BENDING THE VALUE CURVE

Eye-opening Etiologies

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A 5-year-old boy with a history of Trisomy 21, obstructive sleep apnea, moderate persistent asthma, and paroxysmal tonic upgaze (a nonepileptic syndrome of childhood) presented to the pediatrician in the summer with fevers, cough, congestion, and increased work of breathing. He was diagnosed with pneumonia on chest radiograph and treated with amoxicillin, albuterol nebulizers, twice-daily ipratropium nebulizers, twice-daily ipratropium nasal sprays, and oral prednisone as part of his sick plan.

After 1 week of treatment, he was starting to improve when he suddenly developed a fixed and dilated left pupil. The family came immediately to the emergency department, where he was found to have anisocoria (right pupil 3 mm to 2 mm; left pupil 5.5 mm to 5 mm) without ophthalmoplegia or ptosis. The rest of his neurologic examination revealed unremarkable results.

The case was discussed with the ophthalmology and neurology departments, and the decision was made to admit him to the hospital for a sedated MRI. Because of the high volume of patients requiring sedated imaging, he was hospitalized for 2 days for the scan, the results of which were normal. The ipratropium was discontinued on admission; 48 hours later, he demonstrated complete resolution of the anisocoria and was discharged from the hospital.

In cases of anisocoria with an otherwise normal neurologic examination, the differential diagnosis includes both a common pharmacologic side effect and a rare but potentially life-threatening problem.[1] Unilateral pupillary dilatation can sometimes be the only indication of an aneurysm or other subarachnoid lesion impinging on the superficial fibers of the third cranial nerve, although this is a less specific sign in pediatric patients than in adult patients.[2] Pediatric aneurysms have an estimated 19% mortality rate, and only 68% of patients survive without severe disability.[3] However, intracranial aneurysms are extremely rare. Only 2% to 3% of all aneurysms occur in pediatric patients, and the incidence of associated hemorrhage is between 0.05 and 0.09 per 100 000 person-years.[3,4] When there is high clinical suspicion for the benign etiology, prioritizing high-value diagnostic testing is crucial.

Anisocoria is a documented side effect of ipratropium and can lead to premature concern among physicians for cranial nerve impingement. This is particularly true in patients with a difficult neurologic examination, such as young children with developmental delay.[1,5–9] Furthermore, ipratropium is not recommended for asthma control outside of the emergency-department setting.[10] Ipratropium is a muscarinic cholinergic receptor antagonist that inhibits the parasympathetic system responsible for pupillary constriction.[7] It is poorly absorbed and often causes unilateral mydriasis, suggesting it operates by direct contamination.[11] The effect has only been documented after repeated administration of ipratropium, likely because the multidose preparation of ipratropium contains the preservative benzalkonium chloride, which increases corneal permeability in many medications.[8] Facemasks lose

www.hospitalpediatrics.org
DOI:https://doi.org/10.1542/hpeds.2017-0204

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HOSPITAL PEDIATRICS (ISSN Numbers: Print, 2154-1663; Online, 2154-1671).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

Dr Harer drafted the initial manuscript; Dr Alverson reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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~90% of the medication to the surrounding air or left in the chamber.[12] The effect lasts <48 hours, but can persist for 3 weeks.[7]

Pharmacologic mydriasis can be diagnosed with topical administration of the anticholinergic agent pilocarpine. The topical application bypasses the innervation of the pupil and causes pupillary constriction in cases of cranial nerve palsies. Therefore, failure to constrict to 1% pilocarpine suggests either a receptor blockade (pharmacologic mydriasis), structural mydriasis (trauma-induced sphincter rupture or synechial adhesions), or ischemia secondary to high intraocular pressure.[11] This principle holds true for pathologically miotic pupils as well. Topical application of apraclonidine bypasses the innervation of the pupil and causes pupillary dilation from neurologic etiologies (ie, Horner syndrome). Failure to dilate suggests a pharmacologic receptor blockade.[13] In this case, the application of pilocarpine would have revealed no pupillary response, and the patient would have been diagnosed with pharmacologic mydriasis without delaying sedated imaging.

Undiagnosed pharmacologic anisocoria is not a completely benign condition. Dilatation of the iris can obstruct the outflow tract of the anterior chamber in patients and has been known to cause acute closed-angle glaucoma in adults.[14] Increased intraocular pressures are generally not observed in children. However, patients with preexisting narrow angles are at risk for manifesting transient acute angle-closure crises.[14] Increased risk is especially found in patients with iridocorneal dysgenesis, aniridia, Sturge-Weber syndrome, uveitis, aphakia, or traumatic hyphema.[12] Furthermore, B_2-adrenergic agents such as albuterol are almost universally used in conjunction with ipratropium. These agents can stimulate ciliary bodies to secrete aqueous humor, which might potentiate risk of glaucoma.[14]

Finally, pursuit of an alternate etiology with a sedated MRI and/or magnetic resonance angiography is not without risks. Although the pilocarpine test can produce miosis, ciliary spasm, blurred vision, and photophobia, ~20% of children undergoing sedation for computed tomography or MRI scans experience an adverse event related to the sedation.[1,15] Such risks include oxygen desaturation (2.9%), failed or aborted procedures (7%), inadequate sedation (13.1%), or pharmacologic side effects including nausea, vomiting, paradoxical reaction, inadvertent drug overdose, and drug-related rash.[15] Additionally, the incidence of respiratory events such as laryngospasm or the need for airway management is 5.5%. This rate is not negligible in our high-risk patient with Down Syndrome, hypotonia, and obstructive sleep apnea.[15]

In the end, a life-threatening diagnosis such as an aneurism must be eliminated from the differential, but there may be more than 1 way to do so. Recognizing and prioritizing high-value diagnostic testing, even while waiting for more costly interventions, can provide prompt answers that change management. This requires both increased awareness of diagnostic interventions like pilocarpine as well as a high clinical suspicion for the benign etiology. High-value care involves careful consideration of medication side effects both before their administration and after the appearance of unusual symptoms. One must also be open to the possibility that medications intended for the lungs may reach the pupils, particularly in fidgety pediatric patients. In an effort to be conservative and definitively rule out high-risk diagnoses, we must not lose sight of more common etiologies. More extensive testing does not always confer safer care.

REFERENCES

1. Cabana MD, Johnson H, Lee CK, Helfaer M. Transient anisocoria secondary to nebulized ipratropium bromide. *Clin Pediatr (Phila)*. 1998;37(7):445–447
2. Lyons CJ, Godoy F, ALQahtani E. Cranial nerve palsies in childhood. *Eye (Lond)*. 2015;29(2):246–251
3. Sorteberg A, Dahlberg D. Intracranial non-traumatic aneurysms in children and adolescents. *Curr Pediatr Rev*. 2013; 9(4):343–352
4. Blount JP, Oakes WJ, Tubbs RS, Humphreys RP. History of surgery for cerebrovascular disease in children. Part I. Intracranial arterial aneurysms. *Neurosurg Focus*. 2006;20(6):E9
5. Yalcin S, Pampal K, Erden A, Oba S, Bilgin S. Do we really need to panic in all anisocoria cases in critical care? *Indian J Anaesth*. 2010;54(4):365–366
6. Iosson N. Images in clinical medicine. Nebulizer-associated anisocoria. *N Engl J Med*. 2006;354(9):e8
7. Wehbe E, Antoun SA, Moussa J, Nassif I. Transient anisocoria caused by aerosolized ipratropium bromide exposure from an ill-fitting face mask. *J Neuroophthalmol*. 2008;28(3):236–237
8. Sharma NS, Ooi J-L, Papalkar D, Sharma S, Francis IC, Fung VSC. Pharmacological mydriasis secondary to ipratropium bromide: a cause of unilateral dilated pupil. *J Clin Neurosci*. 2008;15(3):320–321
9. Pejic R, Klaric B. Transient anisocoria in a patient treated with nebulized ipratropium bromide. *Am J Ophthalmol Case Rep*. 2017;7:11–13
10. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma-summary report 2007. *J Allergy Clin Immunol*. 2007;120(suppl5):S94–S138
11. Jannun DR, Mickel SF. Anisocoria and aerosolized anticholinergics. *Chest*. 1986;90(1):148–149
12. Watson WT, Shuckett EP, Becker AB, Simons FE. Effect of nebulized ipratropium bromide on intraocular pressures in children. *Chest*. 1994; 105(5):1439–1441
13. Koc F, Kavuncu S, Kansu T, Acaroglu G, Firat E. The sensitivity and specificity of 0.5% apraclonidine in the diagnosis of oculosympathetic paresis. *Br J Ophthalmol*. 2005;89(11):1442–1444
14. Lachkar Y, Bouassida W. Drug-induced acute angle closure glaucoma. *Curr Opin Ophthalmol*. 2007;18(2):129–133
15. Malviya S, Voepel-Lewis T, Eldevik OP, Rockwell DT, Wong JH, Tait AR. Sedation and general anaesthesia in children undergoing MRI and CT: adverse events and outcomes. *Br J Anaesth*. 2000;84(6):743–748

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Hospital Pediatrics 2018;8;300
DOI: 10.1542/hpeds.2017-0204 originally published online April 12, 2018;

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AN OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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