α1-Antitrypsin-levels and phenotypes in Crohn’s disease in the Netherlands

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Summary A group of 310 unrelated patients suffering from Crohn’s disease has been screened for quantitative and electrophoretic variations of α1-antitrypsin (α1AT). A comparison was made between patients and healthy controls. The distribution of electrophoretic α1AT variants in the patients showed no significant deviation from the controls. The α1AT quantities are significantly higher in the Crohn’s disease population than in the controls.

Crohn’s disease, a chronic inflammatory disease of the intestine, is an uncommon condition mainly affecting young adults.

Ever since it was first described, attempts have been made to determine precise clinical and pathological criteria for the diagnosis and to look for factors which could influence or be the direct cause of the disease. Studies on the role of infectious and immunological factors in Crohn’s disease have not yet provided clear answers concerning the cause of the disease. Although genetic factors have been implicated in its pathogenesis, neither a genetic marker nor a biochemical parameter correlated with Crohn’s disease has so far been identified.

α1-Antitrypsin (α1AT, locus Pi) is the main member of a species of inhibitors of proteolytic enzymes occurring in human serum. Genetic polymorphism was discovered by Fagerhol and Braend. The alleles PiP, PiS, PiZ, PiW1, and Pinull are associated with decreased levels of α1AT.

A deficiency of α1AT was found to be associated with a variety of clinical conditions such as chronic obstructive lung disease (COLD), chronic cirrhosis of the liver, coeliac disease, arthritis, uveitis, and ankylosing spondylitis. These last three clinical conditions have been found to be associated with Crohn’s disease. Linkage is shown between α1AT and immunoglobulin G(Gm), whereas other markers revealed no linkage.

We have screened a population of thoroughly investigated Crohn’s disease patients attending the in- and outpatient clinics of the department of gastroenterology at the University Hospital, Leiden, for both quantitative and electrophoretic variations of α1AT in order to explore whether there is (1) a deviation of the distribution of electrophoretic variants of α1AT in Crohn’s disease patients compared with controls and (2) any quantitative change in the α1AT level in the Crohn’s disease patients.

Methods

Three hundred and ten unrelated patients suffering from Crohn’s disease were studied. In about 90% of all the cases the diagnosis was established on the basis of histological evidence; 258 patients have had at least one operation and the specimen resected met the histological criteria of Crohn’s disease; in 22 of 34 patients with Crohn’s disease in the colon determined through the endoscope biopsies showed epithelioid-cell granulomas. In the remaining 18 patients the diagnosis was based upon clinical and radiological findings.

The electrophoretic variations of α1AT in Crohn’s disease patients were compared with those found in 708 healthy Dutch blood donors.

α1AT was typed using two previously described methods: agarose-acrylamide electrophoresis for the initial typing and isoelectric focusing for verifying the variants and for subtyping the M-variant (a combination of the methods of Klasen et al. and Frants and Eriksson.)

α1AT was quantified using the standard radial immunodiffusion technique. The average values of α1AT were expressed as percentage of the standard

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Table 1  Hardy-Weinberg analysis of electrophoretic variants of α1-AT in 310 unrelated patients suffering from Crohn's disease

<table>
<thead>
<tr>
<th>α1-AT allele</th>
<th>α1-AT gene frequency</th>
<th>α1-AT phenotype</th>
<th>Number</th>
<th>χ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>0.00806</td>
<td>FM</td>
<td>5</td>
<td>0.0159</td>
</tr>
<tr>
<td>I</td>
<td>0.00323</td>
<td>IM</td>
<td>2</td>
<td>0.0064</td>
</tr>
<tr>
<td>M</td>
<td>0.94516</td>
<td>M</td>
<td>277</td>
<td>0.0000</td>
</tr>
<tr>
<td>S</td>
<td>0.03065</td>
<td>MS</td>
<td>17</td>
<td>0.0511</td>
</tr>
<tr>
<td>X</td>
<td>0.00161</td>
<td>MX</td>
<td>1</td>
<td>0.0032</td>
</tr>
<tr>
<td>Z</td>
<td>0.01129</td>
<td>MZ</td>
<td>7</td>
<td>0.0223</td>
</tr>
<tr>
<td>Others</td>
<td>0</td>
<td>Others</td>
<td>0</td>
<td>0.6411</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>310</td>
<td>2.4660</td>
</tr>
</tbody>
</table>

For 1 degree of freedom: p = 0.12.

The standard serum was a mixture of several sera from healthy blood donors with the phenotype M. The α1-AT quantity of our standard serum was compared by Dr. M. K. Fagerhol with his serum pool and found to be the same. For comparing the α1-AT levels in the Crohn's disease patients the quantitative data of the healthy controls of Fagerhol were used.

Results and discussion

Typing

Seven phenotypes with six different alleles were found in the Crohn's disease population and, they were shown to be in Hardy-Weinberg equilibrium (Table 1).

The Crohn's disease and blood donor populations showed similar frequencies of electrophoretic variants of α1-AT; none of the seven phenotypes showed a significant difference compared with the controls (Table 2).

Quantification

The level of α1-AT rose in the Crohn's disease patients in all phenotypes, as can be seen in Table 3. In the phenotypes FM, M, and MS the difference reached significance.

Table 2  Distribution of electrophoretic variants of α1-AT among patients and controls.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Patients (N = 310) Controls (N = 708)</th>
<th>χ²</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no.</td>
<td>%</td>
<td>no.</td>
</tr>
<tr>
<td>FM</td>
<td>5</td>
<td>1-6</td>
<td>8</td>
</tr>
<tr>
<td>IM</td>
<td>2</td>
<td>0-6</td>
<td>5</td>
</tr>
<tr>
<td>M</td>
<td>277</td>
<td>89-4</td>
<td>647</td>
</tr>
<tr>
<td>MS</td>
<td>17</td>
<td>5-5</td>
<td>40</td>
</tr>
<tr>
<td>MX</td>
<td>1</td>
<td>0-3</td>
<td>0</td>
</tr>
<tr>
<td>MZ</td>
<td>7</td>
<td>2-3</td>
<td>7</td>
</tr>
<tr>
<td>S</td>
<td>1</td>
<td>0-3</td>
<td>1</td>
</tr>
</tbody>
</table>

†Chi square with Yates correction.

Table 3  Quantitation of α1-AT in Patients and controls

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Patients</th>
<th>Controls</th>
<th>T*</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Mean %</td>
<td>St. dev. %</td>
<td>No. Mean %</td>
<td>St. dev. %</td>
</tr>
<tr>
<td>FM</td>
<td>5 124 30-1</td>
<td>24 98 16-4</td>
<td>2-775 p &lt; 0-01</td>
<td></td>
</tr>
<tr>
<td>IM</td>
<td>2 111 0 5</td>
<td>5 98 11-0</td>
<td>1-579 n.s.</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>277 127 33-1</td>
<td>203 100 17-1</td>
<td>10-627 p &lt; 0-001</td>
<td></td>
</tr>
<tr>
<td>MS</td>
<td>17 104 27-3</td>
<td>54 83 11-0</td>
<td>4-632 p &lt; 0-001</td>
<td></td>
</tr>
<tr>
<td>MX</td>
<td>1 183 1-0</td>
<td>4 63 5-5</td>
<td>1-900 n.s.</td>
<td></td>
</tr>
<tr>
<td>MZ</td>
<td>7 81 36-5</td>
<td>12 61 5-5</td>
<td>1-900 n.s.</td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>1 81 1-0</td>
<td>8 63 11-0</td>
<td>1-900 n.s.</td>
<td></td>
</tr>
</tbody>
</table>

*Student T test.

Table 3 also shows that the phenotypes MS, S and MZ in the controls had a lower average α1-AT quantity than the other phenotypes, especially the M phenotype. This means that when the average quantity is compared between patients and controls the phenotypes should also be taken into account.

Conclusion

The search for linkage or associations of other genetic markers including HLA-DR with Crohn's disease has not so far led to positive results. The present study reveals no association. Patients suffering from Crohn's disease do not differ from the normal controls in their α1-AT phenotype distribution. As α1-AT is an acute phase reactant, the overall increase of the level of α1-AT in the patients is likely to be related to the activity of the disease.

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References

842 Klasen, Biemond, and Weterman

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