PEDIATRIC HYPERLIPIDEMIA

Background

1. Definition:
    - Dyslipidemias are disorders of lipoprotein metabolism and may include:
        - Elevations in total cholesterol (TC), low density lipoprotein (LDL), or triglycerides (TG)
        - Deficiencies of high density lipoprotein (HDL)
2. General Information:
    - Atherosclerosis plays a significant role in progression of cardiovascular disease (CVD), the leading cause of death and morbidity in the US
    - Atherosclerosis may begin in childhood[1,2,3,4]

Pathophysiology

1. Pathology of Disease
    - Cholesterol particles build up in the lining of arteries to form plaques or atherosclerosis.
    - Two causes of atherosclerosis include genetics and environmental factors.
        - Genetic cause: familial hyperlipidemia, characterized by defective LDL-C receptors on the surface of hepatocytes.[5]
        - Environmental causes: include obesity, sedentary lifestyle, diets high in saturated and trans fats, cholesterol and carbohydrates.
2. Incidence, Prevalence
    - Familial hyperlipidemia is a common monogenic disorder with a prevalence of about 1 in 500.[6]
    - 95th percentile for total serum cholesterol is 216mg/dL
    - 75th percentile is 181mg/dl.[7]
3. Risk Factors
    - Increased LDL, decreased HDL
    - Overweight (BMI between 85%-95 %)
    - Obesity (BMI >95%)
    - HTN (BP >95%)
    - Smoking (including exposure to second-hand smoke)
    - Type I and Type II DM
    - Atopy
        - Elevated LDL associated with greater allergic sensitization.[8]
4. Morbidity / Mortality
    - Specific diseases associated with premature CVD include DM, Kawasaki disease and CKD

Diagnostics

1. History
    - Obtain detailed family history including cardiovascular disease status
    - Physical activity history

- Diet history
- Social: Smoking history
- Cigarette smoking is a known risk factor for coronary artery disease, including exposure to second-hand smoke.

2. Physical examination
    - Obtain accurate height and weight measurements to calculate BMI, (weight (kg)/(height (m)^2 or (weight (lb)/(height (in)^2 x 703
        - Plot BMI-for-age growth chart for girls or boys.
    - Blood pressure on three separate occasions and interpreted for age/sex/height
    - If familial hypercholesterolemia is suspected:
        - Eye examination: arcus corneae, deposits of cholesterol creating a thin white circular ring on outer edge of iris
        - Skin examination: tendon xanthomas, palmar xanthomas, eruptive xanthomas, xanthelasma.[5]
    - Complete medical assessment to
        - Identify any underlying syndromes (hypothyroidism, nephritic syndrome, liver disease, renal failure, medications, pregnancy, acute porphyria, anorexia nervosa)
3. Laboratory Evaluation
    - A lipid panel is the recommended approach to screening because there is no currently available noninvasive method to assess atherosclerotic CVD in children.[9]
    - AAP, AHA and NCEP recommends routine cholesterol screening in children, only in those with certain risk factors, including[10]
        - Family history of premature CVD (age 55 or less in men, age 65 or less in women).
        - Unknown family history
        - CVD risk factors (overweight, obesity, hypertension, smoking, diabetes mellitus)
    - Screening should take place after 2 years of age but no later than 10 years of age in children with certain risk factors.
    - USPSTF concludes that evidence is insufficient to recommend for or against routine screening for lipid disorders in infants, children, adolescents, or young adults (up to age 20). (Grade I Statement)[11]
    - Lipid Panel (TC, HDL, LDL, TG)
        - Total Cholesterol and HDL-C can be measured on nonfasting venous or capillary blood samples, LDL-C requires fasting samples.
    - NCEP guidelines for diagnosis:[12]
        - Acceptable total cholesterol is <170mg/dl and LDL <110mg/dl
        - Borderline total cholesterol is 170-199mg/dl and LDL 110-129mg/dL
        - Elevated total cholesterol is >200mg/dL and LDL >130mg/dL
    - AHA guidelines: TG > 150mg/dl and HDL <35mg/dl should be considered abnormal for children.[13]

Therapeutics

1. Acute Treatment:
    - The American Heart Association recommends an adequate trial of diet, along with lifestyle changes for at least 6-12 months, before pharmacologic treatment**.**[13]
    - Pharmacologic intervention should be considered for patients 8 years and older with:
        - LDL >190mg/dl or >160mg/dL with a family history of early CVD or 2 additional risk factors
        - LDL >130mg/dl with DM
    - If children have LDL >190mg/dl, it is unlikely that diet alone will achieve goal LDL.
    - Pharmacologic treatment options for patients <20y/o include bile acid binding resins, statins, cholesterol absorption inhibitors.
    - Statins have been studied mainly in children with familial hypercholesterolemia, and, therefore, applying these results to children with different forms of dyslipidemia may be limited.[14]
    - Statins are an efficient lipid-lowering therapy in children with familial hypercholesterolemia and it seems to be safe in the short term but long-term safety is unknown.[6]
    - Statins or 3-Hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors therapy is safe and effective:
        - First line pharmacologic treatment in lowering LDL for children age 8 and older, according to AAP guidelines.[10]
        - Atorvastatin, Lovastatin, Pravastatin are approved by the FDA for use in adolescents with hypercholesterolemia.
        - Atorvastatin is approved for:
            - Children age 6 and older with homozygous familial hypercholesterolemia, starting with 10-20mg daily dose and increasing Q4 weeks as needed, max 80mg/day.
            - For children with heterozygous familial hypercholesterolemia, approved for ages 10 and older[15]
        - Lovastatin is approved for children age 10 and older (males and postmenarchal females), starting with 20mg daily dose and increasing Q4 weeks as needed. Max 40mg/day.[16]
        - Pravastatin is approved for children 8 and older, starting with a 20mg dose for children 8-13 yo, max 20mg/day. Max 40mg/day for children 14-18yo.[17]
        - Simvastatin is approved for children diagnosed with familial hypercholesterolemia, age 10 and older, starting with 10mg dose and max dose 40mg/day.[18]
        - Potential adverse reactions of statins include:
            - Increased hepatic transaminase levels
            - Myopathy
            - Rhabdomyolysis
            - Teratogenicity.

- Bile-Acid Resins:
  - Previously recommended as first line agent by AAP
  - Adverse reactions limited to gastrointestinal discomfort (constipation, cramping, bloating)
- Niacin should not be used due to side effects of flushing, hepatic failure, myopathy, glucose intolerance and hyperuricemia
- Fibrates should be used with caution in children as they have not been extensively studied in children and the risk of myopathy and rhabdomyolysis is increased when used in conjunction with statin therapy.
- Cholesterol-Absorption Inhibitors (Ezetimibe) have not been well studied in children but their adverse reactions are limited to gastrointestinal discomfort.
- Alternative treatments include daily consumption of plant sterol enriched dairy products which have been reported to reduce LDL-cholesterol in children with primary hyperlipidemia.[19]

2. Long-Term Care
   - NCEP and AAP recommend 2 approaches including:
     - Population-based approach focusing on lifestyle issues for all children
     - Individual approach for children at high risk.
   - Population Approach For all children
     - Children >2y/o should have a balanced caloric intake including fruits, vegetables, fish, whole grains and low-fat dairy products.
     - Balanced diet should be balanced with sufficient physical activity
   - Individual Approach For Children at High Risk
     - All 12month-2y/o who are at risk should use reduced-fat milk
     - Restrict saturated fats to 7% of total calories, trans fats <1% and dietary cholesterol <200mg/dL/day
     - Nutrition Consult
     - Increase physical activity

Follow-Up

1. Return to Office
   - If levels are within normal limits for age, repeat testing in 3-5 years if high risk
   - Borderline LDL levels should be rechecked in 1 year

Patient Education

1. http://familydoctor.org/online/famdocen/home/healthy/food/kids/1045.html

References

1. McGill, Jr; McMahan CA. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *Arterioscler Thromb Vasc Biol*. 2000 Aug; 20(8):1998-2004.
2. Newman WP III, Freedman DS, Voors AW, et al. Relation of serum lipoprotein levels and systolic blood pressure to early atheroscleoros: the Bogalusa Heart Study. *N Engl J Med*. 1986;314 (3): 138-144.

3. Raitakari OT, Juonala M, Kahonen M, et al. Cardiovascular Risk Factors in Childhood and Carotid Artery Intima-Media Thickness in Adulthood: The Cardiovascular Risk in Young Finns Study. *JAMA*. 2003; 290(17): 2277-2283.
4. Davis PH, Dawson JD, Riley WA, and Lauer RM. Carotid Intimal-Medial Thickness is Related to Cardiovascular Risk Factors Measured from Childhood Through Middle Age: The Muscatine Study. *Circulation.* 2001; 104; 2815-2819.
5. Neal, Willliam. Disorders of Lipoprotein Metabolism and Transport, Part X- Metabolic Disease. Chapter 86 In Kliegman, ed.Nelson Textbook of Pediatrics, 18th ed, 2007:33
6. Vuorio A, Kuoppala J, Kovanen PT, Humphries SE, Strandberg T, Tonstad S, Gylling H. Statins for children with familial hypercholesterolemia. Cochrane Database of Systematic Reviews 2010;(7):CD006401
7. Hickman, TB, Briefel RR, Carroll MD, et al. Distributions and trends of serum lipid levels among United States children and adolescents age 4-19 years: date from the Third National Health and Nutrition Examination Survey. *Prev Med* 1998; 27 (6): 879-890.
8. Kusunoki T, Morimoto T, Sakuma M, Mukaida K, Yasumi T, Nishikomori R, Fujii T, Heike T. Total and low-density lipoprotein cholesterol levels are associated with atopy in schoolchildren. *J Pediatr* 2011 Feb;158(2):334-6.
9. Steiner MJ, Brown WD, and E Liles. An Assessment of the New Lipid Screening Guidelines. *Pediatrics* 2008; 122: 904-905.
10. Daniels SR, Greer FR, Committee on Nutrition. Lipid Screening and cardiovascular health in childhood. *Pediatrics* 2008;122:198-208.
11. Haney EM,et al. Screening and Treatment for Lipid Disorders in Children and Adolescents: Systematic Evidence Review for the US Preventive Services Task Force. *Pediatrics* 2007; 120(1): 189-213.
12. National Cholesterol Education Program. Highlights of the report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics* 1992;89(3):495-501.
13. McCrindle BW, Urbina EM, Dennison BA, Jacobson MS, Steinberger J, Rocchini AP, Hayman LL, and SR Daniels. Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents: A Scientific Statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council on Cardiovascular Disease in the Young, With the Council on Cardiovascular Nursing. *Circulation* 2007;115:1948-67.
14. Iughetti L, Bruzzi P, Predieri B. Evaluation and management of hyperlipidemia in children and adolescents. *Curr Opin Pediatr* 2010 Aug;22(4):485-93
15. McCrindle BW, Ose L Marais AD. Efficacy and safety of statin therapy in children with familial hypercholesterolemia or severe hypercholesterolemia: a multicenter, randomized, placebo-controlled trial. *J Pediatr*. 2003; 143:74-80
16. Avis, HJ, Vissers MN, Stein EA, et al. A systemic review and meta-analysis of statin therapy in children with familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol*. 2007;27:1803-1810
17. Wiegman A, Hutten BA, deGroot E, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA* 2004; 292:331-337
18. de Jongh S. Ose L., Szamosi T, et al. Efficacy and Safety of Statin Therapy in Children with familial hypercholesterolemia: A Randomized, Double-Blind, Placebo-Controlled Trial with Simvastatin. *Circulation* 2002; 106:2231-2237

19. Amundsen AL, Ose L, Nenseter MS, Ntanios FY. Plant sterol ester-enriched spread lowers plasma total and LDL cholesterol in children with familial hypercholesterolemia. *Am J Clinl Nutr* 2002;76(2):338-44.

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