Medical Conference: Gaucher's Disease

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Medical Conference:
Gaucher's Disease*

Participants:
Ellis J. Van Slyck, MD,** Lester Weiss, MD,*** and
Robert Waldmann, DO ****

The middle-aged man whose case is discussed here harbored Type 1 Gaucher's disease in subtle form. This hereditary disorder was partly disguised by a long history of peptic ulcer. Still a third cause for anemia was eventually uncovered in a surprise conclusion.

The major discussion deals with the clinical aspects, microscopic pathology, genetics, and biochemistry of Gaucher's disease and related sphingolipidoses.

Case Presentation

Dr. Van Slyck:
The history and other clinical data for this morning's case will be presented by Dr. Waldmann.

Dr. Waldmann:
The patient, R.M., a 52-year-old white male of Jewish background, was seen in the Gastroenterology Clinic on 10/15/73 with the statement, "I have been told that I look pale." He had been feeling weak and tired, but denied melena, hematemesis or abdominal pain. His past medical history included a diagnosis of peptic ulcer made in 1953. At least three episodes of gastrointestinal bleeding, consisting of melena and a drop of 2-3 gms% in his hemoglobin, had occurred from 1953 to 1968. Management had been conservative.

The physical examination was unremarkable except for pallor and sinus tachycardia (rate, 110/min).

Laboratory data showed: hemoglobin 7.0 gm/100 ml, white blood count 4,800 per cu ml, reticulocyte count 1.9%, platelet count 132,500 per cu ml, prothrombin time 12.5 sec (control 11.0), partial thromboplastin time 42 sec (control 35). Radiological films of the upper gastrointestinal tract gave suggestion of an active ulcer near the apex of the duodenal bulb.

The patient was admitted to the hospital on 10/18/73. He was given blood transfusions using four units of packed cells. A repeat
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physical examination revealed an enlarged spleen.

Gastroscopy on 10/23/73 showed no abnormalities. At this time, a consultation was obtained with a hematologist.

Additional laboratory values were: BSP negative, serum iron 22 ugm/100 ml, TIBC 429 ugm/100 ml, all stools positive for occult blood, serum protein electrophoresis: total protein 6.0 gm/100 ml, albumin 3.23 gm/100 ml, gamma globulin 1.45 gm/100 ml. The bleeding time was 14½ min (Duke), prothrombin time 12.5 sec (control 11.0), partial thromboplastin time 37 sec (control 35), prothrombin consumption time 16 sec. Factors V, VII, IX, and X were normal, haptoglobin was 91 ug/100 ml (normal 50-220), immunoglobulins, IgM 134mg/100 ml, IgG 1749 mg/100ml, IgA 148 mg/100 ml. Acid phosphatase 1.04 IU (normal 0-0.7). Bone marrow aspiration was obtained. Liver-spleen scan showed splenomegaly. RBC survival time was 28 days. There was no evidence of hypersplenism on liver-spleen uptake ratio. Patient was discharged with hemoglobin of 11 gms % on 10/26/73.

**Discussion of Case**

**Dr. Van Slyck:**

We had planned to have the patient come from home for an interview; however, over the weekend he developed a gastrointestinal hemorrhage necessitating rehospitalization, and I felt that it was the better part of discretion to keep him quiet in his room.

This patient had been followed for ulcer disease over a period of years, as indicated by Dr. Waldmann. But, when we saw him, we felt there was something unusual about his peripheral blood which did not gibe with the rate of hemoglobin fall or with the current history of bleeding. This fact and the newly discovered splenomegaly compelled us to get a bone marrow. Figure I, a low

![Figure 1](image)

Bone marrow of R.M. showing Gaucher cells. See Text. Leishman stain, x 495
Figure 2
3 Gaucher cells in bone marrow. See Text. Leishman stain, x 1485

power view of Mr. M’s bone marrow, shows a mass of conglomerated cells on the left side. However, on the right half we can see a couple of large cells with single or multiple nuclei with light bluish cytoplasms, suspicious of the pathognomonic cells of Gaucher’s disease.

Figure 2 shows three Gaucher’s histiocytes under higher magnification. We can make out the fibrillar character of the cytoplasm. Under the electron microscope these fibrils can be identified in cross section as tubules. The cytoplasm has sometimes been described as having a wrinkled appearance. The nuclei have been encroached upon by cytoplasmic storage material and, for the most part, are eccentric. The average Gaucher cell size is large, measuring from 20 to 100 microns in diameter. These cells were once considered specific for Gaucher’s disease, but have also been found in chronic granulocytic leukemia1 and thalassemia major.2

Figure 3 shows two more Gaucher’s cells. The one on the right contains more matrix than tubular material. The one on the left contains more of the tubular elements. These tubules have a diameter of 200 to 400 Angstroms, and represent the stored metabolite which is a characteristic of this disease. We know that this material is glucocerebrosidase and its appearance is identical to purified beef spinal cord glucocerebrosidase.3 The matrix in these cells contains excessive amounts of acid phosphatase. Gaucher’s cells are PAS positive. They are negative to fat stains and also do not stain metachromatically with toluidine blue.
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Figures 3, 4
Gaucher cells in bone marrow. See text. Leishman stain, x 3300.
Figure 4 shows still another Gaucher's cell in this patient's bone marrow. Here we can see erythrophagocytosis, which is a constant feature of this disease. Some of the glucocerebroside in the cytoplasm of the Gaucher's cell almost certainly originates from erythrocyte stroma, but it also derives from platelet and leukocyte stroma and from other cells. The iron found in Gaucher's cells is in the ferritin form. In Mr. M's case the iron stains revealed deposition of iron only in the Gaucher's cells at a time in his clinical course when he had iron deficiency by all other criteria. This suggests that ferritin iron is not freely liberated from Gaucher's cells for use by the labile iron pool, contrary to a previous implication in the literature.

Figure 5 is an example of a lipid histiocyte. This cell is found in the marrow of many storage diseases, such as Tangier's disease, Wolman's disease, Niemann-Pick disease, and Gaucher's disease, but also is rather commonly found in normal individuals. Lipid histiocytes, as seen by light microscopy, are not specific for any particular condition. They were present in increased numbers in Mr. M's bone marrow.

Clinical Type I Gaucher's Disease

Patients with type I Gaucher's disease are spared the lethal central nervous system complications of types II and III, probably because they have sufficient
enzyme levels to weather the critical perinatal period of intense activity in ganglioside metabolism. Nonetheless, symptoms may occur in this so-called adult form of Gaucher’s disease in early childhood and, even without the CNS problem, it may be extremely debilitating with marked hepatosplenomegaly, anemia, thrombocytopenia, and pathologic fractures with eventual premature death. As a general rule, in those patients, who do not become clinically expressive of their disease until adult life, as in our patient today, the severity of the disease is milder and consistent with a normal life expectancy. There is also evidence to suggest that the degree of enzyme activity correlates with the age of onset and the mildness of the disease in type I patients. Pingueculae (brownish infiltrates in the nasal corners of the sclerae) are sometimes seen in older patients, as well as a yellowish-brown pigmentation characteristically below the knees to the ankles. Our patient today had neither of these manifestations. Pulmonary infiltrates are frequently seen in patients with Gaucher’s disease. These may lead to a clinical expression of pulmonary hypertension with cor pulmonale. Bony involvement, due to encroachment by Gaucher’s cells leading to osteoporosis and pathologic fractures, is also not uncommon, particularly in the younger type I patient. Figure 6 shows a fracture of the right femur in a young patient, with severe type I disease. Widening of the lower femur
to form an “Erlenmeyer flask” appearance is a frequently cited finding, also seen in this patient.

From the hematologic standpoint, the anemia may be a difficult problem to manage, as it has been in Mr. M’s case. However, the studies that have been done on patients with Gaucher’s disease indicate a normal red cell survival. This proved true by a Cr study done on Mr. M. Normal ferrokinetic clearances and turnovers are found. Earlier, I questioned the ability of the iron-laden Gaucher’s cells to release their iron for ready use by the developing red cells, but there is no precedent for this observation in the literature. Thrombocytopenia is common, generally results from hypersplenism, and is correctable by splenectomy. Leukopenia is occasionally seen but is rarely a clinical problem. The acid phosphatase, which is not inhibited by tartrate, is elevated in the serum of patients with Gaucher’s disease and, as mentioned before, is found in excessive amounts in the matrix of the Gaucher’s cells. It probably is released into the matrix from the primary lysosomes disrupted by the storage phenomenon.

Bleeding problems, seen frequently in Gaucher’s disease, are generally related to the presence of thrombocytopenia. In addition, there have been recent isolated reports of deficiencies in factors V, VIII, IX, and X. In our patient, the poor prothrombin consumption and prolonged bleeding time in the presence of normal prothrombin time and partial thromboplastin time suggest a platelet factor 3 deficiency. This may have contributed to his gastrointestinal bleeding, without being primarily responsible for it.

Dr. Weiss will now discuss the uncommon types II and III Gaucher’s disease.

**Type II and III Gaucher’s Disease**

*Dr. Weiss:*

**Type II:** Type II was first described in 1922 and is known by a number of synonyms. Sometimes it is called acute infantile Gaucher’s, sometimes cerebral Gaucher’s and sometimes malignant Gaucher’s. I personally prefer the term Type II or acute neuropathic Gaucher’s disease. Perhaps neuropathic is more descriptive than the others. Typically, these children are well in the first few months of life and often dead in less than one year. Splenomegaly and elevated serum acid phosphatase are characteristic. There is anemia, thrombocytopenia, trismus, and retroflexion of the head. Most often the children are born at term after an uneventful pregnancy. The affected child appears normal at birth and an average of three months elapses before the first signs appear. There may be any combination of enlarged spleen, enlarged liver and difficulty with swallowing or eating. A chronic cough ushers in the recurrent pulmonary infections that these children have. Sometimes the disease can present as failure to thrive. A small number of infants are obviously affected at birth, while, rarely, a patient has not been considered abnormal until 16 to 18 months of age. The average age of death is nine months, with a range of one to two years. Once the neurologic signs become apparent, death usually occurs shortly thereafter. The immediate causes of death are anoxia and infection related to pulmonary involvement.

By definition, every child with Type II Gaucher’s disease has evidence of progressive central nervous system dysfunction before death. The neurologic deficits usually appear before six months. They tend to be highly stereotyped and therefore can be recognized. These include involvement of the cranial nerves and extrapyramidal tract. Three findings
occur in over 90% of the patients at some time during the disease. These are strabismus, muscular hypertonicity or spasticity, and persistent retroflexion of the head. There is also rigidity of the neck, trismus, dysphagia, increased deep tendon reflexes and pathological reflexes. The children are often apathetic and retarded by the time they die. Therefore, when we see a child with hepatosplenomegaly, who has an ocular palsy, retracted lips and a head held in severe extension, frequently with the arms flexed, the signs are extremely suggestive of Type II Gaucher's disease. The high serum acid phosphatase will almost clinch the diagnosis. However, occasionally, children with other forms of Gaucher's disease may have hepatosplenomegaly and typical cells in the marrow in the first year of life.

**Type III:** There is another type which is probably heterogeneous and will eventually be broken down into several different groups. This is called the subacute neuropathic or juvenile Gaucher's disease. These children are older than
those with Type II and present with hepatomegaly and Gaucher's cells. The clinical course is very variable but ordinarily more protracted than the malignant one seen in Type II. Death usually occurs after two years of age. The largest single group of patients with Type III Gaucher's had 12 patients from an interrelated kindred in Norrbotten, Sweden. Time does not permit me to describe Type III in any detail. Briefly, it can be thought of as Gaucher's disease with neurologic involvement but one which progresses much more slowly than Type II. Some of the patients with this disease were studied when they were 20 years old.

**Genetics:** At least three separate mutations are necessary to explain the different phenotypes. Gaucher's disease without clinical evidence of neural involvement is inherited as an autosomal recessive. The distribution of the gene giving rise to Type I is very wide. One or more cases have been reported in most ethnic groups. There is an unusually high incidence among Ashkenazi Jews. Unequivocal examples of Type I and II have never been reported in the same family. Type II is also inherited as an autosomal recessive trait and has a slight increased prevalence among Ashkenazi Jews, but not as striking as Type I. Type III, as I said previously, is probably a heterogeneous group, a number of different diseases being represented. Certainly the Norrbotten family, in which there is consanguinity and a consistent expression, makes one think of an autosomal recessive mode of inheritance. These various Gaucher types may be different mutations in the same gene. We find this in the hemoglobinopathies, galactosemia, and some inborn errors of metabolism where, in the same gene, we have different mutations resulting in a slightly different functional defect in the enzyme.

**Chemistry of Gaucher's Disease and Related Disorders**

*Dr. Van Slyck:*

Figure 7 modified from Williams\(^\text{5}\) depicts the chemical formula for the class of compounds which make up the sphingolipidoses, into which category Gaucher's disease falls. You will note that sphingosine, which is an amino alcohol, is joined to a fatty acid, forming what is called 'ceramide' and is also attached to a carbohydrate, glucose, to form the specific substrate glucocerebroside found in excess in Gaucher's disease. An absence or deficiency of glucocerebrosidase prevents the splitting off of glucose in the catabolism of this substance. Other disorders involving this group of compounds have enzyme deficiencies which prevent the normal catabolism of other sphingolipids. For instance, the glucose may be substituted by a trihexose or a more complicated carbohydrate radical and the length of the fatty acids may vary with different compounds.

Table I is a partial list of the sphingolipidoses paired with the substrate metabolite that has been identified with each disease. Virtually all of these diseases are characterized by storage of sphingolipid in the macrophages and lymphocytes as well as in the neurones of the central nervous system of affected infants producing early dementia, blindness, and death. The various other clinical manifestations of these diseases are subtle in their differences. We do not have time to discuss these today. You will note that Niemann-Pick disease results from an accumulation of sphingomyelin because of a deficiency of sphingomyelinase. Fabry's disease is, in some respects, similar to Gaucher's disease. Chemically, it can be seen that there is a trihexose instead of a monohexose connected to the ceramide to form the storage metabolite. Tay-
SPHINGOLIPOIDOSIS

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>SUBSTRATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaucher's</td>
<td>Glucocerebroside</td>
</tr>
<tr>
<td>Krabbe's</td>
<td>Galactocerebroside</td>
</tr>
<tr>
<td>Niemann-Pick</td>
<td>Sphingomyelin</td>
</tr>
<tr>
<td>Fabry's</td>
<td>Ceramidetrihexoside</td>
</tr>
<tr>
<td>Tay-Sachs</td>
<td>Ganglioside GM₂</td>
</tr>
<tr>
<td>- Vogt-Spielmeyer</td>
<td></td>
</tr>
<tr>
<td>- Kuf</td>
<td></td>
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<tr>
<td>- Jansky-Bielschowsky</td>
<td></td>
</tr>
<tr>
<td>Generalized Gangliosdosis</td>
<td>Ganglioside GM₂</td>
</tr>
<tr>
<td>Metachromatic Leukodystrophy</td>
<td>Sulfatide</td>
</tr>
</tbody>
</table>

Table 1

Sachs disease contains a much more complicated carbohydrate radical connected to the ceramide portion of the metabolite.

Table 2, taken from Brady, shows some interesting enzyme assay studies on four of these diseases. Type I Gaucher's disease, with which we are dealing this morning, has been found to have about 15% of normal glucocerebrosidase activity in the spleen as compared to 1% in the Type II or neuronopathic form of the disease discussed by Dr. Weiss. Classical Niemann-Pick disease, which is here represented as type A, contains about 5% sphingomyelinase activity in the liver, but the Type B disease, which is the juvenile or later appearing form of the disease, is associated with a somewhat higher percentage of enzyme activity. Arylsulphatase A, which is the defective enzyme in metachromatic leukodystrophy, has been found to have 1-5% of normal activity in brain. In Fabry's disease, the only one in this group which is sex-linked, a clear difference exists between the hemizygous male and the heterozygous female in terms of the
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<table>
<thead>
<tr>
<th>DISEASE</th>
<th>ENZYME</th>
<th>ACTIVITY(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaucher</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>Glucocerebrosidase</td>
<td>15 (spleen)</td>
</tr>
<tr>
<td>Type II</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Niemann-Pick</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type A</td>
<td>Sphingomyelinase</td>
<td>5 (liver)</td>
</tr>
<tr>
<td>Type B</td>
<td></td>
<td>17</td>
</tr>
<tr>
<td>Metachromatic Leukodystrophy</td>
<td>Arylsulfatase A</td>
<td>1-5 (brain)</td>
</tr>
<tr>
<td>Fabry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemizygous</td>
<td>Cerebroside trihexosidase</td>
<td>0.5 (spleen)</td>
</tr>
<tr>
<td>Heterozygous</td>
<td></td>
<td>28</td>
</tr>
</tbody>
</table>

## TABLE II


- Percentage of enzyme deficiency of the cerebrosidase, ceramidetrihexosidase.

In conclusion, I would like to refer you to the chapters on the sphingolipidoses in *The Metabolic Basis of Inherited Disease* by Stanbury, Wyngaarden and Fredrickson for more detailed information. Thank you. Are there any questions?

**Question by Dr. J. P. Olson:**

How often is platelet factor 3 deficiency associated with Gaucher's disease? Is that possibly why bleeding is common in Gaucher patients?

**Dr. Van Slyck:**

The association of Gaucher's disease and platelet factor 3 deficiency has not been described previously. Most Gaucher's disease patients develop thrombocytopenia. Our patient has some degree of thrombocytopenia, but we did not feel it was of sufficient degree to explain his very impaired prothrombin consumption, and so far we have hesitated to think seriously about a
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splenectomy. We have not really decided yet what we are going to do with him. He clearly has a problem with continued GI bleeding, the source for which has not been identified yet. From the x-ray film, we see evidence of older ulcer disease, but I suspect that he has a bleeding lesion more distal. Furthermore, the bleeding may be enhanced by poor platelet function and his somewhat depressed platelet count. That is where matters stand at the moment.

Question By Dr. R. K. Nixon:
The fact that he has iron deficiency certainly makes peptic ulcer an unlikely lesion. You have to look for another lesion, do you not agree?

Dr. Van Slyck:
We have been following him now for four months and he has consistently shown positive stools, in the absence of active ulcer symptoms. At times the source of bleeding seems to me to be further down in the GI tract, because it has been dark red in color. Despite a negative barium enema two months ago, I agree further x-ray investigation is necessary.

Addendum:
Subsequent radiographic re-examination disclosed an "apple core" defect in the right colon. At surgical resection, this was proven to be adenocarcinoma.

References


