Haematological Problems Associated with Gaucher's Disease

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SUMMARY

Five recent cases of Gaucher's disease seen at Groote Schuur Hospital illustrate the haematological complications. The main problem is hypersplenism with secondary thrombocytopenia. Two patients underwent splenectomy for this reason, and one gained lasting improvement. None of the more rare haematological problems was seen in this series.

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Gaucher's disease is an uncommon, inherited metabolic condition in which there is an inability to metabolise glucocerebroside. This defect may cause a variety of symptoms, including haematological problems, as a result of accumulation of abnormal lipids in the reticulo-endothelial system. Although there is some controversy over the exact nosological classification of this disease, it is the adult or chronic form which is considered here. This disease was first described by Gaucher[1] in 1882, when he considered it to be a primary splenic epithelioma.

HAEMATOLOGY

Because of the lack of one of the iso-enzymes of beta glucosidase,[2] the phagocytic cells of the reticulo-endothelial system are unable to metabolise glucocerebroside, so that this and other lipids accumulate in the cells. The bone marrow, liver, and particularly the spleen, become enlarged due to a hyperplasia of the reticulum cells. These Gaucher's cells are large histiocytes, some 20 - 100 μm in diameter, with the cytoplasm full of abnormal fibrillar lipid. In the marrow they displace normal erythropoietic tissue and cause thinning of the bony cortex, resulting in anaemia and pathological fractures; enlargement with secondary hypersplenism in the spleen; and enlargement with failure of function in the liver, resulting in lack of coagulation factors. Involvement of the pulmonary system, with consequent respiratory failure, often results in the terminal stages of the disease.

In a review of 35 cases,[3] the majority of patients were diagnosed under the age of 18 years, and presented initially with splenomegaly, which may be massive—in one case 8 910 g.[4] In fact, it is often the symptoms of hypersplenism, anaemia, and thrombocytopenia which cause the patient to seek attention. Although haematological problems often induce the patient to seek advice, it is usually the pulmonary or orthopaedic complications which limit the prognosis. Other complications that have been reported include coagulation factor deficiencies[5] in which factor IX was much reduced. A rare finding has been that of a leuco-erythroblastic peripheral blood picture due to marrow displacement.[6]

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PATIENTS

Patient 1

This 57-year-old male of Jewish extraction presented initially complaining of a rash on his hands and feet which came on every 2 weeks or so, with no prodromal symptoms, in a crop lasting a few days. The rash was painful, and it consisted of red blotches under the skin of both hands and feet.

Examination revealed a purpuric rash on hands and feet associated with a 3-finger splenomegaly. Platelet count at that time was 58 000/mm^3, and the bone marrow aspiration revealed numerous Gaucher's cells. Because of persistent thrombocytopenia the patient underwent splenectomy with platelet transfusion cover. Recovery was excellent, and the most recent platelet counts have varied from 130 000 to 204 000/mm^3. No exacerbation of the disease was noted.

Patient 2

This 42-year-old male from Lithuania and of Jewish extraction, presented with severe dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, and ankle swelling. He had always had an enlarged spleen and Gaucher's disease had been diagnosed at the age of 8 years.

On examination he was noted to have bilateral pingueculae, marked kyphosis, yellow-brown pigmentation over the upper half of his body, severe congestive cardiac failure, and marked hepatosplenomegaly. Investigation showed peripheral blood with a leuco-erythroblastic picture and thrombocytopenia, and total marrow replacement by Gaucher's cells. An X-ray film of the skeleton demonstrated severe osteoporosis with wedge compression of several lower dorsal vertebral bodies. The femurs showed the classical Erlenmeyer flask deformities. Pulmonary function studies were considerably abnormal, and a chest X-ray film confirmed cardiac failure.

Symptomatic treatment for incipient respiratory failure and congestive cardiac failure provided relief for some

months. However, he died subsequently, after developing arterial gangrene 3 months later.

Patient 3

This 34-year-old female, whose parents were first cousins, emigrated from Lithuania. She presented initially at the age of 16 years with easy bruising on mild trauma and mild menorrhagia. Indeed, her referral to the haematology service was as a result of her desire to be sterilised after the birth of 2 children, the referring doctor wondering whether splenectomy should be undertaken at the same time.

At the time of her examination, apart from a 2-finger splenomegaly, no abnormality was noted. Her platelet count was 144 000/mm^3, and there were no other haematological abnormalities. In view of this, no haematological interference in the form of splenectomy was indicated, and since then she has remained well.

Patient 4

This middle-aged man of Jewish extraction, a known case of Gaucher's disease, was referred for haematological evaluation, having no symptoms at the time.

Although on examination there was a mild splenomegaly, the platelet count was 92 000/mm^3, and the prothrombin index 68%. In view of the lack of symptoms, splenectomy was not indicated and the patient has remained well.

Patient 5

This 15-year-old girl was referred post-splenectomy for follow-up and assessment of respiratory function. She had undergone splenectomy for thrombocytopenia and abdominal discomfort, after Gaucher's disease had been diagnosed before the age of 10 years. At that time she was complaining of respiratory difficulty and 2 recent fractures of her right humerus.

On examination she was small for her age with central cyanosis, and she had a recent fracture of her right elbow. Investigation showed reasonable pulmonary function with an arterial pO_2 of 50 mmHg, indicating a diffusion block. X-ray film showed generalised osteoporosis with 2 fractures of the right humerus. The bone marrow was solidly infiltrated with Gaucher's cells, and the peripheral blood showed 2% normoblasts. Platelets were 49 000/mm^3, and both prothrombin index and cephalin-kaolin time were prolonged, at 68% and 63/48 respectively. Massive hepatosplenomegaly was noted. Therapy was conservative, and she progressed reasonably, though the hypoxia remained a serious problem.

DISCUSSION

These 5 patients illustrate well the problems of Gaucher's disease. The main symptom is hypersplenism with consequent anaemia and thrombocytopenia. Indeed, the hypersplenism required splenectomy in 2 of the 5 cases. A previous review of this form of therapy[7] mentioned low mortality with few complications, though the operation has been reported as risky and technically difficult with such large and friable hilar vessels. Others[3,8] claimed that removal of a large reservoir of lipid aggravates the situation elsewhere. It is interesting to note that splenectomy does not necessarily improve coagulation factor deficiencies[5] or, indeed, thrombocytopenia, as the liver may continue to remove platelets. However, when symptoms of hypersplenism do become troublesome, splenectomy is the treatment of choice, and benefited the first of our cases, although judging from the platelet count of the fifth case, the liver still removes most of the platelets. Splenic transplantation[10] has been attempted, with some favourable results, but rejection problems associated with transplantation of part of the immune system proved insurmountable. Irradiation and steroids have been tried with only very limited results. Considerable scope remains for surgical intervention, since the orthopaedic involvement may cause great problems throughout the patient's life.

Thrombocytopenia is a common reported finding, and was seen in all these cases. In one study,[11] thrombocytopenia was present in 50% of cases with symptoms of purpura and bleeding. Green *et al.*,[9] in a platelet survival study with ^{51}C-labelled platelets, found a half-life of 0,8 days, with marked splenic accumulation, both of which returned to normal post-splenectomy. Electron microscopy revealed whole, intact platelets in the Gaucher's cells, underlining the importance of phagocytosis of increased numbers of these cells in contributing to the thrombocytopenia.

The anaemia often seen in these cases, due to a combination of increased splenic pooling with consequent haemodilution and decreased red cell survival,[12] was not apparent in any of these cases, nor was there any evidence of auto-immune haemolytic anaemia as reported by Wasserman *et al.*[15] It is of interest to note that the source of abnormal lipid, which was thought originally to be due to erythrocyte turnover[12] in view of the iron in the Gaucher's cells, has been demonstrated by Kattlove *et al.*[13] to come from granulocytes. No neutropenia, however, was demonstrated in this series. Only in the fifth and most severe case were any coagulation abnormalities noted, and in this case hepatomegaly was a prominent feature. Other rare complications of multiple myeloma, or monoclonal benign gamopathies,[14] were not present in this series. Only the 2 most severe cases (patients 3 and 5) developed respiratory symptoms and bone changes which, in one of these cases, have already led to death.

As can be seen from this series, the main haematological problem associated with Gaucher's disease is hypersplenism. Splenomegaly is often a presenting symptom, and usually requires treatment. Splenectomy is an excellent form of therapy which resolves most symptoms, but it should be performed only on very definite indications, in view of the risk of exacerbating the disease.[3,8] Certainly it may be of considerable help with the thrombocytopenia, which is the main manifestation of the secondary hypersplenism. The prognosis of the haematological problems is usually good, though pulmonary and orthopaedic involvement may be troublesome.

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