Klebsiella and acute anterior uveitis

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SUMMARY Samples of the faeces of 153 consecutive patients presenting with acute anterior uveitis (AAU), and of 47 controls were examined for the presence of *Klebsiella pneumoniae*. No increase in the carriage rate of klebsiella was found in the AAU patients as compared with the controls. Furthermore no increase was found in any group of patients whether subdivided by HLA-B27 status, sex, or presence of ankylosing spondylitis (AS). No difference was found between patients having their first attack of AAU and those with recurrences.

The factors which may cause the initiation of an attack of acute anterior uveitis (AAU) have been the subject of much speculation and research. The discovery of the association of the HLA-B27 tissue type with AAU¹ has further enabled a particular subgroup of patients with AAU to be isolated and specifically studied. Rahi² has reviewed the possible mechanisms by which the carriage of the HLA-B27 tissue type may increase susceptibility to AAU and in particular the theory of molecular mimicry. This theory suggests that an infecting organism might carry components whose molecular structure mimics that of one of the HLA antigens. This could lead either to an inability of the host to mount a normal immune response to such an organism or to an associated autoimmune reaction being engendered by the organism.

One popular theory has implicated klebsiella species as a possible trigger for the AAU. Evidence supporting this hypothesis has included: (1) cross-reactivity between certain klebsiella species and lymphocytes of HLA-B27+ patients,^{3–7} (2) a significant increase in the faecal carriage rate of klebsiella in HLA-B27+ patients with active ankylosing spondylitis (AS),^{8,9} (3) an increased carriage of klebsiella over controls in patients with AS who developed AAU¹⁰ as well as in patients with AAU who did not have concomitant AS.^{11,12} Further studies which demonstrated immunological similarities between klebsiella extracts and vitreous humour have implicated klebsiella in the development of uveitis in general.^{13,14} However, the above findings have not

been universally confirmed,^{15,16} and specifically there has been a failure to demonstrate lymphocyte cross-reactivity with klebsiella in HLA-B27+ patients with AAU.¹⁷

It is the purpose of the present study to evaluate prospectively the role klebsiella plays as a 'trigger' for AAU by evaluating the prevalence of klebsiella in the faeces of a large group of patients with active AAU both HLA-B27+ and HLA-B27– and to compare this with controls.

Patients and methods

All patients presenting to the casualty unit of the eye clinic at the Leicester Royal Infirmary with AAU over a nine-month period were included in the study. The control group, matched for age and sex, were also chosen from patients attending the casualty unit with unrelated conditions such as corneal abrasions, traumatic hyphaema, and lid lacerations.

All the AAU patients and controls provided a specimen of faeces at or within three days of their first visit to the hospital. This meant that most of the AAU patients provided their specimens very soon after the onset of ocular symptoms and, in the main, within one week. One hundred and fifty-three patients and 47 controls provided specimens. The sex distribution of these groups was 91 males and 62 females in the AAU patients and 27 males and 20 females in the controls.

The laboratory isolation of klebsiella species was undertaken by one author (D.W.) who was unaware at the time which specimens came from AAU patients and which from controls. Primary isolation of the organisms was achieved by plating an emulsion of the

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faecal specimen on to McConkey agar and lactose sucrose urea agar and streaking for single colonies. After suitable incubation klebsiella species were identified by careful examination of colony morphology. Organisms from appropriate colonies were then subcultured until pure. The pure culture thus obtained was then inoculated into the following media: peptone water at room temperature, peptone water at 37°C, phenylalanine malonate broth at 37°C, and Christensen's urea at 37°C. Incubation occurred overnight. Medium 1 was then examined for the presence of bacterial motility. Medium 2 was examined for indole production by the addition of Kovac's reagent, and media 3 and 4 were tested for the presence of malonate production and urease activity respectively. From these properties the presence of klebsiella species was ascertained.

The HLA-B27 status of 134 of the AAU patients (84 males and 50 females) was tested by the tissue typing service of the British National Blood Transfusion Service, Sheffield.

The AAU patients had x-rays taken of their sacroiliac joints and lumbar spine. The presence of AS was determined by the New York criteria for the radiological diagnosis of AS.¹⁸ Bilateral radiological sacroiliitis of grades, 2, 3, and 4 was considered as evidence of true AS.¹⁹

Results

Two hundred specimens of faeces were tested for the presence of klebsiella species, 153 from AAU patients and 47 from controls. A klebsiella was isolated from 27 (18%) of the AAU patients and 12 (26%) of the controls ($p < 0.05$). Table 1 shows the distribution of klebsiella isolation in the patients and controls divided by sex and HLA-B27 status. None of these patient subgroups showed an incidence of klebsiella carriage higher than in the control group.

There was no significant difference in the isolation of klebsiella between those patients suffering a first attack of AAU and those suffering a recurrence (Table 2).

Of 124 patients x-rayed 29 showed radiological evidence of AS, 18 HLA-B27+ males, 5 HLA-B27- males, 5 HLA-B27+ females, and 1 HLA-B27- female. Among these patients with AS only three were shown to carry a klebsiella in their faeces, and these were all HLA-B27+ males.

Discussion

The results of this study do not support the hypothesis that the carriage of klebsiella species in the bowel is incriminated in the initiation or perpetuation of AAU. Indeed in our population of patients with AAU

Table 1 Percentage of patients with AAU and controls demonstrating klebsiella in stools

	HLA-B27+	HLA-B27-	HLA-B27 Tissue type unknown	Controls
	% (n)	% (n)	% (n)	% (n)
Males	15 (39)	24 (45)	14 (7)	26 (27)
Females	17 (23)	11 (27)	17 (12)	25 (20)
Total	16 (62)	19 (72)	16 (19)	26 (47)

(n)=Number of patients in each group.

Table 2 Percentage of patients with AAU demonstrating klebsiella in stools

	First attack of AAU % (n)	Recurrent attack of AAU % (n)
HLA-B27+ males	14 (14)	16 (25)
HLA-B27+ females	20 (10)	15 (13)
Total HLA-B27+ patients	17 (24)	16 (38)
HLA-B27- males	23 (26)	26 (19)
HLA-B27- females	7 (14)	15 (13)
Total HLA-B27- patients	17 (40)	22 (32)

(n)=Number of patients in each group.

the incidence of klebsiella carriage was less than in the control group.

It may be suggested that klebsiella are rapidly eliminated from the gut, and that patients who were carriers at the initiation of their disease were already clear by the time of testing. In this study, however, the time between onset of symptoms and testing was in most cases quite short (less than a week).

An immune response mounted against the klebsiella might remove it from the gut and at the same time initiate an autoimmune attack on the eye. If, however, the organisms were cleared from the gut by such a mechanism, this would contradict the theory that the organism gains protection on the grounds that it possesses an antigen recognised by the host as self. However, it is entirely possible that the immune response may be operating against an antigen on the organism different from the HLA mimic.

Acute anterior uveitis may be triggered initially by a specific antigenic challenge but subsequently may be reinitiated by a variety of non-specific agents. It has been shown that not only 'memory cells' specific to a given antigen may be stimulated to proliferate by that antigen, but through the action of lymphokines a whole range of antibodies can be produced.^{20,21} It is, of course, difficult to be sure that a patient presenting with AAU who denies a previous episode has not, in fact, suffered an earlier undiagnosed attack. In the current study we regarded those patients who on careful questioning denied any previous ocular

symptoms or treatment which would suggest AAU, and who had no clinical evidence of previous AAU in the fellow eye, as having a first attack. We found no significant difference in the incidence of klebsiella carriage between those patients with recurrent disease and those having their first attack.

These negative findings are in contrast to the previous studies where faecal klebsiella carriage was strongly associated with active AS^{8,9} as well as in a single report where klebsiella carriage was reported in 13 out of 17 patients with AAU and concomitant AS.¹⁰ The presence of the klebsiella was, therefore, possibly related to the AS rather than to the AAU, which suggests that AS may behave differently from AAU in this respect.

Our study of 153 consecutive patients with AAU, of which 62 were HLA-B27+, does not support the hypothesis that klebsiella species may play a role in the initiation of AAU especially in HLA-B27+ patients. Klebsiella may be involved in the pathogenesis of AS and perhaps other inflammatory processes associated with the HLA-B27 tissue type, but it seems unlikely that it plays a unique or predominant role in the causation of AAU.

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