Keratoconus and coexisting atopic disease

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SUMMARY The association of keratoconus and atopic disease has been reported on several occasions but the only controlled clinical study that has so far been published found no evidence to support this view. Since it is now known that atopy is often associated with changes in various immunoglobulins, particularly IgE, it was considered desirable to determine the immunological profiles of a large series of keratoconus cases in order to seek evidence for coexistence of the two conditions in one individual. In this study of 182 cases of keratoconus a definite history of atopy was found in 35% compared with 12% in the matched control group. The serum IgE was significantly raised ($P < 0.001$) in keratoconus and markedly so in those cases with associated atopic disease. Serum levels of IgG and IgM were also raised, but contrary to the findings of other observers IgA levels were normal. These findings suggest that atopic traits are more common in patients with keratoconus than in general ophthalmic patients.

Keratoconus (conical cornea) is a progressive non-inflammatory condition characterised by thinning, ectasis, and eventual scarring of the central cornea. Because of the resulting irregular astigmatism there is a marked loss of vision, which for a while can be corrected by contact lenses, but in most cases corneal transplantation is ultimately required. The disease usually becomes manifest during adolescence, and although it has been known from the earliest times its precise aetiology remains obscure.

An association between keratoconus and atopic disease has been reported in a number of uncontrolled studies (Hilgartner *et al.*, 1937; Galin and Berger, 1958; Spencer and Fisher, 1959; Ridley, 1956), the most recent recording the presence of eczema in 32% of keratoconus patients compared with an assumed incidence of 3% in the general population (Copeman, 1965; Longmore, 1970). Lowell and Carroll (1970), however, failed to detect in their small series of 31 cases any significant difference between the incidence of atopic traits in keratoconus cases and a similar number of unmatched controls when both groups were assessed on the basis of a detailed history and skin tests with common allergens. In spite of this conflicting evidence it has remained our firm clinical impression that atopic traits are more commonly associated

with this disease than with other eye conditions. Since it is now known that atopy is often associated with raised levels of IgE together with changes in other immunoglobulins (Taylor *et al.*, 1973) it was considered desirable to study the immunological profile of a large series of keratoconus patients in order to determine the incidence of atopic traits, and in particular to discover whether immunological confirmation of our clinical impressions could be obtained. The present study was undertaken 3 years ago and a preliminary report has already been published (Davies *et al.*, 1976).

Materials and methods

One hundred and eighty-two cases of keratoconus, consisting of 129 males and 53 females were randomly selected from the Contact Lens Department at the High Holborn branch of Moorfields Eye Hospital and assessed for their corneal condition. The general incidence of an atopic state was assessed in only 100 patients, who were also skin-tested when possible. Tears and blood samples were collected from each patient and tested for the following immunological parameters.

The immunoglobulins G, A, M, and D were estimated by radial immunodiffusion techniques using ICL plates. WHO standard sera were used to obtain the reference curve. Because of a skewed distribution the individual values were logarithmically transformed to obtain a Gaussian distribution.

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Immunofluorescence tests were performed on composite block frozen sections consisting of liver, kidney, stomach, oesophagus, and parotid from a rat and the stomach of a mouse. The autoantibodies especially looked for were those against cell nuclei and nucleoli, smooth muscle proteins, reticulin, gastric parietal cells, mitochondria, and microsomes. Rat eye sections were examined for anti-ocular antibodies.

Haemagglutination tests using commercial kits were performed to detect antibodies to thyroglobulin and thyroid microsomal antigens and IgM rheumatoid factor.

IgE in serum and tears was measured by solid-phase radioimmunoassay using a Pharmacia commercial kit.

One hundred age- and sex-matched patients who were suffering from non-inflammatory eye disease at the time of examination and were attending eye clinics at Moorfields Eye Hospital were examined for the presence of atopy and questioned about any past history of hay fever, asthma, allergic dermatitis, urticaria, and vernal catarrh. A baseline was thus obtained for the general incidence of atopy in ophthalmic patients.

Student's *t* distribution was applied to test the significance of the differences of the mean values for IgG, IgA, IgM, and IgE in the control population and in the patients with keratoconus. The incidence of atopy and the percentage of the individuals showing IgE levels ≥ 200 IU/ml were statistically analysed by the chi-square test.

Results

Incidence of atopy: 35% of the keratoconus cases showed atopic tendencies (Table 1) as opposed to the control group, where the incidence was only 12% ($P < 0.001$). The atopic individuals in the keratoconus series showed a male:female ratio of 2:1; the commonest allergic disorder was hay fever followed by asthma and eczema. No case of vernal catarrh was seen in the present series.

The serum IgE was generally raised in keratoconus ($P < 0.001$) but the levels were much higher in the atopic group than in the non-atopic group. The statistical analyses of these levels are shown in Tables 2 and 3.

The geometric mean levels of immunoglobulins G and M were also raised ($P < 0.001$), but IgA levels were not significantly different from those in the control group (Table 4).

Some of these patients showed the presence of a variety of autoantibodies in their sera. But the incidence of antinuclear antibodies (14%), rheumatoid factor (9%), and antibodies to smooth muscle

proteins (20%), reticulin (1%), gastric parietal cells (2%) was not significantly different from the control population (Rahi *et al.*, 1976).

There was no significant difference between the

Table 1 Incidence of atopic disease in keratoconus

Atopic disease	Control population (%)	Keratoconus (%)
Asthma	1	3
Eczema	3	2
Hay fever	8	15
Asthma + hay fever	0	7
Eczema + hay fever	0	3
Asthma + eczema + hay fever	0	5
Total	12	35

$\chi^2 = 14.7$, $P < 0.001$

Table 2 Immunoglobulin E in keratoconus

Serum level	Control population (100)	Keratoconus (182)
Geometric mean (IU/ml)	52	205 ($P < 0.001$)
Range (IU/ml)	10–272	10–4000

Table 3 IgE in keratoconus

Serum level	Control population (100)	Keratoconus, atopic (35)	Keratoconus, non-atopic (65)	Keratoconus, total (100)
<200 IU/ml	94%	14 (40%)	39 (60%)	53%
≥ 200 IU/ml	6%	*21 (60%)	*26 (40%)	*47%

* $P < 0.001$

Table 4 Immunoglobulins in keratoconus

Serum level		Control population (100)	Keratoconus (182)	Significance
IgG (IU/ml)	Geometric mean	121	140	$P < 0.001$
	Range	68–217	71–262	
IgA (IU/ml)	Geometric mean	125	123	Not significant
	Range	55–286	63–460	
IgM (IU/ml)	Geometric mean	151	195	$P < 0.001$
	Range	68–333	60–538	

IgE levels in the tears of the control and the keratoconus groups.

Discussion

The clinical impression that keratoconus for some unexplained reason shows a strong tendency to co-exist with atopic disorders is confirmed by the high incidence of atopy in this large series. The simple electrophoretic study of Manfredi and Romei (1966), which showed raised gamma globulins in keratoconus, was confirmed in the more recent study of 23 cases of keratoconus by Easty *et al.* (1975), who also found that some of these cases had high levels of IgG, IgM, and IgE. Our present study on a much larger group confirms these findings. In addition it detected a variety of autoantibodies in these cases which have not been reported previously, though admittedly their significance is obscure.

Contrary to the findings of Easty and his associates we did not find any statistically significant difference between the levels of serum IgA in keratoconus and those in the control group. Since Easty *et al.* (1975) did not cite their values it is difficult to make any meaningful comparison or to offer any explanation. Although Kaufman and Hobbs (1970) have documented the possible association of high levels of IgE with low IgA levels in atopic adults, this has been questioned by Taylor *et al.* (1973), who showed that, although atopy and raised levels of IgE may be linked with low IgA levels in blood and body secretions, this is true only for the early months of infancy, when the foundations of many allergic traits are being laid down. This transient IgA deficiency is soon replaced by a normal pattern, and in some individuals the IgA concentration may later rise above the normal range. Our findings are in agreement with these workers and indicate that IgA levels are not significantly low in keratoconus despite high levels of IgE, but this does not of course exclude a transient IgA deficiency during infancy.

The significance of these immunological changes in the natural history of keratoconus is uncertain, since the disease is non-inflammatory and it is difficult to see how immunopathological processes can produce changes in the cornea without inducing any inflammatory reaction. It is known, however, that autoimmune gastric atrophy can be produced in experimental animals (Porteous *et al.*, 1974) without any marked inflammatory response, and the kidney in systemic lupus erythematosus may not show any cellular infiltration, though these conditions are the exception rather than the rule in immunopathological disorders.

For some unknown reasons keratoconus seems to coexist with these immunological abnormalities of a

generalised type. Ataxia telangiectasia, with vascular changes in the conjunctiva, the Wiskott-Aldrich syndrome with atopic dermatitis involving the eyelids, and short-limbed dwarfism are all syndromes associated with gross immunological abnormalities. No unifying hypothesis has been produced to explain these remarkable combinations of features, nor is it easy at present to explain the observed immunological changes in keratoconus.

It is possible that keratoconus is a *forme fruste* of a functionally abnormal mesenchymal system, manifesting itself only in the eye, and biochemical and ultrastructural studies seem to support this notion. Keratocytes, which are involved in the synthesis and secretion of collagen and proteoglycans (i.e., the ground substance), which exert molecular constraints on the regular organisation of the corneal lamellae (Borcherding *et al.*, 1975), appear to function erratically in keratoconus. The keratocytes show features of active synthesis as well as gradual degeneration and vacuolation (Pouliquen *et al.*, 1972). The synthesis of collagen takes place in various steps involving translation, hydroxylation, helix formation, glycosylation, secretion, conversion of the precursor, aggregation, and cross-linking. These processes are not only dependent on various enzymes, which are genetically controlled, but on several other factors in the micro-environment which may affect the process of cross-linkage and laying down of the collagen in a regular pattern. A defect in any of these processes will affect fibrillogenesis in the cornea and may lead to the changes so commonly seen in keratoconus.

A close relationship exists between atopy, raised IgE, and several histocompatibility antigens, particularly HLA-B7 and haplotypes A1:B8 and A3:B7 (Goodfriend *et al.*, 1973; Turner *et al.*, 1977). Studies on serum levels of IgE in monozygotic and dizygotic twins suggest an inherited genetic function in IgE production (Hamburger and Bazaral, 1972). It would be interesting to investigate a large number of keratoconus cases to see if this disease (like acute anterior uveitis, in which HAL-B27 predominates) shows a preferential clustering around any particular histocompatibility antigen.

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