

Juvenile Hyperlipemia

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Asymptomatic hyperlipemia occurs in a significant number of American children. It is important to recognize the condition during childhood because of its role as a risk factor in the early onset of coronary artery disease and because early dietary modification may prevent changes leading to premature heart disease.

A predisposition to heart attack exists within families, and now there is significant documentation of familial aggregations of coronary atherosclerosis as a concomitant of genetically determined risk factors such as hyperlipemia, hypertension, and diabetes mellitus.¹⁻³ Of these three conditions, hyperlipemia, which often displays a clearly genetic component, is related most directly to the pathogenesis of atherosclerosis.

The following review will present the characteristics of juvenile hyperlipemia, note the known genetic influences, document its prevalence in children in the United States, and present recommendations for diagnosis and management.

Hyperlipemia is the manifestation of a variety of biochemical abnormalities producing hypercholesterolemia and/or hypertriglyceridemia, both of which are associated with an increased risk of coronary artery disease in adults. Because hyperlipemia occurs in early childhood and may lead to coronary atherosclerosis, the identification and treatment of children with hyperlipemia should receive more attention than it does at present. The definition of hyperlipemia is indistinct; normal blood levels of cholesterol and triglycerides are defined statistically by measurements in apparently healthy children. Although the levels can vary geographically and may be influenced by diet and other factors, "normal limits" have generally been based on 90th percentile fiducial limits calcu-

lated from relatively small samples (Table 1).⁴ A diagnosis of hyperlipemia is justified if lipid or lipoprotein concentrations, measured after a 12-hour fast, are above these "normal limits" on three separate occasions at least two weeks apart. Both cholesterol and triglyceride serum concentrations increase gradually throughout childhood and adolescence. Although the studies are limited, the normal range of cholesterol levels appears to be relatively narrow except during the first year of life when serum cholesterol is especially affected by the type of fat in the diet; consequently, unless the parents are hyperlipemic, diagnostic and therapeutic decisions are best delayed until after six months or one year of age, when a more mixed source of dietary fat is usual and there is a diminished variation of serum lipid concentrations. The changes in serum triglyceride concentrations during childhood are less well defined than are those for cholesterol, although a gradual increase is commonly observed. In children with persistent hyperlipemia, serum lipoprotein should be estimated by electrophoresis, and a survey of other family members is indicated. These additional studies can greatly facilitate a precise diagnosis when it is possible to demonstrate similar findings in a parent or sibling.

The most widely used classification of hyperlipemic diseases is based upon the serum lipoprotein pattern since blood lipids are bound to lipoproteins. The term "hyperlipoproteinemia" is therefore often preferred over "hyperlipemia" or "hyperlipidemia." Six types of primary hyperlipoproteinemia are seen in adults; all except type III have been detected in childhood or adolescence. A useful classification of juvenile hyperlipoproteinemia is illustrated in the Figure.

Hyperlipoproteinemia I, also known as familial hyperchylomicronemia or lipoprotein lipase deficiency, is a rare autosomal recessive trait. The biochemical defect is a deficiency of the enzyme, lipoprotein lipase. In homozygous children the disease is usually characterized by elevated cholesterol and tri-

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TABLE 1
Upper Limits of "Normal" of Plasma Lipid and Lipoprotein Cholesterol Concentrations (mg/100 ml) in Infants, Children and Adolescents

AGE	TOTAL CHOLESTEROL	TRIGLYCERIDE	LDL CHOLESTEROL	HDL CHOLESTEROL	
				MALE	FEMALE
CORD BLOOD	95	65	45	55	55
1-19 yr	230	140	170	65	70

glyceride levels, a deficiency of lipoprotein lipase activity in post-heparin plasma or adipose tissue, chylomicron uptake in the skin and reticuloendothelial tissue, abdominal pain, and pancreatitis which may be fatal. In children with xanthoma or pain the diagnosis is clinically obvious. However, in many children who are asymptomatic the diagnosis may be made

accidentally by a finding of milky plasma, hepatosplenomegaly, or lipemia retinalis. Premature atherosclerosis has not been documented in these patients; however, the other symptoms and debilitating nature of the disease make treatment mandatory.

Hyperlipoproteinemia II, also known as familial hypercholesterolemia or familial hyperbetalipoproteinemia

LIPOPROTEIN PHENOTYPE	LIPOPROTEIN ELECTROPHORETIC PATTERN	LIPOPROTEIN ABNORMALITY	SERUM CHOL.	LIPIDS TRIGLY.	PRIMARY	SECONDARY
I		Chylomicrons	+	++++	Familial hyperchylomicronemia	Diabetes mellitus
IIA		+ LDL	+++	—	Familial hypercholesterolemia	Hypothyroidism Nephrotic syndrome Obstructive jaundice
IIB		+ LDL + VLDL	+++	++	Familial hypercholesterolemia	Hypothyroidism Nephrotic syndrome Obstructive jaundice
III		Abn LDL Abn β-VLDL	+++	+++	Familial dysbetalipoproteinemia	Hypothyroidism
IV		+ VLDL	+ or —	+++	Familial hyperglyceridemia	Diabetes mellitus Nephrotic syndrome Glycogenosis (III) Hypothyroidism
V		Chylomicrons + VLDL	+++	++++	Familial hypertriglyceridemia	Diabetes mellitus Nephrotic syndrome Pancreatitis

Figure—Phenotypic classification of hyperlipoproteinemias.

teinemia, is inherited as an autosomal dominant trait. It is the most common form of juvenile hyperlipemia and is associated with a high risk of premature coronary artery disease. Hyperlipoproteinemia II accounts for many adults with myocardial infarction. Biochemical abnormalities are now believed to be the result of an absence or deficiency of a low-density lipoprotein receptor on cell membranes.^{5,6}

The relatively common heterozygous form, hyperlipoproteinemia II A, has an estimated prevalence of four per thousand⁷; in a Seattle study approximately one out of every twenty adult survivors of myocardial infarction was found to have this condition⁸; in a similar study 38 of 64 survivors had abnormal lipoprotein patterns.⁹ These hyperlipemic fathers, all under 41 years of age, had 85 children of whom 30 also had hyperlipoproteinemia II. Heterozygous infants have plasma cholesterol levels that are two to three times normal by the end of the first year of life. In matings between a heterozygous and a normal parent, the affected children can be identified at birth by cord-blood elevations of low-density lipoprotein cholesterol to values greater than 41 mg/100 ml.¹⁰ Tendinous xanthoma, corneal arcus, and coronary artery disease develop in young adults, usually from 20 to 30 years of age. In about 10% of children with type II disease, there are mildly elevated levels of very low-density lipoproteins and triglycerides along with elevations in low-density lipoprotein cholesterol.¹¹ This less common variation is classified as familial hyperlipoproteinemia II B.¹²

Homozygous children, who inherit a double dose of the mutant gene, are much more severely affected; the disease is often suspected initially because of the strong family history of heart disease. Cholesterol levels, which may range from 500 to 1000 mg/100 ml, are frequently markedly elevated even at birth, and corneal arcus and xanthoma appear before adolescence. Coronary artery disease is clinically apparent before the age of 20 and survival beyond 30 is rare.

In every family with a member who has experienced a heart attack before the age of 50, serum cholesterol and triglyceride levels should be measured in all first-degree relatives. Those with normal lipid values can be reassured about lipid risk factors and a significant number of those with hyperlipemia can be identified and treated early.

Hyperlipoproteinemia III, also known as "broad Beta disease," "floating Beta disease," or dysbetalipoproteinemia, has not been detected in children,

as noted previously. Inheritance is probably either an autosomal recessive or an autosomal dominant with incomplete penetrance.¹³ The condition results in elevated levels of cholesterol and triglycerides with an abnormal cholesterol to triglyceride ratio in the very low-density lipoprotein.¹⁴

Hyperlipoproteinemia IV, is relatively rare in children and is also referred to as familial hypertriglyceridemia or endogenous hypertriglyceridemia. Triglyceride levels are always elevated, ranging from 150 to 1000 mg/100 ml, and in about 20% of patients the very low-density lipoprotein levels may result in a hypercholesterolemia, with levels up to 350 mg/100 ml.¹⁵ Clinical findings commonly include non-ketotic diabetes and, less commonly, subcutaneous xanthoma. Obesity and hyperuricemia are frequent. A significant proportion of adults under the age of 50 with angina or myocardial infarction have primary type IV disease.¹⁵ The condition appears to be heterogeneous. The biochemical abnormality is not known, but studies suggest a defect in very low-density lipoprotein catabolism.^{16,17} It may occur in relatives of patients with type III or type V lipoprotein abnormalities¹³ and in some families genetic transmission follows an autosomal dominant pattern with delayed expression.

Hyperlipoproteinemia V is rare in childhood. Triglyceride levels range from 500 to 6,500 mg/100 ml and cholesterol varies from 150 to 1,500 mg/100 ml. Clinical findings are similar to those with type I disease. Type V disease does not lead to premature atherosclerosis; it is frequently associated with obesity, hyperuricemia, and abnormal glucose tolerance. The inheritance of the primary disease is not known; a family history of diabetes is common and there is a high prevalence of type IV disease in first-degree relatives.

Many chronic childhood diseases are associated with secondary hyperlipemia (Figure). Although infants with hypothyroidism usually have normal lipids and lipoproteins, in older children hypothyroidism is often associated with hypercholesterolemia which can be reduced by adequate thyroid treatment. Most children with the nephrotic syndrome have hypercholesterolemia, with close inverse correlations between cholesterol and albumin levels. In children treated by renal dialysis, the practice of feeding high fat diets to provide sufficient calories for growth may result in secondary hyperlipoproteinemia and acceleration of atherosclerosis. Children with hepatic glycogenosis III have hyperlipoproteinemia, usually

with increases in very low-density lipoproteins. Since many of these children survive to adulthood, early modification of the hyperlipemia by diet is indicated. Children with obstructive liver disease often have hyperlipemia unless the disease is at an advanced stage. Diet and drug management of the hyperlipemia result in diminution in the symptoms and lesions of xanthomatosis. In adolescents and young adults other rare causes of hyperlipemia are pregnancy, alcoholism, adrenal disease, and the chronic administration of adrenal corticosteroid drugs.

Dietary restriction and selection of fats is indicated in all children with primary hyperlipemias (Table 2). Because skin xanthoma are diminished or eliminated in children undergoing treatment, it is reasonable to conjecture that regression of vascular lipid deposits, with a concomitantly decreased risk of coronary artery disease, also occurs. In type I disease a low-fat diet normalizes serum lipids and reduces or prevents abdominal pain and pancreatitis. In type II disease a low-fat, low-cholesterol diet with a high ratio of polyunsaturated to saturated fats normalizes lipids in type II A patients, reduces lipid levels significantly in type II B children, and diminishes xanthoma in both. In type IV children a low-calorie, weight-reduction diet is sufficient to normalize serum lipid. In children with type V disease a low fat, moderate cholesterol diet normalizes serum lipids and prevents abdominal pain.

A low-cholesterol diet, 100 to 150 mg/100 ml, is achieved by eliminating egg yolk, organ and fatty meats, and shellfish, substituting skim milk and low-cholesterol margarine for whole milk and butter, using only cottage cheese among the cheeses and prohibiting products with coconut oil in them.¹⁸

Diet management alone is inadequate in 85% of type II children, and it is often necessary to use cholestyramine, a nonabsorbable anionic resin and bile acid sequestrant, which produces an exchange of chloride ions for bile acids in the intestine. The acids are excreted in the feces, and the reduction in enzyme product inhibition increases the endogenous metabolism of cholesterol, resulting in diminished serum levels of very low-density and low-density lipoprotein cholesterol. In doses of 250 to 800 mg/kg/day, cholestyramine does not cause malabsorption, although constipation, epigastric discomfort, and bloating are common. Because the drug absorbs fat, it can also produce mild steatorrhea and poor absorption of fat soluble vitamins. Its disagreeable taste is masked by using fruit juice or incorporating it into cookies. The surgical treatment of children with type II disease by partial ileal bypass is not recommended at this time.

In homozygous type II B children, the prognosis for effective reduction in serum lipids is poor. Low-fat diets and large doses of cholestyramine, together with the administration of nicotinic acid may be effective.¹⁹ Nicotinic acid, however, is often poorly tol-

TABLE 2
Treatment of Primary Juvenile Hyperlipemia

TYPE	DIET	DRUG	EFFECT
I	Low fat (10-15 g/day) Medium chain triglyceride		Normalizes lipids Prevents pain and pancreatitis
II A HETEROZYGOTE	Low cholesterol (100-150 mg/day) High polyunsaturated/ saturated ratio (2/1)	Cholestyramine (250-800 mg/kg/day)	Normalizes lipids. Reduction of cardiovascular risk possible
II B HOMOZYGOTE	Low cholesterol (100-150 mg/day) High polyunsaturated/ saturated ratio (2/1)	Cholestyramine 500-1500 mg/kg/day Nicotinic acid 25-75 mg/kg/day	Lowers lipids, Xanthoma diminish. Reduction of cardiovascular risk possible
IV	Low calorie weight control		Normalizes lipids. Reduction in cardiovascular risk possible
V	Low fat (20-30 g/day) Moderate cholesterol (300-400 mg/kg/day) Medium chain triglyceride		Normalizes lipids prevents pain

erated because of such side-effects as flushing, gastrointestinal distress, temporary hyperuricemia, glucose intolerance, or hepatic dysfunction.

Nationwide reductions in dietary fat and cholesterol intake have been promulgated by various health organizations. Most advisors recommend a reduction of individual fat intake from 40% to 30% of the total calories and a decrease in cholesterol and saturated fats.

Juvenile hyperlipemia is relatively common in the United States, and most affected children are asymptomatic. Measurements of serum cholesterol and triglycerides are indicated in all infants and children in families with one or more members having a heart attack before the age of 50, because a significant proportion of these children will have hyperlipemia and will require dietary restrictions, and some will need drug treatment. Early recognition and management of juvenile hyperlipemia may diminish the incidence or severity of coronary artery disease decades later.

REFERENCES

- GERTLER MM, WHITE PD: *Coronary Heart Disease in Young Adults: A Multidisciplinary Study*. Cambridge, Harvard University Press, 1954.
- THOMAS CB, COHEN BH: The familial occurrence of hypertension and coronary artery disease, with observations concerning obesity and diabetes. *Ann Intern Med* 42:90-127, 1955.
- SLACK J, EVANS KA: The increased risk of death from ischemic heart disease in first-degree relatives of 121 men and 96 women with ischemic heart disease. *J Med Genet* 3:239-249, 1966.
- LEVY RI, RIFKIND BM: Diagnosis and management of hyperlipoproteinemia in infants and children. *Am J Cardiol* 31:547-556, 1973.
- NEVIN NC, SLACK J: Hyperlipidaemic xanthomatosis. II. Mode of inheritance in 55 families with essential hyperlipidaemia and xanthomatosis. *J Med Genet* 5:9-28, 1968.
- BROWN MS, GOLDSTEIN JL: Expression of the familial hypercholesterolemia gene in heterozygotes: mechanism for a dominant disorder in man. *Science* 185:61-63, 1974.
- CARTER CO, SLACK J, MYANT NB: Genetics of hyperlipoproteinemias. *Lancet* I:400-401, 1971.
- GOLDSTEIN JL, HAZZARD WR, SCHROTT HG, ET AL: Hyperlipidemia in coronary heart disease. *J Clin Invest* 52:1533-1577, 1973.
- TAMIR I, BOJANOWER Y, LEVTOV O, ET AL: Serum lipids and lipoproteins in children from families with early coronary heart disease. *Arch Dis Child* 47:808-810, 1972.
- KWITEROVICH PO, FREDRICKSON DS, LEVY RI: Familial hypercholesterolemia (one form of familial type II hyperlipoproteinemia). A study of its biochemical, genetic, and clinical presentation in childhood. *J Clin Invest* 53:1237-1249, 1974.
- KWITEROVICH PO, LEVY RI, FREDRICKSON DS: Neonatal diagnosis of familial type II hyperlipoproteinemia. *Lancet* I:118-121, 1973.
- BEAUMONT JL, CARLSON LA, COOPER GR, ET AL: Classification of hyperlipidaemias and hyperlipoproteinaemias. *Bull WHO* 43:891-908, 1970.
- FREDRICKSON DS, LEVY RI: Familial hyperlipoproteinemia, in Stanbury JB, Wyngaarden JB, Fredrickson DS (eds): *The Metabolic Basis of Inherited Disease*, ed 3. New York, McGraw-Hill Inc, 1972, pp 545-614.
- FREDRICKSON DS, LEVY RI, LEES RS: Fat transport in lipoproteins—an integrated approach to mechanisms and disorder. *N Engl J Med* 276:34-44, 94-103, 148-156, 215-224, 273-281, 1967.
- HEINLE RA, LEVY RI, FREDRICKSON DS, ET AL: Lipid and carbohydrate abnormalities in patients with angiographically documented coronary artery disease. *Am J Cardiol* 24:178-186, 1969.
- HAVEL RJ, KANE JP, BALASSE EO, ET AL: Splanchnic metabolism of free fatty acids and production of triglycerides of very low density lipoproteins in normotriglyceridemic and hypertriglyceridemic humans. *J Clin Invest* 49:2017-2035, 1970.
- QUARFORDT SH, FRANK A, SHAMES DM, ET AL: Very low density lipoprotein triglyceride transport in type IV hyperlipoproteinemia and the effects of carbohydrate-rich diets. *J Clin Invest* 49:2281-2297, 1970.
- FREDRICKSON DS, LEVY RI, JONES E, ET AL: *The Dietary Management of Hyperlipoproteinemia: A Handbook for Physicians*. Washington D.C., US Department of Health, Education and Welfare, Public Health Service, US Government Printing Office, 1970.
- LANGER T, LEVY RI: The effect of nicotinic acid on the turnover of low density lipoproteins in type II hyperlipoproteinemia, in *Proceedings of the Workshop of Metabolic Effects of Nicotinic Acid*. Berne, Heber Publishers, 1971, pp 641-647.