

The Direction of Specific Efforts with Allergic Conjunctival Diseases in Japan

—From the standpoint of ophthalmologists—

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Hiroshi YOSHIDA*¹, Etsuko TAKAMURA*²

Abstract

Allergic conjunctival diseases include allergic conjunctivitis and spring catarrh (vernal conjunctivitis). The immediate phase of the type I allergic reaction is the essence of the pathology and etiologic mechanism of allergic conjunctivitis, whereas the late phase of the type I allergic reaction is considered to be involved in those of spring catarrh. The use of anti-allergic eye drops is the first-line therapy for allergic conjunctivitis. In cases of pollen allergy, initial therapy with eye drops is effective for relieving symptoms that occur in the pollen season and for reducing the duration of continuing symptoms. If antiallergic eye drop therapy fails to eliminate symptoms, low-concentration steroid eye drops should be combined. Although the basic treatment of spring catarrh also uses antiallergic eye drops, treatment of severe cases should begin with a combination of an antiallergic, steroid, and cyclosporin eye drops, with the concentration and frequency of steroid instillation being gradually reduced as symptoms improve. Self-care is also useful in relieving symptoms in patients with allergic conjunctival disease. A recommended form of self-care is eye washing with artificial tears.

Key words Allergic conjunctivitis, Spring catarrh, Antiallergic eye drops, Steroid eye drops, Cyclosporine eye drops

Introduction

Children with allergic diseases may have a hard time at school even if others do not notice it. In particular, school-aged children with spring catarrh (vernal conjunctivitis) suffer from the repeated recrudescence of keratoconjunctivitis, which may prevent them from participating in various school events and from enjoying their school lives.

This paper outlines the use of therapeutic medications, precautions in daily living, and other information useful for school doctors in relation to allergic conjunctival diseases, particularly allergic conjunctivitis and spring catarrh.

What Is Allergic Conjunctival Disease?

Allergic conjunctival disease refers to broadly categorized allergic conjunctivitis, and is defined as an inflammatory disease of the tunica conjunctiva which presents with various signs and symptoms and in which a type-I allergic reaction is involved.¹ Conjunctivitis associated with type I allergy is included in the category of allergic conjunctival disease, regardless of whether there is accompanying allergic inflammation, such as type IV allergy. On the other hand, conjunctivitis occurring in allergic children is not included in allergic conjunctival disease if there are no peculiar symptoms such as painful, itchy eyes. According to differences in the clinical picture, allergic

*1 Director, Yoshida Eye Clinic, Matsuyama, Japan (hiyoshid@ss.ij4u.or.jp).

*2 Associate Professor, Department of Ophthalmology, Tokyo Women's Medical University, Tokyo, Japan.

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conjunctival disease is classified into allergic conjunctivitis (seasonal or perennial), atopic keratoconjunctivitis, spring catarrh, and giant papillary conjunctivitis. Allergic conjunctivitis is devoid of proliferative changes in the conjunctiva, whereas the condition with proliferative changes in the conjunctiva is classified as spring catarrh or atopic keratoconjunctivitis.

Patients with these conditions complain of subjective symptoms peculiar to allergic conjunctival disease, such as painful, itchy eyes, foreign-body sensation, eye discharge, and lacrimation. Objective findings obtained by slit-lamp microscopy include inflammatory manifestations such as hyperemia, edema, papillae, and follicles in the conjunctiva. Allergic conjunctival diseases common in children are allergic conjunctivitis and spring catarrh.

Mechanism of Onset of Allergic Conjunctival Disease

Mechanism of onset of allergic conjunctivitis (seasonal or perennial)

The essence of allergic conjunctivitis is considered to be the immediate-phase, type-I allergic reaction. When an outside allergen such as cedar pollen enters the tear fluid or attaches to the ocular surface, macrophages in the conjunctiva capture the allergen. This information is transmitted to T lymphocytes, which then convey the information to B lymphocytes, where allergen-specific IgE antibody is produced. When this IgE antibody binds to IgE receptors on the surface of mast cells in conjunctival tissue, an allergen-sensitized state is produced. If the allergen invades the ocular surface again, and a bridge is formed between two allergen-specific IgE antibodies on mast cells, degranulation of the mast cells occurs, causing chemical mediators including histamine to be released locally in the conjunctiva. Primarily, histamine binds to histamine H₁ receptors present in the free terminals of vascular or trigeminal C fibers that transmit the sensation of itching, resulting in the occurrence of hyperemia and painful itching. With this series of reactions, cytokines and adhesion molecules act on subconjunctival blood vessels at the affected site to cause eosinophils to infiltrate into the conjunctival epithelium and tear fluid.

Mechanism of onset of spring catarrh

Late-phase, type-I allergic reaction (allergic inflammation occurring 12–24 hours after exposure to an allergen) is considered to be involved in the pathologic condition of spring catarrh. Predominantly, Th2 cells are produced locally in the conjunctiva, and the aggravation of allergic inflammation occurs at the affected ocular site through the involvement of various cytokines that increase in tear fluid. As a result, fibroblasts proliferate in subconjunctival tissue, leading to the formation of giant, cobblestone-like papillae. Eosinophils, having infiltrated from subconjunctival blood vessels into the affected site, are activated and invade the cornea via tear fluid. Corneal disorders are then created by histotoxic proteins such as eosinophil cationic protein (ECP) and major basic protein (MBP) released from degranulated eosinophils to the affected site.

Diagnosis of Allergic Conjunctival Disease

One representative of seasonal allergic conjunctivitis is cedar pollinosis. Patients with cedar pollinosis suffer painful, itchy eyes, hyperemia, lacrimation, and foreign-body sensation during the pollen season. Perennial allergic conjunctivitis is a type of allergic conjunctivitis that follows a chronic course in response to common indoor allergens, such as mites and house dust. However, in cases of pediatric perennial allergic conjunctivitis, the major complaint may not be painful, itchy eyes, creating limitations in clinical diagnosis.

A diagnosis of allergic conjunctival disease can be established through the detection of eosinophils in ocular discharge. However, since the sensitivity of detection is not high enough, a negative test cannot deny the allergy. To determine the allergen causing the conjunctivitis, the detection of antigen-specific IgE antibody is attempted by serologic examination including radioallergosorbent test (RAST). However, the results reflect the presence of allergy throughout the whole body, and are not restricted to the cause of conjunctivitis. Currently, attempts are underway to make a rapid diagnosis of allergic conjunctivitis through the detection of IgE in tear fluid.² A simple procedure may soon be introduced.

Table 1 Types and dosages of antiallergic eye drops

Chemical mediator release inhibitory eye drops (devoid of antihistaminic activity)	
Sodium cromoglycate (Intal [®])	4 times a day
Amlexanox (Elics [®])	4 times a day
Pemirolast (Alegysal [®])	2 times a day
Tranilast (Rizaben [®] /Tramelas [®])	4 times a day
Ibudilast (Ketas [®] /Ibinal [®])	4 times a day
Acitazanolast hydrate (Zeperin [®])	4 times a day
Histamine H ₁ receptor antagonists (having antihistaminic activity)	
Ketotifen fumarate (Zaditen [®])	4 times a day
Levocabastine hydrochloride (Livostin [®])	4 times a day
Olopatadine hydrochloride (Patanol [®])	4 times a day

Treatment of Allergic Conjunctivitis

The first-line therapy for allergic conjunctivitis is the use of antiallergic eye drops because of their efficacy and safety. In Japan, 9 different antiallergic eye drops have been formulated (Table 1). All of these drugs have been approved and become available as oral medicines or nose drops. These eye drops have almost equal therapeutic efficacy, regardless of whether or not there is antihistaminic activity. Nevertheless, an immediate effect is expected from antihistamine drugs (Histamine H₁ receptor antagonists).³

For pollinosis, initial therapy with eye drops is effective in relieving symptoms during the pollen season and in reducing the duration of symptom manifestations. The frequency of instillation is generally 4 times a day, but pemirolast eye drops are known to be effective at two instillations per day. The regimen of twice a day in the morning and evening is convenient because medication can be carried out at home by children who would find it difficult to administer eye drops at school. In addition, sodium cromoglycate eye drop products that do not contain benzalkonium chloride due to the risk of allergy to the preservative have been formulated. To preclude contamination of the remaining solution after opening, disposable 0.35-ml containers have been adopted. The treatment of allergic conjunctivitis should begin with the use of antiallergic eye drops. Low-concentration steroid eye drops should be added if symptoms persist.

Self-care is useful for alleviating the symptoms of allergic conjunctival disease. A recommended form of self-care is that of washing the eyes with artificial tears to eliminate allergens from the ocular surface and remove eosinophils in eye discharge and their granular proteins, which have been linked to impairment of the corneal epithelium.¹ Frequent eye washing is more effective. Small-sized, preservative-free artificial tear products allow safer use without the possibility of contamination of the remaining solution.

Severe form of Allergic Conjunctival Disease: Spring catarrh

Spring catarrh occurs frequently in children with an atopic diathesis, particularly boys, and follows a severe course characterized by proliferative changes in the conjunctiva. Cases with marked proliferative changes in the palpebral conjunctiva are classified as the eyelid type, and those with marked lesions in the limbus, as the limbus type. Proliferative changes in the palpebral conjunctiva are characterized by giant papillary proliferation 1 mm or more in diameter in the upper palpebral conjunctiva, called cobblestone-like papillary proliferation. Lesions in the limbal conjunctiva are characterized by swelling and bank-like elevation, and are accompanied with corneal epithelial impairment of varying degrees. The impairment of the corneal epithelium is considered to be attributable to activated eosinophils migrating from the conjunctiva and their granular proteins. As conjunctival lesions worsen,

corneal findings follow the process of worsening from superficial punctate keratitis to exfoliative superficial punctate keratitis, corneal erosion, and shield ulcer.*³

Symptoms such as painful, itchy eyes and eye discharge in spring catarrh are severer than those in allergic conjunctivitis due to pollinosis. In addition, if there is accompanying corneal disorder, it may happen that the patient cannot open his or her eyes because of foreign-body sensation, eye pain, or photophobia, or cannot go to school because of reduced visual acuity.

Treatment of Spring Catarrh

The cornerstone of the treatment for spring catarrh is also antiallergic eye drops. Resolving the itch can suppress the scraping involved in the worsening of spring catarrh. Some antiallergic eye drops exert an effect on the late phase of type I allergy. The use of such drugs is more effective. Steroids are currently second to none as anti-inflammatories. While steroid eye drops are combined in usual cases, subconjunctival injection or oral medication may be used for severe cases. The type, concentration, and frequency of instillation of steroid eye drops are chosen according to the severity of the condition. In severe cases, an eye drop product of 0.1% betamethasone, a strong steroid, is used initially, and then changed to 0.1% fluorometholone, a moderate steroid, if symptoms improve. If early improvement is desired in patients who show no improvement of corneal findings, the subtarsal injection of a steroid such as triamcinolone may be carried out. Oral medication of prednisolone 5–10 mg for 1–2 weeks is another option.

A possible adverse effect of steroids is the elevation of intraocular pressure, regardless of the type of steroid, dose, and route of administration. Since this adverse effect is dosage-dependent, topical administration, such as eye drops and ophthalmic ointments, is associated with the highest risk. Although the elevation of intraocular pressure is usually reversible, prolonged administration may result in irreversible elevation. In particular, children may not cooperate with testing, and they are more likely to have increased intraocular pres-

sure after the application of steroid eye drops.⁴ Therefore, caution is necessary in the application of steroid eye drops in children.

In January 2006, prescription of 0.1% cyclosporin eye drops (PAPILOCK Mini[®] ophthalmic solution 0.1%) for spring catarrh was approved. Since this product contains no preservative, 0.4-ml, single-use containers have been adopted; one drop of this solution is given 3 times a day, using one container at a time. Cyclosporine mainly acts on T cells, and inhibits the production of various cytokines from T cells, thereby suppressing allergic inflammation. According to our experience with 0.05% cyclosporine aqueous ophthalmic solution prepared in our institution,⁵ this ophthalmic solution has a slow pharmacologic effect as compared with high-concentration steroid eye drops, but can offer improvement in severe keratoconjunctival findings if combined with steroid eye drops. If symptoms are relieved, reduction or discontinuation of steroid eye-drop therapy is possible.

Treatment of severe spring catarrh begins with antiallergic, steroid, and cyclosporine eye drops, with the concentration and frequency of steroid eye drop therapy being reduced as symptoms improve. Antiallergic and cyclosporine eye drops should be continued for as long as possible. If the therapy is not sufficiently effective, the route of steroid therapy should be changed to subtarsal or oral administration, or surgical treatment including papillary resection should be included.

Ophthalmologists are often asked by patients with allergic conjunctivitis or their families whether they are allowed to enter the school pool. Even during spring catarrh, patients may be able to enter the pool if they are in remission, have minimal corneal problems, and can keep their eyes open. In this case, however, they are recommended to wear swimming goggles to protect the ocular mucosa from the chlorine disinfectant used in pool water. After swimming, it is also recommended to wash the face with tap water and wash the eyes with preservative-free artificial tears. Tap water contains a low concentration of chlorine, and therefore pool-side fountains for eye washing are not recommended as a tool for aggressive eye washing.

*3 Shield ulcer is a condition characterized by deposition of mucin, degenerative epithelium, and inflammatory residue in the defective part of the corneal epithelium. The ulcer base is opacified and grayish white, and the ulcer lesion appears to be enclosed by edematous corneal epithelium. Deposition may increase to produce a white prominence, called plaque, from the corneal surface.

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