Immunoglobulin Abnormalities in Gaucher's Disease
Report of 16 Cases

By Peter W. Pratt, Solomon Estren and Shaul Kochwa

Serum gamma globulin abnormalities have rarely been reported in Gaucher's disease. We recently observed a patient with Gaucher's disease who showed bone marrow plasmacytosis and a homogeneous mid-gamma "spike" on serum electrophoresis. Less than a year earlier, a similar patient had been reported from this hospital by Tyson, et al.1 Search of the literature disclosed two additional patients with similar homogeneous protein elevations. The first showed no evidence of malignancy,2 while the second was considered to have both Gaucher's disease and multiple myeloma.3 Since monoclonal gammopathies and chronic Gaucher's disease are both uncommon disorders, their association in these patients suggested more than merely a coincidental relationship2 and prompted the present study for possible serum protein abnormalities in the sera of 16 patients with known Gaucher's disease.

Materials and Methods

Serum was obtained from each of 16 patients in whom the diagnosis of Gaucher's disease had been made by bone marrow aspiration.

Total protein was determined by refractometry*: Normal values are 6.5-8.4 grams percent.†

Gamma globulin was determined by the modified zinc turbidity method: normal values are 42.2 ± 4.2 turbidity units.4

Quantitation of IgM, IgA and IgG was performed by means of quantitative immunodiffusion. † The normal values are listed in Table 1.6

Cellulose acetate electrophoresis was performed on a microzone electrophoresis apparatus† with quantitation by the Analytrol technic.§

Vertical starch gel electrophoresis was performed in 0.05M tris-versine buffer at pH 8.8 at 400 V. for 6 hours at 4 C.§

From the Department of Hematology, The Mount Sinai Hospital, New York, N. Y.

This study was aided by USPHS grants AM 04434 and CA 04457 from the National Institutes of Arthritis and Metabolic Diseases and the National Cancer Institute, the American Cancer Society and by the Albert A. List, Frederick Machlin and Anna Ruth Lowenberg Research Funds.

First submitted July 5, 1966; accepted for publication, October 15, 1967.

Peter W. Pratt, M.D.: Post Doctoral Fellow, National Institutes of Arthritis and Metabolic Diseases (1-F2-AM30 690-01), Present Address: Danbury Hospital, Danbury, Conn. Solomon Estren, M.D.: Associate Clinical Professor of Medicine, Department of Medicine, (Hematology), Mt. Sinai School of Medicine, New York, N. Y. Shaul Kochwa, Ph.D.: Associate Professor of Medicine, Department of Medicine (Hematology), Mt. Sinai School of Medicine, New York, N. Y.

*Atago serum protein refractometer, Atago, Tokyo, Japan.
†Refractometry values are 10-15 percent higher than values obtained with colorimetric methods.
‡Immunoplates, Hyland Laboratories, Los Angeles, California.
§Beckman Instruments, Palo Alto, California.
Table 1.—Results of Protein Studies

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Total Protein Gms. %</th>
<th>Total Globulin Units</th>
<th>Immunodiffusion</th>
<th>Electrophoresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>8.5</td>
<td>62</td>
<td>42.2</td>
<td>167</td>
<td>51</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>87</td>
<td>5.0</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.2</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.6</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.7</td>
<td>Normal</td>
</tr>
<tr>
<td>Group A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.1</td>
<td>Normal</td>
</tr>
<tr>
<td>1. R. M.</td>
<td>9/M</td>
<td></td>
<td>7.6</td>
<td>32</td>
<td>105</td>
<td>5.0</td>
</tr>
<tr>
<td>2. T. M.</td>
<td>12/M</td>
<td></td>
<td>7.6</td>
<td>27.2</td>
<td>190</td>
<td>4.9</td>
</tr>
<tr>
<td>3. D. B.</td>
<td>16/M</td>
<td></td>
<td>7.2</td>
<td>3.0</td>
<td>145</td>
<td>4.3</td>
</tr>
<tr>
<td>4. D. K.</td>
<td>28/F</td>
<td></td>
<td>8.3</td>
<td>3.0</td>
<td>210</td>
<td>5.1</td>
</tr>
<tr>
<td>5. D. G.</td>
<td>34/M</td>
<td></td>
<td>7.5</td>
<td>3.0</td>
<td>180</td>
<td>4.8</td>
</tr>
<tr>
<td>6. B. C.</td>
<td>48/F</td>
<td></td>
<td>7.8</td>
<td>42.2</td>
<td>125</td>
<td>4.9</td>
</tr>
<tr>
<td>Group B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.3</td>
<td>Normal</td>
</tr>
<tr>
<td>1. R. W.</td>
<td>15/M</td>
<td></td>
<td>8.5</td>
<td>48.5</td>
<td>460</td>
<td>5.0</td>
</tr>
<tr>
<td>2. H. S.</td>
<td>16/M</td>
<td></td>
<td>8.7</td>
<td>55.0</td>
<td>430</td>
<td>4.3</td>
</tr>
<tr>
<td>3. M. S.</td>
<td>19/F</td>
<td></td>
<td>8.1</td>
<td>43.0</td>
<td>550</td>
<td>3.9</td>
</tr>
<tr>
<td>4. T. S.</td>
<td>29/M</td>
<td></td>
<td>7.6</td>
<td>69.0</td>
<td>360</td>
<td>3.7</td>
</tr>
<tr>
<td>5. A. M.</td>
<td>42/M</td>
<td></td>
<td>8.7</td>
<td>90.0</td>
<td>580</td>
<td>3.5</td>
</tr>
<tr>
<td>6. E. S.</td>
<td>70/F</td>
<td></td>
<td>7.0</td>
<td>53.3</td>
<td>180</td>
<td>0.4</td>
</tr>
<tr>
<td>Group C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.4</td>
<td>Diffuse IgG Increase</td>
</tr>
<tr>
<td>1. A. S.</td>
<td>61/M</td>
<td></td>
<td>8.3</td>
<td>110</td>
<td>310</td>
<td>3.2</td>
</tr>
<tr>
<td>2. H. R.</td>
<td>62/M</td>
<td></td>
<td>8.7</td>
<td>138</td>
<td>215</td>
<td>3.3</td>
</tr>
<tr>
<td>3. S. G.</td>
<td>63/F</td>
<td></td>
<td>8.4</td>
<td>93</td>
<td>140</td>
<td>4.0</td>
</tr>
<tr>
<td>4. L. E.</td>
<td>68/M</td>
<td></td>
<td>8.0</td>
<td>82.4</td>
<td>46</td>
<td>3.7</td>
</tr>
</tbody>
</table>

**Quantitation**

- Total Protein Gms. %
- Total Globulin Units

**Immunodiffusion**

- IgA
- IgM mg./100 ml.
- IgG

**Electrophoresis**

- Cellulose Acetate
- Starch
- Immun. Gel

- alb.
- $\alpha_1$
- $\alpha_2$
- $\beta$
- $\gamma$

**Group A**

- Normal
- Normal
- Normal
- Normal
- Normal
- Normal

**Group B**

- Normal
- Diffuse IgG Increase
- Normal
- Diffuse IgG Increase
- Normal
- Diffuse IgG Increase
- Normal
- Diffuse IgG Increase
- Normal
- Diffuse IgG Increase
- Normal
- Diffuse IgG Increase

**Group C**

- $\gamma$ Spike
- Monoclonal IgG type K
- $\gamma$ Spike
- Monoclonal IgG type K
- $\gamma$ Spike
- Monoclonal IgG type K
- $\gamma$ Spike
- Monoclonal IgG type K
Fig. 1.—Distribution of immunoglobulin concentration in three groups of patients. Shaded area represents normal values.

Immunoelectrophoresis was performed with LKB microelectrophoresis apparatus, using monospecific rabbit antisera produced in our laboratory.

RESULTS

The results of the studies are listed in Table 1. On the basis of these studies, the 16 cases could be divided into three groups: Group A: relatively normal serum protein patterns; Group B: diffuse immunoglobulin increases; Group C: homogeneous IgG increases.

Group A included six patients, all under 50 years of age, all of whom had normal immunoelectrophoretic patterns. On immunodiffusion, IgG and IgA levels varied from slightly low in the youngest to high normal in the older patients, while IgM was highest in the youngest and oldest patients. Five patients in this group had low levels of one or more immunoglobulins.

Group B included six patients with diffuse increase of one or more immunoglobulins on immunoelectrophoresis. All six patients in this group had increases levels of IgG, five patients had elevations of IgM, and four patients had IgA elevations (Fig. 1 and Table 1).

*LKB, Stockholm, Sweden.
Fig. 2.—Characterization of serum proteins of case H.R. (C-2). The monoclonal gamma spike is evident on the tracing of cellulose acetate strip and on starch gel electrophoresis. This spike was identified as \( \gamma G \) K on immuno-electrophoresis (arrow). (A WHS = anti whole human serum, A \( \gamma G \) = anti gamma G serum; A K = anti Bence-Jones protein type K; A L = anti Bence-Jones protein type L).

Group C included four patients, all over 50 years of age, whose sera all showed homogeneous peaks on cellulose acetate and starch gel electrophoresis.Immuno-electrophoresis characterized all four peaks as IgG type K. Immunochemical analysis of serum C-2 is given in Fig. 2. On immunodiffusion (Fig. 1 and Table 1), group C patients showed the highest levels of IgG of the various groups, and every patient in group C showed this increase. IgM was elevated in one patient (C-1) and low in another patient (C-4).

Clinically, patients in group A were without symptoms, although patients A-1 and A-2 had a transient upper respiratory illness when serum for protein studies was obtained. The other patients in group A were asymptomatic.

In group B, two patients, (B-2 and B-4), had signs and symptoms of active aseptic necrosis of bone while chronic infection was present in a third patient (B-5). The remaining three patients in group B, (B-1, B-3 and B-6) were asymptomatic.

In group C, patient C-1 had both chronic infection and aseptic necrosis of bone while patient C-2 had had several episodes of urinary tract infections. Patient C-4 had far advanced liver disease and patient C-3 had recurrent pulmonary infections.

Bone marrow specimens obtained from patients in group C showed less
IMMUNOGLOBULIN ABNORMALITIES

than 5 percent plasma cells in three patients and 18 percent plasma cells in one patient (C-1).

The relation of abnormal immunoglobulin levels found in our patients to liver disease, aseptic necrosis of bone and chronic infection may be stated as follows:

Immunoglobulins were always abnormal in patients with hepatosplenomegaly, and all patients with hepatosplenomegaly had either aseptic necrosis of bone or chronic infection or both.

Homogeneous protein increases were found in all patients with hepatosplenomegaly who were over 50 years of age.

Diffuse immunoglobulin elevations were found in patients with hepatosplenomegaly who were under 50 years of age.

Diffuse immunoglobulin elevations were also found in three patients with only splenomegaly. Two of these patients had no evidence of aseptic necrosis, chronic infection or liver disease.

DISCUSSION

In 1950, Goldfarb et al.10 first noted, on serum electrophoresis, a diffuse increase in gamma globulin in four of five patients with Gaucher’s disease, all of whom were under 30 years of age. No further gamma globulin studies were reported until 13 years later when Osserman and Takatsuki2 noted a homogeneous gamma peak on serum electrophoresis in a patient with Gaucher’s disease who was over 50 years of age. In the following two years, two similar patients were reported, each also over the age of 50.1,3 Specific immunoglobulin studies were not detailed in these reports.

Our data show that diffuse elevations of one or more immunoglobulins are quite common in chronic Gaucher’s disease and they suggest that, in older patients, these increases are often monoclonal in nature. Furthermore, progression from monoclonal dysproteinemia to overt multiple myeloma may have occurred in at least one patient with Gaucher’s disease.3

Although coexistent Gaucher’s disease and multiple myeloma has been reported only once, the association of multiple myeloma and abnormal lipid metabolism is well documented.11-16 This suggests that the lipid abnormality may have an irritant or antigenic effect on immunoglobulin production. In BALB/c mice, intraperitoneal injections of pure substance that act as irritants have produced a condition similar to multiple myeloma.17-20 There is obvious plasma cell response to the injected irritants and subsequent excessive elaboration of protein by one or several plasma cell clones.

The evidence for possible antigenic stimulation is conflicting. Joffe et al.21 have shown that glucocerebroside, the major form of abnormally accumulated lipid in Gaucher’s disease, is not antigenic. In contrast, galactocerebroside, a minor component of the accumulated lipid, is quite antigenic.22,23
It is particularly interesting that each monoclonal protein found in our patients was IgG type K. The significance of this finding with only four cases cannot be assessed, since 60 percent of IgG is normally type K.24

Finally, it is of interest that in our series, the only patient over age 50 who failed to show a monoclonal gammopathy had undergone splenectomy five years prior to the present study. Two additional patients from this hospital with splenomegaly due to lymphoma and chronic lymphatic leukemia respectively, had monoclonal gammopathies which disappeared or were markedly decreased following splenectomy. These observations raise the possibility that an infiltrated reticuloendothelial organ, such as the Gaucher spleen, may contribute to the production of the monoclonal protein. Theoretically prolonged contact with large amounts of a weakly antigenic substance could cause a massively enlarged spleen to elaborate significant amounts of antibody resulting in a monoclonal increase. Unfortunately immunofluorescent studies, by ourselves and others, on spleens from three patients with Gaucher's disease and monoclonal gammopathies have failed to show any gamma globulin or complement coating.

Further study of the immunoglobulin abnormalities in chronic Gaucher's disease may help to elucidate the relationship between certain chronic diseases, monoclonal gammopathy and multiple myeloma.

Case A-1. T. M. A 9 year old white male was referred for splenomegaly and thrombocytopenia. Bone marrow examination revealed Gaucher cells and a splenectomy was performed. He is asymptomatic.

Case A-2. R. M. A 12 year old white male, brother of T. M. (Case A-1), was found to have splenomegaly, thrombocytopenia, and Gaucher cells on bone marrow aspiration. A splenectomy was performed. He is asymptomatic.

Case A-3. D. B. A 17 year old white male was found to have splenomegaly on routine physical examination. Bone marrow examination revealed Gaucher cells. He remains asymptomatic.

Case A-4. D. K. A 28 year old white female was originally seen for splenomegaly and thrombocytopenia. Bone marrow examination revealed Gaucher cells and a splenectomy was performed. She is asymptomatic eight years after her splenectomy.

Case A-5. D. G. A 34 year old white male was first found to have splenomegaly at age 21. Bone marrow examination at that time revealed Gaucher cells. He subsequently developed increasing thrombocytopenia and anemia. A splenectomy was performed in 1964 followed by improvement of his anemia and thrombocytopenia. Serum was obtained for immunoglobulin studies at the time of splenectomy.

Case A-6. B. C. A 48 year old white female was first seen at age 39 for joint pain and weakness and diagnosed as having rheumatoid arthritis. Latex fixation titer was 1:1000. Past history included splenomegaly discovered 16 years earlier. Skeletal X-rays failed to reveal characteristic arthritic changes; however, a cystic lesion was noted in the left humerus. Bone marrow examination revealed Gaucher cells. Treatment with phenylbutazone produced marked improvement of her arthritic symptoms. She remains asymptomatic.

Case B-1. R. W. A 16 year old white male was studied because of persistent splenomegaly following an episode of infectious mononucleosis. Bone marrow examination revealed Gaucher cells. He is asymptomatic. Serum was obtained one year after initial diagnosis.

Case B-2. H. S. A 16 year old white male with known splenomegaly secondary to Gaucher's disease had been diagnosed on previous bone marrow examination. Serum was obtained during hospitalization for aseptic necrosis of the right femoral head.

Case B-3. M. S. A 19 year old white female was referred for evaluation of splenomegaly and mild thrombocytopenia. Bone marrow examination revealed Gaucher cells. A splenectomy was recommended but refused. She is asymptomatic approximately one year after diagnosis.
Case B-4. T. S. A 31 year old Negro male developed pain and limitation of motion of the left hip at age 21. On admission to another hospital, he was found to have degeneration and epiphyseal slippage of the left femoral head. A pin was inserted; however, the diagnosis of Gaucher’s disease was not made. At age 31 he developed similar symptoms in the right hip and was admitted to this hospital for a similar procedure. Blood count on admission revealed a mild leukopenia and thrombocytopenia and a hematolgy consultation was requested. At this time 4 cm hepatomegaly and 8 cm splenomegaly were found and subsequent bone marrow examination revealed Gaucher cells and 2 per cent plasma cells.

Case B-5. A. M. A 42 year old white male was seen at age 28 when splenomegaly and thrombocytopenia were first noted. Bone marrow examination at this time revealed Gaucher’s cells. His history also includes “mild colitis” for 14 years with one episode of severe abdominal pain and fever in 1965, which may have represented a small intestinal perforation. In March 1966, blood was obtained during hospitalization for a idiopathic pericarditis, which subsided spontaneously.

Case B-6. E. S. A 70 year old white female was referred at age 64 for evaluation of splenomegaly and thrombocytopenia. Bone marrow aspiration revealed Gaucher cells. A splenectomy was performed at age 65; the spleen showed Gaucher’s disease.

Case C-1. A. S. A 61 year old white male was known to have Gaucher’s disease since 1927, diagnosed on one of the first bone marrow examinations made at The Mount Sinai Hospital. He also had a 27 year history (since age 34) of chronic osteomyelitis of the left femur and bilateral aseptic necrosis of the femoral heads. During the past several years he had developed pancytopenia and hyperproteinemia, with enlarging liver and spleen. Two bone marrow examinations (1965) revealed Gaucher cells with 7 and 18 percent plasma cells respectively. Bone survey showed osteolytic lesions. Spleenectomy, recommended on several occasions, was always refused. The patient died of a myocardial infarction ten months after study.

Case C-2. E. R. A 62 year old white male was admitted with a history of prostatic hypertrophy with increasing obstruction and recent urinary tract infection. Splenomegaly, leukopenia and thrombocytopenia were noted and bone marrow aspiration revealed Gaucher cells and plasma cells were less than 5 percent. Radiologic examination of the skeleton revealed no lytic lesions and the urine was negative for Bence-Jones protein. His urinary tract infection responded to treatment with antibiotics.

Case C-3. S. C. A 63 year old white female with hepatosplenomegaly was found to have a persistently elevated erythrocyte sedimentation rate following an uneventful recovery from lobar pneumonia. Serum electrophoresis revealed a “mid-gamma spike.” Bone marrow examination revealed Gaucher cells and 4 percent plasma cells. No osteolytic lesions were seen on radiologic examination of the skeleton. She has had several recurrent episodes of pneumonia but was asymptomatic at the time of this report.

Case C-4. I. E. (Previously reported.1) A 68 year old white male presented with hepatosplenomegaly, generalized osteoporosis, and lytic areas in both femurs. Bone marrow examination revealed Gaucher cells and 4 percent plasma cells. Post-mortem examination revealed massive infiltration of the liver, spleen, bone marrow and lymph nodes by Gaucher cells. No evidence of multiple myeloma or cirrhosis was found.

SUMMARY

Sera from ten of sixteen patients with known Gaucher’s disease were found to have immunoglobulin abnormalities. Of these, four patients had “monoclonal” IgG type K protein increases. The possible pathogenic roles of lipid accumulation and reticuloendothelial hyperplasia are discussed.

SUMMARIO IN INTERLINGUA

Le seros de dece inter dece-sex patientes cognoscitemente con morbo de Gaucher revelava anormalitates de immunoglobulina. In quatro casos, le anormalitates includeva “monoclonal” augmentos de proteina de IgG typo K. Le rolo possibilmente pathogenic del accumulation de lipido e de hyperplasia reticuloendothelial es commentate.
ACKNOWLEDGMENT

We wish to thank Doctors Leonard Stone, Peter Vogel, Chester Gottlieb, Frank Bassen, Jacob Katz and Louis Wasserman for their cooperation in referring their patients for study and Dr. Jerry B. Finkel for his assistance in compiling clinical data.

REFERENCES


Immunoglobulin Abnormalities in Gaucher's Disease Report of 16 Cases

PETER W. PRATT, SOLOMON ESTREN and SHAUL KOCHWA