Gaucher’s disease

Deborah Elstein, Aya Abrahamov, Irith Hadas-Halpern, Ari Zimran

Case report

The patient was an 18-year old female army inductee of Ashkenazi Jewish ancestry who, after a serious nose bleed, was referred for a haematological consultation because of anaemia. She had had bouts of fatigue, epistaxis, and ecchymoses since early childhood, with onset of bone pains as a teenager. Her anaemia was associated with pronounced hepatosplenomegaly and thrombocytopenia. Identification of Gaucher cells in a bone marrow aspirate (figure 1) lead to the diagnosis of Gaucher’s disease. Over the next 25 years, her symptoms were ongoing and she developed “romantic fractures”—ie, pathological fractures of the ribs incurred while embracing. Vaginal hysterectomy was done at age 39 years because of heavy menorrhagia.

When she presented at our clinic, aged 43 years, her spleen was palpable 30 cm below the costal margin, traversing the midline into the lower right abdominal quadrant. Other findings included pallor, bilateral pinguecula, hepatomegaly (11 cm below the costal margin), and ecchymoses, mainly on her legs. Laboratory findings were dominated by anaemia (haemoglobin 8·9 g/dL with a normal mean cell volume 88·5) and thrombocytopenia (59×10^9/L); prothrombin time (PT) and partial thromboplastin time (PTT) were both prolonged. She also had raised blood concentrations of acid phosphatase and angiotensin converting enzyme (ACE), and polyclonal hyperglobulinaemia. The diagnosis of Gaucher’s disease was confirmed by low β-glucocerebrosidase activity, and molecular analysis revealed the genotype N370S/RecNci.

Skeletal survey showed mild osteoporosis, Erlenmeyer flask deformities in both distal femurs, but no evidence for avascular necrosis in any of the large joints. Computerised tomography (CT) scan showed substantial organomegaly with liver volume of 3070 cm^3 and spleen volume of 3581 cm^3 (figure 2). Bone densitometry of the lumbar spine and at the femoral neck was about 70% of that expected for her age.

In November 1992, our patient was part of the Israeli cohort of a clinical trial with enzyme replacement therapy, using low-dose intravenous imiglucerase (15 IU/kg body weight given fortnightly). After 18 months, liver and spleen volumes were reduced by 40% and 53% from baseline, respectively, and haemoglobin concentrations increased; acid phosphatase and ACE normalised, but there were no changes in PT, PTT, or immunoglobulins. She continued on this treatment for the next 6 years. In February, 2000, she was recruited to a new clinical trial of switch-over to an oral medication for patients who had been treated with enzyme therapy for more than 2 years. At that time, haemoglobin was 11·4 g/dL, (platelets 120×10^9/L), and liver and spleen volumes measured by CT were 1308 cm^3 (decrease 57% from baseline) and 618 cm^3 (decrease 83%), respectively (figure 2).

Genetics, biochemistry, and epidemiology

Gaucher’s disease is an autosomal recessive glycolipid storage disorder, caused by mutations in the β-glucocerebrosidase gene 1q21. This defect leads to reduced enzyme activity with accumulation of glucosylceramide in the macrophages of the reticuloendothelial system. Three clinical subtypes of Gaucher’s disease have been described on the basis of the absence (type I) or presence (types II and III) of a neurological component (panel). All forms are panethnic. However, type I is more common, and is especially prevalent, among Ashkenazi Jews (predicted prevalence is about 1/850). More than 200 mutations have been identified in the β-glucocerebrosidase gene, including point mutations, crossovers, and recombinations, but prediction of clinical course can only be broadly ascribed on the basis of genotyping.
Additionally, only about ten of these alleles have high frequencies in the ethnic groups studied. Generally, the presence of the 1226G (N370S) mutation on one allele is synonymous with type I disease—ie, is apparently protective against neurologic involvement—whereas homozygosity for the allele 1448C (L444P) is invariably correlated with neurological disease. Genotype-phenotype correlation and the role of genetic and environmental modifiers, or both, are areas for future research.

**Clinical manifestations and laboratory findings**

Phenotypic heterogeneity is a hallmark of Gaucher’s disease. Symptomatic disease could develop at any age, but when signs and symptoms are seen in children younger than 5 years, the course of the disease is likely to be more severe than when symptoms develop at an older age. However, many patients, particularly Ashkenazi Jews, might never have any symptoms at all, or might be only mildly affected. Common presenting features include hepatosplenomegaly, anaemia, thrombocytopenia, and often bone pains. Findings might be uncovered incidentally or there might be specific complaints such as abdominal discomfort, early satiety, fatigue, and bleeding tendency.

Before the advent of enzyme replacement, splenectomy was frequently done to minimise secondary effects of hypersplenism, but this often resulted in the aggravation or induction of skeletal disease. Indications for splenectomy in Gaucher’s disease are limited. There is no place for partial splenectomy, since there is both splenic regrowth and induced bone involvement.

Among patients with intact spleens, thrombocytopenia is typically more pronounced than anaemia, and leucopenia is less common. Although hepatomegaly is nearly universal, only a few patients have abnormal liver enzymes or other signs of chronic liver disease; massive hepatic enlargement is only seen in patients who have had splenectomy.

The presence of bone disease is one of the most debilitating signs of Gaucher’s disease. Children might suffer bouts of excruciating pain, termed “bone crises”, which, although self-limiting, are difficult to manage. Pathologically, the major elements of Gaucher’s bone involvement include failure to remodel bone (osteoclast dysfunction), osteopenia and lytic lesions (osteoblast dysfunction), and osteonecrosis (or avascular necrosis). The treatment of choice for avascular necrosis, dependent on the patient’s assessment of decreased quality of life and increased pain, is total joint replacement.

Many children have growth retardation (with linear growth being most affected), although many undergo a compensatory growth spurt at puberty. Girls with Gaucher’s disease can have delayed onset of menarche with consequently decreased oestrogen-induced bone maturation, thereby having a further enhanced risk for osteoporosis.

Symptomatic lung involvement (either of parenchymal or vascular aetiology in a patient with type I disease) can

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Figure 2: Abdominal computed tomography (CT) scans at baseline and after enzyme replacement therapy

Unenhanced axial CT at level of pancreas showing: A) compression of stomach between enlarged liver and spleen (November 1992) and; B) regression in size of liver and spleen (February 2000). Unenhanced axial CT at level of sacrum showing: C) spleen filling up left pelvis (November 1992) and; D) normal organ placement with spleen no longer visible in pelvis (February 2000).
arise at any age, but is uncommon and generally only seen in those with other serious manifestations. Fertility of both sexes is probably unaffected by the disease, but pregnancy itself can affect the patient and, in turn, Gaucher’s disease might affect the pregnancy.3

Several serum markers were identified as valuable for work-up in the past, including raised tartrate-resistant acid phosphatase, serum ACE, and serum ferritin. Classically, formal diagnosis of Gaucher’s disease was based on identification of Gaucher cells (figure 1) in a bone-marrow aspirate, but the current gold standard for diagnosis is enzymatic assay combined with molecular analysis. An important new laboratory marker is chitotriosidase, secreted by activated macrophages, that is raised (often thousands-fold) in patients.4

The acute infantile form of Gaucher’s disease, type II, typically shows the triad of neurologic signs, strabismus, trismus, and retroflexion of the head, within the first months of life. The child goes on to develop seizures, spasticity, dysphagia, and extrapyramidal signs, which herald the penultimate stages, with death occurring before age 2 years.5 There is a neonatal variant of type II, characterised by hydrops fetalis with ichthyosis, which partly resembles an early knock-out mouse model of Gaucher’s disease.4

Type III, the subacute form of the disease, has visceral manifestations with at least one neurological abnormality, most commonly horizontal-supranuclear gaze palsy (also called oculomotor apraxia). Severity of disease in these patients is in direct proportion to degree of neurological and visceral involvement. There is also a unique variant, characterised by minimal visceral involvement, gaze palsy, and progressive calcification of the mitral or aortic valve, or both, which is life-threatening by the late teens. Patients with this variant (including Palestinian Arab, Japanese, and Spanish families) are homozygous for the mutation 1342C (D409H). This variant (also termed type IIIc) is the only type of Gaucher’s disease for which there is good genotype-phenotype correlation.7

**Clinical management**

The advent of enzyme replacement therapy in the early 1990s revolutionised the management of patients with Gaucher’s disease.8 After a decade of experience with alglucerase, the placental derivative, and imiglucerase, the recombinant form, the beneficial effects of enzyme replacement therapy are clear—the new treatment reduces organomegaly, improves haematological and biochemical indices, decreases bone-related pain, and induces compensatory growth in children.

Enzyme replacement therapy greatly improves bone structure as shown by various imaging techniques, although it cannot reverse or halt the course of pre-existing destructive skeletal complications. Skeletal response lags behind visceral and haematological responses, and can take 24–42 months.9 Children who begin treatment with enzyme replacement therapy in childhood have fewer skeletal complications than those who do not. Additional treatment for clinical management of skeletal disease might be treatment with bisphosphonates, which combat both bone loss and secondary bone pain.

Pulmonary hypertension has been noted in some patients on enzyme replacement therapy.10 Although a causal relation with enzyme replacement therapy is controversial, treatment withdrawal might be a possibility.

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**Subtypes of Gaucher’s disease**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
</tr>
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<tbody>
<tr>
<td>Most common genotype</td>
<td>1226G</td>
<td>1226G</td>
<td>1148C</td>
</tr>
<tr>
<td></td>
<td>compound heterozygous</td>
<td>(N370S) homozygous</td>
<td>(L444P) heterozygous</td>
</tr>
<tr>
<td>Ethnic predilection</td>
<td>Ashkenazi Jews</td>
<td>Ashkenazi Jews</td>
<td>Norbottians (Northern Sweden)</td>
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<tr>
<td>Common presenting features</td>
<td>Hepatosplenomegaly</td>
<td>None</td>
<td>OMA</td>
</tr>
<tr>
<td></td>
<td>Hydrops fetalis</td>
<td>None</td>
<td>OMA</td>
</tr>
<tr>
<td></td>
<td>Strabismus</td>
<td>OMA</td>
<td>Myoclonic seizures</td>
</tr>
<tr>
<td></td>
<td>Opiosthotonus Trismus</td>
<td>Opisthotonus</td>
<td>Growth retardation</td>
</tr>
<tr>
<td></td>
<td>Bleeding Bone Pains</td>
<td>Ichthyosis</td>
<td>Cardiac valve</td>
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<tr>
<td>Central nervous system involvement</td>
<td>None</td>
<td>Severe</td>
<td>Slow progressive neurological deterioration</td>
</tr>
<tr>
<td>Bone involvement</td>
<td>Mild to severe</td>
<td>None</td>
<td>Mild</td>
</tr>
<tr>
<td>Lung involvement</td>
<td>None to severe</td>
<td>None</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Enzyme replacement therapy</td>
<td>Indicated and efficient</td>
<td>Not indicated</td>
<td>Recommended for visceral features only</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>Normal</td>
<td>Death before age 2 years</td>
<td>Survival to teenage</td>
</tr>
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OMA=oculomotor apraxia.
in patients who show a progressive increase in tricuspid insufficiency (TI gradient (>30 mm Hg) with treatment during routine echocardiographic monitoring.

The high cost of enzyme replacement therapy affects its availability in many countries, and dosing regimens (ranging from 15 to 240 IU/kg every month) rely less on evidence-based medicine than on national financial and social constraints. Hence, wealthy countries provide high dosage regimens (as much as US $400 000 per patient every year) to mildly affected individuals, whereas poor countries cannot even treat children with life-threatening disease. Innovative treatment modalities are needed, since enzyme replacement therapy entails a life-long commitment to intravenous infusions with its attendant difficulties and inconvenience.

A few patients with type-I Gaucher’s disease have been enrolled in preliminary clinical trials of gene therapy, and others have been treated by non-myeloablative stem cell transplantation. Although these two approaches could be curative, they are far from being incorporated into clinical practice. In the interim, a promising novel approach seems to be that of substrate inhibition with iminosugars such as N-butyl deoxynojirimycin.11 Preliminary results with this new class of drug show proof of principle as monotherapy in naïve patients; the treatment had beneficial effects on key clinical features of type-I Gaucher’s disease.

Our patient is being treated with iminosugar N-butyl deoxynojirimycin in place of enzyme replacement therapy in a trial that addresses the role of substrate balance as a maintenance therapy. Being a small molecule that can traverse the blood-brain-barrier, substrate balance could also be effective for patients with neurological Gaucher’s disease and other lysosomal storage disorders.

The man behind the disease

Gaucher’s disease was first reported in 1882 by Philippe Charles Ernest Gaucher (1854–1918) (figure 3) in his MD thesis entitled “De l’épithélioma primitif de la rate; hypertrophie idiopathique de la rate sans leucémie”. He described primary and idiopathic hypertrophy of the spleen in a young woman, which he attributed to a primary tumour of the spleen with infiltration of the normal parenchyma by large, amorphous nucleated cells. He astutely noted clinical findings of gradual massive splenomegaly, haemorrhage expressed as epistaxis or purpura, secondary liver involvement with jaundice, and overt cachexia. The accuracy of his clinical description led investigators at the Mount Sinai Medical School, NY, USA, to name the condition after him half a century later.

Born in Nièvre, France, in 1854, young Gaucher served in army hospitals in Paris as part of his military service. He also spent some time with his uncle, a doctor in general practice, who persuaded him to apply to study medicine when he failed to obtain a university place in his first choice subject, natural sciences. He was successful as an undergraduate, and was awarded the “interne lauréat” of all Parisian hospitals in 1882, and then, in 1886, “médecin des hôpitaux”. By 1892, Gaucher was enshrined as “professeur agrégé” in the Hôpital Saint-Antoine, and was soon promoted to the Chair of the Department of Dermatology and Syphilology at the University of Paris.

He was a prolific academic writer, contributing several papers on the epidermal, cutaneous, ocular, and nasal manifestations of syphilis. He founded Annals of the Maladies Vénériennes in which he aggressively promoted his theory that poliomyelitis and appendicitis, as well as some congenital malformations, were the result of venereal disease. He also remained committed to military medicine throughout his life and was made an officer of the Légion d’Honneur in 1917 as recognition of his relief work during World War I. Gaucher died in 1918 in Paris aged 73 years.

References


