Serum immunoglobulin levels in gonococcal and non-specific urethritis

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Immunoglobulin responses have been studied in a number of infections and in some diseases specific patterns of diagnostic value have been established. The purpose of this investigation was to study immunoglobulin levels in patients with non-specific urethritis (NSU). This is a clinical entity of uncertain cause or causes; the two most fully investigated possibilities are that it is an infective process either with 'T' strain mycoplasmas (Csonka, Williams, and Corse, 1966) or with Chlamydia (Dunlop, Al-Hussaini, Garland, Treharne, Harper, and Jones, 1965). Another possibility, that of an allergic phenomenon, was investigated by Weston (1965). It is, of course, possible that both infective and allergic mechanisms might operate either separately in different patients or in combination in the same patient; the recurrent pattern of disease seen in some patients tends to suggest an allergic mechanism.

In this investigation the immunoglobulin levels were compared with those found in patients with gonococcal urethritis, a disease in which allergy is not a factor.

Material and methods

PATIENTS AND CONTROLS

Blood specimens were obtained at their first attendance from fifty male patients with non-specific urethritis and 39 patients with gonorrhoea. Eight of the patients with NSU and fifteen of those with gonorrhoea were Negroes, the remainder being European.

None of the patients with NSU had a previous history of the disease or of gonorrhoea and none of the patients with gonorrhoea had had a previous episode of NSU. In each case the diagnosis was made on the basis of the clinical features and confirmed in the cases of gonorrhoea by the identification of gonococci in a Gram-stained urethral smear and in the cases of NSU by their absence. Patients with NSU were treated with a 5-day course of oxytetracycline 1·5 g. daily, and those with gonorrhoea were treated with a single injection of 5 million units crystalline penicillin with 1 g. probenecid orally.

For comparison, serum immunoglobulins were measured in forty normal healthy males, blood donors or hospital staff. The blood samples were allowed to clot and the serum was separated as soon as possible and stored at −20°C.

Immunoglobulin estimations were performed by a radial immunodiffusion technique using 'Immunoplates' (Hyland Laboratories). IgA and IgM plates were incubated at room temperature for 16 hrs, and IgG plates at 37°C. for 4 hrs. The diameter of the precipitin rings was measured to the nearest tenth of a millimetre. All sera were assayed in duplicate on separate plates and repeated if the results differed by more than ± 5 per cent. of the mean; otherwise mean values were taken. The accuracy of the method for the same specimen assayed at different times is ± 10 per cent.; replicate estimations at the same time usually have an accuracy of ± 5 per cent. Sera were suitably diluted with normal saline so that the results fell within the range of the standard line. Standard sera, previously calibrated, were included with each set of estimations, and one standard serum was included in each plate. The plate was discarded if the standard serum did not fall within ± 5 per cent. of the standard line.

STATISTICAL ANALYSIS

Previous observations have shown that the distribution of immunoglobulin levels in normal subjects is approximately log. normal, and this agrees with the observations of Hobbs and Davis (1967). All the results are therefore given on a logarithmic scale. Mean values are given as geometric means and 't' tests were performed in log. units.

Results

The distributions of IgG, IgA, and IgM values for the two groups of patients and the normal subjects are shown in Figs 1, 2, and 3 (overleaf). These data are summarized in the Table (overleaf).

NORMAL SUBJECTS

The distribution of the normal results was comparable with that for a much larger series of normal subjects, both male and female, obtained during 4 years' experience with the method in this laboratory. Serial estimations in 24 normal subjects over a 4-month period have shown that serum immunoglobulin levels do not vary by more than ± 10 per
The mean and 2 S.D. limits for the normal controls are indicated by the solid and broken lines.

Denotes European, and Negro patients.

<table>
<thead>
<tr>
<th>Patients</th>
<th>IgG (mg./100 ml.)</th>
<th>Significance</th>
<th>IgA (mg./100 ml.)</th>
<th>Significance</th>
<th>IgM (mg./100 ml.)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (40)</td>
<td>997</td>
<td></td>
<td>211</td>
<td></td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>Non-specific urethritis (50)</td>
<td>1,360</td>
<td>t = 4.93</td>
<td>280</td>
<td>t = 2.68</td>
<td>128</td>
<td>t = 3.65</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P &lt; 0.001</td>
<td></td>
<td>0.01 &gt; P &gt; 0.001</td>
<td></td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Gonorrhoea (39)</td>
<td>1,317</td>
<td>t = 2.45</td>
<td>317</td>
<td>t = 2.69</td>
<td>139</td>
<td>t = 3.86</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.02 &gt; P &gt; 0.01</td>
<td></td>
<td>0.01 &gt; P &gt; 0.001</td>
<td></td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

The cent. of the mean value, provided that there is no intercurrent illness.

NSU
Although the majority of values fell within the normal range (mean ± 2 S.D.), the mean levels of IgG, IgA, and IgM, were all significantly higher than the normal. 31 patients (62 per cent.) had values for at least one immunoglobulin class above the normal range (mean ± 2 S.D.). Thirteen patients had increased IgG, twelve increased IgA, and twelve increased IgM. Four patients had increases...
in at least two immunoglobulin classes and two patients had increases in all three classes. Seven of the patients relapsed after treatment; three of these had raised IgA levels. None of the patients had any associated diseases likely to alter immunoglobulin levels. Six of the Negro patients had raised IgG levels. It was not possible to relate any of the immunoglobulin changes to particular features of the disease.

GONORRHOEA
Again, although most of the results fell within the normal range, mean levels for IgG, IgA, and IgM were significantly higher than normal. At least one result above the upper limit of the normal range was found in 28 (72 per cent.) of the patients; twelve patients had raised IgG, nine raised IgA, and eleven raised IgM. Four patients had increased levels in at least two immunoglobulin classes; in none were all three classes raised. Five of the Negro patients had raised IgG levels. All the patients made a satisfactory response to treatment although fourteen developed post-gonococcal urethritis. These fourteen patients did not show any specific change in immunoglobulin pattern.

Discussion
Most infections present multiple antigenic challenges and are accompanied by a generalized increase in immunoglobulin levels, although in some diseases, such as infectious hepatitis, and mumps, characteristic patterns are found (Zanussi and Medina, 1968). Where mucosal surfaces are predominantly involved, a selective increase in IgA may occur. In allergic reactions of the immediate hypersensitivity type, increased IgE levels have been recorded (Johansson, 1967) but there is usually no change in other immunoglobulin fractions. In some diseases associated with abnormal immune responses involving humoural antibodies IgG levels alone may be raised.

It is not surprising to find that patients with gonorrhoea have higher mean levels of IgG, A, and M than normal subjects. The localized nature of the disease and the usual absence of systemic effects probably accounts for the relatively small increase. It is of interest that Cohen, Kellogg, and Norins (1969), studying antibody responses in experimental gonorrhoea, found that the antibody response to heat-labile antigens was mainly IgG and to heat-stable somatic antigens mainly IgA. In NSU the immunoglobulin pattern is similar, which would support an infective, as opposed to an allergic, aetiology for this disease. However, this does not exclude an allergic factor in some patients; this series does not include patients with a history of recurrent disease, suggesting that allergy might be involved, and further studies on such patients would be worthwhile.

In both diseases some patients have definitely abnormal levels of one or more immunoglobulin classes, but it does not seem possible to relate these changes to any particular features of the diseases. These results were obtained from specimens taken from patients at their first attendance in the acute stage of the disease and it is possible that specimens taken during convalescence might reveal a more consistent pattern. For example in M. pneumoniae infections a rise in IgM level is not apparent until 2 to 3 weeks after the acute illness (Schonell, 1971).

It is of interest that many of the Negro patients had raised immunoglobulin levels especially IgG. It is known that there is some racial variation in immunoglobulin levels, mainly reflecting the degree of exposure to antigenic challenge, because Negroes domiciled in London have IgG levels which are comparable with those of the indigenous population (Hobbs, 1966). It is not clear from these results whether the raised levels found in the Negro patients are due to higher initial levels or whether they reflect a more marked immune response.

The immunoglobulin changes observed in this study are insufficiently consistent to be of diagnostic value, but they do raise points of theoretical interest and suggest lines of further study.

Summary
Serum immunoglobulin levels were measured in fifty patients with non-specific urethritis (NSU) and 39 patients with gonorrhoea. In both groups of patients the mean levels of IgG, IgA, and IgM were significantly higher than in a normal control group. It was not possible to relate immunoglobulin changes to any characteristic features of either disease. It is suggested that the similarity of immunoglobulin changes in the two diseases supports an infective as opposed to an allergic aetiology for NSU.

We should like to thank Dr. C. S. Nicol and Dr. J. Seale for allowing us to study patients under their care, and Dr. J. D. Oriel for his helpful advice.

References
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— and DAVIS, J. A. (1967) Lancet, 1, 757

JOHANSSON, S. G. O. (1967) Ibid., 2, 951


Taux de l'immunoglobuline sérique dans les urérites gonococciques et non gonococciques

SOMMAIRE

Les taux de l'immunoglobuline sérique furent établis chez 50 malades atteints d'urérite non gonococcique et chez 39 gonococciques. Dans les deux groupes de malades, les taux moyens des IgG, des IgA, et des IgM furent, d'une manière significative, plus élevés que pour un groupe de témoins sains. Il n'a pas été possible de trouver de relation entre les modifications de l'immunoglobuline et un quelconque fait caractéristique de l'une ou de l'autre maladie. On pense que l'allure similaire des modifications immunoglobuliniques dans les deux maladies est en faveur, pour les UNG, d'une étiologie plutôt infectieuse qu'allergique.