mydriasis among TEAEs (5.3% incidence [5th most common TEAE]).[4] The ATMOS-1 and ATMOS-2 clinical trials showed a higher incidence of unilateral (ATMOS-1, 86.7% [13/15 events]; ATMOS-2, 62.5% [10/16 events]) versus bilateral mydriasis.[2] However, post hoc age-stratified analysis showed a higher proportion of bilateral mydriasis in the 9- to 16-year-old subgroup (3/4 events) compared with the older (>16 years) subgroup (5/27 events).[5] These differences were hypothesized to be due to pediatric patients being more likely to touch or rub both eyes after application of medication or possibly due to systemic absorption. Of the 4 pediatric patients who experienced mydriasis, the mydriasis resolved within 2 days in 2 cases, 8 days in another, and 12 days in the final.[5] Among all patients in the ATMOS-1 and ATMOS-2 studies, all TEAEs occurred more commonly earlier in treatment, within the first week in the 4-week studies and within the first 12 weeks in the 44-week extension study, with decreasing incidence thereafter; therefore, it was concluded that TEAEs did not increase with longer duration of exposure.[2-4]

In conclusion, we report, to our knowledge, the first case of pharmacologic mydriasis from glycopyrronium wipes in a child younger than 9 and the first case of a child exposed to the medication through a caregiver. Plausibility of exposure through hand-to-eye contact was suggested in previous studies examining unilateral versus bilateral presentation of mydriasis in pediatric subgroups.[5] Pharmacologic mydriasis is known to occur through inadvertent exposure after handling other topical anticholinergic medications, such as scopolamine patches.[6] Studies have shown that adverse effects of glycopyrronium usually abate within 1 week following exposure.[5]

With the recent approval of glycopyrronium wipes, an increasing incidence of children presenting with inadvertent pharmacologic mydriasis may be expected. Because glycopyrronium is not approved for children <9 years of age, exposure to topical glycopyrronium may not be initially considered by providers. Providers are advised to specifically question patients of any age presenting with otherwise unexplained mydriasis about the use of glycopyrronium wipes. Being a topical wipe, patients

and parents may not consider it a medication; moreover, this case highlights that both patient and caregiver use must be queried. Prescribers of glycopyrronium wipes should be aware of the adverse effects, educate patients about the possibility of inadvertent mydriasis, and instruct thorough handwashing after use. Increased awareness of glycopyrronium and its side effects by healthcare providers evaluating pupillary abnormalities may limit unnecessary, costly, and potentially harmful tests in patients whose history and examination findings are suggestive of mydriasis from glycopyrronium.

Literature Search

PubMed was searched, without date restriction, on July 21, 2019, for English-language results, using the following terms: *glycopyrronium*, *glycopyrronium tosylate*, *glycopyrrolate*, *mydriasis*, *anisocoria*, *side effects*, and *children*.

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