IMPORTANCE OF AN INCREASED GAMMA GLOBULIN LEVEL IN THE DETERMINATION OF Gm GROUPS IN COLLAGEN DISEASES

By

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Since it was demonstrated that some sera of rheumatoid arthritic patients would agglutinate human Rh-positive O-erythrocytes coated with a selected incomplete anti-Rh serum (Grubb, 1956; Waller and Vaughan, 1956), this phenomenon has been extensively investigated (for example, in Finland by Julkunen, Laine, Koskinen, and Tiilikainen, 1958). Grubb and Laurell (1956) showed that this agglutination is inhibited by some human sera. The inhibitory factor has been shown to belong to the gamma globulin fraction of the serum and to be a mendelian dominantly hereditary character. The corresponding phenotype is called Gm (a+), and its frequency in normal population lies between 55 and 95 per cent. (Grubb, 1959).

65 per cent. of a sample of 477 sera from the normal Finnish population were found to be Gm (a+) (Mäkelä and Tiilikainen, 1959), the corresponding recessive character Gm (a−) being found in the remaining 35 per cent.

Present Investigations

Grubb (1959) and Podliachouk, Jacqueline, and Eyquem (1958) studied the Gm frequencies of patients suffering from various collagen diseases, and observed no significant differences in the phenotype frequencies of rheumatoid arthritis, spondylarthritis ankylopoietica (86 patients), gout (8 patients), or psoriatic arthritis (18 patients). However, a Finnish study of collagen diseases has shown a significantly different ratio of Gm groups (Tiilikainen, 1959); of 466 sera, 347 (74·5 per cent.) were Gm (a+) and 119 (25·5 per cent.) were Gm (a−).

Because of the differences between our results and those of the Swedish and French studies, we have made a clinical study of 167 patients.

Diagnosis.—128 of these patients had active rheumatoid arthritis, the diagnosis being based on the criteria of the American Rheumatism Association (Ropes, Bennett, Cobb, Jacox, and Jessar, 1956). Of these 128 patients, thirteen (10 per cent.) had L.E. cells but no further signs of disseminated lupus erythematosus, and nine had juvenile rheumatoid arthritis. All of 25 patients with spondylarthritis ankylopoietica showed radiological changes in both the sacro-iliac joints and the spinal column, and 22 also had signs in the peripheral joints; the Bentonite flocculation test was negative in all cases. In five cases the diagnosis of disseminated lupus erythematosus could be made on the basis of articular signs, skin eruptions, presence of L.E. cells, and positive skin biopsy.

In 142 cases, a serum paper electrophoresis was done.

Method.—The Gm groups of these patients were determined by the same technique and with the same reagents as were used in the study of Gm gene frequencies in the normal Finnish population (Mäkelä and Tiilikainen, 1959). The Gm groups of some samples of normal sera were always included as controls.

Comparison was made with the normal population figures, and the differences assessed in terms of the standard error of the difference.
**GAMMA GLOBULIN LEVELS IN DETERMINATION OF Gm GROUPS** 319

**TABLE I**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Distribution of Gm Groups (per cent.)</th>
<th>No. of Cases</th>
<th>Duration of Disease (yrs)</th>
<th>Mean Erythrocyte Sedimentation Rate</th>
<th>Mean Percentage Gamma Globulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Gm(a-) 24-2</td>
<td>31</td>
<td>5-8</td>
<td>36-5</td>
<td>24-0</td>
</tr>
<tr>
<td></td>
<td>Gm(a+) 75-8</td>
<td>97</td>
<td>6-9</td>
<td>39-4</td>
<td>25-7</td>
</tr>
<tr>
<td>Juvenile Rheumatoid Arthritis</td>
<td>Gm(a-) 22-2</td>
<td>2</td>
<td>8-5</td>
<td>44-5</td>
<td>25-2</td>
</tr>
<tr>
<td></td>
<td>Gm(a+) 77-8</td>
<td>7</td>
<td>2-8</td>
<td>46-7</td>
<td>29-4</td>
</tr>
<tr>
<td>Spondylarthitis Ankylopoietica</td>
<td>Gm(a-) 28-0</td>
<td>7</td>
<td>6-7</td>
<td>61-1</td>
<td>37-2</td>
</tr>
<tr>
<td></td>
<td>Gm(a+) 72-0</td>
<td>18</td>
<td>10-7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lupus Erythematous Disseminatus</td>
<td>Gm(a-) 40-0</td>
<td>2</td>
<td>11-0</td>
<td>26-0</td>
<td>25-3</td>
</tr>
<tr>
<td></td>
<td>Gm(a+) 60-0</td>
<td>3</td>
<td>7-3</td>
<td>88-3</td>
<td>30-9</td>
</tr>
</tbody>
</table>

**Results**

The results of Gm determinations in different types of collagen diseases are shown in Table I.

Gm (a+) tends to appear more frequently in combination with a high gamma globulin percentage in the cases of rheumatoid arthritis, and the duration of disease is longer in the Gm (a+) group.

Table II shows the correlation of the Gm group with the stage of rheumatoid arthritis (Steinbrocker, Traeger, and Batterman, 1949). No significant difference is seen between the two groups.

In Table III the correlation between the Gm groups and the gamma globulin percentage is analysed more closely; the Gm (a+) frequency tends to rise in parallel with the gamma globulin percentage.

**TABLE II**

<table>
<thead>
<tr>
<th>Gm-Group</th>
<th>No. of Cases</th>
<th>Stage of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>I and II (per cent.)</td>
</tr>
<tr>
<td>Gm(a+)</td>
<td>97</td>
<td>31</td>
</tr>
<tr>
<td>Gm(a-)</td>
<td>31</td>
<td>37</td>
</tr>
</tbody>
</table>

**TABLE III**

<table>
<thead>
<tr>
<th>Percentage of Gamma Globulin</th>
<th>Gm(a+)</th>
<th>Gm(a-)</th>
<th>Difference S.E. Difference</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Cases</td>
<td>Percentage</td>
<td>No. of Cases</td>
<td>Percentage</td>
<td></td>
</tr>
<tr>
<td>Under 20</td>
<td>15</td>
<td>68-2</td>
<td>7</td>
<td>31-8</td>
</tr>
<tr>
<td>20-25</td>
<td>21</td>
<td>65-6</td>
<td>11</td>
<td>34-4</td>
</tr>
<tr>
<td>Total Cases with Normal Percentage</td>
<td>36</td>
<td>66-7</td>
<td>18</td>
<td>33-3</td>
</tr>
<tr>
<td>25-30</td>
<td>32</td>
<td>78-0</td>
<td>9</td>
<td>22-0</td>
</tr>
<tr>
<td>30-35</td>
<td>13</td>
<td>81-3</td>
<td>3</td>
<td>18-7</td>
</tr>
<tr>
<td>Over 35</td>
<td>4</td>
<td>100-0</td>
<td>0</td>
<td>0-0</td>
</tr>
<tr>
<td>Total Cases with Increased Percentage</td>
<td>49</td>
<td>80-3</td>
<td>12</td>
<td>19-7</td>
</tr>
<tr>
<td>Normal Finnish Population</td>
<td>310</td>
<td>65-0</td>
<td>167</td>
<td>35-0</td>
</tr>
</tbody>
</table>
Discussion

The Gm group has been shown to be a stable hereditary character. Other workers in Sweden and France have stated that the Gm group frequency in cases of collagen disease is similar to that seen in normal subjects. In Finland, however, a significant difference has been noted between the Gm group frequency in cases of collagen disease and that in normal subjects (Tiilikainen, 1959).

In normal sera the inhibitory potency varies with the individual. The use of selected normal sera for the calibration of the test may be inappropriate in determining the Gm groups in patients with rheumatoid arthritis. Besides the agglutination activating factor there seem to be additional constituents in the rheumatoid sera which disturb the Gm determination; this possibility is also considered by Grubb (1959).

When we look more closely at Table III, where the gamma globulin percentage in 54 patients is below 25, and when we compare their Gm frequencies (a+ 66.7 per cent.; a− 33.3 per cent.) with those of normal subjects whose gamma globulin percentage (by the same electrophoretic technique) is also below 25, we see no significant difference. But, of the 61 patients with a gamma globulin percentage over 25, 80-3 per cent. were Gm (a+) and 19.7 per cent. were Gm (a−). These findings differ significantly from those in the normal Finnish population.* Thus our results do not agree with Grubb's statement that the gamma globulin levels were not correlated with the Gm groups.

However, in Grubb's series, the cases in the Gm (a+) group included 70 per cent. with Stage I and II rheumatoid arthritis and 30 per cent. with Stage III and IV, whereas our Gm (a+) cases included 31 per cent. with Stage I and II disease and 69 per cent. with Stage III and IV. Conversely, Grubb's Gm (a−) cases included 58 per cent. with Stage I and II disease and 42 per cent. with Stage III and IV, and our Gm (a−) cases included 37 per cent. with Stage I and II and 63 per cent. with Stage III and IV. The fact that the disease was more severe in most of our patients may explain the difference in our findings.

In our 25 cases of spondylarthritis ankylopoietica, the ratio of Gm groups also showed a noticeable difference from that in the normal population, but the number of these patients is too small for the difference to be regarded as statistically significant. Of the three patients with vertebral signs alone, two had the phenotype Gm (a+).

Undoubtedly, the high gamma globulin percentage makes it difficult to determine the Gm group in cases of rheumatoid arthritis. This determination depends on the ability of a dilution of serum to inhibit the agglutination of erythrocytes sensitized with anti-Rh. This inhibitory factor is known to be present in the gamma-globulin fraction of serum. Consequently, when the gamma globulin molecules are increased quantitatively in their natural ratios, but are qualitatively "normal", it can be postulated that the molecules or molecule complexes taking part in the inhibition have also increased. It may not be necessary to infer that rheumatoid arthritis patients differ genetically from the normal population, in spite of the apparent phenotypical differences which are found in the high gamma globulin group. When the gamma globulins return to the normal level, some Gm (a+) patients may change to Gm (a−) corresponding to their true genotype. An examination of this hypothesis would exclude the possibility of genetic differences in the Gm groups of rheumatoid patients, if the investigation also extended to the patients' families and a Gm (a+) subject suffering from rheumatoid arthritis could be verified as coming from a family with Gm (a−) parents and siblings. Grubb (1959) also considered that the familial study of series of rheumatoid patients might disclose important data.

Summary

The serum factor Gm (a+) was present in 75.8 per cent. of 128 cases of rheumatoid arthritis, in 77.8 per cent. of nine cases of juvenile rheumatoid arthritis, in 60 per cent. of five cases of disseminated lupus erythematosus, and in 72 per cent. of 25 cases of spondylarthritis ankylopoietica.

Gm (a+) appeared in 80.4 per cent. of the cases of rheumatoid arthritis with a gamma globulin percentage over 25, which is significantly greater than the frequency of 65 per cent. which has been observed in the normal Finnish population.

REFERENCES

Importance du taux augmenté de la gamma globuline dans la détermination des groupes Gm dans les maladies du collagène

RÉSUMÉ
Le facteur sérique Gm (a+) fut présent dans 75,8% des 128 cas d’arthrite rhumatismale, dans 77,8% des 9 cas d’arthrite rhumatismale juvénile, dans 60% des 5 cas de lupus érythématexux disséminé et dans 72% des 25 cas de spondylarthrite ankylosante.
Le facteur Gm (a+) fut décelé dans 80,4% des cas d’arthrite rhumatismale avec un pourcentage de gamma globuline au dessus de 25; ceci représente une fréquence appréciablement plus grande que celle de 65% trouvée parmi la population finlandaise normale.

Importancia de la cifra aumentada de la gama globulina en la determinación de grupos Gm en enfermedades colágenas

SUMARIO
El factor sérico Gm (a+) fue encontrado en un 75,8% de los 128 casos de artritis reumatoide, en un 77,8% de los 9 casos de artritis reumatoide juvenil, en un 60% de los 5 casos de lupus eritematoso diseminado y en un 72% de los 25 casos de espondilartritis anquilo-sante.
El factor Gm (a+) fue encontrado en un 80,4% de los casos de artritis reumatoide con la cifra de gama globulina superior al 25 por ciento: esta frecuencia es significativamente mayor al 65% encontrado en la población finlandesa normal.
Importance of an Increased Gamma Globulin Level in the Determination of Gm Groups in Collagen Diseases
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