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neonate

Hyperalphalipoproteinemia, Birth to Age Two Years

R. C. TSANG, KIRK NEELY, AND C. J. GLUECK[18]

Lipid Research Clinic and General Clinical Research Center, and the Departments of Medicine, Pediatrics, Epidemiology, and Biostatistics, University of Cincinnati, College of Medicine, Cincinnati, Ohio, USA

Summary

Interrelationships of high-density lipoprotein cholesterol (C-HDL) with total plasma cholesterol (TC), triglyceride, and low-density lipoprotein cholesterol, as well as longitudinal maintenance of C-HDL rank order (tracking) from birth to age 2 years were assessed in 76 hypercholesterolemic neonates (cord blood, TC > 95 mg/dl) with focus upon 34 hyperalphalipoproteinemic neonates who had cord blood C-HDL > 61 mg/dl, ≥ the 99th percentile. Cord blood C-HDL correlated closely ($P < 0.01$) with C-HDL at 6, 12, and 18 to 24 months ($r = 0.32$, 0.49, and 0.39, respectively). C-HDL levels at 12 months and 18 to 24 months were closely associated ($r = 0.68$ and $P < 0.01$). C-HDL at birth, 6, and 12 months correlated positively ($P < 0.01$) with TC levels ($r = 0.28$, 0.30, and 0.36, respectively). Conversely, C-HDL at birth, 6 and 12 months correlated inversely with TG ($P < 0.01$) ($r = -0.41$, -0.40, and -0.49, respectively). At birth and at 18 to 24 months, C-HDL correlated inversely ($P < 0.05$) with C-LDL ($r = -0.36$ and -0.31, respectively). Of neonates having cord blood C-HDL in the highest quartile, 38, 56, and 60%, respectively at ages 6, 12, and 18 to 24 months retained C-HDL levels in the highest quartile; 56, 75, and 70%, respectively, retained C-HDL levels > the 50th percentile. Of 13 neonates having the highest initial cord blood C-HDL levels, cord blood C-HDL ≥ 69 mg/dl, nine had one or more C-HDL values > 70 mg/dl (the 90th percentile for childhood), throughout the 12- to 60-month follow-up period. Moreover, where more than one follow-up measurement was available, there was relative stability of elevated C-HDL measurements. Many infants with cord blood hyperalphalipoproteinemia are likely to have persistent elevations of C-HDL at ages 1 and 2 years. If they maintain elevated C-HDL into adulthood, they may, speculatively, be at reduced risk for coronary heart disease, given the strong inverse association of C-HDL with coronary heart disease.

Speculation

Many infants with cord blood hyperalphalipoproteinemia are likely to have persistent elevations of high-density lipoprotein cholesterol (C-HDL) at ages 1 and 2 years. If they maintain elevated C-HDL into adulthood, they may, speculatively, be at reduced risk for coronary heart disease, given the strong inverse association of C-HDL with coronary heart disease.

In a recent study by Frerichs *et al.* (4), as part of a community study of cardiovascular disease risk factors, 1,101 children in four age cohorts (5, 8, 11, and 14 years) were examined during 2 successive years. For lipids and lipoproteins, between 45 and 32% of those children with initially elevated levels remained above the 90th percentile (1). Frerichs *et al.* (4) concluded: "These results suggest the tracking of obesity, blood pressure, and serum lipids and lipoproteins which is known to occur during adulthood is apparent, on an annual basis, in 5 to 15 year old pediatric age groups." In a similar manner, Laskarzewski *et al.* (11) assessed tracking of plasma cholesterol, triglyceride, and high- and low-density lipoprotein cholesterol (C-HDL, C-LDL) in 108 children followed over a 4-year period in the Cincinnati Lipid Research Clinic's Princeton School Study. Initial and subsequent (2 and 3 years later) C-HDL levels were highly correlated ($r = 0.60$ and 0.53) with similar correlations for C-LDL ($r = 0.67$ and 0.61, respectively). Plasma C-HDL levels initially in the top decile generally remained there, with 82% (after 2 years) and 64% (after 3 years) of children initially in the top decile remaining in the top two deciles on follow-up (11). Similar findings for tracking of plasma cholesterol and triglyceride have also been reported from Muscatine, Iowa studies (3). Evaluating Bogalusa, Louisiana infants from a biracial cohort, Berenson *et al.* (1) have also demonstrated significant correlations between cord blood cholesterol, triglyceride, and beta-, prebeta-, and alphalipoproteins and subsequent levels of the same lipids-lipoproteins at ages 6 and 12 months (1). Overall, the studies suggest that plasma lipids and lipoproteins in children track over a broad age range and in diverse socioeconomic groups (1, 3, 4, 11, 13).

The purpose of the current report was to examine interrelationships of C-HDL, total plasma cholesterol, triglyceride, and C-LDL, as well as the longitudinal maintenance of C-HDL rank order (tracking) from birth to age 2 years in 76 hypercholesterolemic neonates (cord blood total cholesterol greater than 95 mg/dl) (15, 16). We focused particularly upon 34 hyperalphalipoproteinemic neonates who had cord blood C-HDL greater than 61 mg/dl (the 99th percentile for unselected neonates) to obtain longitudinal information about the natural history of hyperalphalipoproteinemia during the first year of life.

MATERIALS AND METHODS

SUBJECTS

One hundred and thirty-three hypercholesterolemic neonates were selected from the ongoing Cincinnati population study of lipids and lipoproteins in neonates and their parents (5, 15, 16). For longitudinal follow-up, data were obtained in 76 hypercholesterolemic neonates having cord blood cholesterol greater than 95 mg/dl (6, 15, 16) (Tables 1 and 2), with special focus on 34 hyperalphalipoproteinemic neonates who had cord blood C-HDL greater than 61 mg/dl (Table 3), the 99th percentile for cord blood C-HDL in unselected neonates (10).

After documentation of cord blood hypercholesterolemia, we requested the parents to bring the infants back at 6-month intervals for as long as was practicable. At each 6-month visit, fasting plasma was obtained for quantitation of cholesterol, triglyceride, C-HDL, and C-LDL following methods of the Lipid Research Clinic's Laboratory Manual (12). No instructions for nutritional modification were given, and no detailed nutritional information was obtained at follow-up.

STATISTICAL ANALYSIS

The relationships between initial and subsequent lipid and lipoprotein levels were assessed using both parametric (Pearson's)

Table 1. *Pearson and Spearman correlation coefficients relating serial values of lipids and lipoproteins*

	TC[1]:TC			C-LDL:C-LDL			C-HDL:C-HDL			TG:TG		
	n	(r_p)	(r_s)	*n*	(r_p)	(r_s)	*n*	(r_p)	(r_s)	*n*	(r_p)	(r_s)
Cord *vs.* 6 mos.	76	0.11	0.07	58	0.29[2]	0.24	76	0.32[3]	0.18	58	0.12	0.17
Cord *vs.* 12 mos.	51	−0.10	0.03	45	−0.07	−0.06	51	0.49[4]	0.46[4]	45	−0.12	−0.06
Cord *vs.* 18–24 mos.	45	0.09	−0.02	41	0.30	0.32[2]	45	0.39[3]	0.25	41	−0.05	−0.09
Cord *vs.* 3–5 yr	23	0.13	0.21	23	0.23	0.08	23	0.20	0.28	23	−0.31	−0.12
6 mos. *vs.* 12 mos.	27	0.84[4]	0.50[3]	19	0.62[3]	0.50[2]	27	0.24	0.23	19	0.29	0.56[2]
6 mos. *vs.* 18–24 mos.	12	0.80[3]	0.85[3]	10	0.72[2]	0.29	12	0.51	0.57	10	0.19	0.56
12 mos. *vs.* 18–24 mos.	19	0.52[2]	0.39	14	0.63[2]	0.52	19	0.68[3]	0.48[2]	14	0.48	0.61[2]

[1] TC, total plasma cholesteral; TG, triglyceride; r_p, Pearson correlation coefficient, r_s, Spearman correlation coefficient.
[2] $P < 0.05$.
[3] $P < 0.01$.
[4] $P < 0.001$.

Table 2. *Pearson and Spearman correlation coefficients relating various classes of lipids and lipoproteins*

	C-HDL:TC[1]			C-HDL:C-LDL		C-HDL:TG		TG:C-LDL	
	n	(r_p)	(r_s)	(r_p)	(r_s)	(r_p)	(r_s)	(r_p)	(r_sL)
Cord	133	0.16	0.28[2]	−0.36[3]	−0.62[3]	−0.34[3]	−0.41[3]	0.72[3]	0.50[3]
6 mos.	76	0.26[4]	0.30[2]	0.07	0.19	−0.37[2]	−0.40[2]	−0.12	−0.22
12 mos	51	0.37[2]	0.36[2]	0.18	0.22	−0.37[2]	−0.49[3]	−0.16	−0.16
18–24 mos.	45	0.01	0.01	−0.32[4]	−0.25	−0.30	−0.27	−0.09	−0.06
3–5 yr	23	0.36	0.36	0.17	0.19	−0.46[4]	−0.43[4]	−0.08	−0.11

[1] TC, total plasma cholesteral; TG, triglyceride; r_p, Pearson correlation coefficient; r_s, Spearman correlation coefficient.
[2] $P < 0.01$.
[3] $P < 0.001$.
[4] $P < 0.05$.

Table 3. *Thirty-four infants having highest quartile C-HDL at birth; quartile location of C-HDL on follow-up (n)*

	Quartiles				Total
	Lowest	Second	Third	Highest	Infants
Cord				34	34
6 mos.	3	4	3	6	16
12 mos.	2	2	3	9	16
18 to 24 mos.	3	3	2	12	20
3 to 5 yr	2	0	2	3	7

correlations and nonparametric (Spearman's) rank order correlations (14). Although, for the most part, the trends for both correlations are in the same direction and the levels of statistical significance observed for Pearson's and Spearman's correlations are very similar, both are displayed in Tables 1 and 2 to facilitate comparisons with published data.

RESULTS

CORRELATION BETWEEN CORD BLOOD LIPIDS AND LIPOPROTEINS AND SUBSEQUENT VALUES

Cord blood total cholesterol or triglyceride levels were not significantly correlated with plasma cholesterol and triglyceride levels for any subsequent follow-up period up to 5 years (Table 1). Cord blood C-LDL was positively correlated with C-LDL levels at 6 and 18 to 24 months (Table 1). In contrast, cord blood C-HDL levels were correlated significantly with subsequent C-HDL levels at 6, 12, and 18 months.

CORRELATIONS BETWEEN PLASMA LIPID AND LIPOPROTEIN LEVELS AT 6 AND 12 MONTHS WITH SUBSEQUENT VALUES

Both plasma total cholesterol and C-LDL displayed strong correlations between values at 6 months and those at 12 and 18 to 24 months (Table 1). Plasma total cholesterol and C-LDL levels at 12 months were also significantly correlated with values at 18 to 24 months (Table 1). For C-HDL, there was a significant correlation between values at 12 months and those at 18 to 24 months. For triglyceride, there was a positive correlation between values at 6 months and those at 12 months and between values at 12 months and those at 18 to 24 months. Therefore, all four categories of lipids and lipoproteins, especially total cholesterol and C-LDL, maintained some rank order from one follow-up examination to another, beginning at 6 months. In contrast, tracking relationships between cord blood lipoproteins and lipoprotein levels during the first 2 years of life were present only for C-HDL and C-LDL. In hypercholesterolemic neonates, postnatal measurements for plasma total cholesterol and triglyceride levels may be regarded as more predictive for subsequent measurements than cord blood measurements, whereas C-HDL and C-LDL track reasonably well from birth.

CORRELATIONS BETWEEN CATEGORIES OF LIPIDS AND LIPOPROTEINS: CORD BLOOD AND FOLLOW-UP

As summarized in Table 2, C-HDL values were positively correlated with total plasma cholesterol at birth and at ages 6 and 12 months. There were significant inverse relationships between C-HDL and C-LDL at birth and at 18 to 24 months of age.

C-HDL manifested a very consistent inverse association with triglycerides at birth and at every subsequent follow-up period; the correlation coefficients averaged −0.40 (Table 2). These C-HDL:triglyceride inverse relationships were statistically significant throughout the follow-up period, with exception of months 18 to 24.

Plasma triglyceride was positively and significantly correlated with C-LDL at birth; thereafter, there were no significant relationships between triglyceride and C-LDL (Table 2).

TRACKING FOR HDL CHOLESTEROL IN THE MOST HYPERALPHALIPOPROTEINEMIC NEONATES

In the 133 hypercholesterolemic neonates of this truncated study group, the 25th, 50th, 75th, and 90th percentiles for cord blood C-HDL were, respectively, 41, 51, 61, and 69 mg/dl. In unselected

Table 4. *C-HDL levels on follow-up of 13 neonates with highest initial cord blood C-HDL levels*

	C-HDL on follow-up (mg/dl)						
C-HDL cord (mg/dl)	6 mos.	12 mos.	18 mos.	24 mos.	36 mos.	48 mos.	60 mos.
69		49	70	71			
69	110						
69		76	73	72			
70			38				
71				26	41	41	
71		48	68	70			
73			29				
77						73	78
78	53	71					
78	60	70	71	79			
79	39	43					
84			78				
91	76	79					

Cincinnati births, the cord blood C-HDL 25th, 50th, 75th, 90th, and 99th percentile values were, respectively, for males, 24, 29, 36, 44, and 62 mg/dl and for females, 26, 33, 39, 47, and 61 mg/dl (10).

Table 3 summarizes longitudinal C-HDL data for 34 neonates from this study having top quartile cord blood C-HDL (>61 mg/dl), approximating the 99th percentile for unselected distributions (10). Follow-up data was obtained for 20 infants over 2 years, and their location within their specific quartile distribution was then assessed over time. As summarized in Table 3, six of 16, nine of 16, and 12 of 20 infants followed at 6, 12, and 18 to 24 months, respectively, maintained C-HDL levels in the highest quartile for C-HDL. Moreover, nine of 16, 12 of 16, and 14 of 20, retained C-HDL levels greater than 50th percentile at 6, 12, and 18 to 24 months (Table 3).

Additional studies of tracking at the upper end of the C-HDL distribution were carried out in 13 neonates having the highest initial cord blood C-HDL levels, cord blood C-HDL $\geq$ 69 mg/dl (Table 4). Of these 13 neonates, nine had one or more C-HDL values greater than 70 mg/dl (the 90th percentile for childhood) (7) throughout the 12- to 60-month follow-up period. Moreover, where more than one follow-up measurement was available, there was relative stability of elevated C-HDL measurements. In four neonates, C-HDL levels on follow-up were well below 70 mg/dl, ranging from 29 to 43 mg/dl (Table 4).

DISCUSSION

In this study of hypercholesterolemic neonates, there was tracking of plasma lipoproteins between cord blood values and subsequent values for C-LDL and C-HDL. For total cholesterol, C-LDL, and triglyceride, there was tracking between values at 6 months and those at 12 and 18 to 24 months. The visit to visit correlation coefficients for lipids and lipoproteins were similar qualitatively to those observed in unselected neonates (1) or in older unselected children (3, 4, 11). Moreover, at the extreme of the C-HDL distribution in this study (99th percentile for C-HDL in free-living neonates), there was significant tracking for C-HDL levels.

Prospective studies in adults have shown that even single plasma cholesterol determinations are related to the risk of developing coronary heart disease (CHD) (2, 8, 9). An increased propensity for the development of CHD has also been demonstrated in families of Muscatine, Iowa, children with persistently elevated plasma cholesterol levels (13). Within this framework (2, 8, 9, 13), we speculate that many hypercholesterolemic children with predominant elevations of C-LDL may mature to become hypercholesterolemic adults at increased risk for CHD. However, up to 16% of hypercholesterolemic children have elevated levels of C-HDL, not C-LDL, accounting for their hypercholesterolemia (7), and are probably at reduced, rather than at increased risk for CHD, by virtue of their elevated C-HDL levels (2, 5). We did not assess in this study the tracking characteristics of the ratio of C-LDL to C-HDL which is another method for estimating CHD risk related to lipoprotein levels.

This study reveals relative tracking stability for C-HDL in hypercholesterolemic, hyperalphalipoproteinemic neonates. Their relative tracking stability in the upper quartile or decile for C-HDL may provide, prospectively, groups of children at decreased risk for CHD as adults, given the strong inverse association of C-HDL with coronary heart disease (2, 5).

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18. Requests for reprints should be addressed to: Dr. C. J. Glueck, General Clinical Research Center, Cincinnati General Hospital, 234 Goodman Street, Cincinnati, OH 45267 (USA).
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