Type I Gaucher disease

JACK GOLDBLATT
From the MRC Unit for Inherited Skeletal Disorders, Departments of Human Genetics and Medicine, University of Cape Town Medical School and Groote Schuur Hospital, Cape Town, South Africa.

Type I Gaucher disease, the subject of this article, was initially reported by Gaucher in 1882 as a non-leukaemic splenic epithelioma. The biochemical defect, an autosomal recessively inherited lysosomal glucocerebrosidase enzyme deficiency, was delineated in 1965, and more recently the full length coding DNA sequence has been cloned and characterised.

Gaucher disease is conventionally classified into three types on the basis of neuronopathic manifestations and the natural course of the disorder. In contradistinction to type I Gaucher disease, types II and III have a primary neuronopathic infiltration with a progressive neurodegenerative course. The condition is acute in type II with death in early childhood, while type III is a subacute disorder with survival into adulthood.

Pathogenesis

The undegraded metabolite accumulates in cells of the monocyte macrophage system and hence the major clinical manifestations result from infiltration of the spleen, liver, and bone marrow. Owing to the variable rate of substrate deposition, there is a wide spectrum of clinical involvement (figs 1 and 2) from severely affected infants to asymptomatic octogenarians. This unpredictable natural history complicates genetic counselling and patient management.

Clinical aspects

CLINICAL ONSET
Initial modes of presentation include asymptomatic splenomegaly, complications of pancytopenia owing to hypersplenism, or the orthopaedic sequelae of bone marrow infiltration. Although designated the 'adult' form, the diagnosis is often confirmed in childhood.

HAEMATOLOGICAL
Variable pancytopenia is a consistent feature which manifests with a bleeding tendency and symptoms of chronic anaemia. Despite significant thrombocytopenia, life-threatening bleeding is infrequent because of the functional integrity of the residual platelets.

ORTHOPAEDIC
Skeletal complications cause considerable disability
in the majority of affected persons. Early marrow involvement is shown radiographically by the typical ‘Erlenmeyer flask’ deformities of the lower femora (fig 3) resulting from expansion of the medullary cavity. Episodes of ischaemic necrosis present acutely as a ‘pseudo-osteomyelitic crisis’ or chronically as aseptic necrosis of the femoral heads (fig 4). With disease progression the entire skeleton may be involved causing pathological fractures. Although retarded growth and development are not characteristic of this condition, short stature may occur in the more severely affected children.

GASTROINTESTINAL
Hepatosplenomegaly, usually massive in extent, is invariable and only infrequently have asplenic patients been reported. Hepatomegaly is not usually associated with clinical or biochemical features of hepatic dysfunction until late in the course of the disorder when portal hypertension may develop.

ASSOCIATED FEATURES
Common minor stigmata are ocular pterygia, which are fleshy, brown, bulbar conjunctival nodules, and a diffuse yellow-brown dermal hyperpigmentation. Rarely reported complications, particularly in severely affected post-splenectomy patients, include pulmonary and renal dysfunction from substantial Gaucher cell infiltration.

Differential diagnosis
The diagnosis is confirmed by assaying the specific glucocerebrosidase enzyme in lymphocytes, platelets, or fibroblasts. Associated features include histologically typical Gaucher cells, particularly in liver, spleen, or bone marrow, raised serum acid phosphatase and angiotensin converting enzyme, and the characteristic radiographical features. These findings and the deficient enzyme activity distinguish type I Gaucher disease from the numerous inherited and acquired disorders causing hepatosplenomegaly and hypersplenism. Scattered storage cells histologically similar to Gaucher cells are found in some haematological conditions, such as leukaemia and thalassaemia, but are differentiated by the normal glucocerebrosidase activity in these disorders.

Management and treatment
Enzyme replacement therapy has been unsuccessful.
and allogenic bone marrow transplantation, although potentially curative, is not justifiable in the majority of patients because the risks of the procedure outweigh the benefit offered to the mildly affected patient. Management is therefore aimed at the complications consequent on substrate accumulation.

**H A E M A T O I O G I C A L**

Splenectomy reverses the pancytopenia, but there is considerable controversy concerning the progression of the extrasplenic manifestations after this procedure. In the absence of prospective controlled trials, the role of splenectomy in the natural course of the disorder is uncertain. However, as there are no reliable predictive factors to determine which subjects are at later risk of orthopaedic complications, a conservative policy concerning splenectomy is advocated. This procedure should be delayed until there is life threatening pancytopenia or rarely, in young children, because of cardiorespiratory compromise. Furthermore, if indicated by these criteria,
an attempt should be made to perform a partial splenectomy in the hope of providing a potential storehouse for substrate deposition.8

ORTHOPAEDIC
Bone pain requires analgesia, with care to avoid acetylsalicylic acid and non-steroidal anti-inflammatory agents if thrombocytopenia is present. Episodes of 'pseudo-osteomyelitis' resolve spontaneously over a period of a few days to about two weeks. Symptomatic therapy consists of bedrest and analgesia. It is particularly important to differentiate these episodes from pyogenic osteomyelitis to avoid unnecessary and potentially harmful bone drilling. The chronic sequelae of avascular necrosis of femoral heads with secondary osteoarthritis is managed with prosthetic joint replacement (fig 5) with excellent long term results.9

Genetics
The condition is most prevalent among Ashkenazi Jews with an estimated carrier rate of 0·04 to 0·0810 compared to a carrier rate of 0·0044 in the Afrikaners of South Africa, the highest reported occurrence in a non-Jewish community.11 Heterozygotes are asymptomatic but enzyme assay is available for carrier detection and prenatal diagnosis.12

Future prospects
The isolation of a full length human glucocerebrosidase cDNA clone and its introduction with a retroviral vector into human cells in culture shows the potential for curative gene therapy for type I Gaucher disease.13 Furthermore, this technology should facilitate the large scale production of pure glucocerebrosidase enzyme to allow more concerted attempts at enzyme replacement therapy, which has possibly failed so far because of the paucity of enzyme obtained by current purification techniques.

My work in connection with Gaucher disease has been supported by grants from the Medical Research Council of South Africa, the Maunderger Foundation, the Harry Crossley Foundation, and the University of Cape Town Staff Research Fund.

References

Correspondence and requests for reprints to Dr J Goldblatt, MRC Unit for Inherited Skeletal Disorders, Department of Human Genetics, University of Cape Town Medical School, Observatory 7925, South Africa.