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Gaucher's disease in the Cape Coloured population of the RSA, including a family with 5 affected siblings

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Summary

Nine Cape Coloured children from 4 families with severe non-neuropathic Gaucher's disease are documented. The diagnosis was confirmed histologically in the bone marrow, spleen and liver, and by serum acid phosphatase and leucocyte β-glucosidase assays. This represents a minimum prevalence for Gaucher's disease of 1 in 247 350 in this population and an approximate genetic carrier rate of 1 in 230 for the abnormal gene. A family with 5 affected siblings is recorded.

The severe early clinical expression documented in these coloured patients is similar to that described in the Afrikaner population and differs from the less severe expression of Gaucher's disease in the South African Ashkenazi Jewish population. Gaucher's disease in the Cape Coloured population presents with a precocious onset, causes severe complications and progresses rapidly.

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Philippe Gaucher first reported a patient with hepatosplenomegaly and bone involvement in 1882.[1] The basic defect was elucidated 83 years later by Brady *et al.*,[2] who demonstrated a deficiency of β-glucosidase in an affected adult, with resulting accumulation of glucocerebrosides in various tissues, particularly the reticulo-endothelial system.

Gaucher's disease is conventionally classified into the adult or chronic non-neuropathic type, the acute neuropathic infantile type and the subacute neuropathic juvenile type.[3] The latter two conditions lead to death in childhood due to the accumulation of glucocerebrosides in the brain, while the adult or non-neuropathic form is characterised by a slowly progressive course marked by massive splenomegaly, dyshaemopoiesis and orthopaedic complications.

Chronic non-neuropathic Gaucher's disease has been reported in adults of Ashkenazi Jewish descent[4] in the RSA. Goldblatt and Beighton[5] also documented the presence of a more severe form of the disease among children of the Afrikaner population. The same authors recorded non-neuropathic Gaucher's disease presenting in infancy in 12 children,[6] 3 of whom were of mixed ethnic ancestry and who are included in this report.

Patients and methods

The patients reported here represent all the cases of Gaucher's disease diagnosed at Tygerberg Hospital between 1971 and 1984. During this period the interest of the investigators in this disease became known and patients with suspected Gaucher's disease were referred for opinion.

Each patient was examined clinically. A radiological skeletal survey was performed and the serum acid phosphatase level measured in 8 patients. Bone marrow aspirate was obtained in 7 patients. The spleen was examined histologically after splenectomy in 7 patients and liver biopsy was performed on 4 patients. The typical electron microscopic appearance of Gaucher cells in the liver is illustrated in Fig. 1. Leucocyte β-glucosidase activity at pH 5,5 was measured in 4 affected siblings (patients 6 - 9), their

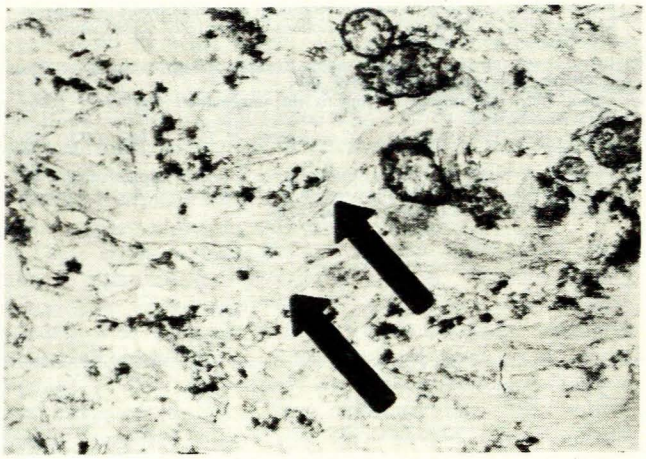

Fig. 1. The ultra-structural studies demonstrate spindle or rod-shaped membrane-bound cytoplasmic inclusions typical of Gaucher's disease in the liver (plate magnification = 10 000; print magnification = 40 000).

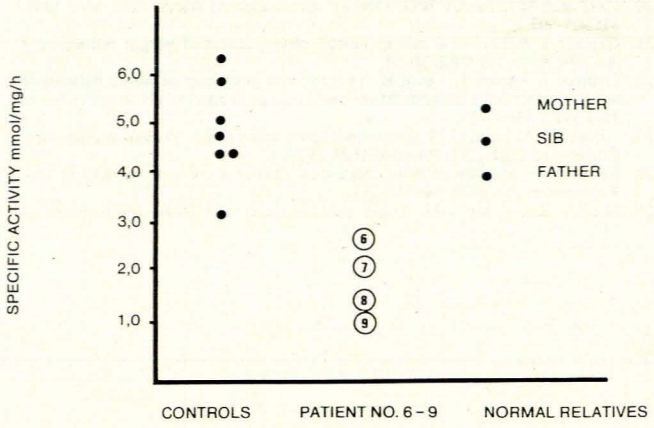

Fig. 2. Leucocyte β-glucosidase activity at pH 5,5 in a family with 5 sibs with Gaucher's disease.

parents, a normal sib and in 7 controls according to the method used by Galjaard.[7] The criterion for hypersplenism was a decreased peripheral red cell, white cell or platelet count in the presence of normal haematopoiesis in the bone marrow. The minimum prevalence of Gaucher's disease in this population was calculated by dividing the total Cape Coloured population (as recorded in the 1980 census) by the number of affected patients.

Results

The leucocyte β-glucosidase activity is shown in Fig. 2 and all the laboratory investigations are listed in Table I.

Nine affected children, 4 boys and 5 girls, were identified. It was discovered that a sister of the 4 sibs with decreased leucocyte β-glucosidase activity had had massive hepatosplenomegaly. She died of presumed splenic rupture secondary to Gaucher's disease before this family came to our notice. Hepatosplenomegaly was very prominent in 8 of the patients. The clinical features of these children are presented in Table II. The age at diagnosis varied from 5 months to 9 years. All the patients except the youngest (patient 9) had massive splenomegaly and some suffered nose bleeds as a result of hypersplenism. Patients 1 - 8 had marked hepatomegaly.

Intermittent bone pain, present in 5 of the 9 children, was due to orthopaedic complications which included aseptic necrosis of the femoral head in 4 patients, pseudo-osteomyelitis in 3 patients and a pathological fracture of the femur in 2 patients. One patient now has a shortened leg. The nervous system and eyes were normal in all patients. There was no history of parenteral consanguinity. Patients 1 and 2 have 4 unaffected sibs, patient 3 is an only child, as was patient 4, and patients 5 - 9 have two unaffected sibs.

An autopsy on patient 4, who died of cardiac failure, revealed no infiltration of the myocardium by Gaucher cells.

Discussion

The assignment of Gaucher patients, especially children, to a clinical subtype should be made only after careful examination for the presence or absence of neurological signs.

The estimated number of the Cape Coloured population is 2 226 160 (according to the 1980 census). Nine affected members in this group therefore gives a minimum prevalence for Gaucher's disease of 1 in 247 350; a minimum gene frequency of 0,0017 with a carrier rate of 0,0034. Therefore, there are

TABLE I. SPECIAL INVESTIGATIONS

Patient	Hypersplenism	Acid Phos. (IU/l)*	Leucocyte ß-glucocerebrosides	Skeletal changes	Histology		
					Bone marrow	Spleen	Liver
1	+	44	Unknown	Erosion femoral head	+	+	+
2	+	45	Unknown	Erosion femoral head	+	+	+
3	+	15,9	Unknown	Erosion femoral head	+	+	Not performed
4	+	35,6	Unknown	Erosion femoral head	+	+	+
5	Not examined	—	Unknown	Erosion femoral head	Unknown	Unknown	Unknown
6	+	161,6	↓	Absent	+	+	Not performed
7	+	67,7	↓	Absent	+	+	Not performed
8	+	163	↓	Absent	+	+	+
9	—	20,2	↓	Absent	Not performed	Not performed	Not performed

*Normal range 4,8 - 13,5 IU/l.

TABLE II. CLINICAL FEATURES IN 9 COLOURED PATIENTS WITH GAUCHER'S DISEASE

Patient	Sex	Year of birth	Presenting symptom	Age at diagnosis (yrs)	Splenectomy	Current status
1	F	1964	Painful hip	5	1970	Died septicaemia, 1970*
2	M	1968	Painful leg	4	1972	Hepatomegaly, bony lesions
3	F	1962	Painful hip	9	1972	Shortened right leg
4	M	1974	Painful hip	1½	1978	Died cardiac failure, 1979
5	F	1967	Painful leg	8	—	Died splenic rupture, 1979
6	M	1972	Nose bleed	4	1979	Hepatomegaly, otherwise well
7	M	1973	Nose bleed	3	1979	Hepatomegaly, otherwise well
8	F	1976	Splenomegaly	2	1983	Hepatomegaly, otherwise well
9	F	1983	—	5/12	—	Asymptomatic

*Did not receive pneumococcal vaccine.

approximately 9 600 clinically asymptomatic carriers of the gene in the Cape Coloured population, i.e. 1 in 230 individuals.

This survey reveals an unexpectedly high frequency of adult-type non-neuropathic Gaucher's disease of precocious onset and rapidly progressive course in Cape Coloured children. One family with a hitherto unrecorded number of 5 affected sibs is included in this series. Non-neuropathic Gaucher's disease in this population differs markedly from non-neuropathic Gaucher's disease in adult Ashkenazi Jewish patients and is similar to non-neuropathic Gaucher's disease in the Afrikaner population.

All the children in this study had surnames denoting Dutch ancestry. It is therefore likely that the same genetic factors causing a progressive form of the disease in the Afrikaner population are present in this coloured population. These findings provide evidence that the disease in these latter groups may be due to a different gene from that in the Ashkenazi Jewish population. This is difficult to explain at present in view of the similar biochemical findings in all three population groups.

The chronic non-neuropathic type was previously designated the 'adult' form of Gaucher's disease. It is becoming increasingly apparent, however, that many patients with onset of signs and symptoms early in childhood belong to this group. The initial signs of this chronic form are usually splenomegaly (although exceptions have been noted), haematological abnormalities attributable to hypersplenism, and bone lesions. The central nervous system is not affected. The course in adult non-neuropathic Gaucher's disease is usually slowly progressive with complications appearing or worsening over a period of years. It is clear that Gaucher's disease in the children of this study does not follow this pattern, thus emphasising the limitations of the original subdivisions of the disease and the need for its reclassification.

Gaucher's disease results from a deficiency of the enzyme β-glucosidase which catalyses the cleavage of glucose from glucocerebrosides, and this defect has been demonstrated in various tissues.[8] Assay of enzyme activity in peripheral blood leucocytes may confirm the diagnosis in suspected cases as in our patient 9, who is still asymptomatic.

The identification of heterozygotes and the prenatal diagnosis of Gaucher's disease from amniotic cell cultures have permitted genetic counselling to families at risk, since all three types of the disease are inherited as an autosomal recessive trait.

Since all but one of the patients had rapid progression of disease with massive splenomegaly, splenectomy was performed in all because of considerable physical discomfort, the presence of hypersplenism and the danger of splenic rupture. All but the first patient received pneumococcal vaccine before or after splenectomy. The splenectomy did not accelerate the natural course of the disease.

The frequency of the gene for Gaucher's disease in the Cape Coloured community approximates that seen in the Afrikaner population. In view of the severity of the condition in the coloured population, this genetic situation has important implications. Antenatal diagnosis is possible and genetic counselling must be made available to any coloured couple who have an affected child. The diagnosis of this disorder should be considered in any coloured child who presents with unexplained hepatosplenomegaly.

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