FAMILIAL HYPERCHOLESTEROLAEMIA (FAMILIAL HYPER-BETA-LIPOPROTEINAEMIA OR TYPE II HYPERLIPOPROTEINAEMIA) IN A CHINESE FAMILY

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SYNOPSIS

Familial Hypercholesterolaemia (Familial Type II Hyperlipoproteinaemia or Hyper-beta-lipoproteinaemia) is an uncommon disorder among the Asians. This paper describes the clinical, biochemical and genetic aspects of this disorder in a Chinese family in Singapore. All twenty members of the family over three generations are studied and ten members are found to have raised serum cholesterol and beta-lipoprotein. The youngest member affected is a two year-old boy and the oldest member affected is the sixty year-old grand-father who also suffers from peripheral vascular disease which is a known complication. The patient and his brother are found to have associated tendinous xanthomas. The study of the family suggests that this disorder is transmitted as mendelian dominance. Dietary treatment with polyunsaturated fat and low cholesterol diet fails to bring about significant reduction in the serum cholesterol level. In addition, all the four affected adults are treated with clofibrate which is only effective in controlling the serum cholesterol level in one patient. The mechanism of the production of increased serum cholesterol and beta-lipoprotein is briefly discussed.

Familial hypercholesterolaemia is a serious disorder characterised by raised serum cholesterol, normal or slightly raised serum triglyceride and xanthomatous lesions in the tendon and skin. Premature coronary heart disease or peripheral vascular disease is the common complication. Pick and Pincus in 1908 first showed a relationship between xanthoma and the high serum cholesterol level but it was Schmidt in 1922 who first described the familial tendency in patients who had xanthoma and hypercholesterolaemia. Various interesting synonyms like hereditary xanthomatosis, hereditary xanthoma tuberosum multiplex, xanthoma tendinosum, xanthelasma multiplex and essential hypercholesterolaemic xanthomatosis appeared not infrequently in medical writings over the years. They were mainly based on the type of skin lesions and simple estimation of serum lipids. But recently it has been recognised that tendo-cutaneous lesions are variable and not reliable and that the measurement of either serum cholesterol or triglyceride level alone is inadequate for proper clinical evaluation of hyperlipidaemic states. Therefore new techniques like ultracentrifugation and paper electrophoresis of lipoprotein are used to provide a better approach to hyperlipidaemic disorders. As the cholesterol-rich lipoprotein of familial hypercholesterolaemia migrates with beta-lipoprotein on paper electrophoresis, it is also known as Familial Hyper-beta-lipoproteinaemia or more commonly as Familial Type II Hyperlipoproteinaemia according to Fredrickson's classification (Fredrickson, 1967).

Although familial hypercholesterolaemia is a fairly common form of inheritable hyperlipoproteinaemia, especially among the Jews and Caucasians, it is rare among the Asians (Frederickson, 1967). Aizawa in 1963 described only few cases of xanthomas and hypercholesterolaemia among the Japanese. In Singapore, Paul (1969) reported one Scottish family with this disorder but so far no Chinese family in Singapore has been reported to have suffered from this similar disorder. This paper describes the clinical, biochemical and genetic aspects of familial hypercholesterolaemia in a Chinese family in Singapore.

CASE REPORT

L.N.Y., a 39 year-old Chinese male gave a history of three attacks of transient loss of consciousness on the day of admission. Each attack was preceeded by giddiness and blurring of vision but there was no associated convulsion. One month earlier, he experienced an attack of central chest pain. An electrocardiogram (E.C.G.) done then did not reveal any abnormality. There was no past history of epilepsy, hypertension or diabetes mellitus but he noticed few small nodules over both of his knuckles which grew bigger gradually

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over a period of 10 years. He smoked about 10 cigarettes a day for last 10 years but he seldom drank any alcohol. A careful dietary history taken did not reveal any excess in consumption of fat or cholesterol. Clinical examination showed a thin man in good general health with a body weight of 120 pounds. He had prominent arcus senilis but no xanthelasma. Two tendinous xanthomas measuring 1·2 cm. in diameter were seen over the right 3rd and 4th metacarpal-phalangeal joint (Fig. 1) and another one over left 3rd metacarpal-phalangeal joint. Heart was not enlarged and no murmur was heard. Pulse rate was 75 per minute and regular. All the peripheral pulses were normal. B.P. was $\frac{100}{70}$. There was no neurological deficit or any evidence of hypothyroidism, nephrotic syndrome or chronic liver disease. Laboratory investigations showed serum uric acid of 5·3 mg. per cent, a fasting sugar of 86 mg. per cent with normal glucose tolerance. Fasting serum cholesterol was 370 mg. per cent and triglyceride of 100 mg. per cent. Paper electrophoresis of lipoprotein showed an increase of beta-lipoprotein band. Serum kept overnight in the refrigerator at 4°C was clear. X-ray chest and E.C.G. were normal. A clinical diagnosis of primary hypercholesterolaemia or Type Two Hyperlipoproteinaemia with xanthomatosis was made.

Fig. 1. Tendinous Xanthomas over the third and fourth metacarpal-phalangeal joints of patient's right hand.

FAMILY STUDY

Patient's 60 year-old father, with 6 years history of mild diabetes mellitus controlled by tolbutamide, was seen in another hospital 3 years ago for occlusive disease of his right axillary artery. An exploratory arterectomy was done and no embolus was found but arterial lumen was found to be small. Though right radial artery became just palpable after surgery, there was residual wasting and weakness of right forearm and hand muscles. His occlusive peripheral vascular disease was quite widespread as the pulses of both his lower limbs were diminished and some even not palpable. He had prominent arcus senilis but no xanthomas or xanthelasma was seen. Laboratory investigations revealed moderate glucose intolerance confirming the diagnosis of diabetes mellitus. His E.C.G. showed ischaemic changes. Fasting serum cholesterol done then was 400 mg. When he was seen again this May, his fasting serum cholesterol was 325 mg.% and triglyceride was 62 mg.%. Paper electrophoresis done for the first time showed an increase in beta-lipoprotein band. Serum kept overnight in refrigerator was clear.

Patient's elder brother aged 40 was symptom free except that he noticed similar nodules over his right knuckle and right Achilles tendon for the last 5 years. Clinical examination confirmed the presence of tendinous xanthomas over the right 3rd metacarpal-phalangeal joint and right Achilles tendon. Arcus senilis was seen but there was no clinical evidences of peripheral vascular disease. E.C.G. was normal. Fasting serum cholesterol was 345 mg.%, serum triglyceride was 78 mg.% and there was also an increase in beta-lipoprotein band. Serum kept overnight was again clear. Blood uric acid was 6·7 mg.%.

Patient's 32 year-old sister was well and had no clinical evidence of coronary or peripheral vascular diseases. Though arcus was present, no xanthomas or xanthelasma was found. Her fasting serum cholesterol was 350 mg.% and serum triglyceride 125 mg.%. Beta-lipoprotein was raised. The other sibling was her 35 year-old brother in China and there was no means of knowing his clinical condition except that his serum cholesterol estimated in China was 283 mg.%.

The other members of this three generation family were asked to come forward for clinical examination and estimation of fasting serum cholesterol, triglyceride and electrophoresis of serum lipoprotein. There was no clinical evidence of cutaneous or tendinous xanthomas, xanthelasma, coronary heart or peripheral vascular diseases in anyone of them. Fasting serum triglycerides were all within normal limit and serums kept overnight were all clear. Among the 11 children studied, 6 were found to have raised fasting serum cholesterol and increased beta-lipoprotein level. The cholesterol levels of all members were clearly indicated in the family tree (Fig. 2). Therefore the familial tendency of the Type Two Hyperlipoproteinaemia was clearly established.

As for the management, all those affected were advised to take a low cholesterol diet of 100-150 mg. per day and substitution of saturated fat with polyunsaturated fat. This was achieved by avoiding

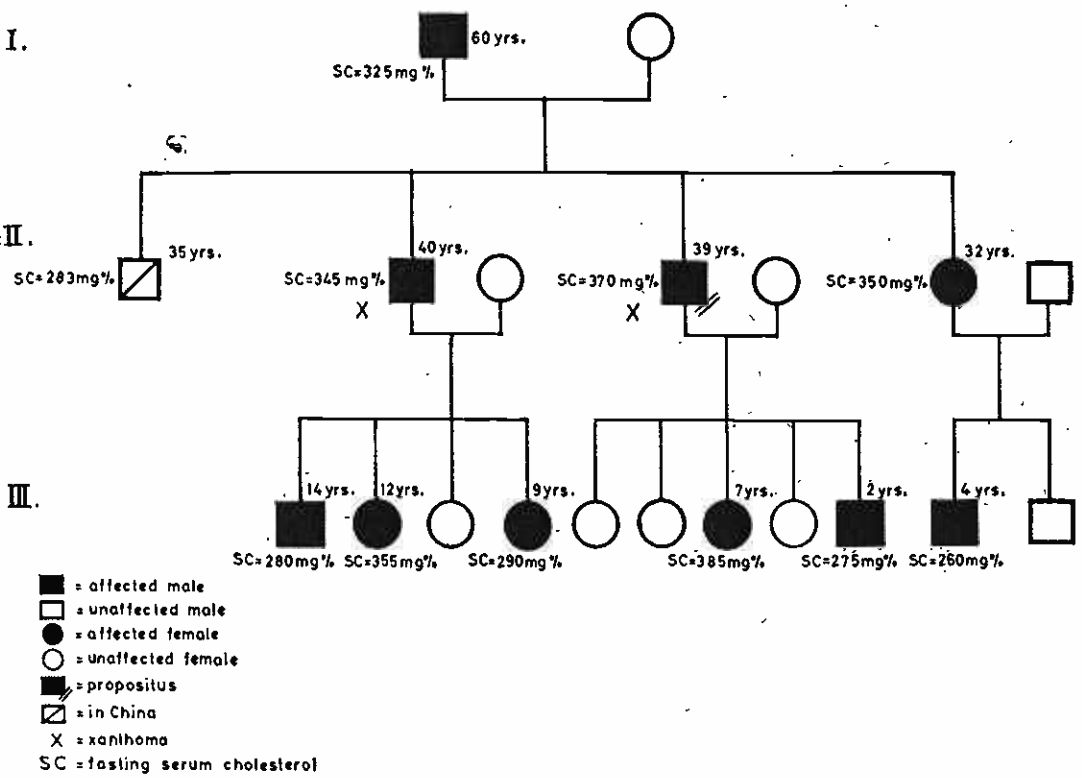

Fig. 2. Family tree of propositus with Familial Hypercholesterolaemia over 3 generations.

TABLE I

CHARACTERISTIC ALTERATIONS IN HYPERLIPOPROTEINAEMIC STATES

Type	Electrophoretic Pattern	Class Predominantly Elevated	Serum Appearance	Serum Triglyceride	Serum Cholesterol	Xanthoma (when Present)
I	Origin	Chylomicron (Sf 400)	Milky	↑ ↑ ↑	Normal or slightly ↑	Eruptive
II	Beta	Low density lipoprotein (Sf 0-20)	Clear	Normal or slightly ↑	↑ ↑ ↑	Tendinous
III	Broad beta	Very low density lipoprotein (Sf 20-100)	Turbid	↑ ↑	↑ ↑	Tuberous Palmar Planar
IV	Pre-beta	Very low density lipoprotein (Sf 20-400)	Turbid	↑ ↑	Normal or slightly ↑	Eruptive
V	Origin and Pre-beta	Chylomicron and very low density lipoprotein	Turbid to milky	↑ ↑ ↑	↑	Eruptive

whole milk and other dairy products, brain, kidney, liver, visible fat on meat, chocolate and cakes, egg yolks and coconut oil. Instead they were advised to use corn oil for cooking and take skim milk, lean meat, fish and special Kraft margarine liberally to maintain a normal nutrition. No restriction on calories or carbohydrate was advised as none of them was over-weight. After 2 months of dietary treatment, the patient's serum cholesterol fell from 370 mg.% to 330 mg.% whereas his brother's and sister's cholesterol fell from 345 mg.% to 295 mg.% and from 350 mg.% to 310 mg.% respectively. There was little or no reduction in cholesterol in other affected members of the family especially the children. Currently the 4 affected adults were put on Clofibrate 500 mg. q.i.d. in addition to dietary treatment. There was little evidence of further reduction in cholesterol level except in the sister whose cholesterol fell from 310 mg.% to 240 mg.% after 3 months of chemotherapy.

DISCUSSION

It is now quite clear that measurement of either serum cholesterol or triglyceride level alone is inadequate for proper clinical evaluation of hyperlipidaemia. Both cholesterol and triglyceride should be regarded as part of lipoprotein, the macromolecular complexes in which the lipid moieties are combined with apoprotein, which also provides a vehicle for transport. Five different lipoproteins have so far been recognised. The protein and lipid content of each type of lipoprotein determine its physical properties like size, density, floatation rate and electrophoretic migration and therefore provides a basis for ultracentrifugation and electrophoretsc separation. Since hyperlipoproteinaemia may result from defective protein as well as lipid metabolism, classification based on lipoprotein characteristics gave a better diagnostic and therapeutic approach to patients with elevated plasma lipids (Fredrickson, 1967). The appearance of the serum kept overnight at 4°C in the refrigerator offers a simpler bedside diagnosis of various hyperlipidaemic states. The more triglyceride a lipoprotein contains, the bigger the capacity for it to scatter light therefore the turbidity of the serum is increased. The various characteristics of different types of hyperlipoproteinaemia are briefly summarised in Table I.

The laboratory diagnosis of Type Two Hyperlipoproteinaemia is characterised by raised fasting serum cholesterol, a normal or slightly increased triglyceride and an increased beta-lipoprotein band on paper electrophoresis. All the 10 affected members in the family possess the above characteristic findings. None of them has increased fasting triglyceride in the serum (Upper limit of normal is taken as 160 mg.%). The raised fasting serum cholesterol ranges from 260 mg.% to 385 mg.% (Upper limit of normal is taken as 250 mg.% for adults). The youngest member affected is a 2 year-old boy whose fasting serum cholesterol is 275 mg.% and the highest cholesterol level of 385 mg.% is found in a 7 year-old girl. It is well known that serum cholesterol level is lower in first and second decades than in adults, therefore these values represent a fairly high cholesterol concentration. The diagnosis of Type Two Hyperlipoproteinaemia in those affected are further confirmed by raised beta-lipoprotein band on paper electrophoresis and also a clear serum kept overnight in refrigerator.

In order to make a diagnosis of familial disorder, primary diseases which can cause a secondary elevation in beta-lipoprotein have to be excluded and a similar disorder must be found in other members of the same family. There was no evidence to suggest that any one of those affected is suffering from hypothyroidism, nephrotic syndrome, chronic obstructive liver disease, myeloma or macroglobulinaemia which not infrequently causes secondary hyper-beta-lipoproteinaemia. There is also no evidence to suggest that the affected take excessive amount of saturated fat with high cholesterol in their diet which can also cause an elevation in beta-lipoprotein. Careful study of the family tree in Fig. 2 suggests autosomal dominant inheritance. This finding agrees with that of Wheeler (1957) who maintained that the disease was transmitted as single mendelian dominance. He observed that increased serum cholesterol was found both in homozygotes and heterozygotes though it was much higher and occurred at an earlier age in homozygotes. The secondary manifestations such as cutaneous or tendinous xanthomas, xanthelasma, arcus and the complications like coronary and peripheral vascular diseases were primarily related to height of the cholesterol and beta-lipoprotein level and also to the duration of the disease irrespective of homozygous or heterozygous state. But homozygote could have xanthomatosis very early in life or even born with them and they not infrequently died in childhood or early adult life because of complications whereas heterozygotes might develop xanthomatosis and cardiovascular complications at a later stage of life. They usually survived the child bearing period. But in 1948, Wilkinson suggested that the hereditary transmission occurred as an incomplete dominant trait and therefore homozygotes would develop complete form of disease i.e. hypercholesterolaemia and xanthomatosis, whereas heterozygotes would develop incomplete form of disease with hypercholesterolaemia as the sole manifestation. But the available evidences at present favour

Wheeler's concept of autosomal dominant inheritance. Both the patient and his elder brother, presumably heterozygotes, have had tendinous xanthomas for 10 and 5 years respectively and arcus senilis are found in all the four adult patients. In none of them is xanthelasma found. As for the cardiovascular complications, the patient may have suffered from transient ischaemic attacks but no definite coronary heart or peripheral vascular disease is noted. His father definitely suffers from occlusive disease of peripheral vessels and ischaemic heart disease. In none other was cardiovascular complication detected.

The massive deposits of cholesterol in the skin and tendons as well as high cholesterol level in the serum show that patients accumulate abnormal amount of cholesterol in their bodies. Biopsy of the xanthoma often shows it contains cholesterol ester. It is not sure whether this is due to defect in the mechanism for removing the cholesterol or due to excessive endogenous synthesis in liver and small intestine. Myant (1970) showed in some studies that there was increased cholesterol synthesis in familial hypercholesterolaemia. But Langer (1969) believed that it was due to delayed catabolism of beta-lipoprotein apoprotein. Recently it was found by Dingham (1972) that this disorder might be due to defect in the adrenal utilization of the cholesterol in the synthesis of steroid thus resulting in the increase of the cholesterol in the blood.

In the Framingham study (Kannel, 1961), it has been clearly established that raised serum cholesterol was the major risk factor in determining the statistical probability of developing coronary heart disease. A 'normal' level of cholesterol of 240 mg. % in 30 to 49 year old men is associated with a risk that is 2·6 times that associated with a level of 200 mg. %. Therefore it is obvious that patients suffering from the familial hypercholesterolaemia need to be treated to prevent cardiovascular complication. Treatment is divided into two main forms: dietary and chemotherapy. Dietary treatment in the form of low cholesterol diet and substitution of saturated fats by polyunsaturated fats offers the safest long range management of hypercholesterolaemia (Conner, 1968) as cholesterol of dietary origin though plays no part in the primary disorder will accumulate beyond the ability of the body to reduce the amount synthesised in the liver and the intestine from endogenous precursors. But unfortunately it has been the experience of Strisower (1968) that familial hypercholesterolaemia especially when associated with xanthomatosis is generally refractory to dietary treatment. But in patients without xanthomatosis and with a moderate elevation of cholesterol and beta-lipoprotein level, dietary restriction of saturated fats and cholesterol is sometimes effective. Because the dietary treatment is safer and more physiological than any form of chemotherapy, diet shall always be given a careful trial before any form of chemotherapy is contemplated. In our present study, all the affected members of the family were started on dietary treatment. After two months, there was about only 10 to 15% reduction in serum cholesterol level in three of the adults. The failure of the children to obtain any reduction is probably due to failure to adhere to the strict dietary restriction. It is obvious that the dietary treatment is not very successful in our patients thus confirming Strisower's (1970) observation that Type II patients have the greater number of dietary treatment failure. This is not surprising as there is no evidence to incriminate excessive saturated fat or cholesterol in the diet as the cause for the elevation of serum cholesterol and beta-lipoprotein in patients suffering from this primary and familial disorder.

As for the chemotherapy of Type II disease, many drugs have been tried before with variable results. They are clofibrate, thyroxine, nicotinic acid and cholestyramine. Except for cholestyramine which is currently found to be most useful (Fallon, 1968) none of the above can bring about significant reduction in the cholesterol level especially in patients who have associated xanthomatosis. Thyroxine in high doses is occasionally useful but this is limited by the side effect of hypermetabolism and risk to patients with coronary disease. Strisower (1966) believed that in some patients thyroxine used properly can bring about a 20% to 25% reduction in the cholesterol level. Nicotinic acid has been used with fair results by Parsons (1965) beginning with 1·5 gm. daily and increasing to 4·5 gm. daily. The side effects are intolerable flushing and itch, activation of peptic ulcer, exacerbation of diabetes mellitus and abnormalities of liver function. The commonly used and safest drug is clofibrate but unfortunately it is least useful in patients who have associated xanthomatosis. But in patients without xanthomatosis and with moderate rise of serum cholesterol, clofibrate can produce a 20-25% reduction in cholesterol and beta-lipoprotein (Strisower, 1970). Therefore this drug should be tried first. Currently all the four adults affected were put on Clofibrate 500 mg. q.i.d. in addition to low cholesterol and saturated fat diet. After 3 months of treatment, it is found that the patient and his brother who have associated xanthoma and the father who suffers also from peripheral vascular disease do not have any significant reduction in the serum cholesterol whereas the sister who has no xanthoma benefits from a further reduction of 75 mg. of serum cholesterol on top of the 40 mg. reduction brought about by diet-

ary treatment alone. Favourable results in other patients are still awaited on continued clofibrate therapy. If this fails, thyroxine, nicotinic acid or cholestyramine shall be tried.

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