Inherited disorders in the black population of southern Africa

Part I. Historical and demographic background; genetic haematological conditions

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Summary

Genetic, geographic and socio-economic diversity has resulted in disparity in the relative prevalence of many inherited disorders and congenital conditions in the populations of southern Africa.

In the first section of a 3-part article an account is given of the historical and demographic background in relation to factors which influence the presence and frequency of faulty genes in the black community. In addition, inherited haematological conditions — in particular haemoglobinopathies, red-cell enzyme and membrane defects — are discussed in terms of their clinical, genetic and anthropological significance. The conditions transmitted by simple genetic mechanisms are documented in Part II, with discussion of those notable for their unusually high or low prevalence. In the final section multifactorial, chromosomal and non-genetic congenital disorders are reviewed and a number of unusual conditions of obscure aetiology are mentioned. In this 3-part overview an attempt has been made to document present knowledge and to provide a bibliography for inherited and congenital disorders in the black population.

In every well-defined population certain inherited disorders occur with unusually high or low frequency. For this reason documentation of the prevalence of genetic conditions in any specific community is essential as a basis for the planning and development of medical services. The ethnic distribution and prevalence of inherited conditions in South Africa were reviewed a decade ago. Further information has now accumulated and a series of articles devoted to the genetic situation in each population group is being prepared. The first of these, on the Afrikaner population, was published in 1983.2,3

The genetic conditions of special importance in the black population of southern Africa have now been analysed. In Part I of this report the anthropological, historical and demographic background is briefly reviewed and, because of their importance in population genetics, an account is given of inherited haematological disorders. Other conditions transmitted by simple genetic mechanisms are presented and discussed in Part II, and multifactorial, cytogenetic and congenital disorders will be presented in Part III of this article.

The black population

Terminology

At a symposium on the people of southern Africa held in 19774 it was decided that the term 'South African Negro' was appropriate for the Bantu-speaking population of this geographical region. However, the alternative term 'black' for Negro has since become acceptable and is currently in vogue. In this review this descriptive designation is thus applied to nearly 17 million Negroes (according to the 1980 census) in the area south of the Orange and Limpopo Rivers. Similarly, the anthropologically acceptable term 'San' has been used for the Bushman group, while 'Khoikhoi' denotes the Hottentot population. The black inhabitants of South West Africa/Namibia, Botswana, Swaziland, Lesotho and Mozambique are excluded for the purposes of this report, not because of a lack of genetic and socio-anthropological affinity, but simply because relevant clinical information is not available.

Demography

The black population consists of tribal groups which differ linguistically and to some extent culturally. The Nguni-speaking group comprises the Zulu, Xhosa and Swazi peoples and constitutes more than half (9.5 million) of the total black population (Zulu over 5.5 million, Xhosa nearly 3 million and Swazi over 850,000). The Northern and Southern Sothos number over 4 million and there are about 1.4 million Tswana. Other tribes individually total less than a million people (Shangaan-Tsonga, Ndebele, Venda, etc.).

Despite their distinctive languages, these black tribes are genetically very similar. Calculations of genetic distance based on red cell and serum protein polymorphisms demonstrate a close biological relationship between South African black peoples. Personal experience with the very discriminating HLA system is in accordance with this concept. Minor differences do occur; for example, there is a higher frequency of certain genetic markers in the Xhosa and contiguous Nguni tribes, which probably indicates a greater percentage of San admixture.5 Similarly, there is a low but detectable prevalence of haemoglobin S among the Venda6 and Shangaan.7 Nevertheless, for the purpose of a general review of inherited diseases and their clinical implications, the South African blacks may be regarded as having considerable genetic homogeneity. This is not so in socio-anthropological terms. For example, consanguinity is very relevant to the frequency of genetically determined autosomal recessive conditions and in this regard there are significant differences between black tribal groups. There is a high percentage of consanguineous matings within the Southern Sotho and the Tswana peoples, in contrast with the
Nguni-speaking groups among whom sexual relations between relatives are not acceptable. This situation may well be responsible for disparities in the relative prevalences of recessive genetic disorders in these groups.8

Historical background

The earliest history of the blacks south of the Limpopo River is obscure and the subject of some controversy. It is of scientific relevance, however, that certain genetically determined haemoglobin disorders, which are protective against malaria and therefore common among blacks inhabiting the malarial belt of subtropical Africa north of the Limpopo, are uncommon or absent in the south. It is thought that the ancestors of South African blacks may have migrated eastwards from the Equatorial forests of the Congo basin and then southwards into southern Africa before the variant haemoglobin genes became established at polymorphic levels in Central Africa. The main arrival at the Limpopo River, which is the northern border of present-day South Africa, probably took place approximately a thousand years ago.9 Early historical records indicate that in 1498 there was a dense population of blacks at a river identified as the Limpopo and that by 1552 blacks had apparently established communities along the eastern Cape coast.10 In 1752 black populations were observed to have settled widely but sparsely as pastoralists in Natal, the Transvaal and along the eastern Cape seaboard as far as the Keiskama River, displacing and partially absorbing the pre-existing San clans along their route. At this time they had already made contact with the Khoikhoi on the east coast and a degree of hybridization had occurred.11 Meetings with parties of white explorers and settlers along the southern and eastern seaboard, were followed by sporadic confrontations which culminated in a series of border wars in the eastern Cape during the 19th century. The rapid extension in South Africa of European modes of agricultural practice in the latter half of the 19th century, followed by the establishment of mines, industries and transport systems, led to detribalization of a large section of the black population and their distribution throughout the country. In recent generations many South African blacks have adopted a westernized lifestyle. Based on census figures, it has been estimated that in 1980 approximately 6,5 million blacks were urbanized and 10,5 million non-urbanized. Those under the age of 20 years numbered over 8,5 million and those over 65 years more than half a million. Of 5,5 million economically active individuals, 4,5 million were labourers, service workers or engaged in farming, forestry, fishing and the like; roughly 175,000 were in professional, technical or related occupations and 370,000 were employed in administrative, clerical or sales work.

Inherited haematological disorders

Many concepts which are central to population genetics are based on investigations of genetically determined normal and abnormal factors in the blood. The main reason for this is that blood is an accessible tissue and that large numbers of specimens can be obtained and studied with comparative ease. In view of their special place in population genetics, haematological conditions are reviewed here.

Coagulation defects

Haemophilia A

The abnormally functioning antihemophilic globulin factor VIII is inherited as an X-linked recessive trait and results in a bleeding disorder of varying severity among males. The condition is not uncommon, and on average about 4 new cases a year are reported to the Medical University of Southern Africa, Pretoria, while about 300 living black haemophiliacs are registered with the South African Haemophilic Society. This obviously is not the total in the country (C. Karabus — personal communication) and because of their demographic and socio-economic situation, it is probable that there are very severe and very mild cases at the ends of the clinical spectrum may be missed. The clinical manifestations of post-traumatic or spontaneous bleeding are generally similar to those in other population groups but black children often present at a late stage when haemorrhage into the joints poses a threat of permanent damage.

Haemophilia B (Christmas disease)

This condition is due to a defect in factor IX. It resembles haemophilia in its mode of inheritance and clinical presentation but it is generally a milder disorder. It is less common than classic haemophilia among all populations and it is distinctly so among South African black patients.

Von Willebrand’s disease

Von Willebrand’s disease is rare among southern African blacks but the occasional case has been encountered. Prevalence figures are not available but, as with other bleeding disorders, it may be underdiagnosed among infants and children in remote rural areas. It is inherited as an autosomal dominant trait of varying expressivity and both sexes may be affected. In this context the only affected person known to us is female.

Haemoglobinopathies

Sickle-cell anaemia

A variety of heritable defective haemoglobins are found unevenly distributed in Central and Northern African populations and several forms are associated with severe disease. Among South African blacks, however, the variant genes responsible for these conditions are far less common. Of the numerous structurally abnormal haemoglobins which result from synthesis of defective globin chains, Hb S (sickle haemoglobin) is of considerable clinical significance in Africa and elsewhere. In South Africa the comparatively harmless heterozygous trait is found mainly among the Venda12 and Shangaan13, two of the less numerous ethnic groups, at the low frequency of 0,2%. Therefore, the occurrence of homozygously determined severe sickle-cell anaemia cannot be a common event among South African blacks and, indeed, seems to be unrecorded in the literature. However, 6 unrelated black people who are homozygous and have sickle-cell anaemia are known to us. In each instance a parent or grandparent originated beyond the northern borders of South Africa.

Thalassaemia

Defective production rates of structurally normal globin α and/or β chains cause the thalassaemia syndromes, characterized by chronic haemolytic anaemia. There is considerable genetic and clinical heterogeneity and several forms occur with varying prevalence among blacks north of the Limpopo. Complete or clinically significant partial failure to produce β chains hardly ever occurs among African populations south of the Limpopo and thus severe homozygous β-thalassaemia is virtually unknown among blacks in South Africa. Only the mildest of the α-thalassaemia syndromes occur among African blacks anywhere on the continent and these disorders are hardly of clinical importance. However, the presence of even the clinically innocuous derangement of α-globin genes is an example of a possible protective factor in hyper-endemic malarial regions and therefore of anthropological interest in the study of African peoples. Normal production of α-globin chains is controlled by 4 α genes. Dysfunction of 1 gene is not associated with haematological abnormality; 2 variant genes produce the harmless α-thalassaemia which may be associated with minor haematological changes without anaemia. This disorder is detectable in the blood of newborn infants by the presence of haemoglobin Bart’s, which results from excess γ chains. In this situation infants may have temporary mild microcytic anaemia. A frequency of 1,6% Hb Bart’s among black infants in the Transvaal has been reported.14 Single α-gene defects can be recognized by modern methods. By means of this technology a frequency of 0,21 of chromosomes with one of the pair of α genes dysfunctioning has been determined in the Venda population.15 These prevalence rates are low compared with those of more northern blacks. Individuals with 3 or all 4 α genes affected have significant or severe anaemia (Hb H disease) or lethal disorders. This genetic situation can only arise when 1 chromosome has abnormalities at both α-gene loci. Since such a chromosome does not seem to be present in any African black populations, including those of South Africa, the severe α-thalassaemia syndromes are not encountered in this region.
Red cell enzyme defects

Several of the enzymes required in the metabolic pathways and physiological functioning of the erythrocyte are liable to heritable defects. These intracorporeal abnormalities are often associated with shortened red cell lifespan and clinically their effects may range from mild haemolytic anaemia to acute, life-threatening haemolysis. Among South African blacks only one such disorder, glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, is prevalent and of clinical importance.

G-6-PD deficiency

There are two types of normally functioning G-6-PD. The B form occurs in all races while the A form occurs in about 20% of all African blacks and their descendants elsewhere. Many abnormal variants are known but the majority of these are rare. These occasional variants may cause chronic haemolytic anaemia sporadically in individuals or single families.

Since G-6-PD deficiency is inherited as a sex-linked trait, the enzyme dysfunction is clearly expressed in males and homozygous females, with very variable clinical expression in heterozygous females. Type B deficiency, which is prevalent in Mediterranean whites, Asians and Jews, is the more severe, with little enzymatic function. The type A deficiency which occurs among African blacks is clinically and biochemically less severe, with 5 - 15% of normal metabolic activity retained in affected individuals.

Type A G-6-PD deficiency occurs in 2 - 9% of South African blacks. Individuals with the deficiency are ordinarily asymptomatic but males, homozygous females and a proportion of heterozygous females are at risk of haemolysis when receiving certain drugs which stress the G-6-PD metabolic pathway. The antimalarial drug primaquine and drugs of the sulphonamide group are particularly dangerous, but many others are capable of producing haemolysis when accompanied by predisposing factors such as infection. Bacterial and viral infections may also cause severe jaundice in G-6-PD-deficient males. This situation is the likely explanation for an unreported episode (M. C. Botha and R. Friedlander — unpublished data, 1966) in which 5 boys (4 black, 1 mixed ancestry) aged 9 - 15 years from three different townships in the Cape Peninsula, in the space of 1 week, required urgent blood transfusion for very severe haemolysis of acute onset. Following transfusion, early presumptive diagnosis of G-6-PD deficiency relied on family studies, especially the mothers who were necessarily deficient because of X-linked transmission. The diagnoses were confirmed 2 - 3 months after recovery when the patients had reconstituted their own blood cells.

Newborn infants with the Asiatic and Mediterranean forms of G-6-PD deficiency are prone to neonatal jaundice. By contrast, black infants with G-6-PD deficiency are thought to have little or no increased frequency of this complication. Nevertheless, in our experience, G-6-PD deficiency is found more often among jaundiced black than in unjaundiced black babies. It is likely that enzyme deficiency predisposes to haemolysis in infants with liver immaturity, infections (especially congenital syphilis), hypoxia or acidosis from whatever cause.

Other red cell enzyme deficiencies

These are much less common in all races and populations everywhere and are virtually absent in South African blacks. In this context, there is a single report of haemolytic anaemia associated with glucose phosphate isomerase deficiency in a black South African child.

Red cell membrane defects

Hereditary spherocytosis

Hereditary spherocytosis (HS) is not rare among the black population of the western Cape and the clinical presentation of haemolytic anaemia in childhood or adolescence and the haematological findings are similar to those of HS in other ethnic groups. Over a 15-year period of investigating all patients with haemolytic anaemia in the Cape Town geographical area, 400 patients were found to have HS. Enquiries at major hospitals in the eastern Cape revealed 4 more affected families. The condition has also been encountered in blacks in the northern Transvaal. Family studies indicate that the condition is inherited in the conventional manner, i.e. autosomal dominant with variable expression.

Hereditary elliptocytosis

An occasional example of hereditary elliptocytosis has been encountered in the black population. This innocent condition does not appear to differ genetically or clinically from the form encountered in other populations.

Discussion

From the foregoing it is evident that several African Negro genes which are capable of producing blood disorders are uncommon in South Africa and increase progressively in prevalence towards Equatorial Africa. These genes are susceptible to the operation of environmental pressures, such as malaria. In this way the ethnic affinities are merely regional reflections of duration and intensity of exposure to exogenous influences. This concept also applies to blacks within South Africa. For example, the marginal genetic differences between the Venda and most other South African black groups reside in the presence of sickle haemoglobin and higher frequencies of G-6-PD deficiency and that grade of α-thalassaemia which presents with minimal haematological characteristics. This situation probably correlates with the subtropical northernmost habitat which links these people more closely in time and space to the West African forest environment. Furthermore, opportunity for hybridization with indigenous Khoisan peoples was restricted at the tail-end of the southwards migration. Thus, the South African blacks who originated from Central African nigroid stock remain, despite minor genetic variation caused by difference in environment or by degrees of hybridization with the Khoisan, part of the sub-Saharan biological population.

We wish to thank Gillian Shapley for typing the manuscript. The research was supported by the South African Medical Research Council, the University of Cape Town Staff Research Fund, the Harry Crossley Foundation and the Mauerberger Foundation.

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