Gaucher's Disease in Southern Africa

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SUMMARY

A review of the clinical features of Gaucher's disease is presented, with particular reference to 17 patients in South Africa. The management, prognosis, mode of inheritance and genetic risks are discussed. It is estimated that there may be as many as 50 affected individuals among the Ashkenazi Jews in South Africa.

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The adult, chronic or non-neuropathic form of Gaucher's disease is an inherited condition in which a deficiency of the enzyme beta-glucosidase leads to the accumulation of cerebrosides in the cells of certain tissues.[1] The major clinical manifestations are the consequence of involvement of the spleen, haemopoietic system and skeleton.

Although rare, this variety of Gaucher's disease occurs with maximal frequency in individuals of Ashkenazi Jewish stock.[2,3] There is a relatively high prevalence of the condition in the Jewish community of South Africa, and we have therefore instituted an ongoing investigation into several facets of the disorder, attempting to examine every affected individual in the country.

In recent months, Gaucher's disease and other inherited conditions have attracted considerable attention in both medical and lay circles. For this reason, we have reviewed the clinical and genetic features of chronic Gaucher's disease, giving details of 17 affected individuals from our series of South African patients.

NOSOLOGY

Gaucher's disease has been classified into infantile, juvenile and adult forms.[4]

The infantile, acute or cerebral variety is a distinct entity, characterised by hepatosplenomegaly, failure to thrive and neurological complications. The condition is progressive and death occurs at an early age. There is no known predilection for any ethnic group.

Patients with the juvenile type of the disorder have mild hepatosplenomegaly with progressive dementia, cerebellar ataxia and extrapyramidal involvement. This condition is rare, but reaches a maximum prevalence in Sweden.[5]

The adult or chronic form of Gaucher's disease is clinically quite distinct and, in particular, neurological changes do not occur. In a proportion of affected adults, a chance finding of splenomegaly has led to confirmation of the diagnosis many years before the development of symptoms. In others, clinical manifestations appeared during childhood. For these reasons, there is terminological confusion concerning the juvenile and adult disorders. However, the clinical presentations are very different, and a correct diagnosis of chronic Gaucher's disease may occasionally be made in childhood.

CLINICAL FEATURES

Gaucher's disease follows a chronic course, and a variety of symptoms may result from splenomegaly, dyshaemopoiesis or skeletal involvement. Hepatic and pulmonary complications may arise in the later stages of the disorder. Dermal and ocular manifestations are of minor clinical importance.

Visceral

Splenomegaly is frequently the presenting feature and is sometimes first detected at routine examination. Resultant abdominal discomfort is of variable severity. Hepatomegaly is a less consistent manifestation and overt defects of liver function are uncommon. Diffuse pulmonary infiltration occurs in severely affected individuals and dyspnoea, cyanosis and right heart failure develop in the terminal stages.

Skeletal

Infiltration of the skeleton leads to a variety of problems, including non-specific bone pain, episodes of acute bony inflammation (pseudo-osteomyelitis), pathological fractures, acute arthritis and collapse of articular surfaces.

Haematological

Hepatosplenomegaly and involvement of the bone marrow lead to dyshaemopoiesis, with anaemia and thrombocytopenia. Petechiae, ecchymoses and abnormal bleeding are common sequelae.

Dermal

Diffuse brown macular pigmentation has been described as a characteristic feature of Gaucher's disease, but undue darkening of the skin on exposure to the sun is more frequently encountered.

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Ocular

In the ocular region, pingueculae and xanthelasmata are not uncommon. Chronic inflammation due to infiltration of the conjunctiva is an infrequent complication.

COURSE AND PROGNOSIS

Gaucher's disease is frequently diagnosed in childhood or early adult life, often following the chance detection of splenomegaly.[6] Years may elapse before the onset of symptoms and the disease is usually slowly progressive with exacerbations and remissions.

In some patients clinical problems are confined to the haemopoietic or skeletal systems, while in others the effects are widespread. In the later stages of illness, health may be impaired by a combination of all the above-mentioned complications.

DIAGNOSIS

Clinical

The diagnosis should be considered if a sibling of an affected individual develops haematological or skeletal problems, or in any patient with unexplained splenomegaly.

Radiological

Radiological findings which support the diagnosis include an Erlenmeyer flask deformity of the long bones, characteristically the lower end of the femur.[7] Alteration of bony trabecular pattern with infiltration and collapse of femoral or humeral heads may also be apparent.[8,9] Evidence of pulmonary involvement may be found later.

Biochemical

The serum level of tartrate-resistant acid phosphate is usually elevated during the active stages of the disorder.[10] Activity of the enzyme beta-glucosidase is absent in peripheral blood leucocytes and skin fibroblasts from affected individuals.[11] Partial deficiency of activity can be demonstrated in clinically normal heterozygous carriers of the gene.[12,13]

Histological

The diagnosis can be confirmed by histological demonstration of the characteristic Gaucher cells in bone marrow, bone biopsy or by splenic puncture, but these measures are rarely indicated.

MANAGEMENT

Splenectomy

Splenectomy has an important place in the management of haematological complications. The precise indications for operation and the timing of this procedure depend upon the evaluation of the haematological investigations or may be indicated for gross abdominal distension or severe discomfort. However, the situation is complex, as some experts consider that splenectomy might accelerate the development of skeletal lesions.

Orthopaedic

Prosthetic replacement of a diseased hip joint has proved to be a satisfactory procedure and long-term results have been excellent.

There is still considerable controversy as to whether pathogenic bacteria are involved in pseudo-osteomyelitis, or whether this complication is simply the result of bony infiltration with medullary haemorrhage or thrombosis. Management of these acute episodes may include the use of antibiotics or steroids, in addition to orthopaedic measures. As secondary infection is a frequent complication, aspiration or surgery should be avoided for as long as possible.[14]

Non-specific arthritis and bone pain, together with pathological fracture and bony deformity, are usually treated in accordance with accepted orthopaedic principles.[15]

Drug Treatment

Analgesics and iron supplements may be required. Apart from a questionable place in the management of pseudo-osteomyelitis, there is no indication for the use of steroids. The sequelae of liver dysfunction and pulmonary infiltration which complicate the late stages of this disorder, are treated on their own merits.

Future Prospects for Therapy

A rational line of therapy for Gaucher's disease would be the replacement of the deficient enzyme. This enzyme can be obtained in small quantities from normal urine, and eventually treatment may be developed on this basis.

Groth *et al.*[16] reported that splenic transplant in a severely affected 24-year-old male resulted in favourable metabolic changes for the first month after operation. However, the graft then ceased to function and the patient died following an exacerbation of the condition. The authors concluded that further attempts at splenic transplantation in Gaucher's disease seemed to be warranted.

GENETICS

Gaucher's disease is inherited as an autosomal recessive.[17] Affected individuals have a pair of abnormal genes, one derived from each parent. In genetic terminology, affected patients are homozygotes, or homozygous for the abnormal gene. Similarly, the parents of a patient, who are asymptomatic carriers of a single abnormal gene, are heterozygotes, or heterozygous carriers.

A couple who have produced an affected child are at a 1-in-4 risk of recurrence in every subsequent pregnancy. However, the majority of families will have been completed before the condition is diagnosed in one of the offspring, and the importance of appreciation of this recurrence risk lies in the fact that the disorder may become manifest in the siblings of an affected individual.

The children of a patient with Gaucher's disease will all be unaffected asymptomatic carriers of the gene and will *not* develop the condition unless the patient's spouse also happens to be a carrier. Similarly, there is a 2 to 1 chance that any sibling of an affected individual will be a heterozygous carrier. However, affected children will be produced by a carrier only if marriage takes place with another carrier. As the carrier state can now be identified biochemically, this situation has considerable practical implications.

The likelihood of two heterozygous carriers marrying can be assessed on a basis of the contention that the carrier rate or gene frequency for chronic Gaucher's disease in the Ashkenazim of Israel is between 1 in 20 and 1 in 30. In general terms, the chances of marriage between two clinically normal carriers of the gene in this community therefore lies between 1 in 400 and 1 in 900. In view of the autosomal recessive nature of chronic Gaucher's disease, there is a 1-in-4 risk that any child of such a marriage will inherit two abnormal genes and manifest the condition. In terms of prevalence of the condition itself, it is estimated that one in every 2 500 individuals in the Ashkenazi community of Israel has chronic Gaucher's disease.

CASE DETAILS

Seventeen individuals with Gaucher's disease have been personally examined. Radiographs and previous medical records were available, and the diagnosis has been confirmed histologically in each instance. Patients with the infantile and juvenile forms of the condition, and those in whom there was any doubt about the precise diagnosis, have been excluded from this report.

The clinical features of the patients in the series are summarised in Table I. For brevity, details of orthopaedic operations and haematological investigations have been omitted.

The presenting feature, age of diagnosis and current health status of the patients are shown in Table II. Details of the patients' personal situation, ethnic background and family history are given in Table III.

The patients were derived from the following population groups:

Ashkenazi Jewish	13
Sephardic Jewish	1
Afrikaans	1
English	1
Zulu	1

None of these patients had affected parents or offspring and none were related to each other. Parental consanguinity was present in one kindred.

Four of the Ashkenazim and the Afrikaner claimed that they had an affected sibling, but as they were not

TABLE I. CLINICAL FEATURES

Sex	Age	Orthopaedic complications: Non-specific bone pain	Pseudo-osteomyelitis	Acute arthritis	Collapse of femoral head	Spinal deformity	Splenomegaly	Splenectomy	Hepatomegaly	Haematological complications	Pulmonary infiltration
F	36	+			+					+	
M	49	+	+	+	+		2″		2″	+	+
F	24	+						1970	4″	+	
M	45	+	+		+	+		1950	5″	+	
M	59							1971		+	
F	34						3″		2″	+	
F	16	+	+	+	+	+		1963	4″	+	+
F	14	+		+	+			1969		+	
F	4						1″		7″		+
M	42						16″				+
M	46	+	+		+		2″		2″	+	
M	33	+	+	+	+		2″		6″	+	
F	32	+			+			1960			
F	28			+	+			1958			
F	37			+	+			1966			
M	42			+	+		1″		1″	+	
F	34	+		+	+			1960		+	

TABLE II. PRESENTATION AND PROGRESSION

Sex	Age	Initial presentation: Age	Initial presentation: Feature	Age of firm diagnosis	Present health
F	36	23	Splenomegaly	23	Episodes of bone pain and anaemia.
M	49	5	Splenomegaly	37	Walks with sticks, otherwise well.
F	24	6	Splenomegaly	20	Walks with limp, otherwise well.
M	45	5	Splenomegaly	17	Poor health; wears spinal brace; walks with sticks.
M	59	42	Splenomegaly (RE)	54	Asymptomatic.
F	34	33	Spontaneous bruising	33	Asymptomatic.
F	16	6	Bleeding and splenomegaly	6	Poor health; severe orthopaedic and haematological complications.
F	14	4	Splenomegaly (RE)	4	Asymptomatic.
F	4	3	Splenomegaly (RE)	3	Asymptomatic.
M	42	2	Splenomegaly (RE)	20	Progressive ill-health. Died in July 1973.
M	46	10	Pseudo-osteomyelitis	28	General health good; problems have all been orthopaedic.
M	33	21	Bone pain	21	General health good; discharging sinus on L thigh.
F	32	18	Abdominal distension	18	General health fair; intermittent pain in R hip.
F	28	13	Splenomegaly	13	Asymptomatic.
F	37	20	Abdominal discomfort	30	Asymptomatic.
M	42	40	Acute arthritis (hip)	41	General health good; hip joint problems.
F	34	21	Acute arthritis (hip)	21	General health good; intermittent anaemia and arthritis.

RE = routine examination.

TABLE III. PERSONAL SITUATION

Sex	Age	Ethnic group	Occupation	Marital status	No. of children	Family history
F	36	Jewish	Teacher	M	3	
M	49	Jewish	Business	M	3	
F	24	Afrikaans	Housewife	M	1	Affected brother
M	45	Jewish	Business	M	—	
M	59	Jewish	Business	M	3	Affected sister
F	34	Jewish	Housewife	M	3	
F	16	Jewish	School	S	—	Nil known
F	14	Jewish	School	S	—	
F	4	Jewish (Sephardic)	—	S	—	
M	42	Jewish	Bookkeeper	S	—	Affected brother
M	46	Jewish	Physician	M	4	Affected sister
M	33	Jewish	Driver	M	1	
F	32	Jewish	Teacher	S	—	Affected brother
F	28	English	Teacher	S	—	No sibs
F	37	Black	Domestic work	M	1	
M	42	Jewish	Business	M	3	
F	34	Jewish	Housewife	M	1	

available for examination, their case details are not given in the tables. Ten other affected adult Ashkenazim are known to us, but not yet fully investigated, and are not included in this series.

COMMENT

The purpose of this article is the presentation of a general review of the clinically important practical aspects of Gaucher's disease. For the sake of clarity, we have deliberately avoided detailed exposition or sophisticated analysis of our data.

Our experience confirms the impression that the course of the condition is very variable. Some individuals remained in good health for many years after initial presentation and diagnosis. Others developed a progressive illness, with or without exacerbations and remissions. Clinical manifestations were confined to the skeleton or haemopoietic systems in some patients, while in others the effects of the disorder were widespread. However, dermal and ophthalmological involvement were not of clinical

significance. It is noteworthy that in some instances bone pains occurred many years before radiological changes became apparent. Conversely, in other individuals bony infiltration was identified radiologically during routine studies in the absence of any bone symptoms.

All the affected individuals mentioned in this report had a definite diagnosis of chronic Gaucher's disease. None of their affected siblings were examined, but in most instances documentary evidence permitted substantiation of the diagnosis. The affected 4-year-old girl is of particular interest, since presentation of the chronic form of the condition at such an early age is unusual, but it is likely that she will remain asymptomatic for many years.

The management of Gaucher's disease is not an easy matter, but modern orthopaedic techniques, such as prosthetic replacement of the hip, have been of considerable value in our patients. Similarly, splenectomy has usually relieved abdominal discomfort and improved the haematological status, if undertaken at the appropriate stage in the illness.

Splenomegaly, often detected at routine examination, was the commonest presenting feature. The time lapse between initial presentation and firm diagnosis was in accordance with the experience of other investigators. However, with increasing awareness of the familial nature and clinical manifestations of Gaucher's disease, diagnosis at an earlier age is to be expected.

Although Gaucher's disease may cause considerable morbidity, the occupational achievements of our patients indicate that their life-styles have not been unduly influenced by the condition. In the same way, the majority have successfully married and raised families. As would be expected in an autosomal recessive disorder, some individuals had affected siblings, but none had affected parents or offspring. In the past, there have been some reports of parent-to-child transmission of Gaucher's disease.[18] However, this apparent autosomal dominant inheritance has probably been the result of marriage between an affected patient and a heterozygous carrier of the gene.

Most of our patients were of Ashkenazi Jewish stock, as has been the case in other series in Israel and the USA.[2,19,20] A considerable proportion of the progenitors of the local Jewish community emigrated to Southern Africa from a relatively circumscribed region in Eastern Europe. It is likely that the abnormal gene was present among these individuals, and it is reasonable to assume that the gene frequency in South Africa is at least as high as that in Israel. There are approximately 120 000 Ashkenazim in South Africa, and if the Israeli figures are applicable to this country, there could be as many as 50 affected individuals in this group. However, some of these homozygotes will still be in the presymptomatic stages of the disorder and may, as yet, be undiagnosed.

Gaucher's disease can be detected prenatally by the examination of cultured amniotic fluid cells.[11] The application of this procedure to all at-risk pregnancies would constitute a valuable measure in the prevention of the condition. Biochemical examination of the relatives of affected individuals also represents a logical step in prevention, and population screening may eventually be feasible.

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REFERENCES

1. Brady, R. O., Kanfer, J. N. and Shapiro, D. (1965): Biochem. Biophys. Res. Commun., **18**, 221.
2. Fried, K. (1958): Bull. Res. Coun. Israel E, **7B**, No 3-4.
3. Groen, J. J. (1964): Arch. Intern. Med., **113**, 543.
4. Knudson, A. D. and Kaplan, W. D. *in* Aaronson, S. M. and Volk, B.W. eds (1962): *Cerebral Sphingolipidoses. A Symposium on Tay-Sachs Disease*. New York: Academic Press.
5. Philippart, M. *in* Bergsman, D. ed. (1973): *Birth Defects—Atlas and Compendium*. Baltimore: Williams & Wilkins.
6. Reich, C., Seife, M. and Kessler, B. J. (1951): Medicine (Baltimore), **30**, 1.
7. Greenfield, G. B. (1970): Amer. J. Roentgenol., **110**, 800.
8. Strickland, B. (1958): Brit. J. Radiol., **31**, 246.
9. Tennent, W. (1945): *Ibid.*, **18**, 356.
10. Crocker, A. C. and Landing, B. H. (1960): Metabolism, **9**, 341.
11. Ho, M. W., Seck, J., Schmidt, D., Veath, M. L., Johnson, W., Brady, R. O. and O'Brien, J. S. (1972): Amer. J. Hum. Genet., **24**, 37.
12. Beutler, E. and Kuhl, W. (1970): J. Lab. Clin. Med., **76**, 747.
13. Beutler, E., Kuhl, W., Trinidad, F., Teplitz, R. and Nadler, H. (1971): Amer. J. Human Genet., **23**, 62.
14. Sacks, S. (1973): J. Int. League against Rheumatism, **3**, 2.
15. Amstutz, H. C. and Carey, E. J. (1966): J. Bone Jt Surg., **48**, 670.
16. Groth, C. G., Dreborg, S., Ockerman, P. A., Svennerholm, L., Hagenfeldt, L., Lofstrom, B., Samuelson, K., Werner, B. and Westberg, G. (1971): Lancet, **1**, 1260.
17. McKusick, V. A. (1971): *Mendelian Inheritance in Man*, 3rd ed. Baltimore: Johns Hopkins Press.
18. Hsia, D. Y-Y., Naylor, J. and Bigler, J. A. (1959): New Engl. J. Med., **261**, 164.
19. Fried, K., Matoth, Y. and Goldschmidt, E. *in* Goldschmidt, E. ed. (1963): *The Genetics of Migrant and Isolate Populations*. Baltimore: Williams & Wilkins.
20. Matoth, Y. and Fried, K. (1965): Israel J. Med. Sci., **1**, 521.