

Atopic Dermatitis and Keratoconjunctivitis

Brett Bielory, MD^a, Leonard Bielory, MD^{b,c,*}

KEYWORDS

- Atopic dermatitis • Atopic keratoconjunctivitis • Ocular allergy
- Blepharoconjunctivitis • Keratoconus

Atopic keratoconjunctivitis (AKC) is a more common chronic inflammatory disorder of the eye than previously appreciated. It is a potentially blinding ocular condition with disabling symptomatology because it involves inflammation of the cornea ("kerato") and the conjunctiva. In 1952, Hogan^{1,2} first described AKC as a bilateral conjunctivitis occurring in five male patients with atopic dermatitis (AD). Other atopic ocular disorders include seasonal and perennial allergic conjunctivitis, giant papillary conjunctivitis, and vernal conjunctivitis (**Box 1**).^{3,4}

IMMUNOPATHOPHYSIOLOGY

The histopathologic findings of AKC are diagnostically specific and include a mixture of mast cell, eosinophil, and lymphocyte infiltration into the conjunctival epithelium that seems to be a hybrid of Th1 and Th2 interactions.⁵ This is further supported by in situ hybridization studies of ocular tissue showing increased levels of mRNA for interleukin (IL)-3, -4, and -5 compared with normal tissue. IL-2 and -5 mRNA expression have been found to be significantly higher in subjects with AKC, as have IL-4 tear levels.⁶ In addition, interferon (IFN)- γ mRNA expression was greater in patients with AKC than in control subjects ($P = .005$).⁷ The increased IFN- γ significantly correlated with corneal involvement, a sign of disease severity, and upregulated intercellular adhesion molecule-1 on conjunctival fibroblasts.⁶ Overall, AKC seems to have a slight

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^a Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, 900 NW 17th Street, Miami, FL 33136, USA

^b STARx Allergy and Asthma Center, 400 Mountain Avenue, Springfield, NJ 07081, USA

^c Center for Environmental Prediction, Rutgers University, 14 College Farm Road, New Brunswick, NJ 08901-8551, USA

* Corresponding author. STARx Allergy and Asthma Center, 400 Mountain Avenue, Springfield, NJ 07081.

E-mail address: drlbielory@gmail.com

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Box 1**History and physical components of AKC***History*

Chronic or chronically relapsing atopic disease

- Dermatitis
- Asthma
- Rhinitis
- Conjunctivitis

Ocular symptoms with little or no seasonal variation (as opposed to vernal conjunctivitis, which is predominantly seen only in warm weather, especially along the Mediterranean Sea basin)

- Itching
- Burning
- Tearing
- Photophobia
- Ropy discharge
- Decreased vision

Physical

Periocular

- Dennie-Morgan folds (linear lid folds)
- Hertoghe sign (absence of lateral eyebrows)

Lids

- Thickening and tylosis, crusting, edema, fissures
- Ptosis
- Staphylococcal blepharitis

Conjunctiva

- Small- or medium-sized papillae
- Hyperemia, edema, excessive mucin
- Limbal Trantas dots (clusters of necrotic eosinophils, neutrophils, and epithelial cells)
- Formation of keratinization, cicatrization, and symblepharon in advanced disease

Cornea

- Punctate epitheliopathy and keratitis
- Extensive peripheral corneal vascularization in later stages
- Persistent epithelial defects
- Higher incidence of keratoconus (16%)
- Shield-shaped ulcers
- Recurrent herpes simplex keratitis associated with AKC
- Anterior stromal scarring
- Micropannus

Lens

- Anterior subcapsular shield-shaped cataracts
- Posterior cataracts (similar to steroid induced cataracts)

Fundus

- Degenerative vitreous changes
- Retinal detachment
- Uveitis (rare)

shift in mRNA expression to Th2-like T-cell cytokine profile.⁷ In addition, tear fluid cytokines including IFN- γ , tumor necrosis factor- α , IL-2, IL-4, IL-5, and IL-10 levels seem to play an important pathophysiologic role in AKC.⁸ IL-5 seems to correlate more closely with the proliferative forms of ocular allergy.⁹

CD4 lymphocytes are increased in various forms of chronic ocular allergy, such as AKC, and seem to require the P-selectin ligand for their direct infiltration into the conjunctiva.¹⁰ Examining specific CD4 subsets, the percentages of naive Th (CD4/45RA+) and memory Th (CD4/29+) cells, and the Th/Ts and memory Th cells/naive Th cells ratios were measured in the blood and tear samples of patients with AKC, atopic patients without ocular involvement, and normal volunteers. The results showed that patients with AKC had significantly higher memory Th cell concentration especially in the tear samples, and Th/Ts and memory Th cells/naive Th cell ratios both in the tear and blood samples compared with normal subjects.¹¹ This further supports that the local ocular environment is important in the development of the more chronic forms of ocular disease, such as AKC. The complexities and the multicellular involvement continue to expand. Additional abnormalities, including conjunctival epithelium of patients with AD with Langerhans cells (CD1a⁺) bearing IgE on its surface, suggest that these cells may also be involved in eliciting the hypersensitivity reaction and may participate in ocular inflammation.¹²⁻¹⁴

A unique finding of the development of an AKC-like disease in four patients who had no history of atopic disorders and who received pluripotent hematopoietic stem cell replacement therapy has been reported, suggesting the potential of some form of adoptive transfer.¹⁵

The relationship of serum levels of IgE, LTB₄, and food allergen sensitivity were significantly increased in AD patients with ocular complications compared with those without ocular complications.¹⁶ In ocular-type AD, serum IgE was significantly increased in patients with cataracts compared with those without cataracts. In other studies, however, development of cataracts or retinal detachment had no relationship to serum IgE levels, personal history of respiratory atopy, the duration of topical corticosteroid use on the face, or treatment with systemic corticosteroids.¹⁷ This suggests that patients who habitually rub their faces strongly tend to develop cataract or retinal detachment at a statistically significant higher frequency. Tear histamine and LTB₄ levels in AD patients with ocular complications showed significant elevations compared with those in patients with pure AD and controls.¹⁶

Other mechanisms of corneal damage include eosinophilic activation and mediator release. There is evidence that sIgA secretion in the tears of patients with AD was significantly lower than that of normal subjects and a higher frequency of *Staphylococcus aureus* in the tears from patients with AD compared with normal subjects.¹⁸ This suggests that the reduced sIgA secretion on the mucous membranes might play a crucial role in the pathogenesis of the ocular lesions. The common finding of *S aureus* colonization in AKC suggests a potential role for the activation of epithelial cells by Toll-like receptor 2 and the receptor for platelet-activating factor.¹⁹ This is further supported in a mouse model of allergic conjunctivitis that demonstrated that inoculation of *S aureus* markedly accelerated the signs of allergic conjunctivitis and was associated with higher levels of IgE in serum. In addition, the mice inoculated with *S aureus* had more IL-4, IL-5, IL-13, and eotaxin secretion than the noninoculated group. In contrast, inoculation of Toll-like receptor 2 (–/–) mice with *S aureus* had no effect on severity of ocular symptoms. The findings further support that activation of Toll-like receptor 2 signaling by *S aureus* induces Th2-type immune responses and accelerates experimental allergic conjunctivitis.²⁰ Another issue is whether the integrity of the ocular surface epithelium in patients with AD is impaired. In a study of AD

patients with blepharoconjunctivitis who were age matched with patients with seasonal or perennial allergic conjunctivitis and normals, the AD plus blepharoconjunctivitis patients showed significantly higher fluorescein uptake in the cornea and bulbar conjunctiva than the normals and patients with allergic conjunctivitis.²¹

Other abnormalities in AKC include epithelial pseudotubule formation and goblet cell hyperplasia,²² increased basophil histamine release, eosinophilia, and elevated serum IgE. Conjunctivae from patients with AKC have a marked increase of CD3⁺ lymphocytes, primarily CD4⁺ phenotype in the substantia propria. In addition, the conjunctivae express increased IL-4 and IL-5. These cells also express the TCR- α/β phenotype. In addition, there is an increase in CD1⁺ Langerhans cells noted in the epithelium and the substantia propria. As expected in patients with AD, the serum IgE is commonly elevated in patients with AKC, but correlates poorly with the severity of disease.²³ The highest levels of serum IgE seem to be found in those patients with atopic cataracts compared with normals.²⁴ Tears from AKC patients may have IgE, eosinophils, and mononuclear cells with a paucity of basophils and mast cells. This is in contrast to patients with atopic blepharoconjunctivitis.

CLINICAL MANIFESTATIONS

Epidemiology and Concomitant Disorders

It is commonly accepted that atopy affects 5% to 20% of the general population. The prevalence of AD in children is as high as 20%, whereas AKC occurs in 20% to 40% of individuals with AD, although it is uncommon to find AKC as a sole manifestation of atopy.^{25,26} AKC is associated a familial history for atopy, such as AD and asthma, and over 95% of AKC patients also have eczema and 87% have a history of asthma. The inverse, however (ie, the reported incidence of ocular involvement in patients with AD), reveals a range of 25% to 42%.^{23,27-29} Although there have been a few case reports of patients diagnosed with AKC as the sole manifestation of their atopy, these patients had a long-standing history of chronic conjunctivitis with bilateral pannus formation. Further evaluation by an allergy specialist revealed that they all had features of a more systemic atopic disorder including AD and asthma.³⁰

The symptoms of AKC commonly include itching, burning, and tearing, which are much more severe than in seasonal or perennial allergic conjunctivitis and tend to be present throughout the year. Seasonal exacerbations are reported in many patients, especially in the winter or summer months,¹⁴ and with exposure to animal dander, dust, and certain foods. There seems to be a trend in AD patients having ocular involvement with increasing levels of IgE and specific IgE to foods, such as rice and wheat and allergic mediators.¹⁶

AKC most commonly involves the lower tarsal conjunctiva and when it involves the cornea, it can lead to blindness. Originally reported to flare with worsening dermatitis, there are reports that some patients' ocular involvement evolves independently of their dermatitis,² whereas other reports reflect a correlation with tear levels of eosinophil cationic protein.³¹

AKC presents in the late teens and early twenties and may persist until the fourth and fifth decades of life.¹⁴ The disorder only occasionally presents before the late teenage years. When AKC is noted to start earlier, however, it is characterized by greater ocular surface epithelial damage.³² Conversely, severe AKC associated with complications, such as blepharoconjunctivitis, cataract, corneal disease, and ocular herpes simplex, occurs primarily in older patients with a peak incidence occurring in the 30- to 50-year-old age group.^{27,33,34}

Ocular complications are seen in over a third of patients with AD, ranging from 31% to 43%²⁷ to 56%.³⁵ Ocular involvement was reported in 41 of 128 patients with AD: 13 had severe conjunctivitis and three had severe keratitis.²⁹ Similarly, in another study, 85 out of 200 patients with AD were reported to have ocular involvement including blepharoconjunctivitis, cataract, corneal scarring, pannus formation, keratoconus, and ocular herpes simplex.²⁷ Severe active AD treated in an ophthalmologic service revealed predominant clinical features of eyelid eczema (66%), AKC, superficial punctate keratopathy (68%), and decreased tear function tests (56%).³⁶

In addition to the cutaneous manifestations of AD, the periorbital skin and cheeks are commonly involved in AKC with eczematoid changes including erythema and thick and dry scales.³⁷ Dennie-Morgan lines involving the skin of the eyelid result in a single or double infraorbital crease secondary to edema or thickening. As with seasonal and perennial allergic conjunctivitis, allergic shiners are common. The absence of the lateral eyebrow is present in many older patients (de Hertoghe sign) and may be caused by the extensive chronic eye rubbing or some form of autonomic dysfunction.^{38,39} Signs include bilateral involvement of the conjunctiva (primarily lower tarsal) in the form of fine papillary hypertrophy of conjunctiva, chemosis, limbal hyperemia, and limbal gelatinous hyperplasia.

In a study reported in 1990 that involved a 9-year retrospective review of 45 patients seen at a large referral center the severity of ocular disease was quite pronounced with subepithelial fibrosis (N = 26), symblepharon or fornix foreshortening (N = 13), and severe keratopathy (N = 34), which included neovascularization in 17 patients. Persistent epithelial defect was another major complication, occurring in 21 eyes and causing severe loss of vision.¹⁴ The description of the more severe forms of AKC is similar to cicatrizing conjunctivitis or cicatricial pemphigoid with subepithelial fibrosis, fornix shortening, and symblepharon formation.²³ Bilateral involvement with abundant mucoid discharge is the rule. Secondary staphylococcal blepharitis is common, caused by the eyelids becoming indurated and macerated. AKC is a chronic inflammatory allergic disease associated with conjunctival and corneal complications that include superficial punctate keratitis, macroerosions, corneal ulceration, plaque formation, corneal neovascularization, and lipid infiltration. The bulbar conjunctiva is commonly injected and chemotic. The corneal epithelium reveals punctate staining with fluorescein and limbal infiltration, Horner points, or Trantas dots. It is the corneal scarring and neovascularization, however, that may result in blindness. Keratoconus occurs in a small percentage (1.5%–16%) of patients with AD^{40,41}; conversely, AD was reported to occur in 16% of patients with keratoconus.⁴⁰ In a recent study of AD, eyelid eczema (66%), AKC, and superficial punctate keratopathy (68%) were the dominant ocular diseases.

COMPLICATIONS

Blepharitis involving predominantly the skin and lashes tends to be staphylococcal or seborrheic in nature, whereas involvement of the meibomian glands may be either seborrheic; obstructive; or a combination (mixed). The pathophysiology of blepharitis is a complex interaction of various factors, including abnormal lid-margin secretions, microbial organisms, and abnormalities of the tear film. Blepharitis can present with a range of signs and symptoms, and is associated with various dermatologic conditions, including seborrheic dermatitis, rosacea, and eczema. The mainstay of treatment is an eyelid hygiene regimen, which needs to be continued long-term. Topical antibiotics are used to reduce the bacterial load. Topical corticosteroid preparations may be helpful in patients with marked inflammation.⁴²

Individuals with AD have frequent colonization and infection with *S aureus*. AD patients have problems with synthesizing defensin proteins (eg, human β -defensin-3) associated with the rapid elimination of *S aureus*.⁴³ AKC patients generate increased α -defensin levels in tears.⁴⁴ It is unclear whether there is a subset of AKC patients with similar problems to those found in the skin that may lead to secondary staphylococcal blepharoconjunctivitis. Other specific ocular complications of AD include cataracts, blepharitis, keratoconus, iritis, and retinal detachment.

Cataracts as an ocular complication of AD were reported in 1914.^{45,46} AKC occurs in 8% to 12% of patients with the severe form of AD, but especially in young adults approximately 10 years after the onset of the AD.^{41,47–51} It is in this more severe population that cataracts are observed.⁵⁰ A unique feature of AKC cataracts is that they predominantly involve the anterior portion of the lens and may evolve rapidly into complete opacification within 6 months. Patients with AD may also develop posterior or nuclear type cataracts that may not be distinguishable from steroid-induced cataracts.^{27,48,52–57} The use of oral or prolonged topical corticosteroid therapy may increase progression of atopic cataract formation or may cause the classical homogeneous posterior cataract. There is a suggestion that high levels of IgE¹⁶ or the rapid rise of IgE levels may portend the development of atopic cataracts.²⁴ In patients diagnosed with an atopic cataract on the first visit, IgE levels were approximately 25,000 IU/mL, whereas those who did not have cataracts had IgE levels of approximately 4000 IU/mL that increased to 13,000 IU/mL at the time of cataract development.²⁴ More recently, the 56T allele in the IFNGR1 promoter resulted in higher IFN- γ receptor 1 transcriptional activity and seems to be a genetic risk factor for atopic cataracts.⁵⁸ Although filaggrin has been associated with more severe forms of AD, hyperlinear palms, and keratosis pilaris, it has not been specifically evaluated for the development of AKC.^{59,60}

Keratoconus is a progressive noninflammatory corneal ectasia that occurs in a small percentage of patients with AD. There is an association between positive allergy skin tests and keratoconus.⁶¹ AD is less common in patients with unilateral keratoconus and keratoconus occurs more frequently on the side of the dominant hand. Although keratoconus patients with and without atopy did not differ significantly with regard to gender, age of onset, or rate of keratoplasty, it has been noted that patients with very high IgE levels were more prone to graft rejection.⁶¹

Postkeratoplasty atopic sclerokeratitis is a potentially severe complication in atopic patients undergoing keratoplasty. In the evaluation of postsurgical complications of patients (N = 247 keratoconus eyes) undergoing keratoplasty, 14% had a history of AD, of which six eyes of five patients (2.4%) developed postkeratoplasty atopic sclerokeratitis. The mean age of postkeratoplasty atopic sclerokeratitis patients was 29 years with the mean onset of postkeratoplasty atopic sclerokeratitis being 26 days. Preoperative atopic blepharitis and corneal neovascularization were identified as risk factors for postkeratoplasty atopic sclerokeratitis.⁶² Inversely, eczema was reported to occur in 16% of patients with keratoconus.⁴⁰

Retinal detachment seems to be increased in patients with AKC and in AD.^{63–66} Additional complications of AKC including blepharoconjunctivitis, cataract, corneal disease, and ocular herpes simplex are commonly associated with older patients and have been reported to be as high as 42.5%.^{25,33,67} Herpes simplex keratitis is often bilateral with high recurrence rates that are more severe. Many patients may develop secondary staphylococcal blepharitis. It seems that AKC patients have a higher incidence of bacterial superinfections, especially with staphylococcus.^{1,68} In a recent study, *S aureus* was isolated from 67% of the AD patients, and finding any type of bacteria was isolated from 86% of the patients was significantly higher

than those of nonatopic control participants (6% *S aureus* and 25% any bacteria). No significant relationship between the frequency distribution of bacteria and the grade of atopy or associated ocular diseases was noted, however, in this small population of AD patients (N = 36).⁶⁹

AKC with significant epithelial disease also demonstrates decreased corneal sensitivity and tear film break-up times, compared with patients with insignificant epithelial disease and controls ($P < .01$).⁷⁰

The dermal and conjunctival irritation associated with staphylococcal colonization was postulated as early as 1937, suggesting that the inflammatory response was induced by a "dermonecrotic factor." It was histologically noted that no lymph follicles or eosinophils were present with several types of keratitis and corneal involvement. Epithelial keratitis can be caused by "toxic mechanisms."⁷¹⁻⁷³ AKC patients have similar findings to those hypothesized from staphylococcal colonization with various degrees of ocular surface alterations that include superficial punctate keratitis, macroerosions, corneal ulceration, plaque formation, corneal neovascularization, and lipid infiltration. These lesions mimic some of the pathologic features seen in asthma, such as Creola bodies, desquamated bronchial linings that have been associated with the deposition of major basic protein. Early studies demonstrated a correlation of tear eosinophil cationic protein levels with severity of ocular disease.³¹ Finding the heavily infiltrated mucosal surface of AKC patients with various inflammatory mediators and cells associated with atopy, such as mast cells, eosinophils, and lymphocytes, has led many to investigate the direct effect of eosinophilic mediators, such as tear eosinophil cationic protein or major basic protein. Studies have shown their presence, their involvement in animal models, and a direct correlation with such treatments as mitomycin C aided papillary resection provided a dramatic decrease in ocular surface inflammation as evidenced by decrease in the number of inflammatory cells and tear eosinophil cationic protein levels with a rapid improvement of clinical corneal and conjunctival findings.⁷⁴ Eosinophils are uncommon in seasonal and perennial forms of allergic conjunctivitis, but are found in AKC. Recent studies show that the incidence of concurrent infection (mainly bacterial infections caused by *S aureus*) strongly correlated with the percent of eosinophilic cells. Concurrent bacterial infection was identified in 26 of 26 cases of the subgroup with the highest percent of eosinophilic cells.⁷⁵ In addition, tear film dysfunction seems to coexist with AKC as demonstrated by tear break-up time values of less than 10 seconds in 62% of the eyes and C 1, 2, and 4 mRNA expression.^{70,76} Impression cytology samples from eyes with corneal ulcers showed significant squamous metaplasia and reduction in goblet cell density compared with eyes without ulcers and eyes of control subjects. Specimens from eyes with corneal ulcers showed periodic acid-Schiff positive mucin pickup and did not stain positive for MUC5AC. MUC5AC mRNA expression was significantly lower in eyes with corneal ulcers compared with eyes without ulcers and eyes of control subjects. MUC5AC mRNA expression was also significantly lower in eyes with AKC suggesting that ocular surface inflammation in patients with AKC has tear film instability and decreased conjunctival mucins in the tear fluid layer that may be important in the pathogenesis of noninfectious corneal shield ulcers in atopic ocular surface disease.^{70,76-78}

NASAL-OCULAR LINKS IN AKC

Various forms of chronic ocular allergy exist, but there are limited studies to demonstrate the significance of the relationship between the chronic forms of allergic keratoconjunctivitis (atopic and vernal) and allergic rhinitis. In a recent allergen nasal challenge, ocular symptoms were collected in addition to the nasal symptoms from

atopic ($N = 15$) showing positive history and skin tests, but responding insufficiently to the local ophthalmologic therapy with a control population of allergic rhinitis ($N = 11$) who did not have a history of ocular disease. It is interesting to note that out of 71 allergen nasal challenges 51 positive nasal responses were noted in 24 patients ($P < .01$), and 43 ($< 80\%$) of the nasal challenges were accompanied by significant ocular response ($P < .01$). No ocular responses were measured during the 26 phosphate buffered saline control nasal challenges ($P > .05$) or during 11 repeated nasal provocations in control subjects ($P > .2$). The results provide additional evidence for possible involvement of nasal allergy in some of the chronic forms of ocular allergy that commonly involve more than just mast cells in the involvement of the cornea (ie, keratoconjunctivitis).⁷⁹ Twenty years earlier the same author had proposed a nasal-ocular linkage.⁸⁰

TREATMENT

Medical treatments for AKC have included mast cell stabilizing agents, such as cromolyn,⁸¹ lodoxamide,^{82,83} *N*-acetylaspartylglutamic acid,⁸³ anti-IgE,⁸⁴ plasmapheresis,⁸⁵ and newer immunomodulatory agents for the treatment of severe AKC.⁸⁶⁻⁹⁰ The use of cyclosporine and tacrolimus has proved effective in the treatment of both AD and AKC in a small number of patients.^{91,92} A topical cyclosporin formula has also been shown to improve subjective and objective symptoms and signs of AKC.^{93,94} In the latter study, 30% of steroid users were able to discontinue topical steroids,⁹⁴ whereas in another study of 18 AKC patients the use of a lower concentration of a topical cyclosporin A 0.05% ointment as a steroid-sparing agent was not found to be better than placebo.⁹⁵

Various reports have described the use of topical calcineurin inhibitors in the treatment of periocular AD.^{91,96} Topical tacrolimus 0.1% ointment reduced signs and symptoms of eyelid eczema.⁹⁷ There are two studies listed focusing on the treatment of AKC using topical cyclosporine in a solution versus the presently approved suspension for tear film dysfunction (<http://clinicaltrials.gov/ct2/show/NCT00884585?term=atopic+keratoconjunctivitis&rank=2>. Accessed December 25, 2009).^{98,99} In the more severe forms, however, systemic treatment with calcineurin inhibitors or daclizumab may be required.⁹⁶

Contact lenses have also been used in some patients with AKC. Specifically, rigid gas-permeable scleral contact lenses were used in the treatment and visual rehabilitation of patients with advanced AKC and demonstrated improved vision with their use for more than 18 months.^{100,101}

SUMMARY

AD is one of the chronic diseases seen by allergist-immunologists that have both dermatologic and ocular manifestations. The occurrence of ocular disease is often proportionately higher than that of dermatologic disease. Even if the skin abnormalities seem well controlled, these patients require ophthalmic evaluation. Optimal management requires a team approach that includes the primary care physician, allergist, and ophthalmologist. AKC in AD patients is characterized by acute exacerbations and requires maintenance therapy for long-term control. Exacerbations need aggressive treatment to limit ocular signs and symptoms and to reduce ocular inflammation that can lead to permanent visual loss. Hygiene cannot be overemphasized because colonization with *S aureus* may be associated with the local release of superantigenic exotoxins generating a form of toxic shock syndrome of the eye that over time leads to more severe complications of AKC. Topical corticosteroid use, although at times

needed, should be minimized to decrease the potential adverse effect on the eye (glaucoma and cataracts). Future studies will continue to emphasize the use of steroid-sparing, immunomodulating agents that have the potential to provide long-lasting anti-inflammatory control with a more favorable side-effect profile. Overall, AKC is more common than previously appreciated, because it was primarily recognized only in the more severe forms, whereas milder forms are seen by practicing allergist-immunologists and these patients need to be identified and treated earlier to prevent disabling visual abnormalities.

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