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Pediatric Screening for Familial Hyperlipidemia

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PERMISSION

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Department Nursing

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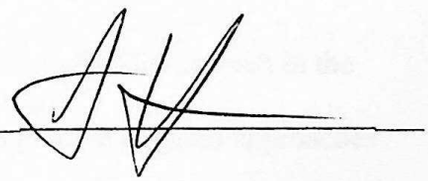
Signature 

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A thorough literature review was performed utilizing the University of North Dakota Harley French library website. PubMed, Cinahl, and Cochrane databases were all explored in an effort to answer the question when to screen for pediatric hyperlipidemia? Key terms used were "pediatric familial hyperlipidemia" and "familial hypercholesterolemia". A large number of articles were found on the subject of pediatric familial hyperlipidemia, the search was narrowed to include the term "screening" in addition to the above terms. A vast majority of these articles pertained to treatment with statin therapy; these articles were excluded for the purposes of this research paper. A total of 23 articles were found for use in this literature review; four cohort studies, two cross sectional studies, one prospective study, five expert consensus recommendations, and eleven expert reviews.

Background

Cardiovascular disease remains the leading cause of death for both men and women in the United States (Centers for Disease Control and Prevention, 2015). Atherosclerosis of the arteries occurs over years, and inflammation and deposition of lipids begins in childhood and progresses throughout the lifespan. Prevalence of lipid disorders in children and adolescents is at an all-time high in the United States (de Farranti, 2012). Hyperlipidemia is a modifiable risk factor in development of coronary artery disease and atherosclerosis (Musters et al., 2011).

Pediatric familial hyperlipidemia is an autosomal dominant disorder that results in limited capacity to clear low-density lipoproteins (LDL) from the circulation (Langslet & Ose, 2013). Familial hyperlipidemia occurs due to loss of function mutations in the LDL receptor genes or the apolipoprotein B gene. It is the most frequently diagnosed inherited lipid disorder in the pediatric population, and confers lifelong risk of atherosclerosis beginning in childhood

(Medeiros, Alves, Aguiar & Bourbon, 2014). Individuals with familial hyperlipidemia have early atherosclerosis from childhood and the only evidence they may be at risk may be family history of premature coronary artery disease (Kirke et al., 2015), so early screening is justified (Medeiros, Alves, Aguiar & Bourbon, 2014). This paper will address the necessity of screening for familial hyperlipidemia in the pediatric population, which is vital for early detection and treatment to prevent premature coronary artery disease and potential death.

Case Report

A 24 year old male presented to clinic for routine health maintenance and a chief complaint of two non-painful 'lumps' to the right knee and left elbow which had developed within the past two months. His past medical history was positive for seasonal allergies and wisdom teeth removal, while family history was positive for hypertension, hyperlipidemia, and coronary artery disease. His father died one month prior to the clinic visit at age 46 of a myocardial infarction. He has one older brother age 26, who is on medications for high cholesterol.

This patient is a college athlete who plays football and exercises four to five times weekly in the off season and six times weekly during football season. His diet consists of a lot of junk food; he does not use tobacco and does drink alcohol one to two drinks per day, two to three days per week, and four to five drinks once a month.

Vital signs were: blood pressure 110/54, heart rate 62, temperature 32.1 degrees Celsius, height 6 feet 1 inches, and weight 200 pounds.

The physical exam was unremarkable except for two small lumps approximately 1 centimeter in diameter located to the right knee and left elbow, both of which were flesh colored,

firm, non-tender, and mobile. No drainage, warmth, or erythema was noted. These findings were highly suspicious for xanthomas. Based on the patient's family history and cardiovascular risk factors as well as physical exam findings, a complete blood count (CBC), basic metabolic panel (BMP) and fasting lipid panel were ordered. The CBC and BMP were both unremarkable, while the lipid panel showed cholesterol 320, triglycerides 140, HDL 60, and LDL 219.

The patient was diagnosed with familial hyperlipidemia and prescribed Atorvastatin (Lipitor) 40 mg by mouth once daily, along with counseling regarding diet and lifestyle modification. He was instructed to increase fruits, vegetables, lean meats and proteins as well as decrease take-out and processed foods in his diet. He was to continue to be physically active, and to follow moderate alcohol consumption. He was instructed to monitor his skin for further changes, for xanthomas he was instructed they would not recede or disappear once formed. Follow-up plan was to recheck a fasting lipid panel in six weeks to assess compliance and monitor changes in the fasting lipid panel.

This patient is at high risk for premature cardiovascular death. A growing body of evidence supports screening for familial hyperlipidemia in pediatric patients versus only adults, as the build-up of plaque in the arteries is cumulative over a period of years. Targeting pediatric patients for appropriate screening, diagnosis, and treatment could prevent premature cardiovascular death and comorbidities such as cerebrovascular accident and myocardial infarction.

Literature Review

Hyperlipidemia is known to be a major cardiovascular risk factor. Familial hyperlipidemia confers a lifetime risk of atherosclerosis beginning in childhood. Early

identification and treatment is associated with a reduction of atherosclerosis (Medeiros, Alves, Aguir, & Borubon, 2014). The case study patient discussed earlier in this paper is demonstrative of the need to screen, identify, and treat patients with familial hyperlipidemia. His risk factors included a positive family history of lipid disorders and premature cardiovascular death, as well as physical manifestations of hyperlipidemia.

The origin of atherogenesis is subendothelial retention of LDL containing lipoproteins (Cook & Kavey, 2011). Lipoprotein molecules carry cholesterol in the bloodstream (Dunphy, Brown, Porter & Thomas, 2011). In normal lipid metabolism, lipoproteins are hydrolyzed to provide energy in the form of free fatty acids to the peripheral tissues (Hussain, 2014). The liver is the final destination for most LDL particles, where they are either cleared and excreted or remain in the circulation (Sniderman, Tsimakas, & Fazio, 2014). Atherogenesis occurs when LDL lipoproteins migrate to inflammatory regions of the vessel wall, where they are oxidized and phagocytized by macrophages to form foam cells, and ultimately form fatty streaks and plaques (Dunphy, Brown, Porter & Thomas, 2011).

Familial hyperlipidemia is an inherited autosomal dominant defect of the low-density lipoprotein (LDL) receptor gene leading to dysfunction of the LDL cell surface. Over 1600 different mutations of LDL-R gene on chromosome 19 have been found. These defects result in reduced uptake of LDL-cholesterol and clearance in the liver cells, increased serum total-and LDL-cholesterol levels and increased risk of atherosclerosis (Langslet & Ose, 2013). Children with familial hyperlipidemia are chronically exposed to high concentrations of plasma cholesterol and are prone to developing premature atherosclerosis and clinically evident disease early in life (Vlahos et al., 2014).

Inheritance of the defective gene from one parent causes heterozygous familial hyperlipidemia. This is more common with an incidence of one per 300-500 births. Heterozygous familial hyperlipidemia should be suspected when LDL levels are greater than 160 mg/dL in children and 190 mg/dL in adults. Patients with heterozygous familial hyperlipidemia have early atherosclerosis from early childhood and the only evidence of risk may be family history of premature coronary artery disease (Kirke et al., 2015).

Homozygous familial hyperlipidemia occurs when defective genes are inherited from both parents. This is a rare disease with an incidence of one per one million births (Langslet & Ose, 2013). Patients with homozygous familial hyperlipidemia have severe hyperlipidemia associated with accumulation of LDL in the plasma, tendons and skin along with accelerated atherosclerosis and coronary heart disease often in the first two decades of life. Untreated LDL levels often exceed 500 mg/dL. High levels of plasma cholesterol are detectable at birth. These patients typically develop valvular or aortic stenosis and die very prematurely of cardiovascular events (Rall, & Santos, 2012).

In childhood, heterozygous familial hyperlipidemia is asymptomatic with elevated total cholesterol and LDL levels. Physical manifestations occur in adults as lipid deposits in the form of xanthomas such as those exhibited in the case study patient, typically on the extensor tendons, especially of the Achilles and fingers (Langslet & Ose, 2013). Corneal arcus is a grayish-white discoloration of the peripheral cornea near the corneoscleral limbus. Arcus deposits tend to start at 6 and 12 o'clock and fill in until becoming completely circumferential. These deposits form as the result of lipid deposition in the deep corneal stroma and the limbal sclera (Macchiaiolo et al., 2014). An estimated five percent of myocardial infarctions in patients under 60 years of age, and

20 percent of myocardial infarctions in patients under age 45 years are attributable to familial hyperlipidemia (Pejic, 2014).

Familial hyperlipidemia is clinically diagnosed by five major criteria, including family history of premature cardiovascular disease, presence of early coronary artery disease in the index case, elevated LDL levels, tendon xanthomas, and corneal arcus. Genetic screening is not needed for clinical management and is not generally covered by medical insurance, but is essential to characterize specific defects. A negative genetic test does not exclude familial hyperlipidemia, because many of these patients will not be found to have a mutation that has been identified (Sniderman, Tsimikas, & Fazio, 2014).

Screening is used to identify unrecognized disease in patients without signs or symptoms. There are two main screening methods, universal population screening and selective screening. Universal screening means screening the entire population. Selective screening is limited to screening individuals who have certain risk factors for familial hyperlipidemia such as positive family history of hyperlipidemia, positive family history of premature cardiovascular disease, or family history unknown with positive risk factors including hypertension, obesity and cigarette smoking. Family cascade screening is performed on close relatives of an individual diagnosed with familial hyperlipidemia, and can be done through fasting lipid panels or genetic screening (Langslet & Ose, 2013). Primary health care is increasingly being seen as an important area for detection of cases of familial hyperlipidemia (Kirke et al., 2015).

In a prospective study by Kirke et al. (2015) in Australia, three methods of case detection were tested: pathology laboratory database search, workplace health checks, and general database search to identify those at risk of familial hyperlipidemia. 1, 316 subjects were

identified and underwent assessment, and 86 were referred to specialty care for high risk genetic screening. In Australia, 83% of the population sees a general practitioner annually, providing an opportunity for screening. In this study, screening in primary care health services was successful in detecting participants with familial hyperlipidemia, which demonstrates utilization of primary care services with a cost effective model of screening.

Noninvasive techniques for early detection of functional and structural vascular atherosclerotic changes may have a place in diagnosis and management of familial hyperlipidemia (Vlahos et al., 2014). Arterial intima media thickness has been shown to be an indicator of atherosclerotic plaque in adults. In a multi-institutional study of 2876 subjects between the ages of 15 and 34 years who died of extraneous causes, autopsies were performed to assess the incidence of intimal lesions of the aorta and right coronary artery. It was found that atherosclerosis begins in youth, fatty streaks and clinically significant raised lesions increase rapidly during the 15 to 34 year age span. Intimal lesions occurred in over half of the right coronary arteries in the youngest age group 15-19 years, and increased in prevalence with age through the oldest group 30-34 years. Elevated LDL levels have been shown to be positively correlated with the incidence of fatty streaks and raised lesions in this age group (Strong et al., 1999).

In a cohort study in the Netherlands of children with heterozygous familial hyperlipidemia between ages eight to 18 years, 214 children were randomized into a single-center two year double blind placebo controlled trial of pravastatin with a ten year follow up to assess carotid intimal media thickness (CIMT). After ten years, mean CIMT was significant in patients with familial hyperlipidemia as compared with siblings without familial hyperlipidemia which served as a control group. In those patients with familial hyperlipidemia on statin

medication, age of medication initiation was significantly associated with decreased CIMT at follow-up (Kusters et al., 2014). Increased CIMT was also demonstrated in study by Vijayasarathi & Goldberg (2014). Ninety pediatric patients with familial hyperlipidemia and/or metabolic syndrome were compared to 84 age matched control group participants, and were found to have increased CIMT as compared to controls.

Currently, no consensus exists regarding standardized screening for pediatric familial hyperlipidemia. Various recommendations have been formulated by different foundations and expert groups. No adequate, non-invasive tool is available for assessing progression of atherosclerosis in children without a family history of hyperlipidemia; instead medical providers have often used cholesterol levels as a surrogate marker for risk stratification. While this is an acceptable approach for adults, there is limited data to support this risk stratification in children; no specific cutoff level has proven predictive of the risk of cardiovascular disease as an adult (Horsely, 2009).

However, a growing body of evidence has identified risk factors for adult cardiovascular disease, including high concentration LDL, low concentration of HDL, hypertension, diabetes mellitus, cigarette smoking and obesity. Research in pediatrics has demonstrated some of these risk factors may be present at a young age and screening and treatment should begin in pediatric patients (Daniels & Greer, 2008).

In the majority of European nations, selective screening strategies are used to identify patients with familial hyperlipidemia, and these index cases then trigger cascade screening (Kusters et al., 2011). The International Familial Hypercholesterolemia Foundation recommends a systematic method of detecting index cases, or first individuals diagnosed, and cascade

screening to identify new cases. Universal screening is stated as being ideal but not feasible due to cost concerns (Watts et al., 2014). The American Heart Association recommends selective screening in children with positive family history of hyperlipidemia, positive family history of premature cardiovascular disease, or unknown family history and other cardiovascular risk factors including obesity, hypertension and cigarette smoking (Langslet & Ose, 2013).

According to the American Academy of Pediatrics, screening in the form of a comprehensive fasting lipid profile at least once in all children over two years of age and adolescents is recommended (Daniels & Greer, 2008). Children with progressive atherosclerosis are most at risk of cardiovascular disease as adults and should be screened (Horsely, 2009). The National Lipid Association Expert Panel on Familial Hypercholesterolemia recommends universal screening for elevated cholesterol for pediatrics and adults. For pediatrics, a fasting or non-fasting lipid profile should be obtained at age 9-11 years. This is the age when atherosclerosis begins to manifest in patients with familial hyperlipidemia (Langslet & Ose, 2013). The National Heart Lung and Blood Institute Expert Panel recommends universal screening of children between the ages of 9-11 with either a non-fasting or fasting lipid profile (McCrindle, 2012).

No standardization exists in screening for pediatric familial hyperlipidemia. Universal screening would have been beneficial for the case report patient discussed earlier. Universal screening would have allowed for him and most likely his brother who is on medication for elevated cholesterol, to be diagnosed and treated in childhood before atherosclerotic changes began in their vessels. Long term lipid deposits in the form of Xanthomas were noted on exam and universal screening would have prevented this through prompt and appropriate screening, diagnosis and treatment. There is the possibility that had this patient been screened as a child, it

would have prompted screening of his family and potentially prevented the premature death of his father.

Learning Points

- Cardiovascular disease is the leading cause of death for both men and women in the United States (Centers for Disease Control and Prevention, 2015).
- Familial hyperlipidemia leads to atherogenesis in pediatrics, and places patients at substantial increased risk of premature cardiovascular death.
- Various screening methods are currently used in the United States and worldwide. Screening strategies range from targeted screening of high risk patients to general screening methods of all patients over age two.
- While more costly, general screening allows for increased identification and diagnosis of pediatric patients with familial hyperlipidemia and allows for appropriate treatment to be instituted.

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