Clinical features and diagnosis of adult atopic keratoconjunctivitis and the effect of treatment with sodium cromoglycate

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SUMMARY This study describes 17 cases of atopic keratoconjunctivitis in adults. In 8 cases the clinical appearances were nonspecific and sufficiently different from vernal keratoconjunctivitis to make diagnosis difficult. These atypical cases often showed a fine papillary conjunctival reaction on the upper tarsus, subconjunctival scarring, and in 1 case severe symblepharon. Corneal features included corneal microcysts, peripheral vascularisation, and various patterns of punctate epithelial keratitis. It was therefore important to establish the atopic status of the patient. A personal or family history of other atopic disease was elicited in every case, and the diagnosis was confirmed by the detection of raised serum IgE level. Uncontrolled clinical assessment suggested that 10 out of 15 patients experienced improvement in symptoms with the use of 2% sodium cromoglycate eyedrops 4 times a day. A subsequent double-masked cross-over trial comparing the same treatment with a matched placebo preparation indicated that 6 out of 9 patients preferred sodium cromoglycate while 1 preferred the placebo. Two patients noted no difference. Cases showing nonspecific or atypical clinical features responded to treatment just as frequently as did cases of typical vernal keratoconjunctivitis.

Vernal keratoconjunctivitis is an atopic reaction and is a specific ocular manifestation of type I hypersensitivity. Other features of atopy include eczema, asthma, hay fever, and rhinitis. Anterior subcapsular cataract and keratoconus occur as less frequent ocular complications. Atopic reactions are mediated by IgE (reaginic) antibody produced in response to numerous environmental allergens which include house dust mite, pollens, and animal danders. IgE combined with antigen attaches to the surface of mast cells in the tissues and causes release of histamine and other agents, which provoke an inflammatory reaction. Eosinophils are prominent in this condition and are probably attracted by the release of the eosinophil chemotactic factor of anaphylaxis (ECF-A) from the sensitised mast cells. It seems the eosinophils exercise an anti-inflammatory role by releasing factors which inhibit histamine and other chemical mediators of the inflammatory response.

Before the immunological mechanisms were elucidated the ocular disease had been exhaustively reviewed by Beigelman and concisely summarised by Duke-Elder. Vernal keratoconjunctivitis or vernal catarrh is a specific clinical diagnosis which can be made with certainty on ocular examination alone. It is usually a disease of childhood, occurring in boys in 80% of cases, and undergoes spontaneous regression at puberty. The clinical features are generally described as tarsal or limbal in distribution, but Jones has indicated the wide variation in corneal changes in vernal disease and that in some cases atypical corneal disturbances may predominate.

There is, however, some uncertainty about the relationship of vernal disease to adult atopic keratoconjunctivitis, though some adult cases are included in descriptions of vernal catarrh. This paper therefore describes 17 adults with diverse types of keratitis and conjunctivitis and also assesses the value of topical sodium cromoglycate in these cases. This mast cell stabilising agent has been shown to have a valuable role in the control of vernal catarrh in children.

Material and methods

Seventeen atopic patients referred to the external eye disease clinic at the Tennant Institute of Ophthalmology were studied between 1975 and 1979. The
presence of atopy was often unsuspected, and all patients were aged 16 years or older. The nature and periodicity of ocular symptoms were recorded, and any personal or family history of eczema, asthma, or hay fever was noted. Ocular examination, including slit-lamp biomicroscopy of the everted upper tarsus, was carried out.

The diagnosis was confirmed by estimation of serum IgE level by radioimmunosorbent technique (RIST, Pharmacia, normal value in adults <150 arbitrary units), and in most cases the peripheral blood was examined for eosinophilia. Bacterial and viral cultures, including examination of conjunctival scrapings for chlamydia, were carried out when clinically indicated, and conjunctival scrapings were examined for the presence of eosinophilia.

The value of 2% sodium cromoglicate eyedrops applied 4 times a day to both eyes was estimated after regular use for over 3 months following the initial acute presentation. Evaluation was based on the patient’s overall subjective report of improvement in ocular comfort, watering, photophobia, and discharge as well as on the author’s assessment of changes in the inflammatory signs seen by slit-lamp biomicroscopy. Sixteen of the 17 patients were available for adequate follow-up, but 1 of these was excluded because he was suffering from severe asthma which required changing doses of systemic steroids for its control.

In addition, a double-masked cross-over trial was conducted with 9 patients in which the same regimen of 2% sodium cromoglicate drops was compared with a matching placebo preparation allocated at random and changed after 6 weeks of treatment. All patients commenced treatment simultaneously and the trial was concluded after 12 weeks. In this controlled trial the patient’s subjective reports were reinforced by the use of diary cards. All patients were examined by the same observer before starting treatment, after the first 6 weeks, and on completion. Every patient had ocular symptoms on entering the trial, but none was suffering a severe exacerbation. All treatment other than test agents was discontinued before starting the trial.

Results

Clinical Features
The 14 male and 3 female patients ranged in age from 16 to 63 years, mean 35. The age at onset of ocular symptoms varied from 13 to 60 years, mean 28, and the duration of eye disease ranged from 1 year to more than 20 years. Every patient had a history of other atopic disease past or present. Fourteen had a history of eczema, though in 1 case this was referred to only as dry itchy skin which had been effectively treated with steroid cream prescribed by the family doctor. Eleven patients admitted to past symptoms of asthma or wheezing, which was sometimes recalled only on detailed questioning. Seven patients suffered from hay fever.

Eleven patients knew of other members of their family affected by similar atopic disorders.

Periodicity of symptoms. Sixteen patients reported perennial symptoms of photophobia, watering, itch, or irritation with periodic exacerbations, but, of these, 2 had seasonal exacerbations confined to summer and 2 confined to winter. In addition 1 patient had symptoms in winter only.

Ocular features. Nine of the 17 cases showed various combinations of abnormalities of lids, conjunctiva, and cornea similar to the tarsal or limbal forms of vernal keratoconjunctivitis in children. These included thickening or ptosis of the lids with oedema in exacerbations and giant or cobblestone papillae of the upper tarsal conjunctiva (Fig. 1). Abnormalities at the limbus were usually associated with active or inactive upper tarsal disease but occasionally occurred alone and usually consisted of focal or confluent inflammatory nodules (Fig. 2) with Horner-Trantas spots in only 2 cases. Three of the 9 cases readily recognisable as vernal catarrh showed the typical indolent ovoid corneal ulcers (Fig. 3) with subsequent plaque formation (Fig. 4), and in 1 case there was deep corneal ulceration adjacent to a limbal nodule (Fig. 5).

In the remaining 8 cases the clinical appearances did not suggest vernal disease, and a fine papillary conjunctival reaction was the usual finding (Fig. 6). In some cases scarring of the upper tarsal conjunctiva suggested pre-existing giant papillary conjunctivitis (Fig. 7), and inactive vascular pannus (Fig. 8) may have been a sequel of more typical limbal disease. One case showed severe obliterator symblepharon. Most of these atypical cases showed punctate epithelial keratitis (PEK) (Fig. 9), and in some intraepithelial microcysts were the most notable features (Fig. 10). These corneal changes were variable but were often limited to the lower third of the cornea. Although many of the atypical cases were of mild or moderate severity, 1 patient presented with severe geographic corneal ulceration initially thought to be of viral origin.

In many cases the features were more severe in one eye than in the other, but in 3 the asymmetry was so marked that the patient’s symptoms were unilateral.

Supplementary investigations. In all cases the diagnosis was confirmed by raised serum IgE level. This ranged from 180 to over 4000 arbitrary units/ml, but individual patients showed fluctuations related to the course of their disease with up to fourfold
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Fig. 1 Giant papillae of the upper tarsal conjunctiva.
Fig. 2 Confluent nodules in typical limbal disease.
Fig. 3 Superficial corneal ulceration stained with fluorescein at the common site in the upper cornea.
Fig. 4 Formation of a calcified plaque after widespread epithelial ulceration.
Fig. 5 Corneal ulceration adjacent to limbal nodules and extending into the stroma with reactive iritis.
Fig. 6 Fine papillary conjunctival reaction common in the atypical cases.
Fig. 7 Subconjunctival scarring of the upper tarsus suggestive of previous giant papillary conjunctivitis.
Fig. 8 Vascular pannus of the lower cornea in an atypical case.
Fig. 9 Punctate epithelial keratitis involving the whole corneal surface.
Fig. 10 Intraepithelial microcysts (arrowed).
increases during exacerbations. In 1 patient the level returned to normal in periods of remission. After allowance is made for these fluctuations in individual cases the highest levels of IgE were found in those patients with the most severe disease, and the morphological features, whether tarsal, limbal, or atypical, did not appear to be related to the level of serum IgE.

In more than half the cases the eosinophil count in the peripheral blood was not raised, and some of these patients showed the highest IgE levels. Similarly the identification of eosinophils in conjunctival scrapings was not a reliable diagnostic test. Although only 6 patients were subjected to this examination, no smears showed convincing eosinophilia. None of the microbiological investigations indicated the presence of pathogenic organisms.

**TREATMENT WITH SODIUM CROMOGLYCATE**

**Uncontrolled assessment.** Ten of the 15 patients reported improvement in symptoms while using sodium cromoglycate, and although occasional exacerbations still occurred these were judged to be briefer and of less severity than before treatment, so that the use of topical steroids was either unnecessary or much reduced. Clinical examination confirmed the reduction in ocular inflammation in all but 1 of these 10 cases, but in none was there complete resolution of the physical signs. Five patients noted no improvement in symptoms, but in 1 of these clinical examination suggested that the eyes were less inflamed while the patient was using sodium cromoglycate.

In the group which showed a good response cases with atypical keratoconjunctivitis appeared as commonly as those with readily identifiable vernal keratoconjunctivitis. The response to treatment showed no correlation with age, sex, severity or duration of eye disease, or level of serum IgE. Transient stinging after application of the drops was reported by 7 patients but was troublesome only during severe episodes of inflammation.

**Double-masked cross-over trial.** All 9 cases completed the 12-week trial. Six patients preferred the active preparation, whereas only 1 preferred the placebo; the other 2 patients detected no difference. On clinical examination 4 were judged to have less ocular inflammation while using the active preparation, but of these only 2 felt their symptoms had improved and 2 detected no change. The ocular appearances of the other 5 patients were similar after each 6–week period.

There was no difference in the response between cases of typical or atypical morphology. Exactly 50% of those who preferred the active preparation and of those who could detect no difference showed keratoconjunctivitis not readily identifiable as vernal disease. The single patient who preferred the placebo showed signs typical of vernal catarrh.

**Discussion**

The sex ratio of these adult patients is similar to that in the childhood form of disease, but by contrast the adult group shows an age of onset of eye disease ranging from the second to the sixth decade of life. None of the patients suffered ocular symptoms in childhood, though a history of infantile eczema or asthma was common. It seems therefore that none of the patients had progressed from childhood vernal catarrh to the adult form of disease. It is generally accepted that vernal catarrh regresses towards puberty, and this has been attributed to spontaneous desensitisation or reduced immunological reactivity. It is also of interest that many of these adult cases had suffered symptoms for a considerable period of time. In 8 cases the ocular features had been present for over 5 years, whereas it is rare for the juvenile disease to last this long. Symptoms of vernal catarrh in children are usually seasonal and occur mostly in the summer months; most of these adult patients reported perennial symptoms with nonseasonal exacerbations. The late onset and longer course with nonseasonal relapses may indicate an as yet undetermined difference in the immunological responses of the 2 groups, and it must be borne in mind that as much as 10% of the population may show some clinical manifestation of atopy. The giant papillary conjunctivitis associated with the wearing of some contact lenses and ocular prostheses may be examples of a latent capacity to produce an atopic response to substances which are usually inert but these studies did not include serum IgE estimations. Whatever the cause, it seems that the duration of the adult keratoconjunctivitis often indicates that the usual optimistic prognosis for spontaneous regression is not justified when the disease starts after puberty.

Notwithstanding these differences 9 out of 17 cases showed typical tarsal or limbal disease which indicated the diagnosis. The remaining 8 cases appeared quite different, and frequently the diagnosis had at first been overlooked because of the atypical clinical features or unilocular symptoms. Various conditions such as keratoconjunctivitis sicca, microcystic dystrophy, viral keratitis, solar keratopathy, keratitis artefacta, and ocular pemphigoid had been suggested without sufficient clinical evidence. In these atypical cases the predominant finding was a fine papillary reaction of the upper or lower tarsal conjunctiva. Giant papillae were not present, though some eyes showed subconjunctival scarring
of the upper tarsus which suggested that giant papillae had been present at some time in the past. Various forms of punctate epithelial keratitis and microcystic keratopathy were often present, but the appearances were not specifically diagnostic. The symptoms of this atypical group were often relatively mild, but in 2 cases acute exacerbations were severe enough to require admission to hospital. Asymmetrical or unilateral disease is not usually associated with allergic ocular reactions, but as it was a feature of 3 of the cases studied it should not be allowed to obscure the diagnosis.

This study has revealed that a substantial number of adults with atopic keratoconjunctivitis have relatively nonspecific ocular signs, yet it is important to establish the diagnosis, as many of these cases benefit from specific treatment with sodium cromoglycate. It was possible to confirm the atopy of all the patients by their history of other atopic reactions, mainly asthma or eczema. In some these other manifestations were obvious and easily elicited on superficial inquiry, but in others only close and direct questioning revealed this information. Likewise a family history of atopy was a valuable piece of evidence to support the diagnosis. The positive family history in 65% of cases in this series is similar to the family history of atopy found in 50–75% of subjects with atopic respiratory disease against only 20% in nonatopic respiratory disease.18

Identification of eosinophils in conjunctival scrapings or raised eosinophil count in the peripheral blood are recognised features in vernal catarrh, but in this series over half the patients showed neither of these features, and the most reliable diagnostic investigation was quantitation of reaginic antibody (IgE) in the serum. This immunoglobulin is increased in the tears and serum of patients with vernal disease,16–19 but the changes in the serum are more marked. Individual patients showed wide fluctuations in this test, and the higher levels seem to reflect the severity of an exacerbation rather than the morphological type of ocular reaction. Certainly 2 atypical cases with very severe symptoms had levels of over 1000 units/ml. This test is now generally available in immunopathology laboratories and requires a 10 ml sample of clotted venous blood. It should therefore become a routine investigation in the diagnosis of external eye diseases. Antigen specific IgE values may be measured on the same sample (RAST). This assay indicates the relative sensitivities to different allergens and may be more convenient than arranging skin testing. In addition some juvenile patients not included in this study have shown a high IgE titre to one specific antigen without elevation of total serum IgE.

The results of both parts of the trial of therapy with sodium cromoglycate eyedrops suggest that 66% of adult patients with atopic keratoconjunctivitis obtained worthwhile relief from itching, watering, and photophobia. Intermittent exacerbation still caused discomfort, but these episodes were reduced in severity and duration. This confirms the therapeutic value of sodium cromoglycate in atopic keratoconjunctivitis in adults and compares favourably with its value in vernal catarrh in atopic children.7–10 One study10 found a poor response to this treatment for vernal keratoconjunctivitis, and the authors suggested that their patients were not atopic. They did not, however, report serum IgE estimations, and they may not have made sufficiently detailed inquiry into a personal or family history of atopy. It is interesting to note that the proportion of patients in the present trial who improved on active treatment is similar to the 62% response to sodium cromoglycate in allergic asthma in adults.21

Seasonal use of sodium cromoglycate is advocated during the high-risk summer months, but the adult patients described in this study are more likely to have periodic exacerbations throughout the year, and therefore continuous use of the drops, perhaps at reduced frequency, may be necessary. Many of these patients have shown complete remission of symptoms for periods of several months, and it has been found satisfactory to allow the patient to discontinue the treatment after being free of symptoms for a few weeks on a twice daily dose. Sodium cromoglycate, however, is only one mode of treatment, and topical steroids, mucolytics, and systemic antihistamines remain valuable in refractory cases or during severe exacerbations. In addition, surgical removal of corneal plaques may be required after episodes of severe corneal ulceration.

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References

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