

Relevance of Hyperlipidemia in Children

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Atherosclerosis, the major pathophysiological sequel of hyperlipidemia starts early in life. This was originally evidenced by the findings at autopsy, of fatty streaks in the arteries of healthy young soldiers who died of war injuries. More recently, studies have revealed endothelial dysfunction in the brachial arteries and increased carotid artery intima-medial thickness in high risk pediatric patients 1. Moreover, many hyperlipidemias have a genetic basis and can be detected early in life 2. It is generally agreed that in hyperlipidemia, the earlier the treatment, the better are the results, hence the importance of early recognition and treatment of hyperlipidemias, starting in the pediatric age group.



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Classification

Table 1 is a list of the different causes of hyperlipidemia in children, classified according to their pathogenesis. The major features of each entity are summarized below:

1. Type 1 Hyperlipoproteinemia (Hyperchylomicronemia)

This is a rare disorder due to a deficiency in the enzyme lipoprotein-lipase or its activator (ApoC-II) resulting in impaired clearance of chylomicra and VLDL. Serum triglycerides are markedly increased (> 1000 mg/dL) and the main manifestation is recurrent pancreatitis starting early in life. The affected children are not obese and the main treatment is a very low fat diet. Niacin and fibrates are ineffective. Some benefit may be obtained from fish oil.

2. Type 2a Hyperlipoproteinemia (Familial Hypercholesterolemia)

This is usually an autosomal co-dominant defect in the LDL receptor or less commonly in the Apo-B-100 protein. Very rarely it can be an autosomal recessive defect in the LDL-receptor gene. The estimated prevalence of the heterozygote state is 1/500 of population, while the homozygote state has an estimated prevalence of 1/250,000. The resulting pathophysiological problem is impaired LDL clearance and internalization, resulting in lack of inhibition of intra-cellular cholesterol synthesis.

Table 2 summarizes the biochemical diagnostic criteria for familial hypercholesterolemia (FH) in adults. The proposed diagnostic criteria in children are based on the combination of the finding of serum LDL-cholesterol > 135 mg/dL and the presence of known family history of FH 3.

Clinical features of FH

The most serious clinical manifestation of FH is the occurrence of coronary heart

disease at any early age. This is most dramatically seen in the homozygote children in whom 100 percent will have major coronary heart disease by the age of 20 years. In fact, those who are untreated will rarely survive beyond the age of 20 years. In the heterozygote patients, more than 50 percent of patients will have major coronary heart disease by the age of 45 years. Another manifestation which can be a clue to the diagnosis are cutaneous or tendinous xanthomata.

Management of Type 2a (FH) in Children

Homozygotes:

As in adults with FH, the benefit on LDL-cholesterol lowering from a low animal fat-low cholesterol diet is limited. The use of bile acids sequestrant resins is of also limited value and suffers from poor compliance because of their unpleasant side effects. Liver transplantation and porta-caval shunting are experimental since they have been tried in only a small number of patients. Lipid apheresis is effective and can significantly lower LDL-cholesterol and Lp(a) as well as adhesion molecules and CRP. However, the main drawback of lipid apheresis is its prohibitive expense especially that it needs to be done regularly every 2-4 weeks. Recently, some encouraging short-term results have been reported from the combined use of high dose statin and Ezetimibe 4, however, more long term studies are needed to assert the safety and efficacy.

Heterozygotes:

The benefit from dietary measures is also limited but better than in the homozygotes, resulting in an average drop of 19 % in serum total cholesterol, 24 % in LDL-cholesterol and 14 % in Apo-B 5. Concern about the impact of a low fat diet on height and growth of children seems to be unwarranted 5. As in the homozygotes, bile-acid binding resins suffer from poor compliance and are rarely well tolerated.

Results from high dose statin therapy are encouraging and have proven in several recent trials, to be safe and effective in children above the age of 8 years, resulting in a drop of 25-40% in LDL-cholesterol levels 6-9. The addition of Ezetimibe to high dose statins results in a further drop of 37-65 % in LDL-cholesterol 10-11 and is also apparently safe. However, there is need for longer term studies on a larger number of patients, to ascertain long-term safety and efficacy of this combination therapy in reducing cardiovascular events.

3. Familial Combined Hyperlipidemia

This is a heterogeneous disorder manifesting with various phenotypes (types IIa, IIb, IV & V) within first degree relatives. It is apparently polygenic and dominantly inherited and its prevalence is about 1 percent of the population. It is associated with early coronary artery disease.

Because the lipid abnormalities of familial combined hyperlipidemia are rarely expressed in childhood, its early recognition in the pediatric age group has been difficult. A recent report from Japan suggests that increased Apo-B is the earliest manifestation in children with familial combined hyperlipidemia 12. There is also a predisposition to increased triglycerides, small dense LDL-cholesterol and low HDL-cholesterol with age, obesity and physical inactivity.

4. Hyperlipidemia of Glycogen Storage Disease

An autosomal recessive disorder due to Glucose-6-phosphatase deficiency.

Main manifestations are:

- Hypoglycemia
- Hypertriglyceridemia
- Lactic acidosis
- Hyperuricemia
- Hepatomegaly

Hyperlipidemia is due to excessive triglyceride and cholesterol synthesis. There is no specific treatment except for

frequent feedings to prevent hypoglycemia.

5. Genetic Disorders of Insulin Receptor

This heterogeneous group of disorders includes more than one genetic defect in insulin receptor. In addition to severe insulin resistance, the following are common manifestations:

- Partial or total lipodystrophy
- Hypertriglyceridemia
- Acanthosis nigricans
- Hypertrichosis

II. Acquired Disorders with a possible genetic predisposition but accentuated by obesity

These are disorders associated with juvenile obesity and include the Metabolic Syndrome and type 2 diabetes that are increasingly occurring in children as part of the worldwide twin epidemic of obesity and type 2 diabetes. Both type 2 diabetes and its precursor, the metabolic syndrome, occur more often in children with a positive family history of diabetes. In both, the lipid abnormalities are related to insulin resistance and are characterized by the atherogenic triad of low serum HDL-cholesterol, increased serum triglycerides and increased proportion of small dense LDL-cholesterol particles. The main manifestations are an increased risk of atherosclerosis especially coronary heart disease

The management of the atherogenic state of the metabolic syndrome and type 2 diabetes starts with life-style changes aiming at weight loss and amelioration of insulin resistance. The results are usually favorable but suffer from poor compliance. Data on pharmacological intervention in children are scarce. Fibrates and niacin that have been shown to be effective in adults, have not been tried in children. The same is true of the use of statins in children but their safety in children above the age of 8 years, can be extrapolated from the trials in familial hypercholesterolemia 6-9.

III. Purely acquired disorders: The hyperlipidemia in children with HIV infection

Although seen more often in adults, hyperlipidemia has also been recognized in HIV-infected children especially in patients receiving protease inhibitor therapy, successful in reducing viral loads and prolonging life. The peak incidence is between 10-15 years of age.

About ten percent of patients develop body fat re-distribution characterized by fat wasting (lipodystrophy) in the face, buttocks and extremities and fat accumulation (lipohypertrophy) in the abdomen or dorso-cervical spine 13.

Dyslipidemia was present in 52 percent of cases and was characterized primarily by hypertriglyceridemia and/or hypercholesterolemia. Although the pathogenesis is unknown, insulin resistance was evidenced by the finding of increased fasting serum C-peptide and the frequent finding of type 2 diabetes or impaired glucose tolerance 13. There is no known treatment.

I. Disorders of purely genetic basis

- a. Type I Hyperlipoproteinemia (Hyperchylomicronemia)
- b. Type 2a (Familial Hypercholesterolemia)
- c. Familial Combined Hyperlipidemia
- d. Hyperlipidemia of Glycogen Storage Disease
- e. Genetic Disorders of Insulin Receptor

2. Acquired Disorders with a strong genetic predisposition

Disorders associated with juvenile obesity

- The Metabolic Syndrome
- Type 2 diabetes in children

3. Purely acquired disorders

Hyperlipidemia in HIV-infected children

Table 1 - Classification of Hyperlipidemia in children

In adults:	LDL-cholesterol mg/dL	TG	HDL-C
Heterozygotes:	> 250	N	N
Homozygotes:	> 500	N	N
In children:			
Combination of LDL-cholesterol > 135 mg/dL and a positive family history has:			
- A 98 % predictive value			
- Good Sensitivity: Only 4.3 % of children with LDL-cholesterol < 135 mg/dL had FH			

Table 2 - Biochemical features of familial Hypercholesterolemia

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