A FAMILY WITH FAMILIAL HYPERCHOLESTEROLAEMIA

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Essential familial hypercholesterolaemia is a hereditable condition, characterised by hyperlipidaemia and hyperlipoproteinaemia, the latter showing increased concentration of low density lipoprotein. There is an abnormality of the homeostatic mechanism regulating plasma cholesterol, but the exact mechanism is not known. Depending on the severity and duration of the hyper-cholesterolaemia, artherosclerosis may develop with involvement of the endocardium and coronary vessels with death at an early age. It is worthwhile recognising disorders of lipoid metabolism, because with proper dietary control, the life span of a patient can be extended. So far in Singapore no case of familial hypercholesterolaemia has been reported and the condition is even rare when it presents in a child. The following is a case report of a nine-year old girl with hypercholesterolaemia where family studies revealed the condition to be present in three generations, the condition being transmitted in a dominant mode of inheritance.

CASE REPORT

K.I. was a nine-year old Scottish girl who was first seen in 1963 for tonsillitis and treated with syrup Penicillin. In June, 1965, she presented for the first time with mild "bagginess" below the eyes. There was no history of swelling of the legs nor a past history of disturbances of micturition. Physical examination revealed a well covered child, weighing 62 pounds. On examination there was minimal puffiness below the eyes, but no oedema of the legs or feet. The heart clinically was not enlarged, and the blood pressure was normal, being 100/70mm. of Hg. No abnormality was detected in the abdomen. The first condition to exclude was acute nephritis and nephrotic syndrome, and the urine was therefore repeatedly examined for albumin. The urine showed no evidence of albumin, the urinary proteins being less than 10 mgm%. The blood urea was 32 mgm%. The serum total protein was 7.8 gm%, the albumin being 4.8 gm% and the globulin 3.0 gm%, there being no reversal of the albumin-globulin ratio. The erythrocyte sedimentation rate was normal, being 8 mm. per hour. The serum cholesterol was very high, being 410 mgm%.

As seen from the above findings, the only abnormality was the persistently high or elevated blood cholesterol, and the urine was repeatedly normal. Besides the serum protein, blood urea and B.S.R. were normal, which makes the case unlikely to be a nephrotic syndrome. Radiographs of the chest reported the heart to be top normal in size, but the electrocardiograph was within normal limits. At first the oedema was thought to be allergic in nature, but as the blood cholesterol was persistently high, it was decided to investigate the family further. The following table shows the results of the blood of the immediate family: (Table I).

From the results, it will be seen that the patient showed an elevated blood cholesterol, the normal for her age being between 115 mgms to 240 mgms per 100 c.c. of blood. The father's blood cholesterol was very high, being 420 mgm%, the normal range for his age being 160 mgm to 320 mgm%. In addition, both the father and the patient showed a raised serum triglyceride, the normal being 120 mgm% and both on electrophoresis showed a very prominent β-lipoprotein band (see Figs. 1(a) & (b)). The father, therefore, was a carrier of the familial hypercholesterolaemia, and he was referred to the

TABLE I

	Blood Cholesterol	Serum Triglyceride	Beta-Lipropotein	S.G.O.T.
Patient	434 mgm%	213 mgm%	Prominent band	161 units
Mother	212 mgm%	Not done	Not done	Not done
Father	420 mgm%	150 mgm%	Prominent band	Not done
Brother	190 mgm%	Not done	Not done	Not done

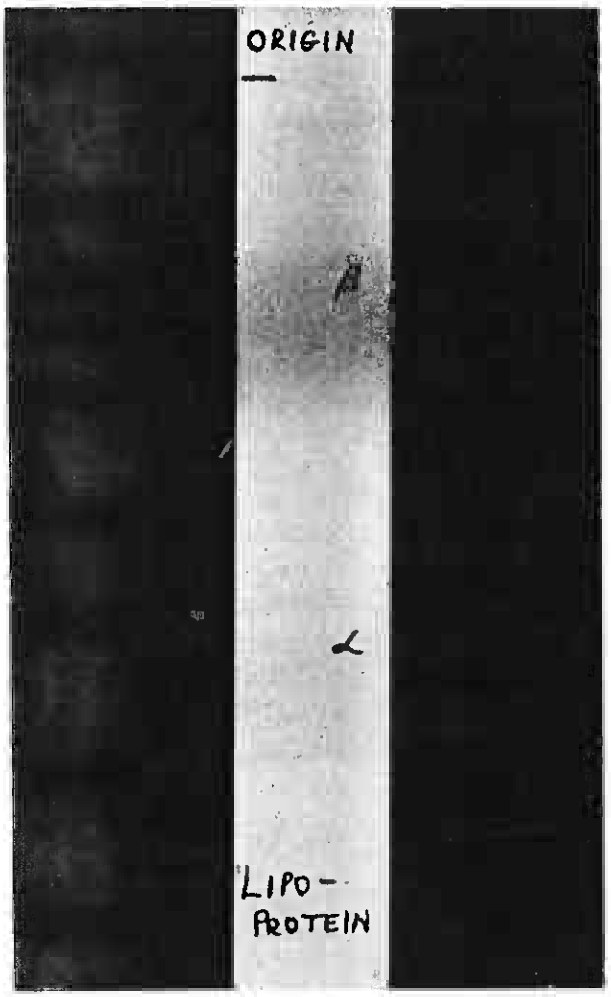


Fig. 1(a). Note the increased band of β lipoprotein on electrophoresis of the patient's blood.

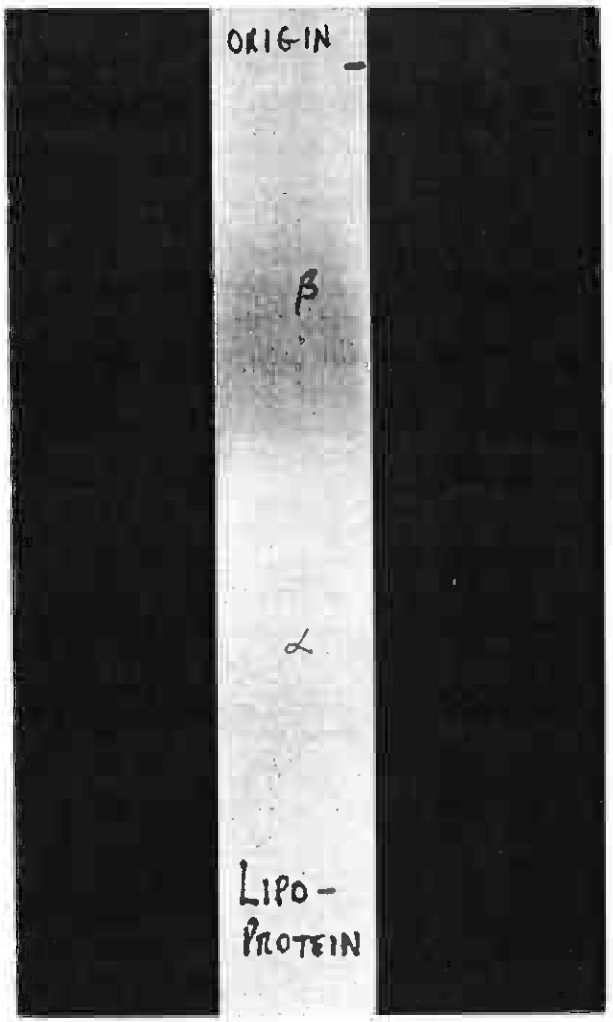


Fig. 1(b). Note the increased band of β lipoprotein on electrophoresis of the patient's father's blood.

Medical Unit for further investigation and treatment. On questioning further it was found that he had two previous attacks of sudden pain in the left-shoulder and an electrocardiographic tracing revealed a raised S.T. segment in the limb leads and the vector leads. (see Fig. 2). It was found on questioning further that two of the father's brothers, aged 39 years and 35 years respectively, had died suddenly of coronary attacks in the United Kingdom. The youngest brother, aged 35 years, had been apparently well, and had died suddenly while trying to catch a bus. The serum cholesterol results of as many members of the family were done, and the following are the results: (Table II).

From the genetic tree (see Fig. 3) it will be seen that there are four affected members, two of whom showed very high cholesterol results, while the other two who died of coronary attacks, presumably had artheroma due to hypercholesterolaemia. The grandfather at 86 years of age is alive, but is subject to anginal attacks and it is not possible to do his blood cholesterol. He is presumably a heterozygous carrier, having transmitted the disease to four of his children, in a typical dominant fashion, and the disease expresses itself in a third generation where the proband showed a high blood cholesterol.

TREATMENT

The patient was put on a 2000 caloric diet restricted in animal fat to 12 to 15 grams a day and where the dietary cholesterol was 200 mgms daily. The diet was restricted in saturated fat keeping the ratio of saturated to unsaturated fat in the proportion of 1:4. The diet, therefore, for the nine-year old patient consisted of 70 grams of protein, 85 grams of fat and 260 grams of carbohydrate, making a total of 2000 calories. All animal products and animal oils were cut off and the substituted oil, therefore, was corn-oil or sunflower oil. Only 'ean meat, fish and chicken were allowed. Skimmed milk was used instead of whole milk. The patient was able to tolerate the diet quite well and within a month of treatment

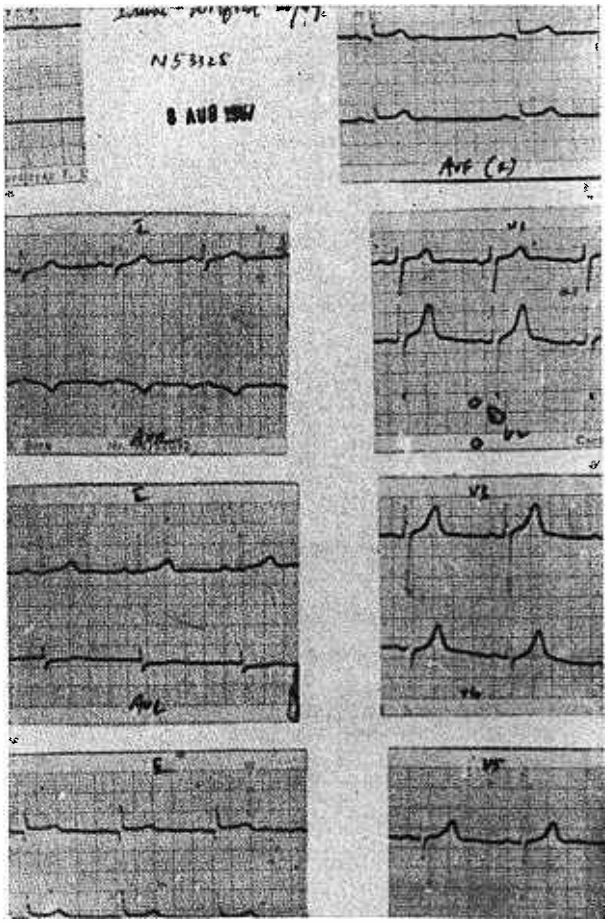


Fig. 2. Note E. C. G. of the father to show elevated ST Segments in leads 1, 3 V_5 and V_6.

the blood cholesterol had dropped from 420 mgm% to 292 mgm%, and two months later the blood cholesterol had dropped to 262 mgm%. The patient's father, who was treated in the Medical Unit, was put on Atromid tablets, (chlorophenoxy-lisobutyric tablets) to lower the blood cholesterol and was progressing satisfactorily, the blood cholesterol having dropped from 325 mgm% to 177 mgm%. In fact the whole family had decided to remain on the same diet as the patient.

DISCUSSION

When confronted with a case of hypercholesterolaemia one has to exclude all secondary causes of hyperlipaemia, e.g. insulin-deficient diabetes mellitus, hypothyroidism, nephrotic syndrome, glycogen storage disease, hepatic disease, chronic pancreatitis, and malignant neoplasms including hepatomas. All these cases of secondary hyperlipaemia would have symptoms and this was not likely in our patient who was practically asymptomless. Secondary hypercholesterolaemia due to hypothyroidism was excluded in this patient, and the protein-bound iodine was 7.5 micrograms%. The patient had not only an elevated blood cholesterol but elevated triglyceride and phospholipids, and these are found in a number of genetic and acquired conditions. The plasma lipids consist of phospholipids, cholesterol, triglycerides, free fatty acids, and miscellaneous ones, e.g. carotenoids, vitamin A and cerebrosides. The phospholipids comprise the largest fraction, the phosphatidyl choline being 70%, spingomyelin being 20% and lysolecithin, phosphatidyl, ethanolamine, phosphatidyl serine, and inositol phosphatide being 10%. Cholesterol forms the second largest fraction, 75% of which is esterified with long chain fatty acids, which are most unsaturated fatty acids, more than 50% being linoleic acid, and the remainder being oleic acid. The next plasma lipids are the free fatty acids which are largely transported in the plasma. The plasma lipids are lipids which unite with protein and aid in their transport. They are classified according to their density

TABLE II

Family Member	Sex	Age	Serum Cholesterol
Grandfather	M	86 yrs	Not done
Grandmother	F	79 yrs	Died
Eldest -	M	39 yrs	Died of coronary attack
2nd - -	M	56 yrs	200 mgm%
3rd - -	M	54 yrs	200 mgm%
4th - -	M	52 yrs	300 mgm%
5th (Father)	M	51 yrs	434 mgm%
6th - -	M	50 yrs	Not done
7th (Mongol)	M	44 yrs	Not done
8th - -	M	35 yrs	Died of coronary attack

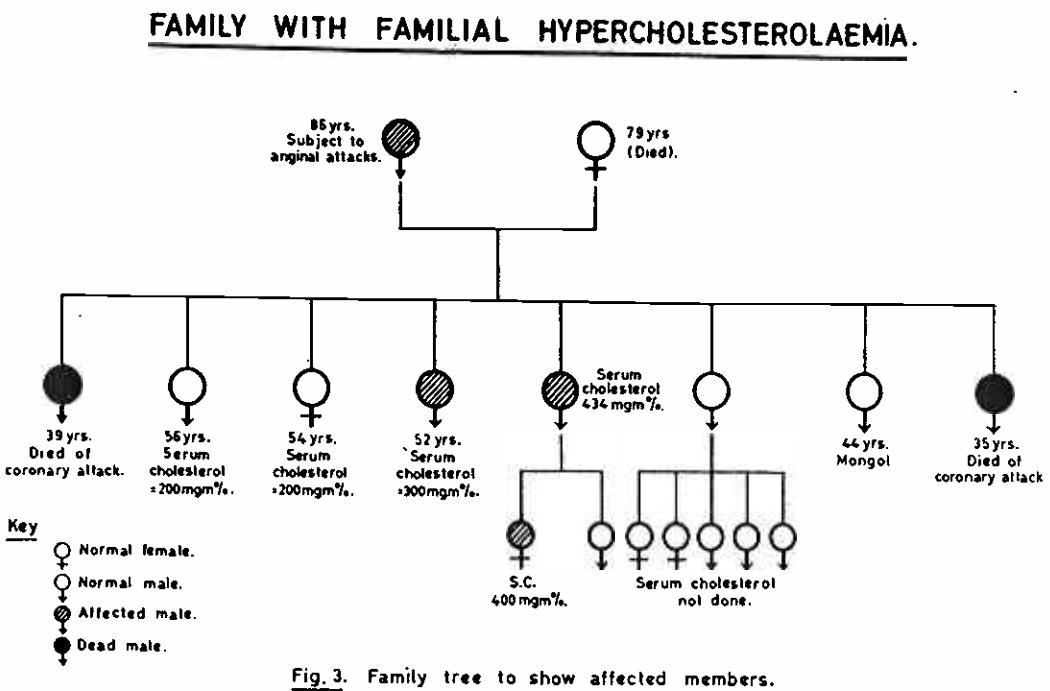
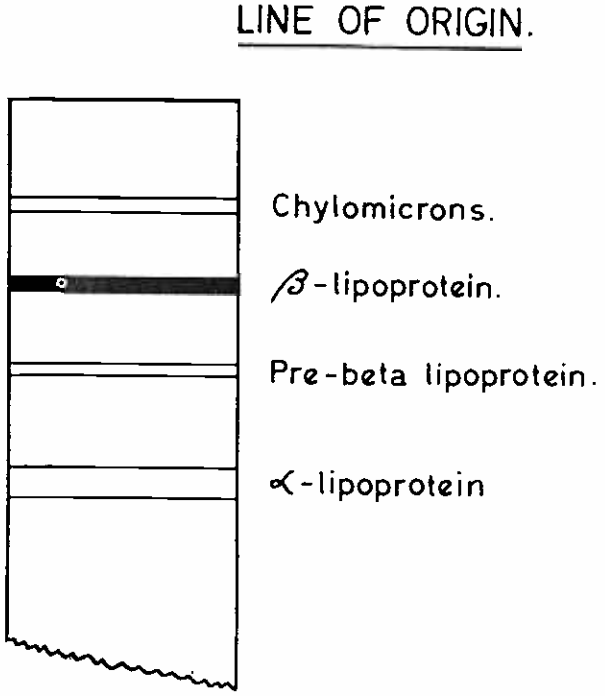


Fig. 3. Family tree to show affected members.

and from the heaviest to the least dense as follows:-



In both the patient and the father the prominent band on electrophoresis was the beta lipoprotein. Depending on the lipoprotein it is possible to divide the lipoprotein into five syndromes: (Table III).

From the table it will be seen that our patient falls into Type II, where the beta-lipoprotein is greatly increased and is due to a dominant mode of inheritance.

In familial hypercholesterolaemia there is hiagh concentration of cholesterol and phospholipid and depending on the severity and duration of hyperlipidaemia, the syndrome is accompanied by cutaneous and tendon xanthomas, corneal arcus and a tendency towards the accelerated development of athero-sclerosis. Stanbury et. al (1960) state that the syndrome is definitely familial and may involve either sex. It may manifest itself in the first years of life, with severe xanthomatous involvement of the skin, endocardium, heart valves. coronary arteries and other organs ending in sudden death from myocardial infarction in childhood, or it may present as nothing more than a slight elevation in plasma cholesterol with no limitation of the normal life-span. The biochemical defect of essential hypercholesterolaemia is not known. The hypercholesterolaemia is inherited as an autosomal dominant trait. Two genetic mechanisms have been described:-

1) That the gene is completely dominant.
2) That the gene is incompletely dominant with the homozygous genotype likely to develop severe hyperlipidaemia and xanthomatosis than the heterozygote.

In the family reported above, the disorder is probably heterozygously manifested, as the proband is only mildly affected. Stanbury reports that there is no uniformly effective therapy for maintaining blood lipid concentrations in patients with essential familial hyperlipaemia. The only form of therapy feasible throughout the life of the patient is dietary modification.

TABLE III

Type	Synonym	Lipid Raised	Genetics
I	Familial hyperchylomicronaemia	Chylomicrons	Autosomal recessive
II	Familial hypercholesterolaemia	β-lipoprotein	Dominant
III	Familial hypercholesterolaemia and hyperlipaemia	β-lipoprotein and pre-lipoprotein	Dominant
IV	Essential familial hyperlipaemia	Pre-beta-lipoprotein	—
V	Mixed hyperlipaemia	Chylomicrons and pre-lipoprotein	—

Basically the diet involves:-

1) Maintenance of an ideal weight.
2) Reduction in the intake of fats, that are saturated in short chain fatty acids, e.g. lard, meat, egg and coconut oil fat.
3) Substitution of more saturated fats, e.g. corn, cotton-seed, peanut, sunflower or corn-oil. Skim milk should be included in diet as sources of calcium, protein and vitamin supplement.

There was no universal agreement about the use of any drug in the treatment of hypercholesterolaemia, e.g. thyroxine, ACTH, nicotinic acid, M.ER - 29, atromid. In the above case it is difficult to say whether the reduction of serum cholesterol in the father was due to the atromid per se, as the father had started on a special low cholesterol diet, before the administration of atromid.

In the differential diagnosis of the condition one would consider familial hyperchylomicronaemia, where the chylomicrons are definitely increased, and the condition is due to an autosomal recessive condition. The exact mechanism for the removal of chylomicrons is not known. It is not known whether the chylomicrons pass into the tissues intact or whether they must be degraded at the capillary level. The tissues capable of removing chylomicrons include liver, heart, skeletal muscle, and adipose tissue; one of the most important factors affecting chylomicron removal appears to be carbohydrate metabolism, according to Stanbury experimentally. Our patient did not fall into this category, as there was no increase in chylomicron level.

In essential familial hyperlipaemia, the syndrome is characterised by hyperglyceridaemia, and elevated concentrations of chylomicrons and low density lipoprotein in the blood. The hyperlipaemia is directed to the intake of fat in the diet. Clinically it is accompanied by eruptive xanthomas, hepatosplenomegaly and abdominal pain. The cause is unknown but appears to be mainly related to the defective removal of chylomicrons from the plasma. In types 3, 4 and 5, i.e. familial hypercholesterolaemia and hyperlipaemia, and essential familial hyperlipaemia and mixed lipaemia, the pre-beta-lipoprotein band would be very marked on electrophoresis, and this was not so in our case.

SUMMARY

The nine-year old patient reported is a very interesting and rare case of essential familial hypercholesterolaemia, transmitted in a dominant mode of inheritance with four affected members. In the patient and her father the blood cholesterol levels have been controlled with an appropriate diet and drugs respectively. It is very early yet to say how effective treatment is, but it is hoped that the complications of artheroma and coronary disease will be prevented.

ACKNOWLEDGEMENTS

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REFERENCE

1. Stanbury, Wyngaarden & Fredrickson (1960): "The Metabolic Basis of inherited diseases.