PAPERS AND ORIGINALS

A host of hypercholesterolaemic homozygotes in South Africa

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Summary and conclusions

From 1972 to 1979 34 patients with homozygous familial hypercholesterolaemia were seen in one clinic in Johannesburg. All were Afrikaners and most lived in Transvaal Province. Their epidemiological, genetic, clinical, and biochemical characteristics were studied. The course of the disease varied considerably among the 34 patients, with no fewer than six surviving into their fourth or fifth decades. In some patients arterial atheroma was severe while cutaneotendinous xanthomas were slight and vice versa.

Coronary heart disease was common but peripheral and cerebral arterial disease was rare. Another prominent finding was high concentrations of low-density lipoprotein cholesterol coupled with low high-density lipoprotein cholesterol values. The prevalences of homozygotes and heterozygotes with familial hypercholesterolaemia in Transvaal Afrikaners, calculated from this group of patients, were 1 in 30 000 and 1 in 100 respectively.

These figures are the highest ever reported and may help to explain why South African whites have the highest death rate from coronary heart disease in the Western world.

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Introduction

South African whites have the highest death rate from coronary heart disease in the Western world.[1] The reasons for this are not clear but one factor may be their high prevalence of familial hypercholesterolaemia (or type II hyperlipoproteinaemia of Fredrickson). This is perhaps most strikingly illustrated by the fact that in a short time in a single clinic we have seen 34 patients with the homozygous form of familial hypercholesterolaemia. We describe here the epidemiological, genetic, clinical, and biochemical features of these patients and discuss the reasons for, and some implications of, the remarkable frequency of familial hypercholesterolaemia in South Africa.

Patients and methods

Thirty-four patients with homozygous familial hypercholesterolaemia from 27 families were seen at the lipid disorders clinic of the Johannesburg Hospital from 1972 to 1979. Twenty families produced one homozygote each and in each of the remaining seven families there were two homozygous siblings. Pedigrees and national origins were studied both in the clinic and by home visits by a trained genetics field worker. During the same period the clinic also registered 351 heterozygotes with familial hypercholesterolaemia belonging to 154 families.

The prevalence of homozygous familial hypercholesterolaemia was estimated in the population at risk and used in the Hardy-Weinberg equation to estimate the prevalence of heterozygous familial hypercholesterolaemia.[2]

Serum lipids measured were fasting total cholesterol and triglyceride, low-density lipoprotein (LDL) cholesterol,[3] and high-density lipoprotein (HDL) cholesterol.[4] Serum HDL cholesterol concentrations are commonly measured by a precipitation method—that is, LDL and very low density lipoprotein (VLDL) are removed from the serum by polyanion precipitation and centrifugation and HDL cholesterol is measured in the supernate. Early on we found that the standard precipitation technique using manganese chloride and heparin sometimes failed to precipitate completely the very large amounts of LDL

found in homozygotes. This resulted in falsely raised values for HDL cholesterol. Using a mixture of sodium phosphotungstate and magnesium chloride[4] we consistently achieved complete precipitation.

Results

GENETIC FEATURES AND DIAGNOSIS OF THE HOMOZYGOUS STATE

Family studies invariably showed an autosomal monogenic dominant pattern of inheritance. Figure 1 shows the pedigree of one of our patients, showing the characteristic vertical transmission of the gene through several generations.

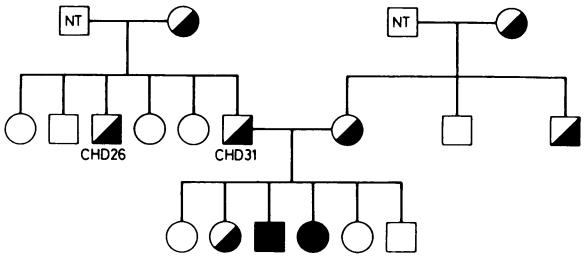

FIG 1—Pedigree of family with two homozygous siblings with familial hypercholesterolaemia (cases 9 and 10). Squares = males; circles = females. White = normal; half-black = heterozygote; black = homozygote. CHD 26 and CHD 31 = death from coronary heart disease at ages 26 and 31 respectively. NT = not tested.

Diagnosis of the homozygous state was based on: (*a*) the presence of serum cholesterol concentrations greater than 14·3 mmol/l (550 mg/100 ml); (*b*) the appearance of xanthomas in the first decade of life; and (*c*) the presence in both parents of hypercholesterolaemia or clinical signs indicative of the heterozygous state (see table). All 34 patients met the first two criteria. In 26 cases both parents were shown to have the required degree of hypercholesterolaemia. In another six the father had died young of coronary heart disease and had had a history of a raised serum cholesterol concentration, and in one of these the mother was known to have had hypercholesterolaemia. The remaining two patients were adopted children. None of the unions of the natural parents were consanguineous.

PREVALENCE OF HOMOZYGOUS AND HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLAEMIA

Of South Africa's 4·5 million whites about 58% are Afrikaans-speaking descendants of immigrants from Holland, France, and Germany; 38% are people of British descent; and the remaining 4% consist of a variety of peoples such as Portuguese, Italians, Greeks, and Jews. A striking feature of our homozygous patients was that all appeared to be of Afrikaner origin. In 32 cases both natural parents were Afrikaners while the two adopted patients were Afrikaans-speaking, having grown up in the homes of Afrikaners in areas populated mainly by Afrikaners. The law governing adoption in South Africa decrees that children are placed in families speaking the same language as that of the natural parents. Of all 181 families affected by familial hypercholesterolaemia in our clinic, about 80% were Afrikaans, 10% British, and 10% diverse but mainly Ashkenazi Jews.

All the patients lived within about 150 km of Johannesburg, most of them in the southern half of Transvaal Province (fig 2). The total white population of this area in 1979 was 1 942 000, of whom 1 146 000 were Afrikaners. Of the Afrikaners 951 000 were under the age of 50 years; and in 1979 28 homozygotes aged 3 to 46 years were alive. The prevalence of homozygotes in this Afrikaner population at risk was therefore 0·00003 or about 1 in 30 000. This figure is conservative since we did not systematically ascertain all the living homozygotes in this Afrikaner population, and we are aware of several other patients diagnosed elsewhere in the area.

Knowing the approximate prevalence of homozygotes in the Afrikaner population at risk, we estimated the prevalence of heterozygotes from the Hardy-Weinberg equation.[2] If the frequency of the allele for familial hypercholesterolaemia is q, its frequency is given as the square root of the frequency of the homozygotes—that is, $\sqrt{0{\cdot}00003} = 0{\cdot}0055$. The frequency of the normal allele, p, is $1-q = 0{\cdot}9945$. The heterozygote or carrier frequency is given by $2pq$, which is about 1 in 100.

CLINICAL CHARACTERISTICS OF THE HOMOZYGOTES

The number of males and females was the same. Their ages in 1979 or at death ranged from 3 to 46 years (see table). Six patients had survived for 30 years or more. Body weights were mostly normal.

Every patient had planar or tendon xanthomas, which had appeared during the first decade of life in all cases. All but the youngest patient had orange or yellow planar xanthomas in the skin over the limbs or buttocks, which, according to Fredrickson,[5] are specific for homozygotes and do not occur in heterozygotes. Nevertheless, the xanthomas varied considerably in extent and distribution, even between affected siblings at comparable ages. Corneal arcus was seen in about a third of patients, mostly those aged over 10 years, while only one patient had xanthelasma.

Coronary heart disease, as evidenced by angina pectoris, myocardial infarction, electrocardiographic changes, or necropsy findings, was noted in 21 cases. The incidences of coronary heart disease in those aged under 9 years, 10-19 years, and 20 years or more were 50%, 53%, and 89% respectively. These must be regarded as minimal figures since we did not do advanced tests of ventricular function or structure. Six patients died from coronary heart disease at the ages of 6, 6, 13, 14, 37, and 40 years. In one boy (case 22) severe aortic stenosis was diagnosed at the age of 9 years and at operation a combination of congenital valvar and atheromatous supravalvar obstruction was found; both lesions were satisfactorily corrected. Arterial bruits were audible in most patients. Functionally significant peripheral vascular disease, however, occurred in only one patient, who suffered from intermittent claudication, while no patient had a major or a minor stroke.

In some patients the degree of xanthomatosis differed strikingly from that of the cardiovascular changes. For example one patient (case 16) had only one planar xanthoma on the knee when she developed angina at the age of 5 years. A few months later she died suddenly. At necropsy there was generalised atheroma with severe disease of the coronary arteries and mitral valve, and histological examination showed extensive subendocardial infarction of the left ventricle. In contrast were our two oldest patients (cases 13 and 14), who were sisters. Both had had extensive planar and tendinous xanthomas for most of their lives. Yet clinical evidence of coronary heart disease appeared only at about the age of 40 and this was limited to effort angina and electrocardiographic signs of ischaemia but not of infarction. Further impressive evidence of the mildness of arterial disease in this family was the fact that both heterozygous parents of the sisters were aged 71 years and were asymptomatic.

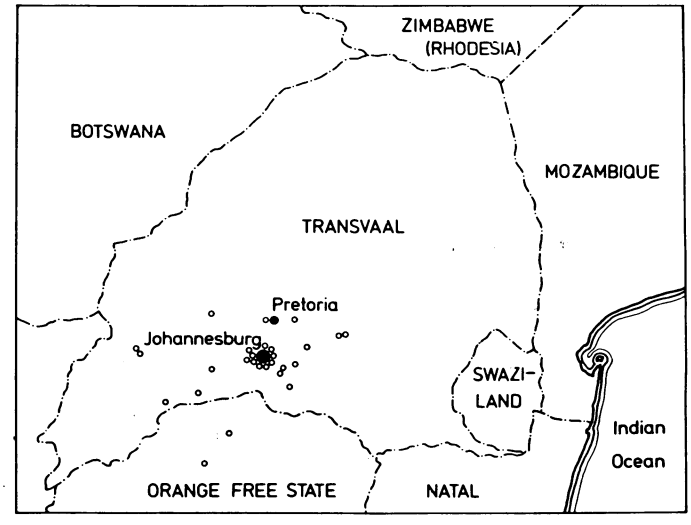

FIG 2—Distribution of 27 FH families with homozygous offspring with familial hypercholesterolaemia in the provinces of Transvaal and Orange Free State of South Africa.

BIOCHEMICAL FEATURES OF THE HOMOZYGOTES

The blood lipid concentrations for each patient shown in the table were the means of at least three determinations. Serum total cholesterol values varied from 14·7 to 28·0 mmol/l (565 and 1077 mg/100 ml) and were unrelated to age or sex. Most of the cholesterol was carried in the LDL form. By contrast, HDL cholesterol concentrations were distinctly low, being on average about half the values of normal subjects of comparable age.[5] The HDL:LDL cholesterol ratios were therefore very low indeed, ranging from 0·02 to 0·06. The ratios varied little, with 21 of the 34 patients having values of 0·02 or 0·03, and did not correlate with the clinical prevalence of coronary heart disease. Normally the ratio varies from 0·2 to 1·0 or more in the earlier decades of life.

Most patients had normal serum triglyceride concentrations, and none were diabetic or hyperuricaemic.

Clinical and biochemical features of homozygotes with familial hypercholesterolaemia and their parents

Case No	Age and sex	Serum total cholesterol (mmol/l)	Serum LDL cholesterol (mmol/l)	Serum HDL cholesterol (mmol/l)	HDL:LDL ratio	CHD	Serum total cholesterol (mmol/l) or CHD death in:	
							Father*	Mother
1	6 M	18·5	17·74	0·52	0·03	Died	12·9	12·0
2	11 M	20·8	20·01	0·47	0·02	–	12·9	12·0
3	7 F	25·7	24·70	0·57	0·02	–	11·9	12·9
4	20 F	26·0	25·16	0·55	0·02	+	11·9	12·9
5	8 F	16·9	16·09	0·62	0·04	+	10·9	8·8
6	18 F	14·7	13·91	0·62	0·04	+	10·9	8·8
7	8 M	16·0	14·33	0·86	0·06	–	9·1	8·7
8	11 M	18·2	16·89	0·80	0·05	–	9·1	8·7
9	10 F	22·9	21·91	0·60	0·03	–	10·3	7·7
10	13 M	18·9	18·20	0·57	0·03	–	10·3	7·7
11	11 F	24·6	23·73	0·57	0·02	–	9·0	8·9
12	14 M	22·6	21·70	0·60	0·03	+	9·0	8·9
13	43 F	21·8	21·04	0·52	0·02	+	10·0	9·3
14	46 F	18·9	17·93	0·67	0·04	+	10·0	9·3
15	3 M	24·7	23·58	0·78	0·03	–	9·7	11·2
16	6 F	18·7	18·08	0·44	0·02	Died	12·7	14·8
17	6 M	20·2	19·40	0·62	0·03	–	11·1	9·6
18	9 M	21·3	20·56	0·52	0·03	+	8·8	8·9
19	10 F	21·3	20·24	0·75	0·04	–	8·8	10·4
20	12 M	15·3	14·13	0·70	0·05	+	Unknown	Unknown
21	12 M	26·0	25·17	0·62	0·02	+	11·4	11·8
22	13 M	21·8	21·01	0·62	0·03	+	10·3	9·4
23	13 F	19·0	18·10	0·67	0·04	Died	High/CHD 42	7·8
24	14 F	17·9	16·75	0·89	0·05	Died	8·9	10·8
25	14 F	28·0	27·18	0·50	0·02	–	10·4	12·2
26	15 M	20·8	20·24	0·39	0·02	+	10·8	9·2
27	17 M	22·1	21·28	0·47	0·02	+	Unknown	Unknown
28	18 F	18·8	17·64	0·66	0·04	–	10·8	8·8
29	24 F	19·5	18·76	0·55	0·03	+	High/CHD 37	Unknown
30	28 M	14·7	13·52	0·83	0·06	+	High/CHD 39	Unknown
31	30 F	21·6	20·89	0·42	0·02	–	High/CHD 35	Unknown
32	31 M	15·7	14·38	0·60	0·04	+	13·0	9·1
33	37 F	17·9	16·85	0·68	0·04	Died	High/CHD 45	Unknown
34	40 M	18·5	17·67	0·52	0·03	Died	High/CHD 49	Unknown
Mean ± SD		20·3 ± 3·43	19·38 ± 3·51	0·61 ± 0·12	0·03 ± 0·01			

Cases linked by braces are siblings in one family.
*"High" indicates a history of raised serum cholesterol concentrations; CHD 42 indicates death from coronary heart disease at the age of 42.
Conversion: SI to traditional units—Cholesterol: 1 mmol/l ≈ 38·6 mg/100 ml.

Discussion

Our estimated prevalences of homozygotes and heterozygotes with familial hypercholesterolaemia in this Afrikaner population are much higher than those in whites elsewhere. For example, Motulsky gives figures for heterozygotes which range from 1 in 1000 to 1 in 200 with a reasonable working estimate of 1 in 500.[6] The generally accepted frequency for homozygotes is 1 per million. We are aware of only one other large series of homozygotes in the world. Khachadurian and Uthman saw 52 such patients in Lebanon over 12 years[7]; 58% of them, however, were born of consanguineous parents, in another 22% the parents came from the same village or district, and no information was available on the prevalence of familial hypercholesterolaemia in the population.

Why is the gene for familial hypercholesterolaemia so common in Afrikaners? We believe that it is common for the same reason that a variety of genetic disorders including porphyria variegata,[8] lipoid proteinosis,[9] and sclerosteosis[10] are common in these people—namely, random genetic drift in the form of founder effect. Today's Afrikaners stem from a few Dutch, German, and French founder families who settled in the Cape during the second half of the seventeenth century. In this bountiful land the founders, who were also fertile and healthy, multiplied rapidly. During the eighteenth century, for example, their numbers increased from about 1200 to 15 000.[11] If one or two of these original founders had happened to possess the familial hypercholesterolaemia allele it could explain the present high frequency of the gene. Dean convincingly showed that such a founder effect accounted for the very high prevalence, about 1 in 250, of porphyria variegata among Afrikaners today.[8] Immigration from European countries, mainly Britain, during the nineteenth century would not have significantly reduced the frequency of the gene by a dilution effect. There was minimal integration and the numbers were small. For example, of the 36 000 emigrants who arrived from the UK before 1869 only half remained. During the nineteenth century South Africa attracted only 0·7% of British emigrants while Australia took 14%.[12]

What is the contribution of familial hypercholesterolaemia to the very high incidence of coronary heart disease in South African Whites? It has been estimated that in a country such as the United States only 1 person in 25 with hypercholesterolaemia (defined as a serum cholesterol concentration falling in the upper 5% of the urban population) would have familial hypercholesterolaemia, a figure based on a heterozygote rate of 0·2%.[6] If we assume a heterozygote frequency of 1% among the Afrikaners (and it might be higher) the proportion of hypercholesterolaemic individuals with familial hypercholesterolaemia would be 1 in 5. This is a substantial genetic contribution to a major risk factor for coronary heart disease and might mean that familial hypercholesterolaemia is the most lethal inherited disorder in this population.

The clinical and biochemical features of the homozygotes indicate that much remains to be learnt about the nature of the metabolic disturbances and the development of arterial disease in familial hypercholesterolaemia. Problems requiring answers include the reason for the consistently low HDL cholesterol values and their role in the accelerated atherogenesis of familial

hypercholesterolaemia. Goldstein and Brown's concept of familial hypercholesterolaemia as a group of disorders characterised by deficiencies or abnormalities of LDL receptors does not provide an obvious explanation.[13] Also if the entire arterial tree and all tissues in all the homozygotes are exposed from an early age to the extremely unfavourable combination of very high concentrations of atherogenic LDL and distinctly low concentrations of anti-atherogenic HDL, how do we explain the variable natural history, the dissociation in severity between the arterial and cutaneous lesions, and the striking predominance of coronary artery disease clinically? Possible explanations include genetic heterogeneity, interactions with other risk factors for arterial disease, and, perhaps most important, the reactivity of the tissues.

We wish to thank the South African Medical Research Council and Atomic Energy Board for supporting this work.

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(*Accepted 24 July 1980*)

Vomiting as a diagnostic aid in acute ischaemic cardiac pain

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Summary and conclusions

The incidence of vomiting before the administration of analgesics was studied in 109 patients admitted to hospital as emergencies with prolonged ischaemic cardiac pain. In transmural myocardial infarction (58 patients) the incidence was 43% (anterior infarction 58%, inferior infarction 41%). Of the 23 patients with myocardial necrosis but without transmural infarction (that is, those with diffuse or subendocardial necrosis) and the 28 with coronary insufficiency but no necrosis, only one patient in each group experienced vomiting.

When vomiting occurs early in association with cardiac pain transmural infarction may be expected in 90% of patients.

Introduction

Detailed descriptions of the symptomatology of coronary occlusion were available before 1912, but until then they were classified under angina pectoris.[1] Subsequently, Hatcher and Weiss[2] reported that vomiting often accompanied both coronary occlusion and angina. More recent reports[3-8] would appear to support this observation, but nobody has carried out a prospective detailed examination of vomiting in the various acute ischaemic cardiac syndromes, although some attempt has been made to identify the role of narcotic drugs in this respect. If there were a significant difference in the incidence of vomiting between acute myocardial infarction and other forms of ischaemic cardiac pain before the administration of analgesics, this would be a useful diagnostic pointer during the initial clinical assessment in general practice and in accident and emergency departments, whose medical staff are often the first to encounter such patients.

The stimulus to vomiting during myocardial ischaemia remains uncertain in man but may be analogous to the van Bezold-Jarisch reflex, which has been extensively studied in experimental animals.[6 7] This reflex is mediated through afferent fibres arising in the heart "substance" and travels in the vagus nerve.[5-7] Since autonomic instability is a common early feature of myocardial infarction, vomiting induced via this pathway might be expected to be associated with other evidence of vagal activity—for example, sinus bradycardia, sweating, and hypotension. Other factors previously thought to be related to vomiting include the site[6] and size[8] of infarction. We carried out a study in which we investigated the incidence of vomiting in various acute ischaemic cardiac syndromes and the relation of the above factors to vomiting.

Patients and methods

One hundred and nine consecutive patients admitted to the coronary monitoring unit of this hospital with acute ischaemic myocardial pain were allocated into three groups: those with proved transmural myocardial infarction (58 patients), those with myocardial

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