

# Allergic reactions to atropine eye drops for retardation of progressive myopia in children

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**Purpose:** To report clinical manifestations of ocular allergy to atropine eye drops used for retardation of progressive myopia in children. **Methods:** Myopic children, who developed bothersome itching that subsided promptly after cessation of atropine eye drops, were included. History of systemic or ocular allergy, preexisting ocular conditions, and clinical features of allergy were noted. **Results:** Six children, age 5–15 years, were included. Four developed allergy to 1% atropine sulfate eye drops and two to 0.01% concentration of atropine sulfate. The onset of allergy was within a month to as late as 4 years after using atropine eye drops. The severity of allergy was higher with 1% concentration. The most common symptoms of atropine allergy were itching and burning. The most common signs were lid swelling and hyperemia. The allergic manifestations promptly reversed with the stoppage of eye drops. Reintroduction was possible in three patients, either by reducing the concentration of atropine or using benzalkonium free formulation. **Conclusion:** Allergy to atropine eye drops in children may develop within a few weeks or after many years of usage. Prompt cessation followed by a reintroduction and continuation of therapy may be possible in few patients.

**Key words:** Allergic contact dermatitis, atropine, eye drops, itching, periocular dermatitis

Atropine eye drops are frequently used for retardation of progressive myopia in children.<sup>[1,2]</sup> Incidence of allergic conjunctivitis and allergic dermatitis (with 0.1% and 0.5% atropine eye drops) is reported to be 4.1% and 1.3%, respectively.<sup>[1]</sup> Contact dermatitis, allergic conjunctivitis, and interface dermatitis (ID) type reactions with 1% atropine eye drops are reported in adults.<sup>[3-6]</sup> A concentration as low as 0.0006% could cause allergy.<sup>[3]</sup>

To our knowledge, this is the first report that describes detailed ocular manifestations of allergy to atropine eye drops in children.

## Methods

Children diagnosed with allergy to atropine drops, between April 2014 and December 2017, were included. Only one patient (patient 1) was recruited prospectively. The diagnosis of eye allergy was based on a history of bothersome itching in or around the eyes that was caused due to instillation of atropine eye drops and subsided promptly following its stoppage.

The patients had used 1%, 0.5%, or 0.01% atropine sulfate eye drops. Single drop was instilled in the lying down or reclining position in the lower cul-de-sac. No specific instructions were given with regards to the technique of the instillation or punctal occlusion or periocular care. Patients

treated with 1% or 0.5% atropine eye drops were prescribed progressive addition photogray lenses.

## Results

Six children age 5–15 years were included [Table 1]. The most common symptoms were itching and burning [Table 2]. The most common signs of atropine allergy were eye lid swelling and periocular redness [Figs. 1-6].

In every patient, the symptoms were reduced within 24 h after stopping atropine eye drops and disappeared within a week. To hasten the recovery, in patient 1, twice a day local application of topical steroid (Chlorocol H eye ointment; Jawa Pharmaceuticals Pvt. Ltd., Haryana, India) was used.

It was possible to reintroduce atropine eye drops and continue the atropine therapy, albeit with a different formulation (Myopin<sup>®</sup>) in patient 3 and patient 4 and at a reduced concentration in patient 5.

An “allergy patch test” in patient 1 [Fig. 7] was weak positive for 1% atropine sulfate (ICDRG allergy patch test classification)<sup>[7]</sup> and negative for 0.01% atropine eye drops. In spite of a negative test, she developed unacceptable itching and redness within 2 weeks of using 0.01% atropine eye drops. It was decided to discontinue atropine therapy.

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**Table 1: General characteristics of the patients with atropine allergy**

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age in years at the time of diagnosis	12	15	5	14	8	9
Gender	Female	Male	Female	Male	Female	Male
Duration of use	7 months	4 years	4 months	1 month	5 months	4 years
Concentration of atropine used	1% and 0.01%	1%	0.01%	0.01%	1%	1% and 0.5%
Brand of atropine	Bell Pino®	Bell Pino®	Prepared by adding injection atropine sulfate (0.6 mg/mL) to 5mL MoisoI® eye drops (FDC, New Delhi, India).	Prepared by diluting 1% atropine sulfate eye drops (Jawa Pharmaceuticals Pvt. Ltd., Haryana, India) with water for injection.	Bell Pino®	1% Atropine sulfate eye drops (Jawa Pharmaceuticals Pvt. Ltd., Haryana, India) and dilution with water for injection.
Frequency of use	Once at night	Once at night	Once at night	Once at night	Once at night	Once in the morning
History of allergic disease	Nil	Chronic allergic rhinitis, chronic allergic conjunctivitis	Chronic allergic rhinitis	Nil	Acute allergic conjunctivitis	Nil
Re-introduction	Discontinued atropine eye drops	Discontinued atropine eye drops	Continued with change in formulation	Continued with change in formulation	Continued after reducing the concentration	Discontinued atropine eye drops

**Table 2: Ocular manifestations of allergy to atropine eye drops**

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Itching	+	+	+	+	+	+
Burning	+	+	+	+	+	Doesn't remember
Swelling of lid	+	+	+	+	-	+
Periocular redness	+	+	+	+	-	+
Conjunctival congestion	+	-	+	-	-	+
Discharge	+	+	-	-	-	+
Loss of eyelashes	-	+	-	-	-	-
Periocular skin erosions	+	+	-	-	-	-
Exaggerated under eye fold	-	-	+	-	-	-
Hypopigmentation	-	+	-	-	-	-
Increased vascularity	-	+	-	-	-	-
Follicular reaction	+	Not examined	Not examined	Not examined	+	Not examined

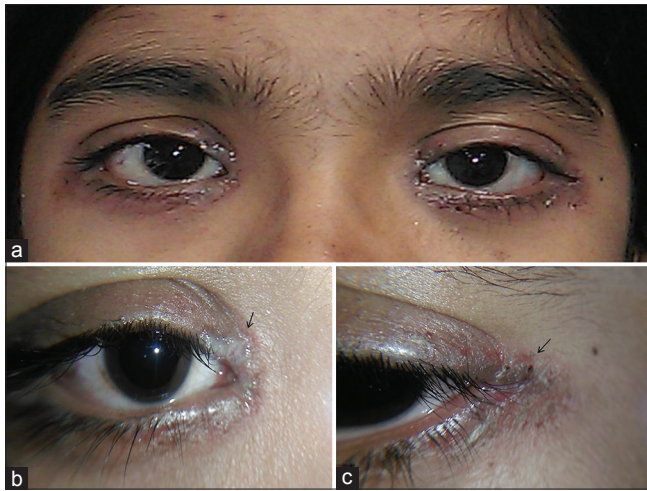
In patient 2, severe periocular hypopigmentation developed in addition to complaints of severe itching and periocular redness [Fig. 2]. An opinion from dermatologists was sought. Two senior dermatologists felt that hypopigmentation was unrelated to atropine use. An allergy patch test [Fig. 8] in him showed absence of reaction to 0.01% and 1% atropine at the end of 48 h. Continued use of 1% eye drops for further 6 months was associated with persistent itching and worsening of hypopigmented patches. 1% atropine eye drops was replaced by reconstituted 0.01% atropine eye drops. His itching and burning significantly reduced, but hypopigmented patches persisted. A therapeutic trial of twice a day topical bimatoprost 0.01% (Lumigan®; Allergan, Bangaluru, India) and tacrolimus 0.1% (Talimus®; Ajanta Pharma, Mumbai, India) was advised to him which resulted in focal areas of repigmentation [Fig. 9]. Nevertheless, he

was asked to stop 0.01% atropine eye drops and continue the follow-up with the dermatologist.

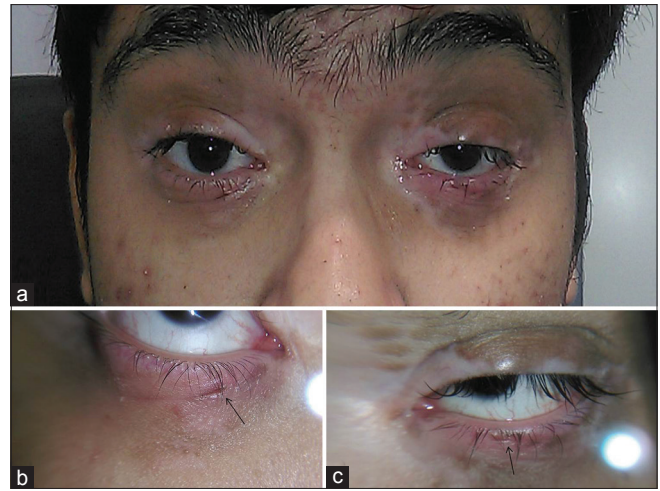
## Discussion

In this study, children developed allergy to atropine eye drops irrespective of their age, gender, or duration of use. The onset was insidious, and the severity was higher with 1% concentration. Reintroduction at a lower concentration, after complete resolution of symptoms, could reduce or eliminate the allergic manifestations.

Manifestations of atropine allergy could be divided into ocular and periocular [Table 3]. Clinicians can differentiate allergy to atropine eye drops from other ocular allergies by stopping the drops in one eye or identifying a lack of typical papillary response seen with other causes of allergic conjunctivitis.



**Figure 1:** (a) Face photograph of patient 1, using 1% atropine eye drops, showing redness, swelling, superficial erosions, and hemorrhagic crusting of both eyes. (b) Picture of right eye showing edema and slough over medial canthus (black arrow). (c) Picture of left eye showing hemorrhagic crusting over lateral canthus area involving periocular skin (black arrow)



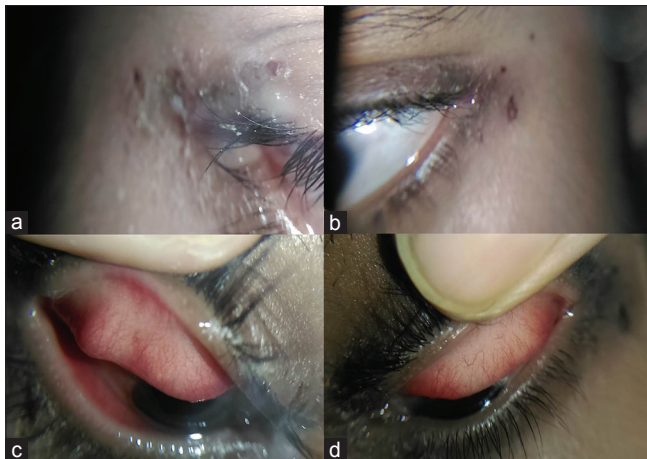
**Figure 2:** (a) Face photograph of patient 2, using 1% atropine eye drops, showing periocular diffuse redness and swelling involving both the lids, skin erosions with focal crusting (black arrow), post inflammatory irregular hypopigmentation around lids, and madarosis of both lower lids, with erosion around lower eye lid. (b and c) Magnified picture of right and left eyes showing the typical signs of periorcular dermatitis



**Figure 3:** Face photograph of patient 3, using reconstituted 0.01% atropine eye drops, showing left eye periocular skin rash and redness with exaggerated under eye fold



**Figure 4:** Face photograph of patient 5, using 1% atropine eye drops, showing edema of both the eye lids bilaterally and crusting over medial canthus in both eyes



**Figure 5:** Photograph of patient 1 after stopping 1% atropine eye drops in the left eye. (a and b) Photograph showing reduction of lid swelling, erosion, and crusting in the left eye. (c and d) Photograph showing minimal follicular reaction in the upper tarsal conjunctiva



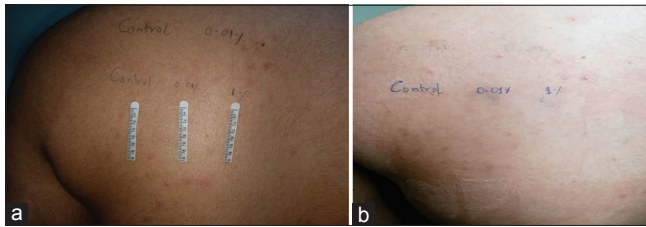
**Figure 6:** Photographs of patient 1 showing complete resolution of the allergy 10 days after discontinuation of 1% atropine eye drops

History of allergy was present in 50% children in this series. It is possible that patients with preexisting ocular or systemic

allergy or ocular comorbidity, namely, dry eye disease, meibomian gland dysfunction, or patients using multiple eye drops may be at a higher risk of allergy.<sup>[3-6]</sup> It is not known why patients develop allergy to the very drug that they have



**Figure 7:** Allergy patch test in patient 1. (a) Picture showing a patch containing atropine 0.01% on the right side of the back of the patient and 1% atropine on the left side. (b) Picture showing absence of reaction to 0.01% atropine and an erythematous reaction (6.2 cm x 4.2 cm) to 1% atropine



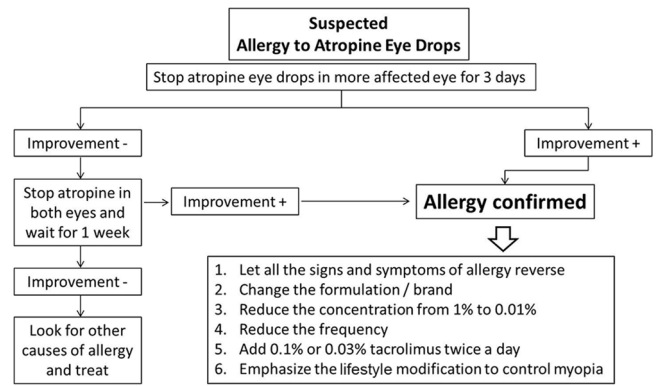
**Figure 8:** Photograph of patient 2 demonstrating (a) allergy patch test with control (distilled water), 0.01% atropine and 1% atropine. (b) Lack of hypersensitivity reaction after 48 h



**Figure 9:** Photograph of patient 2, showing serpinginous depigmentation around the left eye with areas of repigmentation (black arrow) after discontinuation of 1% atropine eye drops and 6 weeks application of topical bimatoprost and tacrolimus while continuing 0.01% atropine eye drops

tolerated for many years. The ophthalmologist should advice the parents to put drops with punctal occlusion and wipe of the excess from periocular skin.

Elimination of preservatives benzalkonium and chlorbutonol was associated with successful reintroduction of atropine therapy in two patients. Allergic contact dermatitis and irritant contact dermatitis are known to occur with benzalkonium chloride, thimerosal, and alcohols, such as chlorobutanol.<sup>[8]</sup> Changing the preservative to a stabilized oxychloro complex has resulted in significantly better tolerance of topical medication.<sup>[9]</sup>



**Figure 10:** Clinical algorithm for management of patients with allergy to atropine eye drops

**Table 3: Clinical classification of atropine eye allergy**

	Symptoms	Signs
Ocular	Itching, burning, conjunctival redness, discharge, eyelash matting, light sensitivity	Follicular conjunctival reaction, hyperemia, reduced tear film break-up time
Periocular	Swelling, itching, redness	Lid edema, hyperemia, papules, macules, vesicles, excoriation, madarosis, hypopigmentation, dry scaly lichenified plaques

As such, it may not be recommended to make diluted atropine solution from injectable atropine due to chances of contamination, inaccuracy of mixing the two preparations, change in the shelf life, and introduction of BAK/chlorbutol/ other excipients.

Hypopigmented patches in the periocular area following the use of topical atropine eye drops are uncommon. The ophthalmologist must immediately stop using the drops and seek dermatological opinion. The diagnostic accuracy of patch test in ocular allergy is not known and patients may continue to be symptomatic despite a negative result.

Once developed, hypopigmented patches may take very long to recover. Permanent hypopigmentation of periocular skin following chronic use of eye drops can happen.<sup>[10]</sup>

There are two major limitations of our study. (1) The study included only patients with history of itching. We might have missed patients with irritant contact dermatitis who may present with only burning or pain with minimal or no itching. (2) Only one patient was recruited prospectively during the active phase. Hence, the data regarding the incidence of allergy to atropine eye drops were not available.

Nevertheless, the ophthalmologists should suspect an allergy to atropine eye drops in patients with bothersome itching and/or burning and promptly discontinue its use for a quick reversal of symptoms. It might be possible to reinstitute the therapy after a change in formulation or with a reduced concentration of atropine drops.

**Table 4: Current available market formulations of atropine eye drops**

Drug	Pharmaceutical	Active ingredient	Preservative
Bell Pino	Bell Pharma	Atropine sulfate 1%	Chlorbutol
Atropine eye drops	Jawa	Atropine sulfate 1%	Chlorbutol
Myopin	Appasamy	Atropine sulfate 0.01%	Stabilized oxychloro complex
Myatro	Entod Pharma	Atropine sulfate 0.01%	Stabilized oxychloro complex
Atroped	Sunways	Atropine sulfate 0.01%	Stabilized oxychloro complex
Pinocort	Bell Pharma	Atropine 1% and hydrocortisone 0.5%	Chlorbutol

## Conclusion

The ophthalmologists should follow a specific clinical algorithm [Fig. 10] to diagnose and manage the patients suspected to have allergy to atropine eye drops. One may restart the eye drops in one eye after a few days or after a patch test and watch for the response. In case of recurrence, change in formulation [Table 4], reducing the concentration, or frequency of application and a simultaneous use of immunomodulator, namely, tacrolimus may help. In some cases, where it may not be possible to reinstitute the therapy, lifestyle modifications should be emphasized to slow the progression of myopia.

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## Conflicts of interest

There are no conflicts of interest.

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