CORONARY HEART DISEASE IN THE YOUNG

NEONATAL FAMILIAL TYPE II HYPERLIPOPROTEINEMIA: CORD BLOOD CHOLESTEROL AND FOLLOW UP STUDY IN 1.323 BIRTHS

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Lipid research in recent years has made substantial contributions to our understanding of the pathophysiology of hyperlipoproteinemia. But lipid analysis of plasma, including total lipid, triglyceride and cholesterol determinations, are known to be of restricted diagnostic value unless they are carried out in conjunction with an elucidation of the so-called "lipoprotein pattern". This is reasonable since all plasma lipids circulate in form of plasma lipoproteins.

Considering our latest knowledge in the differentiation of inherited hyperlipoproteinemia 6 different types can be distinguished. Fig. 1 summarizes some of the characteristic features of these types.

The type I is characterized by milky plasma, persistence of chylomicrons, extremely elevated triglycerides, while the plasma cholesterol is often within the normal range. The type II hyperlipoproteinemia has recently been divided into two types: Type II a and type II b. Both are characterized by strongly elevated beta-lipoproteins and cholesterol concentrations. While in type II a the triglycerides and prebeta-lipoproteins are normal, in type II b these fractions are also elevated.

The type III shows an abnormal plasmalipoprotein rich in triglycerides and cholesterol with beta-mobility on electrophoresis but within the VLDL density class.

The type IV shows a turbid plasma, elevated triglycerides and pre-beta-lipoproteins while cholesterol and beta-lipoproteins are normal.

The type V hyperlipoproteinemia is a mixed type and shows chylomicrons as the type I and elevated pre-beta-lipoproteins as the type IV. The plasma of these patients is milky, their triglycerides elevated, the cholesterol concentration often normal.

In this presentation, I should like to devote myself entirely to the type II hyperlipoproteinemia, since we have increasing evidence that the hyper-beta-lipoproteinemia accompanying this disease is a major cause or factor in the acceleration of atherosclerosis and, in particular, of coronary sclerosis. In attempts to identify neonatal and familial type II hyperlipoproteinemia and to evaluate the incidence of this disease, we measured umbilical cord blood total cholesterol and beta-cholesterol in 1.323 consecutive unselected births from 4 obstetrical departments in the Heidelberg area (Heidelberg: 343, Mannheim: 110, Ludwigshafen: 280, Pforzheim: 590).

The beta-cholesterol fraction, which is the most important criterion in the diagnosis of type II hyperlipoproteinemia was determined as follows:

The first step is the determination of total serum cholesterol designated A.

The serum is then submitted to ultracentrifugation at a density d 1.006g/ml and centrifuged for 22 hrs. with 105.00 x g. In this procedure the very low density lipoproteins (VLDL) will float, while the low density lipoproteins (LDL) and the high-density lipoproteins (HDL) will sediment. The second cholesterol determination (designated B) is then performed on the bottom fraction after ultracentrifugation and accounts for the LDL + HDL cholesterol.

The third cholesterol determination is performed on the filtrate after heparin precipitation of the serum designated C, which accounts for the HDL cholesterol content. From the obtained data, the beta-cholesterol concentration can be calculated by

B minus C.

In most instances cord blood is devoid of VLDL and therefore ultracentrifugation is not required. In this case the beta-cholesterol value can be calculated directly from

A minus C.

which is a great advantage and makes this type of study possible in every laboratory.

The statistical analysis of our data revealed a normal range of total cord blood cholesterol between 40 — 100mg/100ml with a mean of 60mg/100ml and for cord blood beta-cholesterol a normal range between 15 and 60 mg/100ml with a mean of 35mg/100ml.

Total cord blood cholesterol values above 100mg/100ml representing the upper two standard deviation range or cord blood beta-cholesterol values above 60mg/100ml, also representing the upper two standard deviation range were identified as abnormally elevated.

In 92 subjects elevated values were found, 6 of these had only an elevation of total cholesterol, 49 an elevation of total plus beta-cholesterol and 37 patients showed only an elevation of the beta-cholesterol value.

For the diagnosis of a familial type II hyperlipoproteinemia it is important to also study the parents of the affected subjects. We were able to examine both parents in 73 cases and found a type II hyperlipoproteinemia in 10 of these parents.

Since it is unknown so far, whether all newborns suffering type II hyperlipoproteinemia show the characteristic elevation already at birth, a strictly randomized control group of 81 new-borns with normal total cholesterol and normal beta-cholesterol were investigated in parallel. Both parents could be studied from all cases in the control group, and in three parents a type II hyperlipoproteinemia was established.

After one year both, the affected and the control group, were re-examined in order to evaluate, whether the preliminary diagnosis made at birth would also hold after one year. Of 73 infants suspicious for type II hyperlipoproteinemia at birth 61 (85%) and of 81 control infants 65 (80%) could be followed-up after a one year period. The statistical analyses of

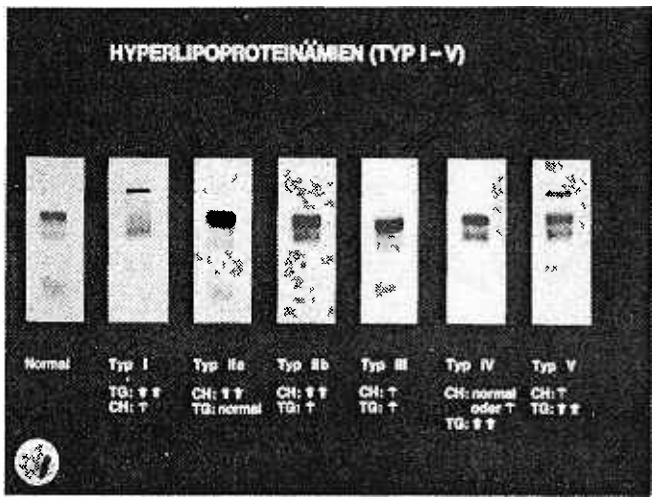

Fig. 1.

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NUMBER OF UNSELECTED BIRTHS

HEIDELBERG	340
LUDWIGSHAFEN	280
MANNHEIM	110
PFORZHEIM	590
	1,320

Fig. 2.

INVESTIGATION OF PARENTS

A SUSPICIOUS GROUP	B CONTROL GROUP
92 Neonates with elevated cholesterol	81 Neonates with normal cholesterol
73 Parent pairs studied	81 Parents pairs studied
10 FATHER/MOTHER TYPE 11	3 FATHER/MOTHER TYPE 11

Fig. 5.

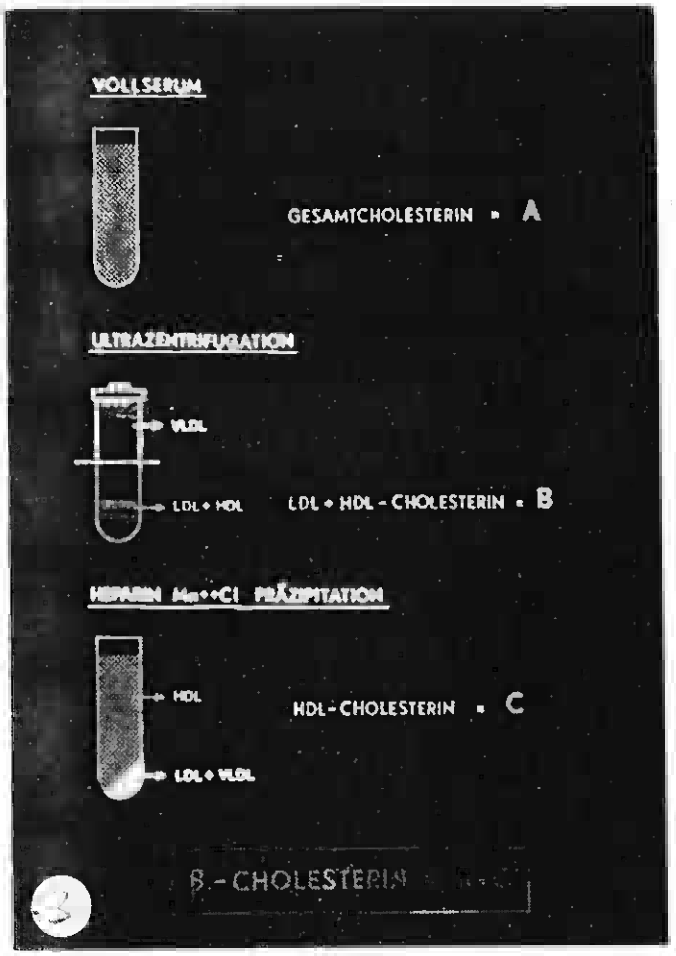

Fig. 3.

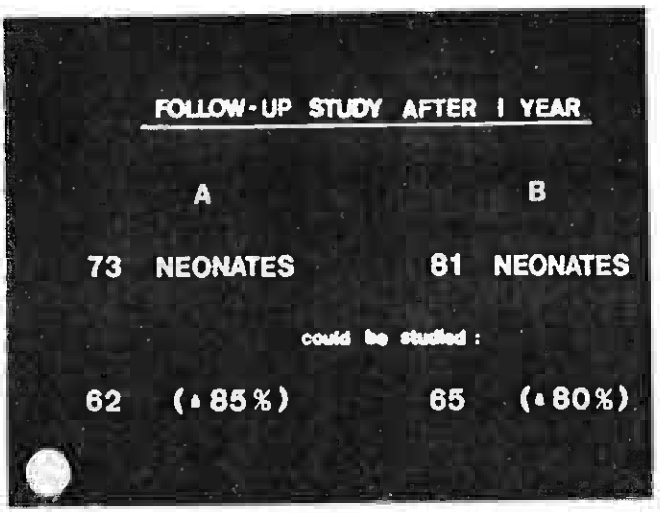

Fig. 6.

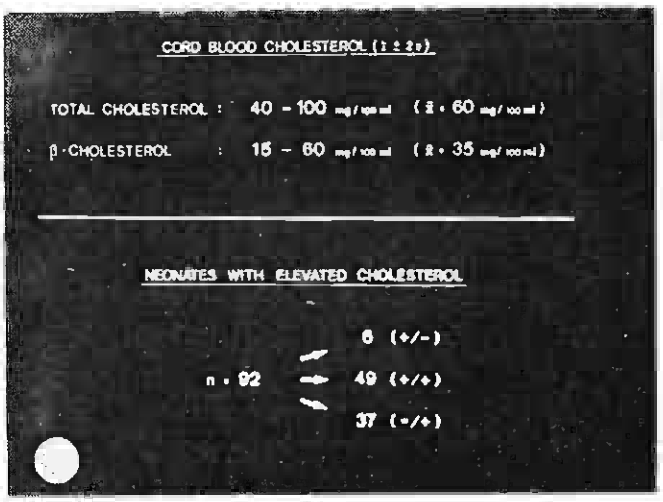

Fig. 4.

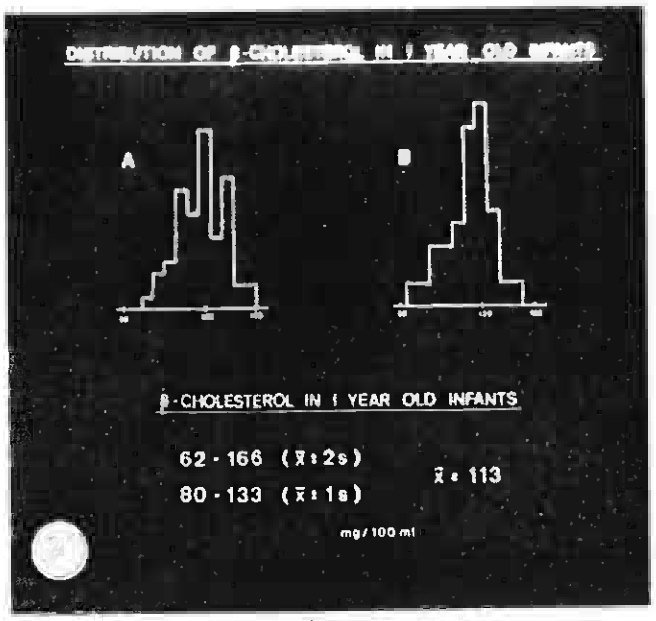

Fig. 7.

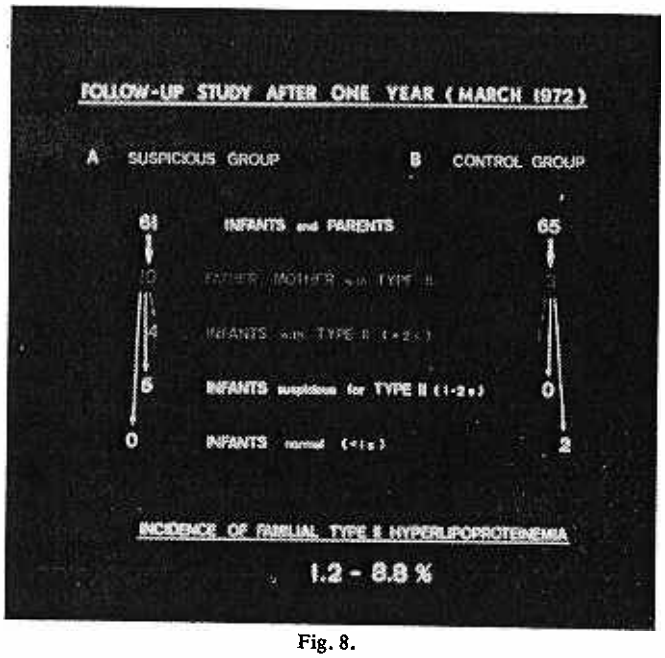

Fig. 8.

the obtained data for beta-cholesterol concentration in one year old infants, revealed a normal range between 62 and 166mg/100ml on the basis of the two standard deviation ranges with a mean of 113mg/100ml. All children within the upper 1-2 standard deviation range corresponding to beta-cholesterol values of 133-166mg/ml were classified as suspicious for type II hyperlipoproteinemia after one year, and all children above the upper two standard deviation range corresponding to beta-cholesterol values above 166 mg% were defined as definite type II hyperlipoproteinemics.

From the group suspicious of type II hyperlipoproteinemia at birth here designated as A, 61 and their parents were re-examined after one year. In ten cases a type II hyperlipoproteinemia could be diagnosed in one of the parents. Four children of these parents revealed pattern definite and five suspicious for type II hyperlipoproteinemia. One child could not be re-examined. From the control group with normal total and beta-cholesterol concentrations at birth, here designated as B, 65 and their parents were re-examined after one year. In three parents of these children a type II hyperlipoproteinemia was found and one child of the three parents had elevated beta-cholesterol values after an age of one year. On the basis of the definite diagnosed familial type II hyperlipoproteinemics an incident of 1.2-8.8% of this disease was calculated in our population.

IN SUMMARY, our study indicates that

1. the determination of beta-cholesterol and the investigation of the parents of affected children is necessary for the diagnosis of familial type II hyperlipoproteinemia in cord blood.
2. Many, but not all infants with familial type II hyperlipoproteinemia can already be diagnosed at birth.
3. The incidence of familial type II hyperlipoproteinemia ranges from 1-8% for a German population.