

## $\alpha_1$ -Antitrypsin phenotypes in acute anterior uveitis

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**SUMMARY** The  $\alpha_1$ -antitrypsin phenotype PiMZ has been reported to have a higher than normal incidence in patients with acute anterior uveitis, indicating an important role in the immunogenetics of this condition. We have determined the incidence of this phenotype in 72 patients with acute anterior uveitis. It was found to occur in four patients (5.6% of the total), with the highest incidence (3/34 or 8.8%,  $p < 0.001$ ) in patients negative for HLA B27 and without sacroiliac joint disease. The incidence in HLA B27 positive patients was normal. No correlation was found with the severity, bilaterality, or recurrence of uveitis. Although this increased incidence is statistically significant in comparison with the normal population incidence of 2.6%, its direct clinical significance is questionable; the most likely explanation for it includes possible linkage with other immunoregulatory genes. We also found a lower than expected incidence of the phenotype PiMS, and discuss the relevance of this finding.

The association between HLA B27, ankylosing spondylitis (AS), and acute anterior uveitis (AAU) has been known for over 14 years.<sup>1</sup> This tissue type, which is found in 7 to 8% of the general population, occurs in virtually all patients with both anterior uveitis and ankylosing spondylitis but only 45 to 50% of patients who have anterior uveitis without systemic disease.<sup>2,3</sup> Furthermore, only 0.15% of the HLA B27 positive population will ever get anterior uveitis. It is therefore apparent that there must be some alternative genetic or environmental factor which predisposes an individual to attacks of acute anterior uveitis.

In 1978 Brewerton *et al.*<sup>4</sup> demonstrated a substantially increased incidence of the  $\alpha_1$ -antitrypsin phenotype PiMZ (associated with relatively lower blood levels of this major protease inhibiting enzyme) in patients with anterior uveitis, occurring in 30% of those with anterior uveitis and ankylosing spondylitis and 21% of those with anterior uveitis alone. The  $\alpha_1$ -antitrypsin phenotypes are internationally annotated by an alphabetical method, prefixed by Pi (protease inhibitor), with one letter for each allele (some of which have several subtypes, annotated numeric-

ally). Some 59 different alleles have been recognised, the most prevalent being M (hence PiMM is the most common phenotype). As the Pi gene locus is on chromosome 14 while that of the HLA system is on 6, this suggested a hitherto unrecognised inherited susceptibility to anterior uveitis capable of operating independently of HLA B27 through insufficient inhibition of inflammatory proteolysis by  $\alpha_1$ -antitrypsin.

Although these findings have been confirmed by some authors,<sup>5,6</sup> albeit with lower incidences, they have been refuted by others.<sup>7,8</sup> The result is a lack of a definitive understanding of whether a deficiency of  $\alpha_1$ -antitrypsin is of clinical importance in the susceptibility of an individual to anterior uveitis. We now present our data from a well-defined group of 72 patients with acute anterior uveitis who presented to St Thomas's Hospital, London, between 1984 and 1986, and who were classified according to race, HLA B27 status, sacroiliac joint disease, recurrence, bilaterality, and severity of inflammation.

### Subjects and methods

In this study acute anterior uveitis is defined as an acute, non-granulomatous inflammation of the

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anterior uveal tract. It was usually unilateral, and characterised by a history of pain, photophobia, and blurring of vision, with circumcorneal injection, keratic precipitates, and cells and flare in the anterior chamber.

The 72 patients who presented to the Eye Casualty Department with anterior uveitis were studied in our uveitis clinic, where we recorded their age (range 16 to 73 years, mean 43), sex (41 male, 31 female), and race. Other details included whether it was a first or recurrent attack of AAU and whether it was unilateral or bilateral. The severity of inflammation at presentation was clinically graded as mild, moderate, or severe. In those patients seen when convalescent these details were obtained from the records.

Tissue typing, in order to ascertain HLA B27 status, was carried out on a 20 ml sample of citrated venous blood.

α<sub>1</sub>-Antitrypsin phenotyping was performed at the Protein Reference Unit of the Royal Hallamshire Hospital, Sheffield, by the established technique of isoelectric focusing of serum samples on polyacrylamide gels, in accordance with Brewerton's study.<sup>4</sup> Incidence values for the normal south-east England population were used as controls in this study.<sup>9</sup>

Radiological assessment of the patients' sacroiliac joints was carried out according to New York criteria<sup>10</sup> by a member of the Department of Radiology, St Thomas's Hospital, who was not informed of their HLA B27 status or any relevant history other than the fact that all had anterior uveitis. Patients scoring 2 or more out of 4 by this method were classified as having sacroiliac joint disease.

The results were analysed by χ<sup>2</sup> tests.

**Results**

The incidences of the major phenotypes in our study group are displayed in Table 1, which also shows the results divided into different ethnic groups. The

Table 1 *Incidences of the major Pi phenotypes found in our study group compared with those of the UK population as controls (percentage in parentheses)*

Phenotypes	n	PiMM	PiMS	PiMZ	PiFM*
UK incidence		(86.5)	(9.3)	(2.6)	(0.7)
Study group	72	65 (90.3)	2 (2.8)	4 (5.6)	1 (1.4)
Caucasian	56	50 (89.3)	2 (3.6)	3 (5.4)	1 (1.8)
Negro	7	7 (100)	-	-	-
Asian	5	4 (80)	-	1 (20)	-
Oriental	4	4 (100)	-	-	-

\*No known clinical significance.

Table 2 *Phenotype incidences in HLA B27 positive and negative patients, and in those with and without evidence of sacroiliac joint (SIJ) involvement (percentages in parentheses)*

Phenotypes	n	PiMM	PiMS	PiMZ	PiFM
B27 negative	34	30 (88.2)	-	3 (8.8)	1 (2.9)
B27 positive	38	35 (92.1)	2 (5.3)	1 (2.6)	-
SIJ neg*	57	53 (93.0)	-	3 (5.3)	1 (1.8)
SIJ pos†	15	12 (80.0)	2 (13.3)	1 (6.7)	-
B27 positive, SIJ neg	23	23 (100)	-	-	-

\*Twenty three HLA B27 positive and 34 negative.

†All HLA B27 positive.

normal values for the United Kingdom are given as controls. As can be seen, the study population as a whole was an atypical sample (p<0.05) owing to a possibly higher incidence of phenotype PiMZ (5.6%, p=0.10) and a slightly lower incidence of PiMS (2.8%, 0.05<p<0.10). When the group was subdivided according to ethnic origin, only the Caucasian group (n=56) was large enough to warrant valid statistical analysis, and the results of this group mirrored those of the study group as a whole, with a PiMZ incidence of 3/56 (5.4%) and a PiMS incidence of 2/56 (3.6%).

When the patients were divided into those who were HLA B27 positive and negative, and those who did and did not have radiological evidence of sacroiliac involvement (Table 2), it was found that our sample population showed a typical distribution of the incidences of HLA B27 (38/72, 52.8%) and sacroiliac disease (15/72, 20.8%) for patients with anterior uveitis (p>0.50). Analysis of the individual groups showed that the B27 negative patients followed the trend of a possibly lower incidence of PiMS (0.05<p<0.10) and a higher incidence of PiMZ (p<0.025) when compared with the normal United Kingdom population. When the B27 positive group was considered as a whole, it showed a normal distribution of phenotypes (p>0.75), with no significant difference between those who had evidence of sacroiliac disease and those who did not. Those patients who had no sacroiliac involvement (irrespective of HLA B27 status), like the B27 negative group, also showed a lower incidence of PiMS (p<0.025) and a possibly higher incidence of PiMZ (0.05<p<0.10). Those who did have sacroiliac involvement (all HLA B27 positive) had an essentially normal distribution of phenotypes (p>0.75).

Our results showed no significant difference in the phenotype incidences when the severity of anterior uveitis was expressed in terms of bilateral or recurrent disease (Table 3). Only seven of the 72 patients had bilateral disease, and all were PiMM, the remaining 63 (laterality not recorded in two patients) having

the same phenotype incidences as the whole group. There was no significant difference between those who had recurrent inflammation and those presenting for the first time, nor between those presenting with clinically mild, moderate, or severe inflammation.

Table 3 *Phenotype incidences in bilateral and recurrent, and mild, moderate, and severe acute anterior uveitis (percentages in parentheses)*

Phenotypes	n	PiMM	PiMS	PiMZ	PiFM
Unilateral	63	56 (88.8)	2 (3.2)	4 (6.3)	1 (1.6)
Bilateral	7	7 (100)	-	-	-
Not recorded	2	2 (100)	-	-	-
First attack	37	33 (89.2)	1 (2.7)	2 (5.4)	1 (2.7)
Recurrent	33	30 (90.9)	1 (3.0)	2 (6.1)	-
Not recorded	2	2 (100)	-	-	-
Mild	21	20 (95.2)	-	1 (4.8)	-
Moderate	39	34 (87.2)	2 (5.1)	2 (5.1)	1 (2.6)
Severe	12	11 (91.7)	-	1 (8.3)	-

Of the four patients with the PiMZ phenotype only one was HLA B27 positive, and she presented as a severe, recurrent, unioocular inflammation with grade 2 radiological evidence of sacroiliac disease. The remaining three were all B27 negative, with no evidence of sacroiliac involvement. Two presented with moderate inflammation (one of whom had recurrent anterior uveitis), and one had a mild first attack. All three were unilateral.

## Discussion

There are at least 59 different alleles for the  $\alpha_1$ -antitrypsin gene, only two of which, Z and (to a lesser extent) S, are associated with a deficiency of the enzyme. Severe deficiency produced by homozygote PiZZ or PiSS, and associated with primary emphysema and juvenile cirrhosis, is well documented.<sup>11</sup> Heterozygote phenotypes for Z and S, occurring with M or 0 (null), have been suggested to be associated

Table 4 *Comparisons of our results with the PiMZ incidences in other studies of acute anterior uveitis, with and without sacroiliac joint (SIJ) disease (percentages in parentheses)*

Study group	SIJ disease negative	SIJ disease positive
Fearnley <i>et al.</i>	3/37 (5.3)	1/15 (6.7)
Brewerton <i>et al.</i> <sup>4</sup> (later reappraised)	10/47 (21.3)	10/33 (30.3)
LeClerq <i>et al.</i> <sup>6</sup>	9/64 (14.1)	15/52 (28.8)
Wakefield <i>et al.</i> <sup>5</sup>	4/30 (13.3)	4/29 (13.8)
Grabner <i>et al.</i> <sup>8</sup>		3/80 (3.8)
Brown <i>et al.</i> <sup>7</sup>		3/65 (4.6)
		0/133 (0)

with less severe hepatic and pulmonary disease, juvenile arthritis,<sup>12</sup> and psoriasis,<sup>13</sup> as well as anterior uveitis.

An increased incidence of phenotype PiMZ was seen in our patients when taken as a whole, with values ranging up to 8.8% depending on which subgroup is considered. In none of these cases, however, does it occur with the frequency described by some workers (Table 4). Although our results are just statistically significant when compared with the normal south-east England incidence of 2.6%,<sup>9</sup> it is difficult to argue their clinical significance in proving that the relatively lower levels of  $\alpha_1$ -antitrypsin associated with phenotype PiMZ do predispose to anterior uveitis. This argument is further confounded by the fact that uveitis is not a major clinical feature in those who have the PiZZ genotype.<sup>11</sup>

Those authors whose results failed to show any significant difference in the incidence of phenotype PiMZ in anterior uveitis<sup>7,8</sup> have suggested that this might be due to differences in the ethnic make-up of the various sample populations. It is known that the incidence of PiMZ can vary between 1 and 4% for different populations (it occurs much less frequently in Negroes and Asians), but this is not enough to explain the magnitude of the discrepancies seen between different study groups (Table 4). Our population came from the same area as that of Brewerton *et al.*<sup>4</sup> in London, and, although it is moderately heterogeneous, one would expect a closer correlation between our results. Instead we found almost the opposite, with no particular correlation between the incidence of PiMZ and sacroiliac joint involvement (all HLA B27 positive), as one might expect if the Pi system was independent of the HLA system. Brewerton himself thought that such differences seen might be due to the more rigorous selection techniques used in his studies,<sup>14</sup> but we have used similarly rigorous selection techniques ourselves with our study group. Indeed, by using only radiological criteria to assess sacroiliac disease, we have probably created several false negatives (patients who have early sacroiliac involvement but have not yet developed radiological evidence of it), which would serve only to enhance the incidence reported in those patients who were diagnosed as having sacroiliac disease. Not only did we fail to demonstrate such a high incidence of PiMZ in anterior uveitis, but we also found no significant difference in its incidence between those uveitic patients who also had sacroiliac joint disease and those who did not.<sup>4,14</sup> In fact, the incidence of PiMZ in our study group was higher in cases of B27 negative anterior uveitis without sacroiliac involvement. We were similarly also unable to show any difference within our group in the incidence of PiMZ with increased clinical severity of

uveitis, bilaterality, or relapse, in contrast to the findings of Wakefield *et al.*<sup>5</sup>

One unusual finding which some workers<sup>5,6</sup> have also reported, but failed to comment on, is the relatively low incidence of the phenotype PiMS in anterior uveitis patients, as this is normally the next most frequently occurring phenotype (9.3%) after PiMM (86.5%) in the United Kingdom. As the genotype PiSS has been associated with severe deficiencies of  $\alpha_1$ -antitrypsin in much the same way as PiZZ, it might be expected that the incidence of PiMS should also be increased in anterior uveitis. Our results, if anything, show a negative correlation of PiMS with acute anterior uveitis, possibly implying a protective role similar to that seen with some tissue types in other disease.<sup>15</sup>

The theory of a PiMZ association with anterior uveitis is an attractive one, as it provides a potential genetically determined immunochemical mechanism for disease susceptibility. It is becoming increasingly clear, however, that its potential role as a predisposing gene is at best part of a far more complex immunogenetic mechanism, and it might even be merely a marker for an alternative, as yet unidentified, gene. Chromosome 14 is known to contain several genes associated with immunoglobulins and their synthesis, and there has recently been some interest in the possible role of the IgG heavy-chain (Gm) allotypes in determining susceptibility to anterior uveitis. The gene locus for the Gm allotypes is on chromosome 14q, in close proximity to that of the Pi system,<sup>16</sup> with which it occurs in autosomal linkage,<sup>17</sup> and it was argued that the PiMZ phenotype was only a genetic marker for a specific Gm allotype.<sup>18</sup> An association between such specific allotypes and anterior uveitis has, however, since been refuted<sup>19</sup> and retracted.<sup>20</sup>

At present, research into the immunogenetics of acute anterior uveitis and other inflammatory diseases<sup>21</sup> has mainly served to emphasise the complexity of the systems involved and the likelihood that these are controlled through a multiplicity of endogenous and exogenous factors which have yet to be correlated with each other.

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