

Familial Hyperlipidaemia in Malaysian Children

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Summary

This paper highlights two cases of paediatric familial hyperlipidaemia (hypercholesterolaemia and hypertriglyceridaemia). The first case was an 11 year old Chinese boy, a "homozygous" (Type II) hypercholesterolaemic patient. He had extremely high blood cholesterol level (19.4mmol/l), severe multiple xanthoma and abnormal resting electrocardiogram. He had repeated heart attacks and died at the age of 15 in spite of early intervention, treatment and follow up. The second case was a 2½ years old girl who had severe hypertriglyceridaemia. She had raised cholesterol (6.2mmol/l) and extremely high triglycerides (14.8mmol/l). The patient did not resemble Type I lipoproteinaemia which is classically seen in childhood. On the contrary, the patient exhibited clinical and biochemical manifestations of a Type V lipoproteinaemia which often occurs in adults. Apart from a Type V lipoprotein pattern, the patient had low post hepatic lipase activity (PHLA), Apo C II and Apo E2/E3 phenotype. In addition, the lipid profile of her family members (both the parents and brothers) had raised triglycerides and thus ruled out the Type I lipoprotein inheritance pattern, which is an autosomal recessive condition.

The issue of paediatric hyperlipidaemia, their management and treatments are discussed.

Key Words: Familial (Type II and Type V) hyperlipidaemia, Hypercholesterolaemia, Hypertriglyceridaemia, Xanthoma, Children, Coronary artery disease, Pancreatitis

Introduction

Familial hyperlipidaemia, an inherited lipid disorder which causes raised blood lipids, have been described in the Malaysian population¹⁻⁶ and the disorder was known to be confined to adults.

Lipid problems in children and adolescents are uncommon. However, hyperlipidaemia before adulthood is of concern because atherosclerosis begins in childhood.

Children and adolescents with cholesterol elevation are more likely than their peers in the general population to

have cholesterol elevation in adulthood. Marked hyperlipidaemia in childhood presents itself as coronary artery disease and acute pancreatitis.

This paper highlights two cases of familial hyperlipidaemia namely, hypercholesterolaemia and hypertriglyceridaemia in children with details of their clinical history and manifestations, therapeutic measures and responses, family study and genetic defects. The implications of the findings will be discussed in relation to the diagnosis, treatments and management of these paediatric lipid disorders.

Severe Hypercholesterolaemia

Case A

CSN was an 11-year-old Chinese boy who was born in 1962, the product of normal pregnancy and delivery. He was found to have a small spot at the gluteal cleft at birth. He developed a lump over the right gluteal region at the site of an antibiotic injection for a scalp abscess at the age of eight months. This increased progressively in size. The left gluteal region developed a similar lump at the age of three years. At the age of six, he had additional lumps over the knees and elbows. He was referred by his general practitioner to the General Hospital in Taiping where a blood test showed a total cholesterol value of 19.4mmol/l. He was advised to reduce the intake of saturated fats to increase intake of polyunsaturated fats and to avoid foods rich in cholesterol. He was treated with clofibrate 1g daily. On March 1972, he had his first myocardial infarction and on June 1977, his second one. He was referred to the General Hospital, Kuala Lumpur on March 1973 at the age of 11.

Clinical Examination

On admission to the General Hospital, Kuala Lumpur, the 11-year-old patient weighed 19.1kg and measured 123cm in height. Figure 1 depicts the physical findings, which consisted of generalised distribution of xanthomata over the limbs, trunk as well as bruit over the neck, chest, abdomen and both femoral arteries. There was bilateral arcus senilis involving the whole circumference. A slightly raised plaque of xanthoma planum covered the whole of the child's back. Xanthoma tuberosum was present over the elbows, buttocks, popliteal fossae, and knees and over the tendo achilles and the extensor tendons overlying the metacarpals. His blood pressure was normal.

The liver was enlarged - 1.5cm breadth below the margin. Blood test revealed elevated total cholesterol (15.1mmol/l), triglycerides (2.0mmol/l) and uric acid (8.4mg/dl). Electrocardiogram showed deep Q waves in V2-3, ST elevation in lead 3 and ST depression in lead 1.

Biopsy of the tuberos xanthoma overlying the tendo achilles showed epidermal collection of foam cells and cholesterol clefts separated by fibrous tissues. There were also scattered Touton giant cells.

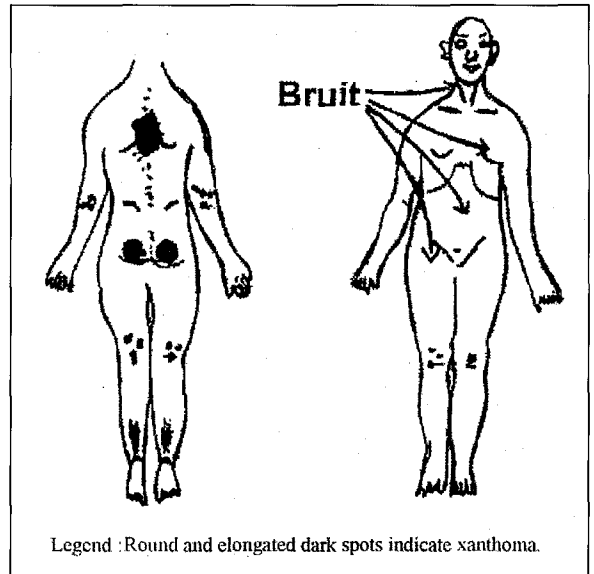


Fig. 1: Distribution of xanthoma and bruits in the hypercholesterolaemic patient, CSN.

Other physical, clinical and blood tests were normal. There was no evidence of diabetes mellitus, hypothyroidism or renal diseases.

Therapeutic Measures

The results of therapy with low cholesterol diet and cholesterol lowering drugs over a period of three months in hospital showed a marked clinical improvement in response to diet and drug combination of 32g cholestyramine and 6g nicotinic acid daily (Fig 2 & 3). By the time he left the hospital, he was 3.6kg heavier than on admission and his serum lipids were: total cholesterol 8.8mmol/l and triglycerides 0.64mmol/l. He was seen at the monthly follow-up clinic and was prescribed the same dietary and drug treatments as in the hospital. As the serum cholesterol remained above 7.8mmol/l, over the next six months, d-thyroxine 4mg was added to his medication. This brought the serum cholesterol down as low as 5.8mmol/l with some fluctuation but the cholesterol never touched 7.8mmol/l. During this period, the serum triglycerides fell in tandem with the serum cholesterol from 2.0mmol/l on admission to less than 0.6mmol/l.

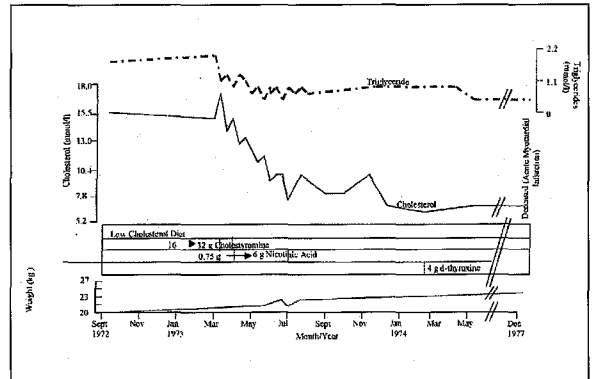
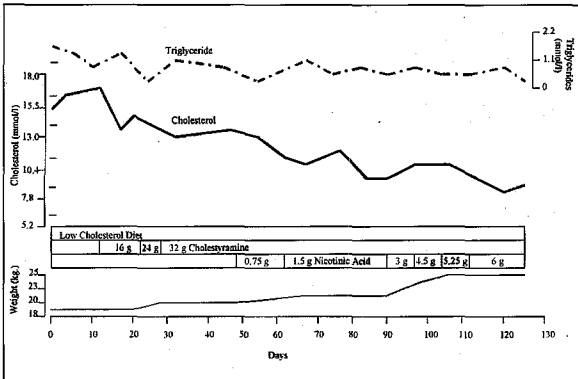


Fig. 2: Response of diet and drug therapy in a Type II homozygote, CSN. (Age: 11 years)

Fig. 3: Treatment of a Type II homozygote, CSN, over 4 1/2 years. (Age: 11 years)

The Double Master's test done on 31st July, 1973 whilst the patient was in hospital showed marked ST depression of 4mm in the anterior chest leads and reverted to normal, 6 minutes after the exercise.

The tuberous xanthoma of the gluteal region, elbows and knees showed marked regression two and a half years after the start of intensive treatment (Fig. 4a & 4b). Three years after intensive therapy, he was doing

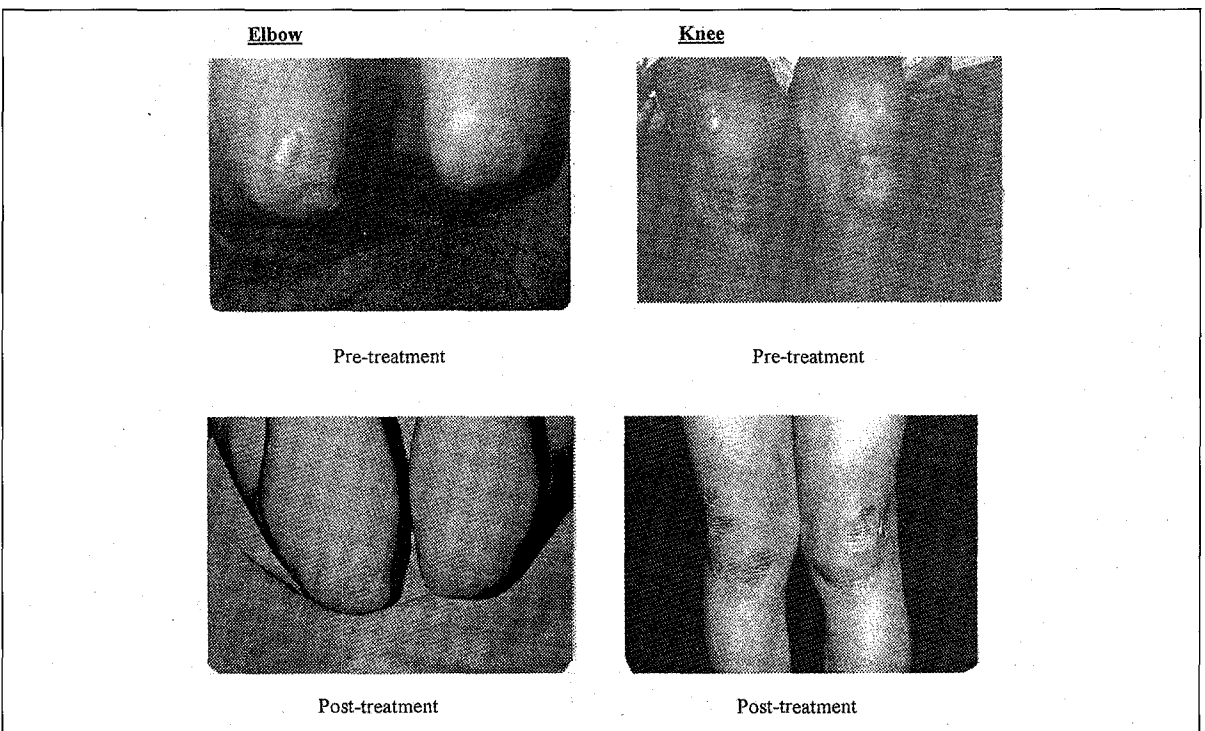


Fig. 4a: Regression of tuberous xanthoma in CSN.

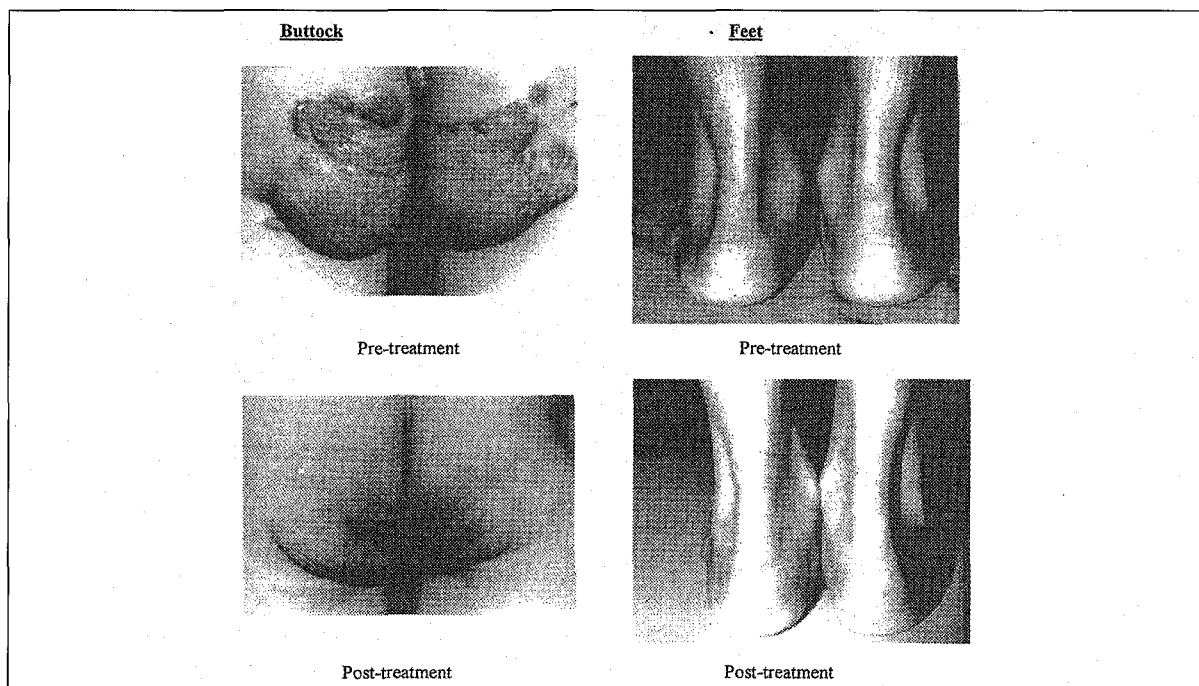


Fig. 4b: Regression of tuberous xanthoma in CSN.

very well in school in spite of his handicap, having been away from school for almost two years due to his illness. However, he was slightly retarded in physical growth weighing 30.9kg, standing at 141.6cm for a child of 14 years old.

In November 1977, the patient had a third myocardial infarction and died at the age of 15.

Family Study & Genetic Defect

The pedigree (family) tree of the patient is shown in Fig. 5. A couple who were both found to have hypercholesterolaemia gave birth to the patient in addition to five other children. The father aged 44 years had marked arcus cornealis and tedinous xanthoma of the tendo archilles and had elevated cholesterol of 8.9mmol/l. His Double Master's test showed ST depression and died of myocardial infarction at the age of 49. The mother was unrelated to the father (non-consanguinity). She had mildly elevated cholesterol (7.1mmol/l). The patient had three brothers aged 1, 5 and 6 with elevated cholesterol of 9.3mmol/l,

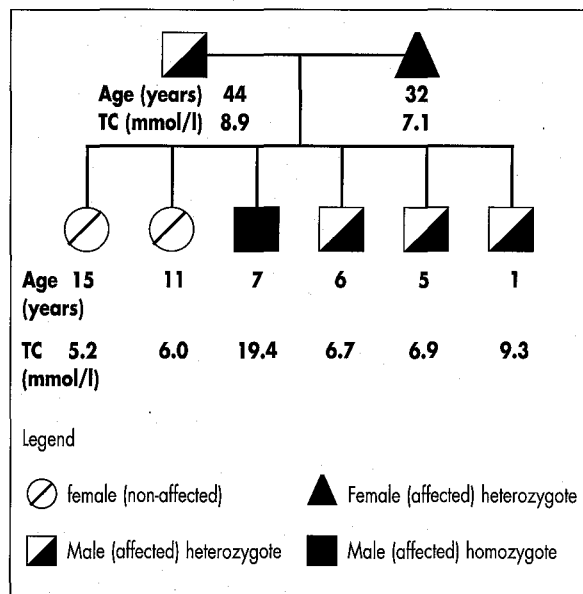


Fig. 5: Family tree of a homozygous Type II hypercholesterolaemic patient - CSN.

6.9mmol/l and 6.7mmol/l respectively. He had two sisters aged 11 and 15, with normal cholesterol levels. The patient's cholesterol level was extremely raised at 19.4mmol/l when he was 7 years of age.

Based on the family tree and the segregation of the hypercholesterolaemic trait from the presumed familial heterozygote parents, it can be postulated that the patient is likely to have inherited both the affected (autosomal dominant) traits from his parents, suggesting it is a familial homozygote for Type II hypercholesterolaemia. A segregation ratio of expected 1:2:1 ratio for AA, Aa and aa respectively in the offspring further reinforce the above hypothesis.

Familial Hypertriglyceridaemia

Case B

The patient, a Chinese girl Jq. W, aged 2½ years old, was referred for evaluation of her lipid management in the year 1977. The presence of neonatal jaundice led to the discovery of hyperlipidaemia. Her jaundice cleared and she remained well during the first year of her life with no history of episodes of abdominal pain. Hypertriglyceridaemia was confirmed by a paediatrician, who advised on a low-fat diet and more recently, medium-chain triglyceride was introduced. Apart from a rather variable appetite, the child seemed active and healthy.

The previous lipid tests showed raised total cholesterol and highly elevated triglycerides in the first 10 months. Subsequently, the lipid levels declined with dietary advice (Table I).

Clinical Examination

On examination, the 2½ years old girl weighed 10.8kg with a height of 87cm. She had three reddish papular rashes on the trunk and arm, which could possibly represent eruptive xanthomas but were not diagnostic. The only other clinical abnormality was slight enlargement (1cm) of the left lobe of the liver.

Family Study & Genetic Defect

The patient was born to a couple who were unrelated but both had hyperlipidaemia. In the case of the father, this was diagnosed 20 years ago and he was treated with the fatty omega-3 acid, namely, eicosa pentaenoic acid (EPA) and lovastatin. He also had late onset diabetes mellitus. Her mother was hypertriglyceridaemic and was also on EPA. One of her uncles (mother's brother) had a myocardial infarction at the age of 47. The patient had a brother, aged 4½ years, who did not get frequent attacks of abdominal pain and was known to be slightly hypertriglyceridaemic.

The lipid profile of the family members of the patient is given in Table 2a and 2b. From the family data and the specific lipid investigation (Fig. 6 and Table III), it appears that she had not inherited either lipoprotein lipase deficiency or Apo-lipoprotein CII deficiency traits from her parents, the usual situation in patients with hyperchylomicronaemia (Type I hyperlipoproteinaemia). However, her type V hyperlipidaemia was undoubtedly inherited.

There was a suggestion that her hypertriglyceridaemic condition might be attributed in part, to her Apo E2/E3 phenotype with the overproduction of triglyceride-rich lipoproteins as well as decreased clearance of the lipoproteins.

Table I
Lipid Profile of JQ. W. Since Birth (5/11/94)

Date	Age (Month)	TC		TG		HDL-C	
		mg/dl	mmol/l	mg/dl	mmol/l	mg/dl	mmol/l
10/11/94	0.2	111.9	2.9	1486.8	16.8	-	-
05/09/95	10	316.5	8.2	1486.8	16.8	23.2	0.6
23/06/96	19	200.7	5.2	1283.3	14.5	15.4	0.4
08/11/96	24	239.3	6.2	1725.8	19.5	7.7	0.2

Table IIa
Lipid Profile of JQ. W. Family

Parameter	Father (59 yr.)		Mother (40 yr.)		Brother (4 yr.)		Patient (2 yr.)	
	mg/dl	mmol/l	mg/dl	mmol/l	mg/dl	mmol/l	mg/dl	mmol/l
Cholesterol	206	5.3	145	3.8	164	4.2	238	6.2
Triglyceride	193	2.2	318	3.6	255	2.9	1729	19.5
HDL-C	34	0.88	-	-	-	-	8	0.21
LDL-C	133	3.4	-	-	-	-	-	-
Apo A1	150	-	115	-	131	-	118	-
Apo B	140	-	116	-	116	-	469	-

Table IIb
Lipid Profile of JQ. W'S Father Before and After Treatment

Date	Age (Year)	Weight (kg)	Glucose mmol/l	TC mmol/l	TG mmol/l	Treatment
01/07/77	40	70	5.5	8	2.1	NA
13/07/78	41	71	4.6	4.1	3.7	NA
02/08/79	42	73	4.4	5.9	3.5	NA
27/08/80	43	71	5.1	8.8	22.3	NA
06/08/84	47	71	5.1	8.8	22.3	NA
15/01/91	54	-	5.8	8	6.6	Mevacor
06/03/91	"	-	-	6.6	2.9	Mevacor
07/09/91	"	-	-	7.8	5.3	Mevacor
02/05/92	55	-	-	7.7	3.5	Mevacor
25/07/92	"	-	4.9	6.5	3.5	Mevacor
12/09/92	"	-	-	6.0	2.5	Mevacor
28/11/92	"	-	-	6.7	3.0	Mevacor
20/03/93	56	-	-	5.0	2.2	Zocor
16/10/93	"	-	-	5.8	2.8	Zocor
22/01/94	57	-	4.9	5.5	2.3	Zocor
20/07/94	"	-	-	4.8	1.7	Zocor
24/06/95	58	67	-	4.7	1.9	Zocor
03/02/96	59	69	5.0	5.2	2.9	Zocor

Apo E2/E3

Lp(a): 4mg/dl

NA : Not available

Presumably as well, along with the E2 allele she had also inherited familial combined hyperlipidaemia and/or familial hypertriglyceridaemic alleles from both parents. This means that she might have a combination of at least three genetic defects, the exact nature of which, apart from the E2 defect, we have to delineate and define.

Therapeutic Measures

From the point of view of future management, it would be reasonable to suggest a trial of omega-3 fatty acid, EPA, in an effort to reduce the VLDL component of her hypertriglyceridaemia as initial dietary treatment had produced some favourable results (Table IV). This could

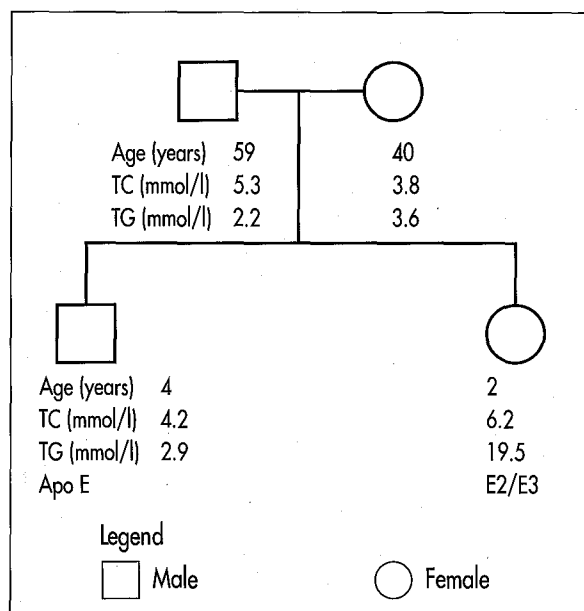


Fig. 6: Family tree of a Type V hyperlipidaemic patient (JQ.W.).

be instituted initially, assuming that the patient could swallow the fish oil. When the patient reaches the age of five, a trial of fenofibrate in a dose of 5mg daily can be recommended. This drug is licensed for use in children and the presence of an Apo E2/E3 phenotype is often predictive of a good response. The outcome of the therapeutic responses should be reviewed and appropriate treatment should be followed up.

Discussion and Conclusion

Familial hyperlipidaemia in children is not common. When the lipid disorder occurs, it is usually severe as most cases are often due to a homozygous defect. This means that intensive diet and drug therapy is required for the management of the disorder. In spite of the intensive therapy, they are known to run a galloping and unfavourable course.

Familial Type II hypercholesterolaemia, a genetic disorder caused by LDL-receptor defect, is known to be controlled by autosomal dominant inheritance. This

**Table III
Lipid Profiles and Other Tests for JQ. W. on**

Parameter	Value or Status	Reference Value
Total Cholesterol	6.2 mmol/l	4.0 - 6.5
Triglycerides	14.8 mmol/l	0.00 - 1.5
HDL Cholesterol	0.32 mmol/l	0.95 - 2.20
Total : HDL Ratio	19.4	Ideal <5
Apo A-I	78 mg/dl	112 - 201
Apo B	81 mg/dl	55 - 144
Lp(a)	<5 mg/dl	< 30
Lipoprotein type	Type V	
Apo E phenotype	E2/E3	
Apo C II	Present	
Post heparin Lipolitic Activity ;FFA/ml/hr (Intravenous heparin 1000 IU):		
Total Lipase	33.5 mmol/l	62.8
Lipoprotein Lipase	22.9 mmol/l	36.3
Hepatic Lipase	10.5 mmol/l	26.5

**Table IV
Effect of Dietary Treatment of JQ. W**

Treatment Status	Total Cholesterol mmol/l	Triglyceride mmol/l	HDL-Cholesterol mmol/l
Pre-treatment ^a	5.8	16.9	0.4
	(2.4 - 8.2) ^b	(14.5 - 19.5) ^b	(0.2 - 0.6) ^b
Post-treatment	3.7	5.2	0.4

^a Pre-treatment data collected from 10th. Nov. 1994 to 10th. Apr. 1997

^b refers to minimum - maximum values

disorder exhibits a condition of raised cholesterol and it is often associated with xanthomatosis. Khoo³ reported in his earlier study that majority of the patients with lipid disorders were of Type II hypercholesterolaemia and were mostly found in adults which were likely to be heterozygous in their genetic defect. The "homozygous" hypercholesterolaemic patient reported in this study is of rare occurrence and it is the first case documented in this country.

The present case of Type II hypercholesterolaemic patient, an 11-year-old boy, CSN, presented himself as a typical case of homozygous familial hypercholesterolaemia, has fulfilled the criteria for familial type II homozygous hypercholesterolaemia⁷ as follows:

1. the serum cholesterol of the index case was about twice that of the heterozygotes in the same kindred.
2. both parents were affected (hypercholesterolaemic).

The minor criteria for homozygous was also present in this case:

Serum cholesterol being above 13mmol/l, xanthomatosis appearing before the age of 19 years and vascular lesions before 20 years. In this current age, LDL receptor gene analysis would have been done to confirm the diagnosis.

The clinical features, biochemistry and the natural history of this patient was similar to homozygotes reported in Lebanon⁸, United States⁷ and Japan⁹.

For the homozygous Type II hypercholesterolaemic child, the risk of premature death from coronary heart disease is so high that vigorous measures to reduce the plasma lipids are obligatory. This applies similarly to both the parents and majority (3/4) of the children with this lipid disorder, albeit less severe due to their heterozygous state. They too, particularly the parents, may die of premature coronary heart disease or develop medical problems in the course of their life. All these will add more tension, suffering and economic problems to the family. Thus, the strain on the whole family can be severe and the physician's role may not be limited to administering therapy alone, but other forms of support such as counselling can be expected of him.

The Type V hyperlipidaemia was at one time not so well defined and had caused some confusion in terms of its phenotypic expression and genetic inheritance. It is a genetic disorder of lipoprotein metabolism with elevated fasting chylomicronaemia and elevated level of VLDL¹⁰. This lipoprotein abnormality might be a primary familial disease, or it may be secondary to a variety of conditions, such as diabetes, alcoholism, nephrotic syndrome or hypothyroidism. Depending on

the degree of hypertriglyceridaemia, the fasting plasma appeared opalescent to milky, and the clinical pictures show similarities to familial lipoprotein lipase (LPL) deficiency. Biochemically, the Type V disease seemed closely related to Type IV. This is because, by an appropriate treatment, Type V pattern could be converted to Type IV. On the other hand, there were a number of arguments suggesting that primary Type V hyperlipoproteinaemia was a genetic syndrome, (certainly not a single disease) separate from familial Type IV hypertriglyceridaemia.

Type V is a relatively uncommon disorder but not as rare as familial LPL deficiency. In population screenings of small scale, it was often not found at all, since the prevalence among males was 0.2 to 0.3 percent¹¹⁻¹³. A higher frequency was found among populations that were selected on the basis of ischaemic heart disease¹⁴.

The early description of primary Type V were under different names and were not clearly distinguished from Type I and Type III hyperlipoproteinaemia before the introduction of the lipoprotein classification system. There were also some confusion in the separation of primary and secondary forms of Type V. Such a separation is not feasible without family screening and remain ambiguous even after that because factors causing secondary hyperlipidaemia can be superimposed on a primary genetic trait.

The first three kindred with defined familial Type V hyperlipoproteinaemia were reported by Fredrickson, Levy and Lees¹⁵.

The presenting symptoms of Type V are related to excessive chylomicronaemia and are thus similar to those seen in patients with familial LPL deficiency, including eruptive xanthomatosis and episodic abdominal pains with or without established pancreatitis. The two disorders differ in many aspects which may give important clues for diagnosis. In contrast to Type I, the onset of symptoms in Type V patients date to adulthood and even to middle age. Occasionally, children with familial Type V were reported^{7,16,17,18}. This disease usually manifested itself when the patient was between 20 and 50 years of age, males presenting earlier than females. The onset of clinical symptoms may be associated with

some factor which itself causes hypertriglyceridaemia such as pregnancy, use of oestrogenic hormones, excessive alcohol consumption, rapid gain in body weight from appearance of uncontrolled diabetes mellitus.

The diagnosis of familial Type V hyperlipoproteinaemia cannot be made by exclusion of other causes only; it must be based on lipid and lipoprotein analysis of first degree relatives, preferably of adults. Differentiation between, Type I and V made by specific assays of LPL activity from either post-heparin plasma or adipose tissue or preferably both¹⁹. The currently available methods are relatively simple and specific. Post heparin plasma LPL activities of less than 10 percent of the mean level of normolipaemic controls of similar age and sex are usually diagnostic for LPL deficiency, while values between 10 - 20 percent of the control mean, are suspect. Low values should be further checked, by adding normal serum (or Apo C-II) to the assay mixture in order to exclude the possibility of Apo C-II deficiency. If the activity is significantly increased by the addition of normal serum, the latter diagnosis is likely and it can be confirmed by assaying Apo C-II.

In our Type V case study, both parents and an elder brother have raised triglycerides favouring Type V. As in Type I, the proband have normal or slightly elevated triglycerides. The patient has slightly low LPL and slightly low hepatic lipase. In addition, she has a Type V phenotype on lipoprotein electrophoresis rather than Type I. The presence of hyperlipidaemia in both parents is also against the diagnosis of lipoprotein lipase deficiency, which is a recessive disorder.

Thus, the presence of Apo E2/E3 probably contributed partly to her hypertriglyceridaemia.

Childhood familial Type V hyperlipidaemia is unique and uncommon because majority of the Type V cases were described in adults^{20,21}. A few cases of familial Type V hyperlipidaemia adults were also documented in Malaysia^{1,3,4}. It is therefore essential to carry out further investigations and follow-ups with such cases to ascertain the precise nature of the genetic defect and therapeutic responses.

In general, the diagnosis and management of childhood lipid problems requires the teamwork of paediatricians, cardiologists, dieticians and social workers with specialised lipid laboratory back-up.

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