

# Association between keratoconus and atopy

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**SUMMARY** Sixty-seven patients with keratoconus were classified according to atopic status. Keratoconus patients with and without atopy did not differ significantly with regard to sex, age of onset, or rate of keratoplasty, but patients with very high IgE levels were more prone to graft rejection. Atopy was less common in patients with unilateral keratoconus, and keratoconus occurred more frequently on the side of the dominant hand. There was a significantly lower frequency of HLA B7 in the keratoconus group than in the controls. No abnormalities of essential fatty acid metabolism were found in keratoconus patients with or without atopy. There was no social class bias in the group. The study included a brother and sister with keratoconus and atopy, and a non-atopic patient whose identical twin did not have keratoconus.

Keratoconus is a disease of unknown aetiology, although several studies have demonstrated an association with atopy.<sup>1-9</sup> Excessive eye rubbing has been considered a reason for this association, on the assumption that atopic patients are prone to conjunctival itching and irritation,<sup>3,4,7</sup> but some form of shared inheritance of the two conditions has also been proposed.<sup>7</sup> Other suggested aetiological factors include genetic mutation due to increased parental age.<sup>10</sup> Increased and decreased frequencies of certain HLA antigens have been found in patients with keratoconus.<sup>11-15</sup>

In this study 67 patients with keratoconus were classified according to the presence or absence of atopic conditions, and the clinical progress of patients with and without atopic disease was compared. The patients were investigated for other possible associations with keratoconus, in particular HLA A, B, and DR antigens and increased parental age. Levels of essential fatty acids were estimated, as an abnormality of essential fatty acid metabolism has been found in some atopic patients, but keratoconus patients had not previously been studied. An association was also sought for unilateral keratoconus, atopic status, and hand dominance. The study included a sister and brother with keratoconus, and a patient whose identical twin did not have the disease.

## Patients and methods

Sixty-seven patients with keratoconus attending the Bristol Eye Hospital participated in the study. The great majority were attending the contact lens department or corneal clinic or had undergone keratoplasty. All were seen by one examiner (RJH). Information was obtained about occupation, parental age, a family history of keratoconus, a family history of asthma, eczema, or hayfever (parents and siblings only), and a personal history of these conditions. The age of onset, contact lens wear, and keratoplasty were noted. Patients who had undergone keratoplasty were questioned about episodes of graft rejection, and further information was sought from the hospital notes. The patients were examined on a slit-lamp and with a keratometer to confirm the diagnosis of keratoconus. When the patient had undergone keratoplasty, the diagnosis was histopathologically confirmed.

Blood was taken for serum IgE, HLA typing, and essential fatty acid estimation.\* Essential fatty acid levels were compared with those of samples from 35 normal subjects taken under similar conditions. Patients were also prick tested for 16 common allergens by means of the Bencard testing solutions.

In the absence of an agreed definition of atopy a

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\*Essential fatty acids were determined by gas liquid chromatography analysis of the methyl esters at the Efamol Research Institute Laboratory in Nova Scotia, Canada.



Table 3 Essential fatty acids (mean plasma levels)

		Atopic n=21	Possibly atopic n=16	Non-atopic n=16	Total n=59	Controls n=35
Linoleic (18:2,n6)	Mean	27.08	26.07	27.67	27.02	26.74
	SD	5.26	3.99	3.92	4.42	3.30
Dihomo-γ-linolenic (20:3,n6)	Mean	2.62	2.52	2.75	2.64	2.86
	SD	0.59	0.56	0.52	0.54	0.70
Arachidonic (20:4,n6)	Mean	10.96	10.49	10.81	10.76	11.10
	SD	1.67	1.23	1.96	1.62	1.55
Docosatetraenoic (22:4,n6)	Mean	0.316	0.287	0.275	0.300	0.334
	SD	0.18	0.19	0.13	0.17	0.20
Docosapentaenoic (22:5,n6)	Mean	0.222	0.263	0.218	0.240	0.314
	SD	0.17	0.22	0.12	0.17	0.26

linoleic (18:2,n6) and α-linolenic (18:3,n3) pathways were measured. The mean plasma levels of linoleic (18:2,n6), dihomogamma-linolenic (20:3,n6), arachidonic (20:4,n6), docosatetraenoic (22:4,n6), and docosapentaenoic (22:5,n6) acids, the polyunsaturated fatty acids in the linoleic pathway, are shown in Table 3. The plasma levels of dihomogamma-linolenic acid (20:3,n6) were lower in keratoconus patients than in controls, and levels in the atopic and possibly atopic subgroups were lower than the non-atopic group, but none of these differences were significant.

SOCIAL CLASS AND PARENTAL AGE

The social class of 65 patients was determined according to the Registrar General's classification and compared with data from the 1981 census for the South West Region (Table 4). Patients with keratoconus in this study did not show any social class bias. The year of birth ranged from 1908 to 1967, and the mean year of birth was 1953 (SD 11.75). The mean paternal age at time of patients birth was 31.4 years (range 19-57 years, SD 6.44) and the mean maternal age was 28.4 (range 18-42 years, SD 5.40).

KERATOPLASTY AND GRAFT REJECTION

The atopic status of patients who had undergone keratoplasty is presented in Table 5. Keratoplasty was more frequent in atopic patients, but this was not significant. Nine patients – five atopic, two possibly

atopic, and two not atopic – had at least one graft rejection episode, but there was no correlation between atopic status and graft rejection. Four of the five atopic patients with graft rejection had IgE levels >1000 U/ml, compared with only nine of all the 26 patients classified as atopic. This difference was significant (χ<sup>2</sup> test, p<0.05).

UNILATERAL AND BILATERAL KERATOCONUS, ATOPY AND HAND DOMINANCE

Keratoconus was bilateral in 46 patients. In 37 of these patients the disease developed simultaneously in both eyes, and in the remainder occurred in the second eye within five years. The duration of the disease in the bilateral group was from less than one to 35 years. Unilateral keratoconus was found in 21 patients, and the duration of the disease ranged from one to 57 years (Fig. 2). When the atopic status of these two groups was compared, atopy was less common in the unilateral group (Table 6). If patients with unilateral keratoconus for three years or less are excluded from the analysis, the differences in atopic status are significant (χ<sup>2</sup> test, p<0.05).

Unilateral keratoconus occurred in the right eye of 13 patients and in the left eye of only four, a difference that was significant (χ<sup>2</sup> test, p<0.05). This prompted a search for an explanation, so patients were sent a questionnaire about hand dominance and eye rubbing, and 48 replied. Two patients denied eye rubbing, and a third who was handicapped was unable to give reliable information. Of the remaining 45 patients 31 stated that they used both hands to rub

Table 4 Social class: keratoconus patients compared with the 1981 census results for the South-west Region (10% sample, persons by head of household)

Social Class	I	II	III	IV	V	Unclassified
Keratoconus patients, no.	4	16	29	8	2	6
%	6.2	24.6	41.5	12.3	3.0	12.3
South-west Region %	6.2	26.7	44.3	14.5	4.1	4.2

Table 5 Keratoplasty and atopic status

	Atopic	Possibly atopic	Non-atopic
Keratoplasty patients (numbers)	10	4	5
Keratoplasty patients (%)	52.6	21.1	26.3
Whole group (%)	44.1	27.1	28.8

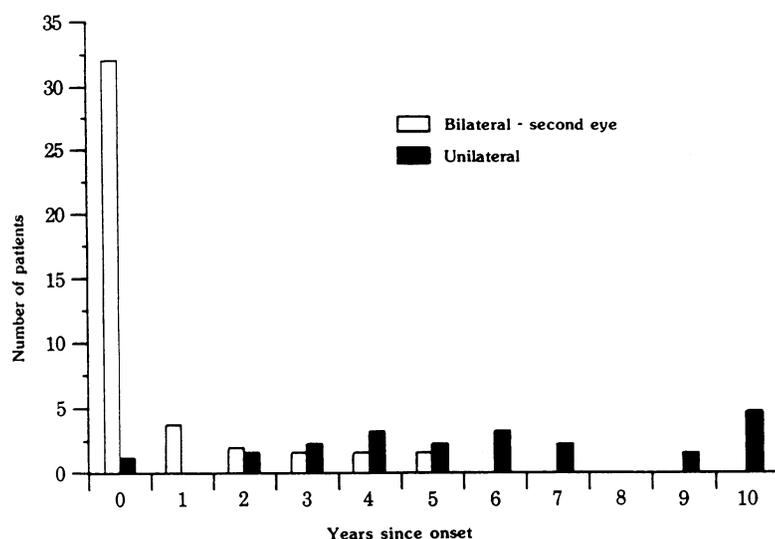


Fig. 2 Unilateral and bilateral keratoconus.

their eyes, 11 used their dominant hand, two used their non-dominant hand, and one ambidextrous patient used his right hand. In reply to the question about the eye mostly rubbed, 24 of 28 patients (85.7%) with bilateral disease felt they rubbed both eyes equally, compared with 10 of 16 (62.5%) with unilateral disease. This difference is significant ( $\chi^2$  test,  $p < 0.05$ ).

Over three-quarters of patients with unilateral keratoconus (13 of 17) developed keratoconus on the same side as their dominant hand, a finding that is significant ( $\chi^2$  test,  $p < 0.05$ ). Of the four patients who developed keratoconus on the opposite side, one stated that he used his non-dominant hand to rub the eye on the same side, two used, respectively, the dominant and both hands to rub both eyes, and only one stated that he developed keratoconus in the eye that he did not rub.

**FAMILY HISTORY OF ATOPY AND KERATOCONUS**

A family history of atopic disease in parents and siblings was reported in 86.4% of atopic patients, in 84.6% of possibly atopic patients, and in 23.1% of non-atopic patients. Two patients were sister and brother. The sister had suffered severe eczema from infancy and could remember being scolded for

rubbing her eyes as a child. She developed bilateral keratoconus at the age of 14 and underwent keratoplasty aged 30. Her younger brother developed eczema at the age of 20 and bilateral keratoconus the following year. He gave no history of excessive eye rubbing and was a successful contact lens wearer. Both brother and sister had high IgE levels ( $>1000$  U/l and 800 U/l respectively). They shared one HLA haplotype, A31; B18; DR2.

One patient with a nine-year history of unilateral keratoconus had a twin who did not have keratoconus. Their physical appearance was strikingly similar, and their HLA type was identical. Both twins denied eye rubbing and neither was atopic, though both suffered contact dermatitis but from different irritants.

**Discussion**

The incidence of atopic disease in the general population is variously assessed as between 2 and 20%, and the proportion of the apparently non-atopic population that may suffer from atopic disease under suitable conditions is unknown.<sup>16</sup> The presence or a previous history of atopic disease was noted in more than half the patients (56.7%) who participated in this study, and a further eight patients (11.9%) had evidence of atopy without clinical disease. Most previous studies have also found a high incidence of atopic disease,<sup>3,4,6,7,9</sup> though some studies have failed to demonstrate an association.<sup>11,17</sup>

Explanations for the high incidence of atopy in keratoconus patients have included an association or linkage between the genetic determinants of the two conditions, or eye rubbing stimulated by ocular

Table 6 Unilateral and bilateral keratoconus and atopy

Keratoconus	Atopic	Possibly atopic	Non-atopic	Total
Bilateral	22	8	11	41
Unilateral	4	8	6	18

itching or discomfort resulting from atopic disease,<sup>3,4</sup> or a combination of both.<sup>7</sup> Investigation for a possible genetic association presents particular difficulties, for while the atopic tendency is undoubtedly inherited the type and severity of atopic disease and the age of onset are variable even within a family group, and some individuals may have an atopic tendency demonstrated by a type 1 immune response on stimulation with low doses of common allergens (such as a positive skin test) in the absence of clinical disease.<sup>18</sup> For this reason we used a set of criteria that distinguished the definitely atopic from the non-atopic, with a third intermediate group. The usefulness of this classification needs to be established by further studies, but it was encouraging to find that patients with normal levels of IgE but with evidence of atopy had levels mostly above 31 kU/l, while the opposite was true of patients without evidence of atopy: this did suggest that distinct groups had been delineated. A Swedish study of atopic and non-atopic populations found that a serum IgE level of 50.1 kU/l best discriminated the atopic and non-atopic groups.<sup>19</sup>

The hereditary nature of the atopic condition is well established, and a family history is obtained in about 70% of cases.<sup>16</sup> It seems probable that at least three independent genetic systems operate in the acquisition of allergic illnesses.<sup>18</sup> There is one (clearly critical) gene which predisposes certain individuals to develop one or more of the atopic diseases, but its chromosomal location and the mechanism of action of its translated products are unknown. A second genetic system controls total serum IgE levels and is not linked to either the genetic system mentioned above or the HLA system. Some workers have proposed that a single mendelian gene R/r plays a major role in the individual's IgE level, with the 'high IgE phenotype' corresponding to the rr genotype and the 'low IgE phenotype' corresponding to the RR and Rr genotypes.<sup>20</sup> Thirdly, there is a measure of HLA-linked genetic influence, and it has been postulated that several different Ir (immune response) genes associated with HLA type permit specific IgE synthesis in responders having high IgE phenotypes but that only one (or a very few) of such Ir genes allows response in people with low IgE phenotypes. This hypothesis would explain the strong association between particular HLA antigens and allergic responses to highly purified antigens in patients with low levels of IgE, but not in patients with high IgE levels.<sup>20</sup> Although an increased incidence of certain HLA types has been noted in some patients with an immune response to a particular antigen, no HLA associations have been demonstrated in atopic patients as a whole. It seems unlikely, therefore, that HLA associations found in keratoconus patients are

connected with HLA associations in atopic patients, unless atopic keratoconus patients showed a greater frequency of response to certain antigens than atopic patients without keratoconus. Although levels of HLA B7 were significantly decreased in our study, no independent associations between atopic status or IgE levels could be demonstrated. A statistically significant increase in the frequency of HLA B5,<sup>12</sup> HLA A9, A10, and A12,<sup>13</sup> and HLA Bw21<sup>14</sup> has been found in keratoconus patients, but other studies have found normal HLA frequencies.<sup>11,15</sup>

Although research into atopy has naturally concentrated on the immunological aspects of the condition, there is some evidence that a disorder of fatty acid metabolism may be an aetiological factor. Essential fatty acids are the precursors of prostaglandins and leukotrienes, and are also important structural components of cell membranes. Reduced levels of an essential fatty acid derivative, dihomo- $\gamma$ -linolenic acid, have been found in patients with atopic eczema and a deficiency of the  $\delta$ -6 desaturase enzyme has been postulated.<sup>21</sup> Patients treated with long-chain fatty acids to bypass this enzyme block have shown clinical improvement.<sup>22</sup> If reduced levels of dihomo- $\gamma$ -linolenic acid could be demonstrated in keratoconus patients, a genetic association between keratoconus and atopy could be proposed. Although we found reduced levels of dihomo- $\gamma$ -linolenic acid in keratoconus patients which were lower in the atopic and possibly atopic groups than in the non-atopic group, these differences were not significant.

Karseras and Ruben,<sup>4</sup> Woodward,<sup>10</sup> and Ihalainen<sup>23</sup> noted a bias towards the higher social classes in keratoconus patients, but this was not found in our study. Woodward<sup>10</sup> also found a significantly higher maternal age in keratoconus patients than in the general population and argued that the social class bias was secondary to increased parental age, suggesting that a genetic abnormality related to parental age might contribute to the aetiology of the disease. Ihalainen found no maternal age bias,<sup>23</sup> and maternal age in our study was significantly lower than in the Woodward study. Details of this work have been published elsewhere.<sup>24</sup>

Differences in the clinical course of keratoconus in atopic and non-atopic patients were compared in the hope that this might shed light on the nature of the association between keratoconus and atopy. Contrary to our clinical impression atopic patients did not have a significantly earlier onset of disease or higher rate of keratoplasty than non-atopic patients, nor were they more prone to graft rejection, though high levels of serum IgE may be a specific risk factor for rejection. The only significant clinical difference we found was a negative association between the more severe atopic manifestations and longstanding unilateral disease.

The proportion of unilateral cases in this study, at 31.3%, is comparable with other studies, where the proportion has varied from 5.8 to 41%.<sup>8,9,11,25</sup>

Evidence for excessive eye rubbing as a causative factor in keratoconus has been found in a number of studies.<sup>13,4,7</sup> There are obvious difficulties in quantifying the degree of eye rubbing either by observation or questioning patients, so we sought more indirect but objective evidence for it. Patients were questioned about age of onset of atopic symptoms and keratoconus, and in only one patient did keratoconus predate the onset of atopic symptoms. All but two atopic patients (who had asthma only) suffered with hayfever or eczema, the conditions most likely to cause ocular itching. To our knowledge no previous studies have reported a preponderance of right eyes in cases of unilateral disease. This preponderance, combined with the information that most patients use their dominant hand to rub their eyes, does support the view that eye rubbing influences the course of the disease. Patients with unilateral disease for more than three years were more likely to be non-atopic or possibly atopic, perhaps suggesting that eye rubbing in these patients was habit driven, whereas atopic patients were more likely to rub their eyes in response to bilateral ocular itching.

Keratoconus in identical twins has been reported previously,<sup>26</sup> as has keratoconus in one identical twin.<sup>27</sup> The occurrence of keratoconus in only one twin suggests that environmental factors are important, though the environmental factor most commonly suggested, excessive eye rubbing, was denied by both twins in our study. The frequency of inheritance of keratoconus has been found to vary between 6 and 19%.<sup>8,9,23,25,28</sup> The sister and brother in our study both had high levels of IgE, but the range of IgE levels in this study does not support a genetic linkage between high IgE production and keratoconus. The onset of keratoconus was earlier in the sister who gave a history of excessive eye rubbing than the brother who denied excessive eye rubbing, suggesting that keratoconus is inherited with eye rubbing as an exacerbating but not a primary causative factor. Sister and brother had a common haplotype. Ihalainen reported on 15 families with more than one affected child and excess of haplotype sharing between the affected parent and children.<sup>23</sup>

## Conclusion

The relative contributions of genetic and environmental factors to the aetiology of keratoconus are poorly understood. An association with atopic disease was confirmed in this study, but the nature of this association is uncertain. A significantly decreased frequency of HLA B7 was found, but this showed no

independent association with atopic disease. Conflicting evidence for and against a genetic aetiology was provided by a patient with an identical twin who did not have the disease, and a brother and sister who were both atopic. There was some evidence that eye rubbing may contribute to the aetiology of keratoconus, as unilateral keratoconus occurred more frequently on the side of the dominant hand.

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