Primary disorders of lipoprotein metabolism in childhood*

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Four major classes of lipid are found in human serum: cholesterol and its esters, triglyceride, phospholipids and non-esterified fatty acids. They exist in aqueous solution because they are combined with protein to form lipoprotein complexes. The non-esterified fatty acids are bound to albumin, and the other lipids are associated with certain serum globulins. The nomenclature of the lipoproteins derives from the methods used for their separation. The simplest method is paper electrophoresis (Salt & Wolff, 1957; Fredrickson, Levy & Lees, 1967a) and using this technique four lipoprotein fractions are identified (Fig. 1). Chylomicra remain at the point of application of the serum to the paper and are normally present only during fat absorption; β-lipoprotein and α-lipoprotein have the mobility of β- and α1-globulins, respectively; pre-β-lipoprotein, which is not present in significant amounts in normal fasting serum, moves ahead of β-lipoprotein towards the position of α2-globulin. The chemical composition of the lipoproteins can be determined if they are separated in a preparative ultracentrifuge (Table 1). It will be appreciated that all lipoproteins contain some cholesterol, triglyceride and phospholipid, although in different proportions. Estimations, therefore, of the total serum triglyceride and cholesterol concentrations cannot alone identify a lipoprotein abnormality, but this becomes possible if electrophoresis is used in addition. Interpretation is facilitated if blood is taken in the fasting state (to avoid post-prandial chylomicronaemia), and the serum should not be stored or frozen, either of which procedures may alter the lipoprotein pattern.

Classification

Table 2 gives a classification of primary lipoprotein disorders according to the individual lipoprotein involved. Current terminology, however, is often based on the individual lipid which is most affected, and where appropriate this terminology is also given.

Lipoprotein deficiency states

Abetalipoproteinaemia

This rare condition is characterized by absence of β-lipoprotein from the serum, failure to form chylomicra from dietary fat (with consequent accumulation of triglyceride in the intestinal mucosal cell and malabsorption of fat), abnormally shaped red cells (acanthocytes), and the development of a pigmentary retinopathy and an ataxic neuropathy. The primary gene defect probably concerns the synthesis of the protein moiety of

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\( \beta \)-lipoprotein, and the condition is inherited as an autosomal recessive. Heterozygote individuals show no clinical abnormality and usually have a normal lipoprotein pattern (Farquhar & Ways, 1966), although reduced levels of \( \beta \)-lipoprotein have been demonstrated in one family (Salt et al., 1960).

The disease usually presents with steatorrhea, and symptoms appear during the first few months of life. Growth is retarded and secondary vitamin and mineral deficiencies may occur. The intestinal symptoms lessen in severity during later childhood and adolescence, but during this period the retinitis and ataxic neuropathy appear and result in progressive disability. Mental retardation has been present in a few patients but in the majority mental development is normal. Life expectancy is limited and cardiac arrhythmia resulting in death has been reported (Sobrevilla, Goodman & Kane, 1964).

The diagnosis is made on the lipoprotein pattern together with the typical red cell appearances. The total serum cholesterol concentration is very low, usually below 40 mg/100 ml, and on paper electrophoresis no \( \beta \)-lipoprotein can be detected; \( \alpha \)-lipoprotein is reduced. The lipoprotein deficiency can be confirmed by immunochemical and ultracentrifugal techniques. Acanthocytosis of the red blood cells (acanthus = horn or sharp point) is always present but may be missed or misinterpreted unless a fresh wet undiluted blood film is examined. The misshapen cells and the failure of rouleaux formation are then obvious. The cells have a slightly shortened survival time but a haemolytic anaemia is uncommon. The phospholipid composition of the red cell membrane is abnormal, with an increase in the ratio of sphingomyelin to lecithin (Ways, Reed & Hanahan, 1963). Acanthocytes themselves are not pathognomonic of abetalipoproteinaemia and may occur in hepatic disease (Smith, Longergen & Sterling, 1964) and in patients with deficiency (as distinct from absence) of \( \beta \)-lipoprotein (Kuo & Bassett, 1962).

Treatment is symptomatic. The steatorrhea usually responds to a low fat diet. Large doses of water-miscible preparations of vitamins A and E should be given together with supplements of vitamins D and K.

**Familial abetalipoprotein deficiency (Tangier disease)**

This condition was first described by Fredrickson in 1960 and named Tangier disease after the Chesapeake Island Bay home of the first two patients. A total of nine cases have so far been reported (Fredrickson, 1966; Kocen et al., 1967; Engel et al., 1967). The most striking abnormality is the deposition of cholesterol esters in the reticuloendothelial system which is manifest clinically by enlarged tonsils having a unique yellow-orange appearance. Lymphadenopathy and hepatosplenomegaly may be present and a peripheral neuropathy may develop in early adult life (Kocen et al., 1967; Engel et al., 1967).

The concentrations of cholesterol and phospholipid in the serum are reduced, but triglyceride is raised. \( \alpha \)-Lipoprotein cannot be detected by paper electrophoresis, but more sensitive techniques reveal the presence of a small amount which, however, has an abnormal protein moiety (Levy & Fredrickson, 1966).

The disease is inherited as an autosomal recessive and the majority of heterozygote individuals can be shown to have reduced concentrations of \( \alpha \)-lipoprotein.

**Hyperlipoproteinaemias**

**Hyperchylomicronaemia (familial fat-induced hypertriglyceridaemia)**

This condition is due to failure to clear chylomicra from the serum at a normal rate and is thought to be due to a deficiency of the enzyme lipoprotein lipase. The disease is inherited as an autosomal recessive. It is probably rare, only about thirty-five well-documented cases having been reported (Fredrickson & Lees, 1966). The incidence of the gene in the population is not known owing to the difficulty in identifying the heterozygote state.

The clinical manifestations include eruptive xanthomata which may appear at any age, attacks of abdominal pain, more common in childhood, hepatosplenomegaly, and lipaemia retinalis. Occasionally symptoms are absent and the condition is discovered during examination of the serum for another purpose.

The serum is characteristically grossly turbid, even in the fasting state, and there is marked elevation of triglyceride (often to more than 3000 mg/100 ml) with only moderate elevation of cholesterol in keeping with the composition of chylomicra. Lipoprotein electrophoresis shows that most of the lipid remains at the origin; the amount of both \( \beta \)- and \( \alpha \)-lipoprotein are reduced but there is usually some pre-\( \beta \)-lipoprotein present. Lipoprotein lipase activity in the plasma after intravenous heparin (Fredrickson, Ono & Davis, 1963) is low.

The response of the condition to reduction in dietary fat is rapid and confirms the diagnosis. Within a few days of starting a diet in which the daily fat intake is less than 5 g the fasting serum becomes clear and chylomicron material can no
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Although the levels range.

In the concentration is elevated, infarction in and elbows, knuckles symptoms disappear when the fat intake can usually be increased to about 20 g a day, although there is considerable invididual variation in the amount of fat that can be tolerated. The clinical response is excellent; xanthomata disappear within a few weeks, the liver and spleen return to normal size, and general health and well-being improve (Lloyd & Wolff, 1967). The palatability of a low-fat diet can be greatly enhanced by the use of medium-chain triglycerides, the fatty acids of which are absorbed directly into the portal circulation and thus bypass the chylomicron route.

The natural history of the untreated condition is not as benign as earlier observations have suggested. The abnormality is persistent and xanthomata and abdominal crises can occur at any age. There may also be problems due to increased blood viscosity and impaired tissue oxygen uptake from the lipaemic serum (Joyner, Horwitz & Williams, 1960). There is as yet no definite evidence that coronary artery atherosclerosis is accelerated (Fredrickson et al., 1967a).

Hyperbetalipoproteinaemia (familial hypercholesterolaemia)

Familial hyperbetalipoproteinaemia is characterized by elevated levels of \( \beta \)-lipoprotein in the serum and the development of xanthomata and accelerated atherosclerosis in a high proportion of affected subjects. It is inherited as an autosomal dominant. The gene frequency in the population is not yet known.

In the homozygous form the clinical manifestations are usually severe and appear in childhood. Xanthomata are of the tendinous or tuberous type and typically appear over the tendo-Achilliss, elbows, knuckles and backs of the knees. Symptoms of coronary artery disease may occur as early as 7 years of age and death from cardiac infarction in later childhood and adolescence is not uncommon. The serum cholesterol is grossly elevated, usually above 700 mg/100 ml, and lipoprotein electrophoresis shows a marked increase in the \( \beta \)-lipoprotein fraction. The serum triglyceride concentration is generally within the normal range.

In the heterozygote form serum cholesterol levels are usually between 300 and 500 mg/100 ml. Although the lipoprotein abnormality is present in childhood, clinical evidence of the disease is rarely manifest until adult life when xanthomata and coronary artery disease may develop at a relatively early age.

Lowering serum cholesterol levels by diet and drugs in heterozygous adults with established coronary artery disease has not been found to influence the prognosis (Oliver & Boyd, 1961; Rose, Thomson & Williams, 1963), but no studies have yet been made of the results of treatment started before the onset of atherosclerosis, that is in childhood. Until more evidence is available, and especially in families in which there is a history of the early development of coronary artery disease, dietary treatment to lower \( \beta \)-lipoprotein levels should be instituted in childhood or early adult life (Lloyd & Wolff, 1967; Fredrickson, Levy & Lees, 1967b). A diet in which at least 80% of the normal fat is replaced by polyunsaturated fat is usually successful in lowering cholesterol concentrations to near normal levels. Drugs such as \( \alpha \)-throxine, nicotinic acid, cholestyramine and oestrogens have side effects which limit their value in long-term therapy, and have not proved superior to dietary treatment for the heterozygous state. Unfortunately no therapy has yet proved effective in the treatment of the homozygous patient, but the prognosis for these individuals is so poor that the combined use of diet and drugs together with consideration of more radical measures to interfere with cholesterol metabolism, such as ileal bypass operations (Buchwald, 1965; Davis et al., 1966) is probably justified.

Prelipoproteinemia (carbohydrate-induced hypertriglyceridaemia)

In 1961 Ahrens, Hirsch, Oette, Farquhar & Stein described a group of hypertriglyceridaemic patients who responded to a reduction in dietary carbohydrate intake, and named this condition carbohydrate-induced hypertriglyceridaemia. It is now clear that pre-\( \beta \)-lipoproteinemia with excessive endogenous triglyceride synthesis is not a single entity but represents a group of conditions. Nevertheless, patients have certain features in common: the development of atherosclerosis is accelerated, obesity and abnormalities of carbohydrate tolerance are frequently found and eruptive xanthomata may occur if the hypertriglyceridaemia is severe. Serum cholesterol levels are raised to a variable extent and lipoprotein electrophoresis shows a pre-\( \beta \) band, and reduction in \( \alpha \)-lipoprotein. The incidence of pre-\( \beta \)-lipoproteinemia appears to increase with age (Fredrickson, Levy & Lees, 1967a, b, c) but the condition has been recognized in childhood (Segall, 1967).

Treatment is by reduction in the intake of
dietary carbohydrate. The type of carbohydrate eaten may be important as sucrose tends to produce higher levels of serum triglyceride than starch (Kuo & Bassett, 1965). In obese patients there will usually be a marked improvement after weight reduction (Fredrickson, Levy & Lees, 1967c). Clofibrate (chlorphenoxysobutyrate) is likely to be the most effective drug for the treatment of this type of hyperlipoproteinaemia (Strisower & Strisower, 1964).

References


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