

Unilateral Fixed Dilated Pupil in A Child with Critical Asthma: When A Nebulized Therapy Causes A Worrisome Sign and Rare Side Effect

(Short Title: Ipratropium bromide-induced anisocoria in a child)

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Citation: Alfraij A, Alseadawy M, Hasan W (2024) Unilateral Fixed Dilated Pupil in A Child with Critical Asthma: When A Nebulized Therapy Causes A Worrisome Sign and Rare Side Effect. *Anna Clin Rev Cas Rep*: ACRCR-129.

Received Date: 06 July, 2024; **Accepted Date:** 16 July, 2024; **Published Date:** 23 July, 2024

Abstract

Background: New onset anisocoria is a scary sign that may often suggest a life-threatening condition. Reservable causes of anisocoria include medication and herbal exposure. Eye contamination with ipratropium bromide mist may cause anisocoria by inducing unilateral mydriasis.

Methods: We are reporting a case of critical asthma triggered by a viral illness treated with an intensive nebulization regimen inside the pediatric intensive care unit. The child developed a new onset of unilateral fixed dilated pupil despite a normal neurological examination.

Results: The anisocoria resolved within a day after stopping ipratropium bromide, and pupils returned to normal without any sequela. Life-threatening causes in the brain were ruled out using a CT scan.

Conclusion: Despite the fact that ipratropium bromide nebulization is a standard therapy used in asthma cases, but anisocoria is a rare side effect that could be underreported due to its benign nature. Increasing awareness of this side effect and ensuring the appropriate seal of the nebulization mask can help reduce unnecessary investigation.

Keywords: Unequal pupils, Anisocoria, ipratropium bromide, PICU, Pediatrics.

Abbreviations

ICP: Intracranial pressure
PICU: Pediatric intensive care unit
HFNC: High-flow nasal cannula
CRP: C-reactive protein
GCS: Glasgow coma scale
MDT: Multidisciplinary team

Introduction

Anisocoria is a condition where a person has unequal pupils [1]. It could be a normal variant present in approximately 10-20% of people or a sign of a life-threatening condition [2]. Pathological anisocoria may indicate sympathetic or parasympathetic pathways nerve supply problems, or direct iris injury [3]. Pharmacological, which is a temporary-type anisocoria, can occur when a medication affects the pupillary dilator or sphincter muscles in one eye, causing a unilateral mydriasis or miosis. Agents causing pupils to dilate (mydriasis) include atropine, ipratropium bromide, tropicamide, cyclopentolate, scopolamine patches, and glycopyrrolate [4].

Ipratropium bromide is an anticholinergic agent (muscarinic antagonist) very commonly used in pediatrics, especially for acute asthma treatment. In 1986, anisocoria caused by ipratropium bromide was first reported [5]. The unilateral pupil dilation from ipratropium bromide nebulization is caused by the

medication aerosol that reaches the eye directly [6,7]. This could happen when the nebulizer mask is poorly fitting, loose, or broken [8]. Also, it may occur when high doses of ipratropium bromide are used or if spillage of the medication directly into the eye [6,9]. Here, we present a case of a temporary unilateral fixed dilated pupil from nebulized ipratropium bromide that was resolved within 24 hours after stopping the nebulization. Our aim from this case report is to increase awareness of a worrisome rare side effect from a common practice of using ipratropium bromide for asthma cases.

Materials and Methods

A 15-month-old previously healthy girl was admitted to the pediatric intensive care unit (PICU) with acute respiratory distress associated with a fever requiring a high-flow nasal cannula (HFNC). Diagnosis of bronchiolitis vs. reactive airway disease was raised after ruling out other differentials. Despite the absence of a history of atopy, her presentation with severe lower obstructive airway symptoms led to the decision to use bronchodilator therapy. An improvement was noticed, and the reactive airway disease (i.e., asthma of early infancy) triggered by viral infection became top of the diagnoses list. A systemic steroid and ipratropium bromide nebulization (based on pediatric dosing every 6 hours) were started. Blood workups were within the normal range, and C-reactive protein (CRP) was negative. A Boca virus was detected in the nasopharyngeal swab. Chest x-ray revealed hyperinflated lungs.

After 12 hours of her admission, she developed a new onset of unequal pupils noticed in routine PICU round. Her consciousness level, central nervous system examination, and Glasgow coma scale (GCS) remained normal and unchanged.

She was looking around with no ptosis. The pupillary examination revealed a left pupil diameter of 3 mm reacting to light. The right pupil was dilated and measured 6 mm in diameter with no reaction to light, as shown in Figure 1.

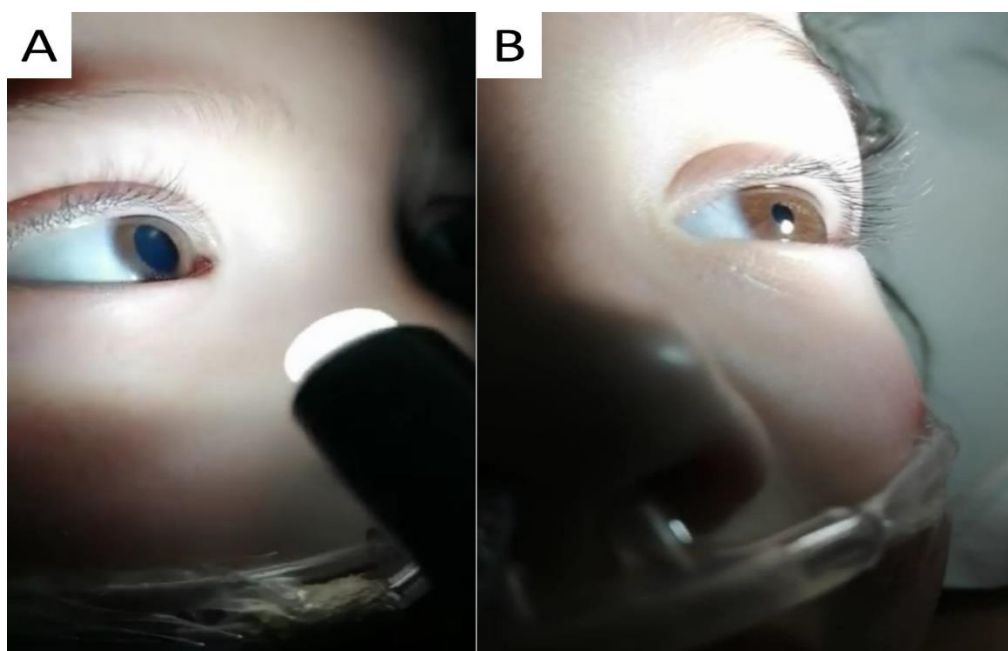


Figure 1: The pupillary examination of the patient's pupils, which was taken at the same moment that showed. **A:** The right pupil is dilated and measured 6 mm in diameter with no reaction to light. **B:** The left pupil has a diameter of 3 mm and reacts normally to light.

Complete neurological and ophthalmologic examinations were performed immediately, with no abnormality detected except for the anisocoria. Given the acute onset of the anisocoria, an urgent multidisciplinary team (MDT) meeting between pediatric intensivists, pediatric neurologist, and ophthalmologist was conducted, and an urgent brain imaging (CT scan) was recommended.

Results

The child underwent an urgent CT brain, which was unremarkable. A local eye effect of ipratropium bromide was suspected, and the medication was stopped. Within 24 hours after discontinuing the nebulization, the pupils returned to be equal, and the anisocoria's concern was entirely resolved.

Discussion

Anisocoria is an alarming sign that may lead, most of the time, to extensive and expensive neuroradiologic investigations, especially when it is acutely happening [10]. Normally, both pupils dilate in the dark and constrict in bright light. When anisocoria becomes prominent in the dark, it indicates that the small pupil is abnormal, i.e., sympathetic pathway affection. Conversely, if anisocoria becomes prominent in light, it indicates that the dilated pupil is abnormal; therefore, the problem is with the parasympathetic pathway (figure 2,3) [11]. If the relative difference in pupillary size is the same in both dim and bright illumination, the patient likely has physiologic anisocoria [11].



Figure 2: Anisocoria is prominent in light, indicating that the dilated pupil (Left eye - Arrow) is **abnormal**, i.e., the problem is in the parasympathetic pathway. [This hand drawing by Mr. Samran Alrashidi is made for the use of this article].



Figure 3: Anisocoria is prominent in the dark, indicating that the constricted pupil (Right eye - Arrow) is **abnormal**, i.e., the problem is in the sympathetic pathway. [This hand drawing by Mr. Samran Alrashidi is made for the use of this article].

Anisocoria can be classified based on the etiology into physiological, pathological, or pharmacological [10]. The commonest cause of unequal pupil sizes is physiologic anisocoria (also known as simple anisocoria) [2]. It is a benign condition with a settle pupillary size difference of less than or equal to 1 mm, and a normal response to light [12]. Anisocoria with a normal ocular examination but a nonreactive pupil to light is usually due to either oculomotor (third) nerve palsy or medication-induced. A careful history of parasympatholytic or sympathomimetic medications and plant exposures should be elicited; moreover, pupillary size and extraocular movements should be examined in all cases. Ptosis, “down and out” gaze in the ipsilateral eye, and loss of accommodation may support the oculomotor nerve palsy diagnosis. The life-threatening cause of acute-onset anisocoria is raised ICP due to a space-occupying lesion or infection, which compresses the parasympathetic fibers located superficially in the pupillary innervating nerve [13]. Brain imaging remains essential to rule out structural causes of acute anisocoria. Another etiology is direct trauma to the eye.

Pharmacologic anisocoria can be caused by administering agents acting on the pupillary dilator or sphincter muscles. Ipratropium bromide is a derivative of atropine that antagonizes acetylcholine at muscarinic cholinergic receptors [14]. A local effect on one eye from mist due to an improper mask seal may lead to a dilating pupil in that eye, causing anisocoria condition. Though its respiratory effect peaks at 30 to 60 minutes after administration, and the duration of action is 3 to 6 hours [15]; However, it took almost 1 to 2 days for ipratropium bromide-induced mydriasis to resolve after discontinuing the agent [16]. The effect might be prolonged on rare occasions and lasts up to 21 days [9]. Apart from that local effect, nebulization has no systemic effect on infant’s and children’s eyes, as demonstrated by several studies.

Bedside pupils’ examination before nebulization and adequate mask fitting can help not only in reducing the untoward adverse effect of ipratropium-bromide, but also reduce unnecessary investigations. Furthermore, a bedside test may help confirm the pharmacologic (anticholinergic drug) cause of mydriasis using 1% pilocarpine eye drops [17]. When 1% pilocarpine is administered topically to the conjunctiva, it will cause local-effect miosis in patients with dilated pupils. However, when mydriasis is due to an anticholinergic agent like ipratropium bromide, miosis will not occur and the pupil will remain dilated

as the muscarinic receptors are already blocked [8]. Moreover, increased intraocular pressure or damage to the sphincter muscle may also cause the pupil to be unresponsive to this test. So, ruling out eye trauma is crucial before performing this test [9]. It is uncommon to use this test due to undesirable pilocarpine effects, including ciliary spasm, blurred vision, and photophobia [18].

In our case, we could not use pilocarpine as it was not available in our facility at that time. With the reassuring brain imaging CT scan and normal neurologic examination, the decision to discontinue ipratropium bromide was taken. With careful monitoring, the anisocoria was resolved in 24 hours. The unnecessary exposure to imaging could have been avoided by considering the child's history and her previous neurological condition with a proper examination of the pupils pre- and post-nebulization. Also, closely monitoring the neurological status would be of great help in detecting any new changes that require rapid intervention and action. The monitoring should include the heart rate (mainly if bradycardia occurs), respiratory rate/pattern, blood pressure, level of consciousness, GCS, motor assessment, and other eye manifestations besides the anisocoria, which were all remained normal in our patient. Changes in these clinical signs with the presence of a new onset anisocoria should raise suspicions of intracranial pathology that may necessitate imaging and urgent intervention.

Conclusion

Using ipratropium bromide nebulization in patients with asthma is a usual practice. Though anisocoria induced by this therapy is uncommon, the new-onset anisocoria may be worrisome and may lead to unnecessary investigations. Given the level of the case report and the limitation to conclude a generalizable statement, physicians may cautiously consider ipratropium bromide-induced anisocoria, especially in the absence of other neurological or ophthalmological signs and symptoms in a patient receiving this medication.

Acknowledgment

We thank Mr. Samran Alrashidi for his hand drawing (figures 2 & 3) that was made for this article.

Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article.

Contributors' Statement

Abdulla Alfraij: conceptualization, methodology, data curation, writing – original draft, writing – review and editing and supervision

Mohamed Alseadawy: conceptualization, methodology, data curation, writing – original draft;

Walid Hasan: conceptualization, methodology, writing – review and editing;

All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Conflict of Interest Disclosures (includes financial disclosures): The authors declare that there is no conflict of interest regarding the publication of this article.

Funding/Support: No funding was secured for this article.

Consent for Publication:

Written informed consent was obtained from the child's parents to publish this report in accordance with the journal's patient consent policy.

Learning Points:

- The acute onset of unequal pupil in any patient requires immediate attention and a high index of suspicion.
- Pediatricians should remember that ipratropium bromide nebulization could result in anisocoria from eye contamination of medication mist.
- Eye patches or protective goggles may help prevent eye contamination with medication mist.
- More evidence is required to generate an approach to acutely isolated anisocoria in children to avoid unnecessary radiation exposure from brain imaging.

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