Familial Type II Hyperlipoproteinaemia

CLINICAL FEATURES AND RESULTS OF TREATMENT IN CHILDREN AND YOUNG ADULTS

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SUMMARY

Thirty-four patients with familial type II hyperlipoproteinaemia were seen over an 8-month period at a lipid disorders clinic for children and young adults. Of the 34 patients, 5 were classified as homozygous, 27 as heterozygous type IIa, and 2 as heterozygous type IIb. Clinical manifestations of the disease were present in all 5 homozygous patients and in 12 of the 29 heterozygotes. The most common physical finding was Achilles tendon xanthoma. The high incidence of physical signs in our patients stresses the importance of such features in the young. For the purpose of treatment the heterozygotes were divided into 2 groups: (*a*) children under the age of 15 years; (*b*) young adults from 16 to 25 years of age. Patients in both groups received a minimum of 6 weeks' dietary treatment followed by combined dietary and cholestyramine therapy (Questran; Mead Johnson). The decrease in serum cholesterol on diet alone was similar in both groups. On combined therapy, the children showed a decrease in serum cholesterol of 27% compared with 15% in the young adults. A general fall in the serum cholesterol of 36% was achieved in the children, compared with 19% in the young adults. In 3 homozygotes diet alone produced a fall in serum cholesterol similar to that found in the heterozygotes. In 2 patients who had cholestyramine added to the diet, a further decrease of 20% in serum cholesterol was achieved.

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In South Africa the incidence of coronary thrombosis in the White population is among the highest in the world.[1] It has been recently demonstrated[2] that the contribution of hereditary lipoprotein disorders towards this high incidence of ischaemic heart disease in the younger age group is greater than has hitherto been supposed. Furthermore, while many patients with familial hyperlipoproteinaemia (HLP) are seen by physicians throughout the country, there has not, until recently, been any centre available to screen, classify, and effectively treat such patients. The need for a specialised centre is twofold: firstly, because the disease is usually latent for the first 3 decades of life, physicians, especially paediatricians, are generally unaware of its existence until complications such as coronary thrombosis occur. Secondly, the financial costs involved in the thorough investigation and long-term follow-up and treatment of patients, are often beyond the average family's means.

In the 8 months since the formation of a familial lipoprotein disorders centre, 34 patients with type II HLP, among others, have been investigated and treated. Only patients under the age of 25 years are admitted to this centre. The reasons for restricting the study to type II HLP in this communication are, firstly, preliminary investigation into the incidence of the disease in the different racial groups in South Africa indicates that the White population has a high incidence of familial type II HLP;[2] the number of possible patients requiring treatment in the future is, therefore, likely to be large. Secondly, of all the lipoprotein disorders, familial type II probably carries the worst prognosis. Homozygotes seldom reach the fourth decade of life before they die of ischaemic heart disease.[3] Of the heterozygote males, 5% have ischaemic heart disease by age 30, 61% have it by age 50, and 85% have it by the time they reach 60 years of age.[4] The risk for females with the disease is slightly lower. It was felt that by concentrating on children and young adults, vigorous treatment aimed at lowering the serum cholesterol might prevent or delay the ultimate complications of the disease.

This report stresses some of the problems encountered in dealing with a population consisting of children and young adults on long-term treatment for familial type II HLP. It also emphasises clinical findings encountered, in the hope that physicians and paediatricians will become aware of these features at an early stage.

PATIENTS AND METHODS

Patients

Many of the patients were referred to the clinic because of a strong family history of premature coronary artery disease. Further cases were diagnosed after screening relatives of the propositi. The 34 patients could be traced back to 10 original family lines (Fig. 1). The age range varied from 4 days to 25 years. In some cases both the parents and their children were affected and fell into the age requirements for treatment at the centre (Fig. 1; families III, VI, VII and X). At the time of their first visit all patients had been following their normal dietary pattern for at least 3 weeks. Patients from both groups then received a low cholesterol, limited saturated fat, and high polyunsaturated fat diet[5] for a minimal period of 6 weeks. This was followed by 6 weeks of cholestyramine therapy in addition to the diet. The dosage of cholestyramine varied from 8 g to 16 g daily. The homozygotes received the same dietary treatment. The dose of cholestyramine in the 2 homozygotes who received drug therapy, was 20 g daily. Venous blood was collected after a 12 - 14-hour overnight fast, and allowed to clot in a plain glass tube for 2 hours to complete clot retraction. All estimations were carried out within 6 hours of collection. At least 2 serum levels, 1 week apart, were taken at each stage of treatment.

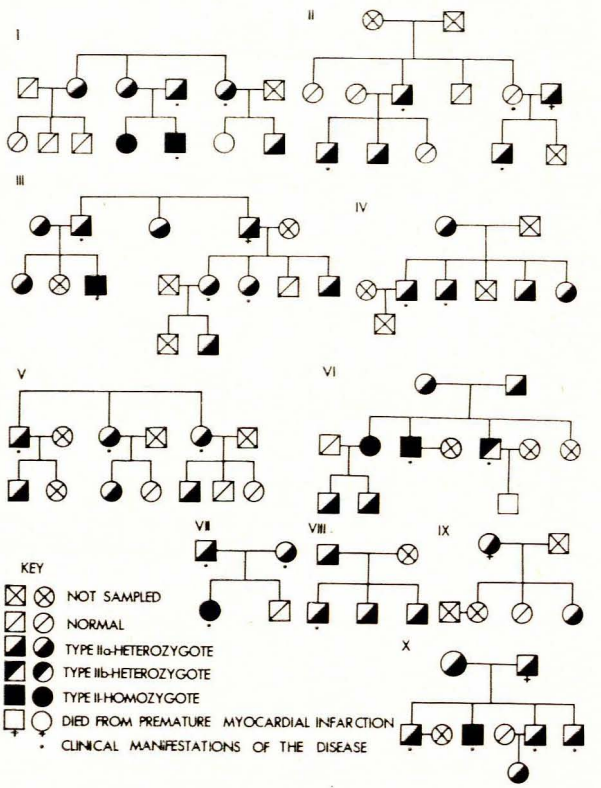

Fig. 1. Ten kindred in which familial type II hyperlipoproteinaemia was diagnosed and treated in children and young adults.

Methods

Initially, total cholesterol, triglycerides and lipoprotein electrophoresis were determined; later high-density lipoprotein cholesterol (HDLc) was measured and low density lipoprotein cholesterol (LDLc) calculated.[6] Cholesterol was determined by the method of Carr and Drekter[7] and compared with the standard method of the Technicon Auto-Analyzer II using a Lieberman-Burchard reagent.[8] The correlation coefficient was 0,99.

LDLc was calculated from the formula: LDLc = total cholesterol — ($\frac{\text{triglyceride}}{5}$ + HDLc).[6]

HDLc was estimated after both the very low density lipoprotein (VLDL) and the LDL had been precipitated with sodium phosphotungstate and magnesium chloride.[9]

Serum triglycerides were measured by the method of Carlson and Wadström.[10] The values obtained by this method were compared with those obtained by the Technicon AutoAnalyzer II.[11] The correlation coefficient (r) was 0,99.

Lipoprotein electrophoresis was performed on fresh serum in a barbital buffer, pH 8,6, using a Beckman Microzone tank and Cellogel (Chemtron, Milan) membranes. The membranes were stained with Fat Red 7B and scanned on a Beckman Microzone densitometer.

RESULTS

Of the 34 patients, 5 were homozygous and had severe clinical manifestations of the disease. The findings included gross skin and tendon xanthoma, arcus corneae and cardiovascular involvement, as typified by a long loud ejection murmur over the aortic area and radiating into the neck (Table I). Of the heterozygotes, 41% (12 out of 29) had clinical manifestations of familial type II HLP (Table I). Achilles tendon thickening was present in 11 cases. Other features were arcus corneae, skin xanthoma, and cardiovascular involvement. The initial biochemical findings in the 29 heterozygotes are summarised in Table II. For the purpose of reporting results of treatment, this group was divided into 2 groups: children below the age of 15 years (group I), and young adults from 16 to 25 years of age (group II). Twelve patients in group I received dietary treatment. A mean fall in serum cholesterol of 11,6% (from 362 mg to 320 mg/100 ml) was recorded (Table III). Nine patients in group II were treated similarly and a mean decrease in their serum cholesterol of 9% (398 mg to 361 mg/100 ml) was found (Table III). Ten patients in group I received cholestyramine in addition to the diet. A further decrease after dietary treatment of 27% (338 mg to 246 mg/100 ml) was recorded (Table IV). If the effect of both diet, and diet combined with cholestyramine, is considered in group I, a fall in serum cholesterol of 36% (383 mg to 246 mg/100 ml) is found (Table IV). In group II the fall in serum cholesterol was 15% (392 mg to 333 mg/100 ml) after addition of cholestyramine to the dietary treatment (Table IV). A general fall in serum dietary and cholestyramine therapy was found in group II cholesterol of 19% (413 mg to 333 mg/100 ml) after combined dietary and cholestyramine therapy, was found in group II (Table IV). In cases where the LDLc was measured before and after treatment, the fall in total cholesterol was paralleled by the fall in LDLc. The 5 homozygous patients had high cholesterol values (Table V) and severe clinical manifestations (Table I). Response to dietary treat-

TABLE I. CLINICAL FEATURES FOUND IN 34 CHILDREN AND YOUNG ADULTS WITH FAMILIAL TYPE II HYPERLIPOPROTEINAEMIA

Type II	No.	Achilles tendon xanthoma	Arcus corneae	Skin xanthoma	Cardio-vascular
Homozygotes	**5**	**5**	**4**	**4**	**4**
Heterozygotes	**29**	**11**	**3**	**1**	**1**

TABLE II. INITIAL BIOCHEMICAL FINDINGS IN 29 CHILDREN AND YOUNG ADULTS WITH THE HETEROZYGOUS FORM OF FAMILIAL TYPE II HYPERLIPOPROTEINAEMIA

No. of cases	Sex		Mean age (yrs)	Total serum cholesterol (mg/100 ml)	Serum triglycerides (mg/100 ml)
	M	F			
29	**19**	**10**	**15**	**363 ± 71**	**122 ± 116**

TABLE III. RESULTS OF 6 WEEKS' DIETARY TREATMENT IN HETEROZYGOTES WITH FAMILIAL TYPE II HYPERLIPOPROTEINAEMIA

No. of cases	Mean age (yrs)	Sex		Predietary cholesterol (mg/100 ml)	Postdietary cholesterol (mg/100 ml)	Mean decrease (%)
		M	F			
12	**11***	**10**	**2**	**362**	**320**	**11,6**
	(5-15)			**(242-460)**	**(210-416)**	
9	**21†**	**5**	**4**	**398**	**361**	
	(19-24)			**(282-525)**	**(180-514)**	**9**

* Group I.
† Group II.

TABLE IV. RESULTS OF 6 WEEKS' DIETARY TREATMENT FOLLOWED BY 6 WEEKS OF COMBINED DIETARY AND CHOLESTYRAMINE TREATMENT IN HETEROZYGOTES WITH FAMILIAL TYPE II HYPERLIPOPROTEINAEMIA

No of cases	Mean age (yrs)	Sex		Predietary cholesterol (mg/100 ml)	Postdietary cholesterol (mg/100 ml)	Mean decrease (%)	Postdrug cholesterol (mg/100 ml)	Mean decrease (%)	Mean total decrease (%)
		M	F						
10	**11***	**8**	**2**	**383**	**338**	**12**	**246**	**27**	**36**
	(5-15)			**(299-460)**	**(239-416)**		**(177-330)**		
5	**21†**	**4**	**1**	**413**	**392**	**5**	**333**	**15**	**19**
	(20-24)			**(340-525)**	**(324-514)**		**(262-384)**		

* Group I.
† Group II.

TABLE V. HOMOZYGOTE FAMILIAL TYPE II HYPERLIPOPROTEINAEMIA IN 5 PATIENTS SHOWING THE TOTAL SERUM CHOLESTEROL LEVEL AT TIME OF DIAGNOSIS, AFTER 6 WEEKS' DIETARY TREATMENT, AND AFTER COMBINED DIET AND CHOLESTYRAMINE THERAPY

Patient	Age (yrs)	Sex	TCL at diagnosis (mg/100 ml)	TCL after diet (mg/100 ml)	Decrease (%)	TCL after drug (mg/100 ml)	Decrease (%)	Total decrease (%)
1	5	M	900	812	10	650	20	28
2*	11	M	690	650	6	529	19	23
3	21	M	520	456	12			
4†	25	M	647					
5	2	F	840					

* Ileal bypass at age 6 years, surgical removal of gross pendulous xanthoma on feet, hands and elbows at ages 8 years and 2 years.
† Ileal bypass in 1969, full reconstitution of bowel length in 1971 due to chronic diarrhoea.

ment was similar to that of the heterozygotes. In 2 patients who received cholestyramine, a decrease in serum cholesrol of 20% was found (Table V).

DISCUSSION

The number of patients already attending the familial lipoprotein disorders centre, and the steady inflow of new families, indicates that familial type II HLP in the White population of South Africa is not as rare a disorder as was previously thought.[12] The incidence on neonatal cord blood screening has been shown to be in the region of 1 : 60 live births.[2] Although clinical features are easily detected early in the homozygotes, few authors have stressed the fact that clinical signs of the disease may be found in heterozygotes in the first 2 - 3 decades of life. Fredrickson *et al.*[3] found that the incidence of clinical features in a series of heterozygotes below the age of 30 years was less than 10%. However, since over 40% (12 out of 29) of the heterozygotes in the present series had features of the disease in childhood and late adolescence, it is thought that more careful clinical examinations should be carried out in patients with a family history of premature coronary thrombosis. Assessment of cardiovascular involvement in the young patient presents a problem. Although an ejection systolic murmur may be present, suggesting cholesterol deposition in the aorta, the severity and nature of the deposit in the young heterozygote is difficult to determine.

While results of dietary treatment recorded here are not as impressive as those reported by other authors,[13,14] we think this may be due to certain local sociological, psychological, and familial problems connected with the patients seen at the clinic. Many are from rural areas where meat and dairy products constitute a considerable portion of the diet. This traditional diet makes it difficult to adapt to an entirely new one. Furthermore, children cannot comprehend the nature of the disease and its long-term implications. Consequently, keeping them on a restricted diet for any length of time is not an easy task. The difference in the results of treatment between the 2 groups (Tables III and IV) suggests that younger patients are more responsive to therapy. However, this may also be explained by the fact that the patients in the younger group were subjected to more stringent control by their parents, and were less inclined to rebel against the treatment given. For example, the older group consisted of many patients who confessed to 'forgetting' to take 1 or 2 doses of the cholestyramine a week. The results obtained on the homozygotes (Table V) are encouraging, since the dose of cholestyramine was not large and could be increased 4-fold[13] before other drugs need be considered. Cholestyramine is fairly well tolerated by most patients. The slightly unpalatable taste has caused difficulties and disguising it in foods such as instant puddings, soups and skim milk, is common. Other side-effects include constipation and nausea. The incidence of constipation was far lower in younger patients than in adults. The introduction of both dietary and drug treatment as early and as vigorously as possible is now well accepted for the homozygous form of the disease. As far as the heterozygotes are concerned, the introduction of dietary treatment as soon as diagnosis is confirmed, is also well established.[15] The question of when to introduce drug therapy is still being debated. Cholestyramine therapy has only been instituted in the patients when their cholesterol levels remain above 250 mg/100 ml after dietary treatment. Eight of the patients are now controlled at cholesterol levels below 230 mg/100 ml either on diet, or on diet combined with cholestyramine. Only long-term treatment and follow-up will show whether the maintenance of a normal cholesterol level in patients with familial type II HLP will decrease the risk of coronary thrombosis.

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