Familial hypo- β -lipoproteinaemia

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Fosbrooke, A., Choksey, S., and Wharton, B. (1973). *Archives of Disease in Childhood*, 48, 729. **Familial hypo- β -lipoproteinaemia.** A 2-year-old boy investigated because of small stature, had low serum levels of cholesterol (74 mg/100 ml) and β -lipoprotein cholesterol (20 mg/100 ml). Faecal fat, jejunal biopsy, red cell morphology, and plasma growth hormone and thyroxine were normal, and it was concluded that the small stature was hereditary.

A family study showed a similar lipoprotein abnormality in the patient's mother; her serum cholesterol was 83 mg/100 ml and β -lipoprotein cholesterol 34 mg/100 ml. Analysis of the β -lipoprotein fraction in both child and mother showed it to have an abnormal lipid composition; the cholesterol/phospholipid ratio was 1.0 and 0.8, respectively (normal 1.7), and within the phospholipid components the proportion of sphingomyelin was markedly reduced (11% and 5%, normal 30%). These findings differ from previous reports that the composition of β -lipoprotein is normal. Familial hypo- β -lipoproteinaemia has been shown to be inherited as an autosomal dominant, and our findings are in agreement.

Although a few individuals with this condition have been reported to have some of the features associated with α - β -lipoproteinaemia, neither our patient nor his mother had any gastrointestinal, haematological, or neurological abnormalities.

The familial occurrence of low concentrations of serum β -lipoprotein has been reported in one Dutch (van Buchem *et al.*, 1966), one French (Richet *et al.*, 1969), and two American families (Mars *et al.*, 1969; Levy *et al.*, 1970). In one patient there was severe neurological disease (Mars *et al.*, 1969), whereas the other patients and their families were symptom free. The condition is inherited as an autosomal dominant. We have found a low concentration of β -lipoprotein in a 2-year-old boy in the course of investigations for diarrhoea and small stature, and subsequently we have established that this was a familial condition. We made more detailed studies to determine the lipid composition of the β -lipoprotein fraction in the patient and to compare this with the composition found in some patients with other causes of a low β -lipoprotein concentration.

Patients and methods

Patient. The child was born at term weighing 2.0 kg and was discharged from hospital 4 weeks later at 2.3 kg. At 22 months he was admitted with diarrhoea and vomiting, and oral rehydration was necessary. His small size was noted (height and weight below 3rd centile) but, in view of his low birthweight and the parents' shortness of stature (mother 150 cm, father 160

cm), further investigation was not considered necessary. After discharge from hospital, however, he failed to gain weight during 2 months observation and there were further episodes of diarrhoea. He was therefore readmitted for a more detailed assessment. The serum cholesterol was 75 mg/100 ml, and it was thought this finding together with his small stature and diarrhoea might indicate malabsorption. No other evidence of malabsorption or of intestinal disease was found (faecal fat, jejunal morphology including fat stain, jejunal disaccharidase levels, resting pancreatic enzyme levels in duodenal juice, stool sugars, and serum levels of iron, folate, vitamin E, vitamin A, protein, calcium, alkaline phosphatase, and magnesium, were all normal); plasma growth hormone, thyroxine, urinary concentrating ability, and amino acid chromatography were also normal. Studies of plasma lipids in other members of the family were then carried out.

The child has subsequently grown well (during 3rd year of life, height velocity 25th centile, weight velocity 25–50th centile) and there have been no further episodes of diarrhoea. At 3 years of age his faecal fat and serum concentrations of vitamins E and A were again normal. Neurological development is normal and there is no peripheral neuritis or retinopathy.

The child's mother, a healthy woman aged 23, had no history of serious illness and on examination did not have peripheral neuritis or retinopathy.

The child's father, maternal grandfather, 3 maternal aunts and their children were alive and well. They were

TABLE
Serum lipids

Subjects	Whole serum (mg/100 ml)			β -lipoprotein			
	Cholesterol (C)	Phospholipid (P)	Triglyceride (TG)	C	P	C/P ratio	TG
Patient	74	88	11	20	21	1.0	3
Mother	83	101	21	34	43	0.8	4
Father	213	239	58	124	72	1.7	10
Case 1 (heterozygous α - β -lipoproteinaemia)	153	165	30	59	34	1.7	5
Case 2 (cord blood)	66	122	19	19	18	1.1	5
Case 3 (cord blood)	63	91	23	30	28	1.1	7
Case 4 (pancreatic hypoplasia)	90	115	32	31	19	1.6	6
Normal children*	189	187	46	98	58	1.7	11
mean (and range)	(160-232)	(150-241)	(34-87)	(48-136)	(33-76)	(1.2-2.1)	(5-16)

*14 healthy children 1-12 years of age.

†PC, phosphatidyl choline; S, sphingomyelin; PE, phosphatidyl ethanolamine; LP, lysophosphatidyl choline.

seen and blood samples were obtained from them, but a clinical examination was not performed. The maternal grandmother had died at age 62 after a 'stroke'.

Cases with other causes of low serum β -lipoprotein.

Case 1. Aged 42, no symptoms, mother of an only child with α - β -lipoproteinaemia (Salt *et al.*, 1960). Has reduced serum lipid concentrations as does the child's father. This appears to be an expression of the heterozygous condition for α - β -lipoproteinaemia.

Case 2 (female) and Case 3 (male). Babies of normal weight born at 40 weeks' gestation from whom umbilical cord blood samples were obtained.

Case 4. A boy aged 13. Pancreatic dysplasia with neutropenia, steatorrhoea (faecal fat 18 g/day), and reduced serum lipid concentrations, presumed secondary to fat malabsorption.

Methods. Venous blood was collected after a 12- to 14-hour overnight fast and serum lipoproteins were separated the same day by electrophoresis on agarose gel (Johansson, 1972), and by density gradient ultracentrifugation (Cornwell *et al.*, 1961). For the fractions separated by ultracentrifugation we use the terms β -lipoprotein for the sf_{3-9} fraction, and α -lipoprotein for the high density fraction. Cholesterol was estimated by a ferric chloride autoanalyser method (Fosbrooke and Pringle, 1970); triglyceride concentration and the fatty acid composition of triglyceride and cholesterol ester were determined by gas-liquid chromatography (Fosbrooke and Tamir, 1968). Thin-layer chromatography (method similar to that of Skipski *et al.*, 1967) was used to separate the phospholipids into 4 classes, phosphatidyl choline, lysophosphatidyl choline, sphingomyelin, and phosphatidyl ethanolamine; and lipid phosphorus was estimated colorimetrically (Bartlett, 1959).

Results

Patient and parents. The Table shows the serum lipid concentration in the patient and his parents. Both he and his mother had reduced serum concentrations of cholesterol, phospholipid, and triglyceride; the values for his father were normal. Fatty acid composition of triglyceride and cholesterol ester and the serum concentrations of vitamins A and E in the child and mother were normal. Separation and lipid analysis of the lipoprotein fractions showed marked reductions in β -lipoprotein and slight reductions in α -lipoprotein for the patient and his mother.

FIG. 1.— β -lipoprotein, lipid composition (top); phospholipid composition (bottom) in patient, his mother, and normal children. PE, phosphatidyl ethanolamine.

hypo- β -lipoproteinaemia

9) lipids (mg/100 ml)				α -lipoprotein (high density) lipids (mg/100 ml) serum							
Phospholipids† (% distribution)				C	P	C/P ratio	TG	Phospholipids† (% distribution)			
PC	S	PE	LP					PC	S	PE	LP
82	11	6	1	47	77	0.6	6	75	14	3	8
92	5	2	1	38	73	0.5	5	71	18	4	7
				74	141	0.5					
48	33	13	5	70			7				
62	19	3	16	46	95	0.5	5	65	18	3	14
61	25	6	9	29	62	0.5	4	60	26	5	9
69	22	4	6	50	109	0.5	14	64	16	7	13
64	30	4	2	72	119	0.6	11	71	17	4	7
(57-66)	(28-34)	(3-6)	(0-3)	(52-102)	(86-176)	(0.5-0.7)	(6-19)	(63-74)	(9-23)	(3-10)	(1-11)

Fig. 1 shows the lipid composition of β -lipoprotein; in both patient and mother there was a disproportionate reduction in the amount of cholesterol (cholesterol/phospholipid ratios 1.0 and 0.8, respectively, compared with the normal mean value of 1.7). Serum obtained from the patient 2 hours after eating fat contained normal chylomicrons. Fig. 1 also shows the composition of the phospholipid in β -lipoprotein. There was a deficiency of sphingomyelin and relative excess of phosphatidyl choline. Both the lipid composition and the phospholipid composition of α -lipoprotein were normal in patient and mother, and the results are given in the Table.

Family. Fig. 2 shows the family tree and the serum cholesterol concentration of each member. The cholesterol concentrations were normal in all cases apart from mother and child.

Cases 1-4. The results for some patients having nonfamilial hypo- β -lipoproteinaemia are included

FIG. 2.—Family tree showing serum cholesterol concentrations (mg/100 ml) in the patient's relatives. ■ male, ● female.

in the Table for comparison. The findings are similar to those in the patient in that (a) whole serum concentrations of cholesterol, phospholipid (except Case 1), and triglyceride are reduced; (b) these reductions are more evident in the lipids of the β -lipoprotein fraction; (c) cord blood samples show low cholesterol/phospholipid ratios in β -lipoprotein; (d) there is a less marked reduction in the lipids of the α -lipoprotein fraction; (e) the cholesterol/phospholipid ratios are normal in α -lipoprotein and the phospholipid composition is the same as or similar to the normal.

The findings are dissimilar to those in the patient in that (a) Cases 1 and 4 have normal cholesterol/phospholipid ratios in β -lipoprotein; (b) the proportion of sphingomyelin in β -lipoprotein is either normal (Case 1) or only slightly reduced (Cases 2, 3, 4); (c) the proportion of phosphatidyl choline is either normal (Cases 2 and 3) or only slightly increased (Case 4); (d) lysophosphatidyl choline is increased, particularly in the cord blood samples, but this could be an artefact arising from some delay before analysing the serum.

Discussion

Previous studies of familial hypo- β -lipoproteinaemia have reported no abnormality in lipid composition of lipoproteins apart from an observation by van Buchem *et al.*, 1966, that the serum of his patient contained more sphingomyelin and less phosphatidyl choline than normal. Since normal α -lipoprotein contains a lower proportion of sphingomyelin than β -lipoprotein, this finding for whole serum is unexpected.

At birth the concentration of serum β -lipoprotein

is low and increases swiftly with feeding in the first days of life, and at the same time the cholesterol concentration has doubled by the end of the first week (Darmady, Fosbrooke, and Lloyd, 1972). Since there is evidence in familial hypo- β -lipoproteinaemia of a reduced rate of synthesis of β -lipoprotein (Levy *et al.*, 1970), this could possibly represent a persistence of the fetal situation into later life. Our patient had serum lipid concentrations similar to those in cord blood, and comparison of the composition and concentration of the lipoprotein fractions shows some common features: the concentration of β - was reduced more markedly than that of α -lipoprotein, and the ratio of cholesterol to phospholipid in the β fraction was low. However, we did not find the marked changes in phospholipid composition (deficiency of sphingomyelin and excess of phosphatidyl choline) in the cord blood β -lipoprotein, and it is therefore unlikely that familial low levels of β -lipoprotein do represent a persistence of the lipoprotein situation at birth.

The low concentrations of β -lipoprotein present in both parents of the child with a- β -lipoproteinaemia probably represent the heterozygous state for this disease. Comparison between the β -lipoprotein from such a heterozygote and that in our patient shows dissimilarities in the lipid composition; the ratio of cholesterol to phospholipid was normal, and there was no deficiency of sphingomyelin and/or excess of phosphatidyl choline in the heterozygote. Furthermore, in the patients with a- β -lipoproteinaemia the consistent abnormality of phospholipid composition was an excess of sphingomyelin (Ways, Reed, and Hanahan, 1963). It is unlikely, therefore, that familial hypo- β -lipoproteinaemia is merely the heterozygote expression of a- β -lipoproteinaemia, and it seems that the two conditions are genetically distinct.

Low concentrations of β -lipoprotein are found in patients with fat malabsorption. Such patients (e.g. Case 4 in the Table), however, do not have the altered cholesterol/phospholipid ratio nor the marked deficiency in the proportion of sphingomyelin found in our patient.

The low concentrations of β -lipoprotein in our patient and in his mother are presumably genetically determined. Our results show that the lipid composition is different from that found in subjects having low β -lipoprotein concentration of different

aetiology. Neither mother nor child has signs or symptoms, and the child's small stature is adequately explained by hereditary factors and low birthweight. The prognosis for the child seems good, but in view of the association between low plasma lipids and neurological disease, we shall continue supervising his progress.

Professor J. D. L. Hansen, University of the Witwatersrand, Johannesburg, saw one of the aunts and her two children and estimated their serum lipids. Drs. G. McCarthy, M. Robards, M. Rossiter, T. Matthews, and Sister L. Robertson helped in the management of the patient. Professor O. H. Wolff and Dr. J. K. Lloyd allowed us to study Cases 1 and 4. We are grateful to the patient's relatives, and to Miss C. Jackson for secretarial help.

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