Gaucher's disease in South Africa

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SUMMARY The adult non-neuropathic form of Gaucher's disease has been identified in 32 patients in 25 Ashkenazi Jewish kindreds in South Africa. The minimum prevalence in this population is 1 in 5000, with a gene frequency of 0.014 and a carrier rate of 1 in 36. On correction for bias resulting from possible under-ascertainment, these minimum figures become 1 in 4000, 0.0166, and 1 in 36, respectively.

Confirmation of autosomal recessive inheritance was obtained by segregation analysis by the 'a priori' and 'simple sib' methods.

The Ashkenazim of South Africa have their origins in Lithuania and it is evident that the high gene frequency in South Africa is a reflection of the genetic constitution of the immigrant population. The localisation of the Gaucher gene to Lithuania represents a further step in the determination of the early geographic distribution of the genetic disorders of the Jewish race.

The adult chronic or non-neuropathic form of Gaucher's disease is an autosomal recessive disorder in which activity of the enzyme β -glucosidase is defective. The condition runs a fluctuant but progressive course and the main clinical problems are splenomegaly, dyshaemopoiesis, osteitis, and collapse of weight-bearing joints (Matoth and Fried, 1965).

This type of Gaucher's disease is relatively common in the Ashkenazi Jewish population of South Africa (Beighton and Sacks, 1974). During the course of a nationwide survey we have attempted to ascertain and investigate every affected person, and in a 5-year period we have studied 32 patients in 25 Jewish kindreds. Our findings concerning the prevalence of the condition, the frequency of the abnormal gene, and the historical and geographic origins of the disorder are presented and discussed in this paper.

Classification

Gaucher's disease is conventionally classified into infantile, juvenile, and adult forms, which have also been given numerical designations. These conditions differ in the chronology of their clinical presentation and in their manifestations, course, and prognosis.

In the infantile form, death usually occurs in early childhood after infiltration of the central nervous

system, spleen, and bone marrow with cerebroside. Affected subjects have been encountered in many different ethnic groups.

The juvenile form is characterised by progressive dementia, cerebellar ataxia, and extrapyramidal dysfunction. The majority of patients have been reported from Sweden.

The adult chronic or non-neuropathic type, which forms the subject of this paper, usually presents in early adulthood. Lack of involvement of the central nervous system and a predominance in people of Ashkenazi Jewish stock are the main distinguishing features (Fried *et al.*, 1963). The fact that this type of Gaucher's disease is sometimes diagnosed in childhood has been the source of considerable semantic and nosological confusion. However, the situation may be clarified by the use of the term 'non-neuropathic' and the avoidance of the designation 'adult'.

The Jewish population of South Africa

The immigration patterns of South Africa's Jewish community fall into a number of distinct periods. Before 1800 a few Jewish settlers, who were rapidly assimilated into the Christian community, came with the ships of the Dutch East India company. Between 1800 and 1880 several thousand Jews arrived from Germany, Holland, and England. They were more communally orientated than the original settlers and organised religious congregations. However, they also were assimilated into the Christian majority.

that few, if any, practising Jewish descendants of these families remain today.

The Jewish community of South Africa was largely fashioned by the mass immigration of Eastern European Jews between 1881 and 1910, who left their countries of origin, especially Lithuania, because of pogroms and persecution. Whole communities came in this way, bringing their distinctive traditions and culture.

In the 1930s, further immigration of Jews from Germany and other Nazi occupied countries took place, but the arrival of individual Jews since this period has been a very insignificant factor in population growth of the Jewish community. It has been estimated that between 1880 and 1940 about 40 000 Ashkenazi Jews entered this country from Eastern Europe. This movement ceased in 1937 after the passing of the Aliens Act.

The present day South African Jewish community of approximately 120 000 is largely derived from Eastern European ancestors. In a survey of Johannesburg Jews (50% of South Africa's Jewish population), it was found that 70% were descendants of parents or grandparents born in Eastern Europe, or were themselves born there.

Methodology

A circular letter requesting patient referrals was sent to every medical colleague in South Africa who was likely to care for patients with Gaucher's disease. These included orthopaedic surgeons, physicians, and general practitioners who served the Jewish community. The investigation was publicised in a national medical newsletter, in an article in the South African Medical Journal, and at national congresses. The Jewish community have an active interest in genetic problems and the condition was discussed at meetings of various cultural groups, in lay magazines, and in radio broadcasts. Hospital records and pathology and radiology museums provided further information.

The authors travelled throughout South Africa in order to investigate affected subjects, and clinical, radiographic, and laboratory studies were undertaken in most instances. A detailed family history was obtained, with particular reference to the geographic origin and ethnic background of the patient's progenitors.

Fresh samples of venous blood were obtained and transported by air, if necessary, to the genetic biochemical laboratory of the Medical School, Cape Town. β -glucosidase activity was determined in the white cells of the respondents and their sibs by the method of Beutler and Kuhl (1970). Before these special studies, the diagnosis had already been

confirmed in the majority of patients by demonstration of the typical foamy Gaucher cells in bone marrow biopsy specimens.

Results

Thirty-two Ashkenazi Jewish patients in 25 kindreds were ascertained. Of these, 24 in 21 families were examined and investigated, while firm medical evidence permitted a positive diagnosis in 4 sibs of these subjects who were abroad or deceased. Medical data were also available concerning 4 other affected Jews in South Africa, who were not available for examination in the survey.

PREVALENCE

On a basis of the 24 living patients with Gaucher's disease in a total Jewish population of 120 000, the minimum prevalence of the disorder in this group is about 1:5000. This figure rises to approximately 1:4000 if the 4 patients who were not examined are included in the calculation.

GENE FREQUENCY

Taking the figures of 24 homozygotes in a population of 120 000, with a prevalence of 1:5000, the gene frequency (q) is 0.014. Therefore, the frequency of heterozygotes ($2pq$) is 0.028 (1/36) and the number of heterozygotes in the population of 120 000 is 3346.

If these figures are recalculated with the inclusion of the 4 patients who were not examined, together with an estimate of existing undiagnosed cases, based upon average age of presentation, birth rate, and population size, the minimum prevalence becomes 1:4000, with a gene frequency of 0.0166, and a carrier rate of 1 in 30 or 0.332.

GEOGRAPHIC ORIGINS

Information concerning the geographic origins of immigrant progenitors was available from 20 kindreds. In 13, both paternal and maternal families had lived in Greater Lithuania during the 19th century. In 6, only one side of the kindred came from this area, the others originating in Russia (4), Holland (1), and Czechoslovakia (1). In one family, both parents had emigrated to South Africa from Germany and had no known ancestral connections with Lithuania. The area of origin of the Gaucher's disease gene in Europe is shown in Fig. 1, in relationship to the distribution of other genetic disorders which reach their highest prevalence in the Ashkenazim, as determined by Meals (1970).

PEDIGREE DATA

Abbreviated pedigree data concerning the 21

kindreds are shown in Fig. 2. There were 15 male and 13 female patients.

There was no generation to generation transmission. Known consanguinity was present in one kindred.

The results of segregation analysis on 21 informative kindreds by the 'a priori' or Apert method were in accordance with autosomal recessive inheritance (21 sibships, 71 sibs, 28 affected, 28.98 expected, SE 2.69). Analysis by the simple sib method, after deletion of the proband, gave 7 observed, 12.5 expected, with a variance of 6 (limits 6.5 to 18.5), thus confirming the autosomal recessive mode of inheritance.

Fig. 1 Initial European localisation of Gaucher's disease and other autosomal recessive disorders of the Ashkenazi Jews (Meals, 1970).

Fig. 2 Abbreviated pedigree data from 21 kindreds with Gaucher's disease.

GAUCHER'S DISEASE IN OTHER POPULATIONS IN SOUTH AFRICA

Information was available on a few subjects of non-Jewish stock, all with the non-neuropathic form of Gaucher's disease: 11 Afrikaners, 2 African Negroes, 2 British, and 2 sibs of mixed ancestry. Though no attempt was made at complete ascertainment in these populations, it is probable that a significant proportion of diagnosed cases would have come to our notice. The prevalence of the disorder in the British community (2 in 1.5 million) and the African Negro group (2 in 16 million) was very low. In the Afrikaners, the minimum prevalence was 1 in 200 000, with a gene frequency of 0.0022 and a carrier rate of 1 in 220. Approximately 9000 heterozygotes are present in this community (Goldblatt and Beighton, 1979).

Discussion

The progenitors of the Jewish population of South Africa had their origins in Lithuania and the prevalence of Gaucher's disease in this group reflects the genetic status of the early immigrants. The reason for the high frequency of the Gaucher gene in Lithuania is unknown and, superficially at least, heterozygotes do not seem to possess any biological advantage.

The recognition of Gaucher's disease in the Negro and British population of South Africa is not unexpected, as the condition occurs with low frequency in many non-Jewish groups. The comparatively high prevalence in the Afrikaner population is probably explicable on the basis of the founder effect, as this community is descended from a relatively small number of immigrants of Dutch stock.

Though activity of the enzyme β -glucosidase is defective in affected subjects in all populations the manifestations of the disease develop earlier and are more severe in the Afrikaners. At a fundamental level, it is not known whether the abnormal genes in the different communities are identical, allelic, or situated at different loci.

The high frequency of the Gaucher disease gene in the Jewish population of South Africa is of potential importance from the point of view of screening and prevention. However, laboratory procedures for detection of heterozygotes are complex, and present population screening is not feasible.

From the clinical point of view, the high prevalence of Gaucher's disease in this community is important in terms of differential diagnosis. Indeed, unexplained splenomegaly or orthopaedic problems in a young adult of South African Jewish stock immediately raise the possibility of Gaucher's disease (Goldblatt et al., 1979).

There have been numerous reports concerning the geographic origins of autosomal recessive disorders of the Ashkenazi Jews (Bearn, 1960; Barker *et al.*, 1964; Myrianthopoulos and Aronson, 1967; Meals, 1970). The localisation of Gaucher's disease to Lithuania represents a further step in the elucidation of this complex pattern.

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