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Case Report

Nebulized ipratropium bromide in fixed dilated pupil: three cases report and review of literature

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Abstract: This study is to identity the clinical characteristics of mydriasis derived from nebulized ipratropium bromide in neurosurgical patients. We presented 3 patients with inhalation of ipratropium bromide associated mydriasis and reviewed the pertinent literature. Mydriasis was caused by nebulized ipratropium bromide leak from the mask into ipsilateral eye. When the medication was discontinued in the 3 patients, the pupillary abnormality was resolved in 2 patients, but 1 patient's pupil was not recovered. Ipratropium bromide blocks muscarinic acetylcholine receptors in sphincter pupillae. It absorbs through the cornea and conjunctiva, blocking the sphincter pupillae cholinergic M receptor antagonist lead to mydriasis, if lasts for a long time it will compress anterior chamber angle, impede real water reflux, cause increased intraocular pressure, induce glaucoma and ocular pain. It should quickly identify mydriasis reason in the clinical work, avoiding unnecessary invasive operation and imaging examination, to reduce the burden of patients.

Keywords: Ipratropium, mydriasis, nebulize

Introduction

Mydriasis is a vital method of Department of Neurosurgery, especially for serious patients with unilateral mydriasis, which needs to immediately conduct a comprehensive clinical examination, assessment, diagnosis and treatment. Without timely diagnosis and treatment, it can even cause death for patients. Common causes for mydriasis are transtentorial hernia, optic nerve, oculomotor nerve paralysis disease, meningitis. But, inhalation drug associated mydriasis was unusually happened and was paid little attention. Now we summary 3 cases for patients with inhalation of ipratropium bromide associated mydriasis in the Neurosurgery Department of our hospital as follows from 2011 February to 2014 April.

Case report

The 1st case, a 67 years old male with sudden headache, was unconsciousness for 6 hours. Physical examination showed: moderate coma, GCS4, fixed right pupil mydriasis. The diameter of right pupil was 5 mm, the diameter of left pupil was 3 mm. And all light reaction was disappeared. The left side was hemiplegia. Brain CT for admission to the hospital showed: the right basal ganglia cerebral hemorrhage was into ventricles. middle line shift to left. The amount of bleeding was about 80 ml. We performed the right basal ganglia intracerebral hematoma and bone flap decompression. Then the patient was sent to intensive care room and was treated by intravenous drug infusion, inhalation of ipratropium bromide 0.5 mg q6h (Shanghai Bolinge Yingehan Pharmaceutical Co., Ltd.). After 5 days, GCS of patient was 5. The right pupil was 3.5 mm diameter and unresponsive to light. Left pupil was 2.5 mm and responsive to light. The tension of decompression window flap in right operation area was not high. Brain CT showed clearance for brain hematoma (**Figure 1A**). Acute intracranial hypertension and cerebral hernia were excluded for the reason of mydriasis. 10 day after operation, patients were bilateral mydriasis (5 mm in diameter) without all light reaction. And decom-

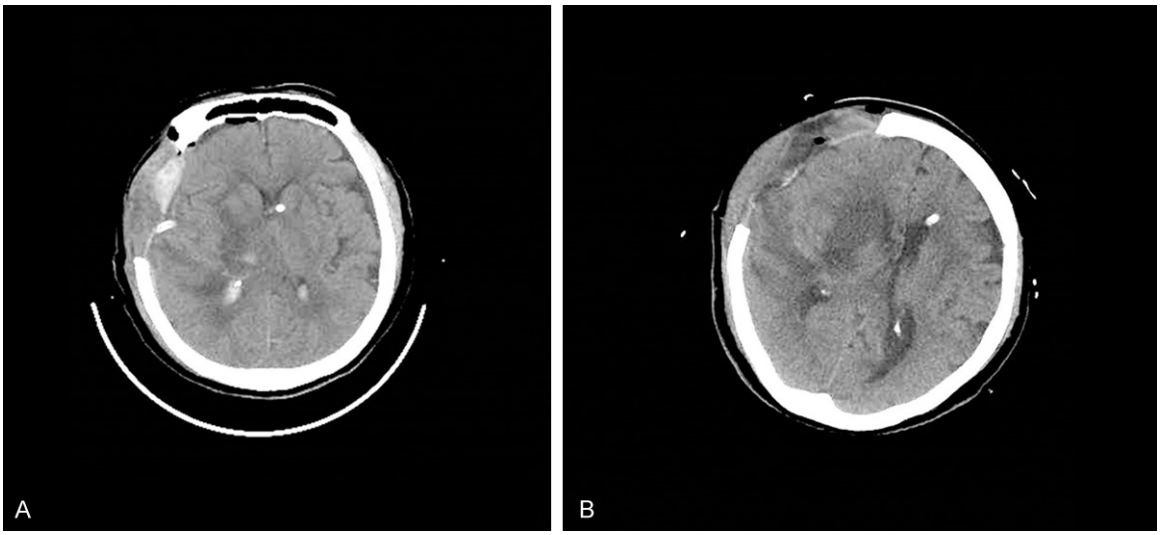

Figure 1. Case 1: A. 5 days after right basal ganglia intracerebral hematoma plus bone flap decompression operation, that the brain CT showed in the brain hematoma was satisfied; B. 10 days after operation it was found in patients with bilateral mydriasis, recheck brain CT showed intracranial no hemorrhage, hydrocephalus.

Figure 2. Case 2: A. Preoperative brain CT showed left temporal lobe brain contusion and hematoma; B. After 1 day of operation recheck brain CT which showed intracerebral hematoma removal was thorough; C. 5 days after operation found that patients with left mydriasis, recheck brain CT displayed no intracranial hemorrhage.

pression window flap tension was not high. GCS was 6. Recheck of brain CT showed that no intracranial hemorrhage, hydrocephalus and cerebral hernia (**Figure 1B**). Intraocular pressure was normal. Diseases were excluded for the cause of mydriasis by Department of Ophthalmology. Patient suffered persistent dilated pupil. At the 24th postoperative day, GCS was with 6. Intraocular pressure was increased, which was suspected to be glaucoma. Ipratropium bromide was found to be the cause of complications. And drug leakage was into the eye when inhalation. So we discontinued ipratropium bromide and conduct intraocular pressure lowering treatment. Then, the dilated pupil of patient was not restored. Finally the patient gave up the treatment and discharged from the hospital.

The 2ed case, a 45 years old male, was admission to the hospital after 12 hours for accident with head injury. Physical examination showed: lethargy, GCS 11, bilateral pupils were same size circle, diameter was 3 mm, sensitive to light, normal activities for limbs. Brain CT showed left temporal lobe brain contusion and hematoma, and hematoma volume was about 40 ml (**Figure 2A**). We performed temporal straight craniotomy for intracerebral hematoma. After 1 days of operation, the brain CT showed intracerebral hematoma was completely cleared (**Figure 2B**). Patient with aspiration pneumonia was treated with atomizing inhalation of ipratropium bromide 0.5 mg q6h (Shanghai Bolinge Yingehan Pharmaceutical Co., Ltd.). On the postoperative 5th day, left mydriasis was found (5 mm in diameter), and

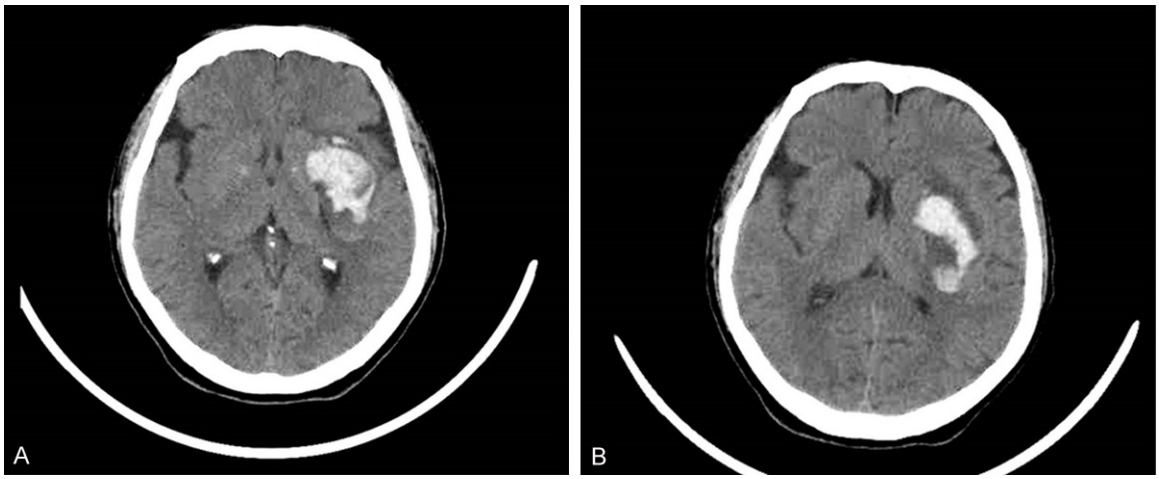

Figure 3. Case 3: A. Brain CT after 6 h for left basal ganglia intracerebral hematoma; B. Patients after 7 days drug treatment appeared the right side of mydriasis, recheck brain CT showed intracranial no fresh bleeding.

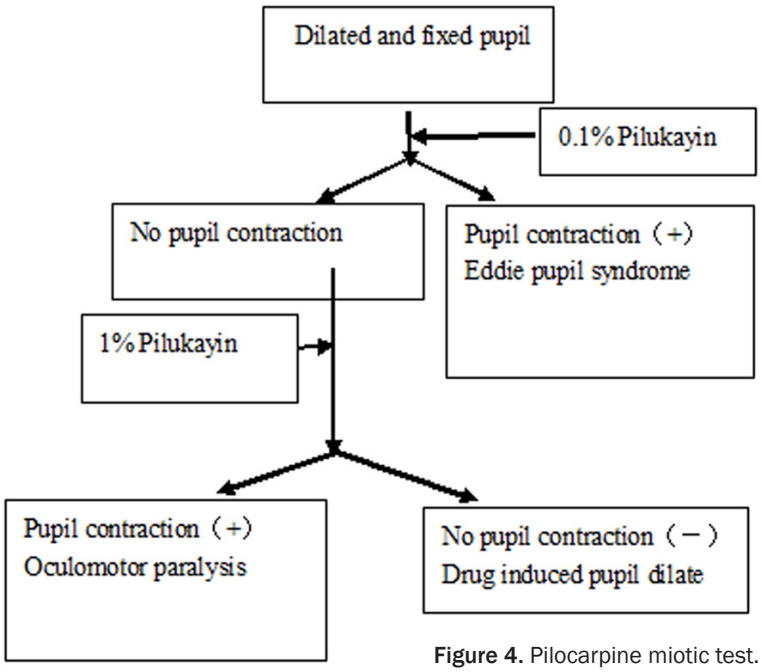

Figure 4. Pilocarpine miotic test.

light reaction was disappeared. The right pupil diameter was 3 mm, sensitive to light. And the patient was conscious without other neurological dysfunction. Brain CT displayed no intracranial hemorrhage, and midline structure was centered (**Figure 2C**). But it was showed that drug leakage to the eye after the mask inhalation, then we treated the discontinuation of ipratropium bromide. After discontinuation for 8 hours, the dilated pupil returned to normal size. Bilateral pupil diameter was 3 mm and sensitive to light. When we used protective mask during aerosol ipratropium bromide, mydriasis symptoms disappeared.

The 3rd case, a 65 years old female, had sudden headache and right hemiplegia for 6 hours. Physical examination showed: sanity, GCS 15, bilateral pupils were same size and circle, diameter was 3 mm, sensitive to light, right limb muscle strength was grade II, left limb activity was normal. Brain CT showed left basal ganglia intracerebral hematoma, and hematoma volume was about 20 ml (**Figure 3A**). Patient was with asthma. We conducted conservative treatment, and treated by inhaled ipratropium bromide 0.5 mg q6h for asthma (Shanghai Bolinge Yingehan Pharmaceutical Co., Ltd.). On 7th day after treatment, right mydriasis was found (5 mm in diameter), light reaction disappeared. And left pupil was 3 mm diameter and sensitive to light. The patient was conscious without new neurological dysfunction. But there was drug leakage to the eye when mask inhalation. We conducted 1% pilocarpine dropped right eye, and the eye with mydriasis did not appear miotic. So, it was confirmed as drug induced mydriasis. Then we discontinued ipratropium bromide. After discon-

tinuation for 16 h, left mydriasis of patient returned to normal size. And bilateral pupil was 3 mm diameter and sensitive to light. Brain CT showed no new intracranial hemorrhage, and midline structure was centered. Brain CTA examination showed no cerebral aneurysm (**Figure 3B**).

The follow up time of all three cases was 10 months. Bilateral mydriasis of the first case was not recovered. And the reaction of light was disappeared. The intraocular pressure was high. For the second and third cases, bilateral pupil returned to normal size and sensitive to light. The intraocular pressure was normal.

Discussion

Mydriasis is one of the important emergency signs in Department of Neurosurgery, which needs for timely diagnosis and treatment. Causes for the clinical common mydriasis are: (1) The oculomotor nerve palsy manifests as: mydriasis, disappeared the light reflection, superior rectus, medial rectus, inferior rectus and inferior oblique muscle activity obstacle and eyelid ptosis. It can be visible in the posterior communicating artery aneurysm, intracranial hypertension caused tentorial hernia. (2) The diseases of ophthalmology: acute angle closure glaucoma, optic nerve paralysis, paralysis of traumatic iris. General eyeball showed normal activities. The fundus showed optic atrophy or retinopathy. (3) Cervical sympathetic nerve diseases: Stimulated Cervical sympathetic nerve appears mydriasis, light reflection, expanded eyelid, exophthalmos, no eye movement disorders. It can be visible in the neck with tumor, inflammation, trauma, syringomyelia, cervical sympathetic neuritis. (4) Eddie syndrome: a syndrome of unknown etiology. The disease is typically characterized by sudden unilateral mydriasis, pupillary reflex abate or disappear, blurred vision, eye pain. Tendon reflex accentuated or disappeared, especially for the ankle and knee jerk reflex. (5) Drug caused mydriasis: anticholinergic drugs and sympathomimetic drugs may cause mydriasis, in which the mydriasis has the characteristics of self limiting.

Severe patients in Department of Neurosurgery were always complicated by pulmonary infection, which commonly used ipratropium bromide inhalation to relax bronchial smooth muscle and promote expectoration with auxiliary treatment of pulmonary inflammation. Ipratropium bromide is a powerful highly selective anticholinergic drugs, which mainly control bronchial spasm through the vagal inhibition of M cholinergic receptor. And it has a strong role in bronchial smooth muscle relaxation. Ipratropium bromide still can control mucus glands secretion and improve the cilia movement. Its effect on sputum volume is strong, thereby it can reduce sputum obstruction to improve ventilation, which is widely used in ICU of Neurosurgery. Clinical common side effects of ipratropium bromide include headaches, nausea, dry mouth, hand tremor, heart palpitations, whereas adverse reaction of the eye such as mydriasis and increased intraocular pressure is paid little attention in clinic. When ipratropium bromide was leaked from aerosol mask into the eyes, it is absorbed by the cornea and conjunctiva, blocked the sphincter pupillae cholinergic M receptor antagonist and acetylcholine further, leading to mydriasis. If it lasts for a long time, anterior chamber angle and real water reflux will be inhibited, causing increased intraocular pressure, glaucoma and ocular pain.

Ipratropium bromide is an anti-muscarinic drug, which is similar with atropine. After effecting on eyes, it can cause mydriasis and inhibit ciliary muscle. Discontinuing ipratropium bromide can recover mydriasis. In literatures before 2014 [1-5], there were 27 cases of mydriasis after inhalation of ipratropium bromide, in which 7 cases were children. The minimum age was a 6 months male children with pneumonia, who was treated by atomizing inhalation of ipratropium bromide after 1 day of unilateral mydriasis. Brain CT didn't show nervous system disorders. When inhalation leakage of ipratropium bromide into the eyes was found, discontinuing related drugs recovered mydriasis. In 27 cases, mydriasis of 26 cases was recovered after 24 h discontinuation of the drugs. Another 1 case was recovered in 48 h. All patients had not eye organic complications. For the first case in this study, mydriasis was not recovered and glaucoma occurred, because the reason of mydriasis was not diagnosed timely.

The mydriasis was induced by improper placement of nebulizer mask and atomized medicine ipratropium bromide leakage. Farrow etc. [6]

intended to leak ipratropium bromide leakage into eyes when atomization inhalation, but it did not appear mydriasis. So, he raised objections on the mydriasis by atomization medicine ipratropium bromide. Sharma etc. [7] found that the reason for the different consequences was the formulation types for aerosolized drug ipratropium bromide. Clinical commonly used composite solvent contained preservative benzalkonium chloride. Benzalkonium chloride was a powerful cation cleaning agent, which could increase the permeability of the cornea and promote drug absorption. Benzalkonii chloridum contained ipratropium bromide could promote corneal penetration and absorption of drugs, leading to mydriasis. Cornea permeability absorption for aerosolized drug without benzalkonium chloride was was little, and the occurrence of mydriasis was little. The mydriasis, induced by ipratropium bromide, was positive correlated with the use of dose and frequency.

It should quickly identify the reason for mydriasis in clinical work, avoid unnecessary invasive operation and imaging examination. Pilocarpine miotic test is important for diagnosis of mydriasis. Pilocarpine was a sympathomimetic drug, which played a role on muscarinic receptor in the iris sphincter muscle, amydriasis, reduced intraocular pressure. Pilocarpine miotic response is effective after 20 minutes administration and lasts for about 4-6 hours. Pilocarpine had miotic effect for the normal pupil and mydriasis which caused by neuropathic reasons. But for ipratropium bromide induced mydriasis, it has no obvious miosis effect (**Figure 4**). Drug induced mydriasis patients were no unconsciousness, loss of neurological functions, eyelid ptosis or eye movement muscle disorder.

If the drug was discontinued as early as possible, ocular symptoms would disappear within 24 hours. If mydriasis lasted for a long time, it would had complications: (1) blurred vision. (2) acute angle closure glaucoma: conscious person could have eye pain, blurred vision. unconsciousness one was not easy to be found in early time. If it last for a long time, the patient will loss permanent vision. So, patients were recommended to use oral catheter atomizing inhalation, or closed to the face during masking. Correct positions can prevent drug leakage and locally absorbed by cornea. For high risk patients, it was best to use protective eyewear.

Conclusions

In conclusion, unilateral mydriasis in an unconscious patient is an important clinical sign and a differential diagnosis must be quickly performed in order to rule out structural and pharmacological causes. Physicians should keep in mind that cholinergic antagonists agents administered via nebulizers can cause this unusual effect.

Disclosure of conflict of interest

None.

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