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Familial hypobetalipoproteinaemia in 9 children diagnosed as the result of cord blood screening for hypolipoproteinaemia in 10 000 Danish newborns

G. E. ANDERSEN, K. BROKHATTINGEN, AND P. LOUS

Neonatal Department, Rigshospitalet, and the Department of Clinical Chemistry, Bispebjerg Hospital, Copenhagen

SUMMARY Out of 10 440 children, 266 with low (<2·5 centile) values for very low-low density lipoproteins in cord serum were chosen to be followed up to find out how many came from families with familial hypobetalipoproteinaemia (FHBL). In 176 families (66% of 266 families), FHBL was diagnosed in 9 children and their families.

Familial hypobetalipoproteinaemia (FHBL) is a genetic disorder which differs from classical abetalipoproteinaemia (ABL) by the presence in the serum of abnormally low, immunochemically identifiable, low density lipoproteins (LDL) in the propositus and in at least one first-degree relative (with no disease to which hypobetalipoproteinaemia could be secondary). An autosomal dominant mode of inheritance is likely (Herbert *et al.*, 1978). FHBL has been described in homozygous and heterzygous forms (Cottrill *et al.*, 1974). Homozygotes are biochemically indistinguishable from patients with ABL having no apolipoprotein B (apo B) or LDL, but they lack the severe neuromuscular degeneration typical of ABL (Salt *et al.*, 1960; Cottrill *et al.*, 1974; Biemer and McCammon, 1975; Muller and Lloyd, 1977; Herbert *et al.*, 1978).

The heterozygous condition is normally asymptomatic; there are however data which suggest that the low serum LDL-C levels may defer the development of coronary heart disease (CHD), thus prolonging life expectancy (Glueck *et al.*, 1976a). This makes FHBL of interest in regard to CHD prevention. So far only two children have been reported born with low levels of total cholesterol (T-C) and LDL-C who were found to have FHBL (Glueck *et al.*, 1976b; Stein, 1977). We describe 9 more such children.

Patients

In our screening programme for hyper- and hypolipoproteinaemia, cord blood was obtained from 10 440 infants (Andersen and Gry Nielsen, 1976). 266 (2·5%) of the 10 440 infants with the lowest VLDL-LDL values were chosen to find out whether they came from families with FHBL.

176 (66%) of the 266 families joined the study after informed consent. Venous blood samples were taken from all 176 fathers and 176 mothers after a 12-hour fast and at least 3 months after birth of their children. Serum lipid and lipoprotein values were determined for each, and if serum T-C was found to be below the sex- and age-adjusted 5th centile value for normal Danes (Andersen and Friis-Hansen, 1976), they were estimated at least three times more, and all other members of the family were invited to join the study so that their serum lipids and lipoproteins could also be determined. In the children <2 years venous blood was taken after an 8-hour fast, in the children >2 years it was taken after a 10- to 12-hour fast.

Methods

Cord serum VLDL-LDL was measured by a modification of the $CaCl_2$-heparin turbidimetric method

Abbreviations:

FHBL:	Familial hypobetalipoproteinaemia
ABL:	Abetalipoproteinaemia
apo B:	Apolipoprotein B
CHD:	Coronary heart disease
T-C:	Total cholesterol
TG:	Triglyceride
VLDL:	Very low density lipoproteins
LDL:	Low density lipoproteins
HDL:	High density lipoproteins

Neonatal Department, Rigshospitalet, Copenhagen
G. E. ANDERSEN
K. BROKHATTINGEN
Department of Clinical Chemistry, Bispebjerg Hospital, Copenhagen
P. LOUS

of Burstein and Samaille (1959), on a Greiner Selective Analyser II using 20 μl serum and 1000 μl $CaCl_2$-heparin-precipitation solution. After 5 minutes at 37°C the sample was read at 578 nm against a sample blank. Concentration of VLDL-LDL was expressed in arbitrary units corresponding to the extinction. A frozen (−20°C) stock solution of pooled cord serum (VLDL-LDL concentration: 45 arbitrary units) was thawed and included in over 100 runs. Coefficient of variation was 1·6%, T-C was measured enzymatically on a Greiner Selective Analyser II as described by Borner and Klose (1977). Two cholesterol standards (K-77 and Pathonorm) were included in over 250 separate runs; coefficients of variation were 3·1 and 4·0% respectively. VLDL-LDL-C was measured manually after $CaCl_2$-heparin-precipitation in duplicate (Andersen and Gry Nielsen, 1976). VLDL-C was measured manually in duplicate after ultracentrifugation in a 40·3 rotor, Beckman type L ultracentrifuge at 10°C at 40 000 rev/min for 20 hours. Tubes were sliced. HDL-C values were calculated as the difference between T-C and VLDL-LDL-C.

Serum TG was measured manually in duplicate using the enzymatic method of Eggstein and Kreutz (1966). Two Liponorm triglyceride standards were included in over 100 separate runs. Coefficient of variation was 3·6% (for the 0·42 mmol/l triglyceride Liponorm) and 2·0% (for the 2·50 mmol/l triglyceride Liponorm). Nonparametric statistics (Siegel, 1956) were used.

Results

The serum lipid and lipoprotein values were analysed in the first 200 parents who joined the study. Eight of these 200 parents had serum T-C below the sex- and age-adjusted 5th centile value for normal Danes (Andersen and Friis-Hansen, 1976) and so were assessed for FHBL. Serum lipid- and lipoprotein values in the remaining 192 parents and their 17 children aged 5–19 years are given in Table 1.

Table 1 *Centile values for T-C and LDL-C in the reference groups*

Age groups (years)	*n*	*Centile values*									
		5		*10*		*50*		*90*		*95*	
		T-C (mmol/l)	*LDL-C (mmol/l)*	*T-C (mmol/l)*	*LDL-C (mmol/l)*	*T-C (mmol/l)*	*LDL-C (mmol/l)*	*T-C (mmol/l)*	*LDL-C (mmol/l)*	*T-C (mmol/l)*	*LDL-C (mmol/l)*
1–2	190	3·48	1·58	3·69	1·83	4·75	2·61	5·77	3·42	6·08	3·67
3–4	64	3·40	1·51	3·69	1·92	4·72	2·47	5·75	3·43	6·07	3·82
5–19	17			3·89	1·50	4·30	2·09	5·56	3·02		
20–29											
Women	64	4·31	1·82	4·41	1·96	5·20	2·64	6·62	3·91	7·07	4·14
Men	52	4·22	1·85	4·33	2·12	5·13	2·64	6·57	3·70	6·72	4·07
30–39											
Women	33	4·57	2·04	4·64	2·23	5·38	2·81	6·30	3·90	6·94	4·76
Men	43	4·46	2·14	4·70	2·33	5·46	2·99	6·73	3·95	6·88	4·15

Conversion: SI to traditional units—cholesterol: 1 mmol/l ≈ 38·6 mg/100ml..

Table 2 *Lipid and lipoprotein-cholesterol values in parent/child pairs with familial hypobetalipoproteinaemia*

Kindred	*Age (years)*	*T-C (mmol/l)*	*VLDL-C (mmol/l)*	*LDL-C (mmol/l)*	*HDL-C (mmol/l)*	*TG (mmol/l)*
1 III 4	28	3·56	0·12	0·96	2·48	0·42
1 IV 4	1·4	3·16	0·09	0·81	2·26	0·39
2 III 2	26	4·03	0·11	1·28	2·64	0·40
2 IV 1	2·3	3·34	0·58	0·95	1·81	1·34
3 IV 2	32	4·09	0·09	0·97	3·03	0·42
3 V 2	1·1	2·94	0·08	0·73	2·13	0·49
4 III 2	26	3·68	0·06	0·99	2·63	0·49
4 IV 1	1	2·10	0·27	0·49	1·34	0·44
5 III 7	29	3·82	0·47	1·93	1·42	1·17
5 IV 5	1·3	2·76	0·08	1·24	1·44	0·62
6 III 1	32	3·58	0·13	1·10	2·35	0·55
6 IV 3	2	3·25	0·40	1·03	1·82	1·04
7 III 2	24	4·01	0·15	1·31	2·55	0·58
7 IV 1	1·1	2·54	0·36	0·68	1·50	0·76
8 III 4	19	3·97	0·09	1·36	2·52	0·39
8 IV 1	1·3	3·31	0·04	1·13	2·14	0·39
9 II 1	46	3·47	0·47	1·75	1·25	1·23
9 III 10	1·6	3·37	0·20	1·33	1·84	0·89

Conversion: SI to traditional units—triglyceride: 1 mmol/l ≈ 88·5 mg/100 ml.

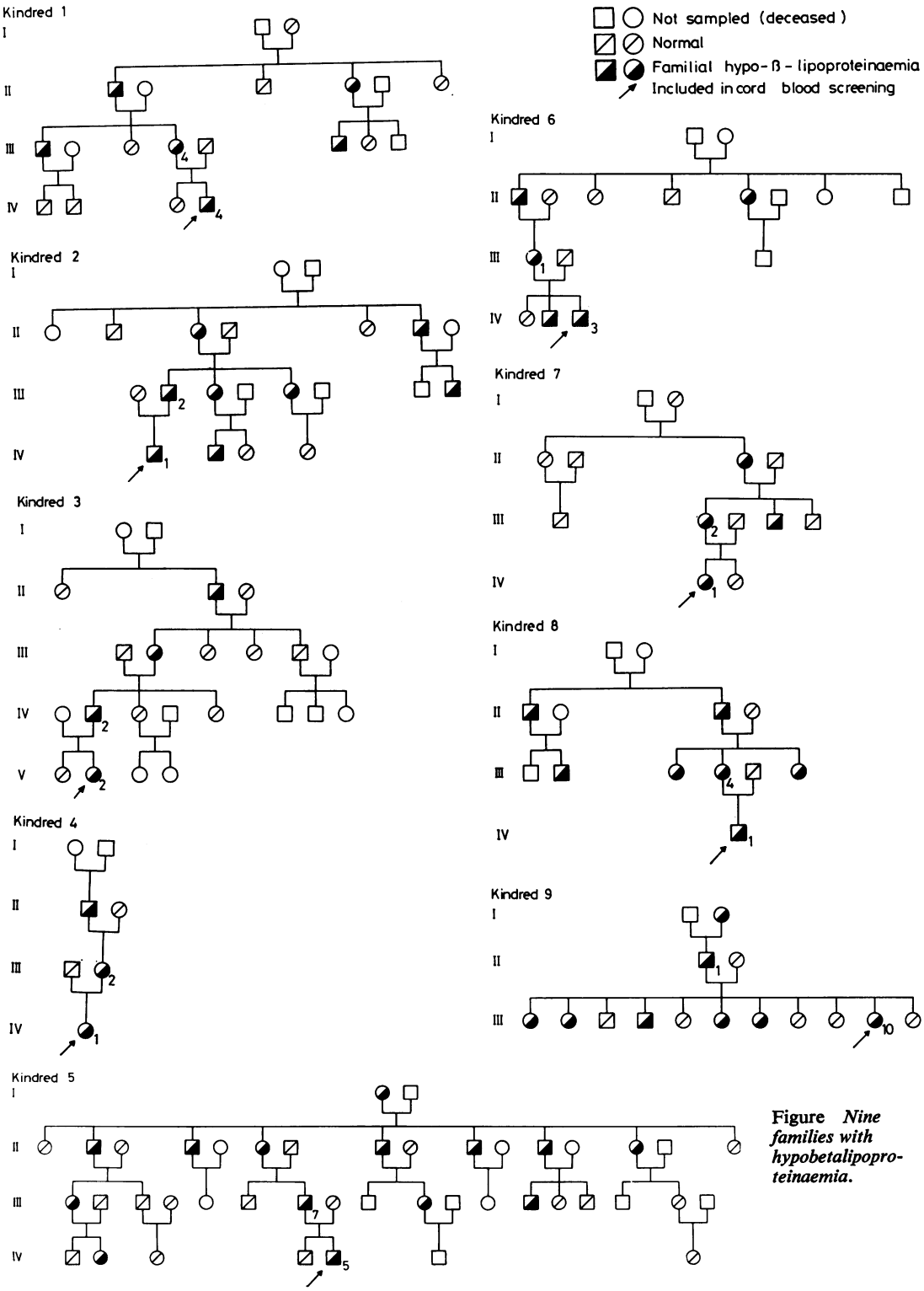

Figure *Nine families with hypobetalipoproteinaemia.*

Table 1 also gives the serum lipid- and lipoprotein values in 190 children aged 1–2 years described by Andersen *et al.* (1979a), and in 64 children aged 3–4 years described by Andersen *et al.* (1979b).

FHBL was found in 9 of the 176 families followed up. These 9 families are shown in the Figure, and the corresponding lipid- and lipoprotein values in parent/child pairs are given in Table 2. None of the parents or grandparents had been known to have FHBL before the study.

Discussion

The distribution of serum T-C values in 20- to 29- and 30- to 39-year-old men and women in the study is almost identical with that found earlier in similarly aged Danish fathers and mothers, in whom the 5th centile value for serum T-C was 4·26 and 4·42 mmol/l respectively (Andersen and Friis-Hansen, 1976).

The study did not allow precise calculation of the incidence of FHBL in Danish children, as only 66% of newborn babies with <2·5 centile values for cord serum VLDL-LDL were studied. As out of 10 000 consecutively born infants we found 9 with a three-generation vertical transmission of hypocholesterolaemia, this gives an incidence of at least 0·09%.

Hitherto only two children with FHBL had been reported with low cord serum T-C and/or LDL-C. The child described by Glueck *et al.* (1976b) had a normal cord serum T-C of 1·37 mmol/l and a low LDL-C of 0·23 mmol/l. In the child described by Stein (1977) cord serum T-C was 1·29 mmol/l and LDL-C 0·44 mmol/l. In the present study where only the cord serum VLDL-LDL was determined by the turbidimetric screening method, we show that in newborn babies with low values of cord serum VLDL-LDL, FHBL can be diagnosed at follow-up in at least 0·09% of the children and their families. The condition is therefore by no means a rare inborn error of metabolism.

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Correspondence to Dr G. E. Andersen, Neonatal Department, GN 5024, Rigshospitalet, 9 Blegdamsvej, DK-2100 Copenhagen, Denmark.

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