

Vernal keratoconjunctivitis in an Israeli group of patients and its treatment with sodium cromoglycate

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SUMMARY Vernal keratoconjunctivitis (VKC) is usually considered as an allergic eye disorder of type I, and in most therapeutic trials it has been shown to yield to topical treatment with sodium cromoglycate. This has been confirmed in the present study of VKC patients from Israel. However, some of the cases seemed not to benefit from this treatment. In a survey of IgE levels in VKC patients in Israel tear IgE levels were significantly increased in 63.5%, but in 29% of the patients both tear and blood IgE levels were normal to low. The possibility that some of the cases diagnosed as VKC might have another cause than IgE-mediated atopy is discussed.

Vernal keratoconjunctivitis (VKC) is usually considered to be an allergic, IgE-mediated disorder.^{1,2} Outbreaks, exacerbations, and recurrences cluster in the spring together with hay-fever, spastic bronchitis, or asthma. A large proportion of VKC patients suffer from other atopic conditions or give a history of familial allergy. Microscopic examination of the inflammatory exudate shows consistently increased numbers of eosinophilic leucocytes. High levels of total IgE³ and of antipollen specific IgE⁴ in tears have been reported for VKC patients.

In spite of the possibility that VKC might be only one facet of a multisystem atopic condition, therapeutic trials have put emphasis on topical treatment with anti-inflammatory drugs or even by surgical correction. The topical application of corticosteroids gives considerable benefit, but it must be restricted owing to their effect on the intraocular pressure⁵ or to their suppression of the defence mechanism against infections. The use of vasoconstrictors and antihistamines seems reasonable but has often proved to be ineffective, at least in severe cases.

Topical application of the nonsteroid antiallergic drug sodium cromoglycate (SCG) has been reported to be strikingly or moderately effective,^{5–10} but a well-controlled trial from Israel¹¹ led to a negative evaluation of this drug. The divergent results might be due to the particular character of VKC in Israel. A

comprehensive survey of patients from Israel¹² has indicated that the disease in this country is less dependent on season than has been reported elsewhere, and no connection with systemic atopy could be demonstrated. Similarly, in a report from Egypt only 5 out of 83 patients (6%) showed symptoms of other allergic conditions.⁵ If this indicates that VKC in this subtropical zone is not always an allergic disorder, no effect of SCG should be expected in some of the patients. It should also be noted that in the previous Israeli study¹¹ a 1% solution of SCG was used, whereas other studies have been carried out with a 2% solution.

For these reasons a reappraisal of the nature of VKC in Israeli patients and of the therapeutic effect of topical SCG drops seemed to be needed.

Materials and methods

PATIENTS

Nineteen patients with VKC were treated with 2% sodium cromoglycate in a solution of 0.01% benzalkonium chloride, 0.4% phenylethyl alcohol, and water. The drops were instilled 4 times a day to one of the diseased eyes, and the fellow eye was concomitantly given a placebo solution—that is, the same preparation without SCG. No other medication was used during the observation period.

All the patients that participated were considered to have typical VKC either at their first attack or at a fresh attack after a quiescent period of the disease.

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Treatment was started in 12 out of the 19 patients during the July-August period. Only one patient had a history of another atopic condition (spastic bronchitis). Of the 19 patients 14 were males (74%) and 5 females. Seventeen were 4–10 years old, one was 12, and one 20 years old.

The eye to be treated was chosen at random by the ophthalmologist, who knew the content of the bottles, though the patients or their parents did not. Ten of the patients were admitted to hospital for control of treatment and better evaluation of its effect during the first 5–10 days. The patients or their parents were in all cases carefully told how to administer the drops and how to record the subjective symptoms (itching, photophobia, lacrimation). In spite of this the parents of 5 patients were unable to give clear information about the subjective feeling of their children. In the eye clinic the patients were subsequently examined by the same physician several times during a period of 2–8 weeks. The state and alterations of the following conditions were particularly noted and used as the basis for the evaluation of the effectiveness of the treatment: mucoid discharge, Trantas spots, epithelial keratitis, and ulceration of the cornea. The state of each symptom was graded in a scale from 0 to 3 according to severity, and it was also recorded by a drawing in the patient's journal. The compound papillary hypertrophy of the upper tarsal conjunctiva (cobblestones), a constant finding, and limbal hyaline masses which are less dynamic than the others mentioned, were not included for evaluation. Of the treated 19 eyes 6 were, according to the above symptoms, evaluated as severely, 8 as moderately, and 5 as mildly diseased. Two of the treated eyes had corneal ulcerations. Of the 19 eyes that received placebo drops 4 were graded as severely, 9 as moderately, and 6 as mildly affected; none of these eyes were ulcerated.

LABORATORY INVESTIGATIONS

Conjunctival scrapings were examined for cells and stained with Giemsa's stain. Tear samples, and in most cases also blood samples, were obtained from the patients, and examined for serum albumin and immunoglobulins. Most of these studies were performed by radial immunodiffusion as described.¹³ IgE levels were determined by solid-phase radio-immunoassay (Prist, Pharmacia Ltd, Uppsala, Sweden).

Results

THERAPEUTIC TRIAL WITH SODIUM CROMOGLYCAT

The overall results of the therapeutic trial with topical SCG are summarised in Table 1. The alterations in

Table 1 Clinical evaluation of topical treatment with sodium cromoglycate (SCG) in 19 patients of vernal keratoconjunctivitis. One eye was treated with SCG and the fellow eye with placebo drops.

		No. treated eyes	No. untreated eyes
Objective evaluation*			
Improvement	+	13	4
Questionable	±	1	2
No alteration	0	1	6
Aggravation	-	4	7
Total		19	19
Subjective evaluation†			
Improvement	+	9	6
Questionable	±	1	2
No alteration	0	1	2
Aggravation	-	3	4
No information		5	5
Total		19	19
Subjective and objective improvement‡	+/+	8 of 14	3 of 14

*The results were tested by Fisher's exact test and were statistically significant ($p < 0.01$) both when the questionable cases were counted as improved and when they were counted as not improved.

†Results not significant ($p > 0.1$).

‡Results at the border of statistical significance ($p = 0.06$).

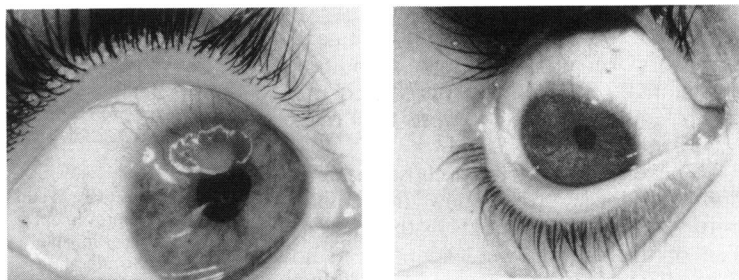
the clinical condition were fairly easy to evaluate in most cases, since improvement or aggravation was usually concordant in all the markers chosen, namely, itching, photophobia, and lacrimation for the subjective evaluation, and mucoid discharge, Trantas spots, epithelial keratitis, and corneal ulcer for the objective evaluations. The cases in which one of the symptoms was unaltered and the others improved are indicated in Table 1 as ± (questionable).

Table 1 shows a definite improvement in 13 out of 19 treated and 4 out of 19 untreated eyes according to the assessment of the objective clinical markers. If ± is counted as improved, 14 treated eyes and 6 untreated eyes were improved. The difference between treated and untreated was in both cases statistically significant ($p < 0.01$) by Fisher's exact test.

According to the subjective parameters, 9 out of 14 treated and 6 out of 14 untreated eyes were reported to have improved, whereas in 5 cases no useful information was obtained. The difference here is not statistically significant. Of the 14 patients with full evaluation, 8 treated and 3 untreated eyes were improved according to both their subjective feelings and the objective observations. The significance of the difference between the treated and the placebo groups was $p = 0.06$.

These results indicate a favourite effect of cromoglycate, and in some cases the rapid and clear-cut improvement after this therapy was remarkable. It should, however, be emphasised that in other patients this treatment clearly did not control the inflammatory

Fig. 1 Right eye of patient, case 2. Left before, right after, treatment with SCG.



eye disease. This difference between the patients seemed obvious, and could lead to speculation about differences in the aetiology of the disease, although the cases were clinically similar. The following observations will illustrate this point further.

Case 1

A 6-year-old boy had suffered from VKC for the last 3 years. He had severe papillary hypertrophy of the tarsal conjunctivae, epithelial keratitis of both eyes, itching, and lacrimation. Previous therapeutic trials with topical corticosteroids were unsuccessful. Conjunctival scrapings from both eyes showed a large number of neutrophilic and eosinophilic polymorphonuclear granulocytes. Treatment with SCG to the right and placebo drops to the left eye was given between 4 June and 8 August 1979. The right eye improved rapidly, whereas the condition of the left eye became worse. From August onwards SCG was prescribed for both eyes for 1½ years, but the parents reported that the treatment was not applied regularly. During this time the child experienced one

severe attack of VKC and several periods with mild inflammation. Tear albumin levels were high throughout, 240–1044 mg/100 ml (2.4–10.44 g/l). The tear IgE levels exceeded by far the value for the geometric mean in healthy eyes + 2 SD (Table 2) and reached even 1237 IU/ml. The serum IgE level was 1700 IU/ml, which is also higher than the geometric mean of the control group + 2SD.

Comments. The immediate effect of SCG was clearly beneficial, whereas the long-term effect was difficult to evaluate, since the SCG drops were not instilled regularly. The eosinophilia observed in conjunctival scrapings as well as the abnormally high levels of tear and blood IgE may indicate that this child suffered from a type I allergic eye disease.

Case 2 (Fig. 1)

A 6-year-old boy who had suffered from VKC during the previous 2 years was twice admitted to hospital owing to the severity of the condition. He had several times had corneal ulceration of the right eye. In May 1979 he presented with a severe bilateral attack of VKC with giant tarsal papillae, diffuse epithelial keratitis and Trantas spots, and a marked corneal ulceration of the right eye. Conjunctival scrapings showed abundant eosinophilic leucocytes. The peripheral leucocyte count was $11.9 \times 10^9/l$ with 14% eosinophilic granulocytes. Treatment with SCG was applied to the right eye for 6 weeks, and the left eye was concomitantly given placebo. In the course of 3 weeks a marked improvement in the condition of the right eye was observed, and the ulceration disappeared completely, whereas no alteration in the state of the left eye was noticed. After 6 weeks the SCG treatment was extended to both eyes, and since then—1½ years—the boy has been under observation. Relatively mild recurrent attacks of the disease were observed in August 1979, April 1980, and April 1981. Tear IgE levels have been high throughout, higher than the geometric mean + 2 SD, and reached 1800 IU/ml. The IgE concentration in the blood was also high (1650 IU/ml).

Comments. The boy had already experienced several severe attacks of VKC when SCG was applied

Table 2 Levels of IgE (IU/ml) in tears and blood of vernal keratoconjunctivitis patients (VKC) and healthy controls

	Tears		Blood	
	Controls	VKC	Controls	VKC
No. samples	40	129	20	47
GM	0.92	7.88	88.92	113.63
Range	<0.42–6.6	<0.42–1350	12–485	<0.42–1700
GM + 2 SD	3.21	614.71	1024.29	2643
No. < GMC	27 (67.5%)	37 (28.6%)	10 (50%)	19 (40.4%)
No. > GMC				
+ 2 SD*	2 (5%)	82 (63.5%)	0	4 (8.5%)

GM = Geometrical mean. GMC = Geometrical mean of control.

*The differences between the controls and VKC group were significant ($p < 0.001$) according to the chi-square test for tears and significant ($p > 0.05$) for blood samples.

Levels of IgE < 0.42 IU/ml could not be determined exactly. They were calculated as 0.21 IU/ml. The levels of IgE in tears from VKC patients were significantly different ($p < 0.01$) from the levels in the control group (Student's *t* test). The corresponding difference in blood levels was at the limit of statistical significance ($0.025 < p < 0.05$). Calculation of *t* test was based on the arithmetic mean.

to the right eye. A raised eosinophil count in the peripheral blood and strikingly increased levels of IgE in tears and blood might indicate a type I atopic condition. SCG seemed in this patient to be clearly beneficial in the short term. It is possible that the mild nature of subsequent attacks may be due to this therapy.

Case 3

This was a 4-year-old boy with a 2-year history of VKC. The patient had previously been under treatment with topical steroids in 2 other hospitals, and had been skin-tested twice with a series of commercial allergens; all skin tests gave negative results. The patient presented on 21 August 1979 in our clinic with red, severely itching eyes, photophobia, and lacrimation. Examination of repeated conjunctival scrapings did not reveal eosinophilic leucocytes. The child was treated on the right eye with SCG and on the left eye with placebo. No essential alteration of the condition was observed in either of the eyes during the next months. The child suffered particularly on hot days ('hamsin'). During October the inflammation faded slowly in both eyes. The child was now put on SCG for both eyes during the next year and a half. New attacks were experienced in April, August, and November 1980 and April 1981. Tear levels of IgE were determined on 6 occasions and were consistently <1.75 IU/ml. Blood levels of IgE were examined on 2 occasions and were 54 IU/ml and 56 IU/ml.

Comments. In this case no indication of an allergic aetiology was obtained. Skin tests with commercial allergens were negative on 2 occasions, and no eosinophilic leucocytes were found on examination of conjunctival scrapings. IgE levels of tears were low and of blood serum below the geometrical mean of normal adults (see below). The onset of the disease did not seem to depend on the season, though hot weather perhaps aggravated it.

LEVELS OF IGE IN VKC

Table 2 shows the levels and the geometric mean of IgE levels in tears and blood of VKC patients. The control group was composed of young adults, since we have no IgE determinations on healthy children at the age of most of the VKC patients. It is of particular interest that in 63.5% of the VKC patients, the tear levels of IgE were above the geometric mean of normal persons (GMC) + 2 SD, and in 4 VKC patients the blood levels of IgE were above GMC + 2 SD. 29% of the VKC patients had tear IgE levels below GMC. All patients with tear IgE levels less than GMC, had blood IgE levels below the GMC. Of the patients with tear IgE levels greater than GMC + 2 SD 12% had blood IgE levels above the GMC + 2 SD, whereas 35% had blood levels below the GMC.

These results show that although the geometric mean of IgE levels in tears of VKC patients was far above the GM + 2 SD, a significant proportion of our patients had low IgE levels in both tears and blood. In this group the eye disorder may not be IgE mediated, and it might possibly be expected that SCG treatment of these patients would not be effective.

Discussion

VKC is usually considered to be a type I allergic disorder.^{1,4,14} High IgE levels in the tears and in the blood,³ a high proportion of pollen-specific antibody in the tear IgE,⁴ a high incidence of other atopic conditions (spastic bronchitis, eczema, hay-fever, etc.) among VKC patients⁸ and persistent eosinophilia of conjunctival scrapings¹⁵ are all features supporting the generally accepted opinion that VKC is a type I allergic disorder. The incidence of the disease seems to be particularly high in Israel, and especially in younger children (4–10 years old), but apparently some of its features are at variance with those reported from temperate zones. Neumann *et al.*¹² have given a comprehensive record of a group of 400 Israeli patients. It should particularly be stressed that the incidence of atopic disorders in other organs was only 11%, not more than among other children of the same age group. Likewise in a recent report from Egypt⁵ the incidence of VKC patients with other atopic conditions was extremely low. Hyams *et al.*¹¹ have found that treatment with SCG is unsatisfactory in their patient material and have postulated that the reason might be the particular nature of VKC in the subtropical zone.

We report here a statistically verified effect of SCG treatment, and our impression from clinical observations is that SCG is beneficial in most VKC patients. However, in some patients this treatment seemed to have no effect.

This is the first study of tear and blood IgE levels in VKC patients from this geographical region. The results may indicate that the cases clinically diagnosed as VKC vary in their aetiology. In 63.5% of the patients the levels of IgE in the tears were extremely high and IgE blood levels were above GMC + 2 SD in some of the patients. Serum IgE levels above GMC + 2 SD are rare in nonatopic patients,¹⁶ but we have not seen corresponding records of tear levels of IgE. However, in our cases the difference between the number of healthy and VKC eyes with such levels is significant. On the other hand, in 29% of the patients we found low IgE levels (below GMC) of tears and blood. It should be emphasised that in some patients with low tear IgE levels repeated examinations during recurrence of the disease showed persistently low IgE values. One example is case 3. In this child no

eosinophilic leucocytes were observed in repeated conjunctival scrapings, and skin testing with commercial allergens was twice negative.

This raises the question whether the clinical diagnosis of VKC is based on a uniform pathological entity. If it is not, the rational treatment of the non-atopic patients may have to await advancement in our understanding of the real nature of their eye disorder.

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