5-5-2016

Universal Screening for Hypercholesterolemia in Primary Care

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UNIVERSAL SCREENING FOR HYPERCHOLESTEROLEMIA IN PRIMARY CARE

by

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Bachelor of Science in Nursing, University of North Dakota, 2009

An Independent Study

Submitted to the Graduate Faculty

of the

University of North Dakota

In partial fulfillment of the requirements

for the degree of

Master of Science

Grand Forks, North Dakota

May 2016

PERMISSION

Title	Effectiveness of universal screening for hypercholesterolemia in primary care
Department	Nursing
Degree	Master of Science

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Abstract

Familial hypercholesterolemia (FH) is a common genetic condition that can have serious implications in adulthood such as premature coronary disease, stroke, and peripheral vascular disease if not adequately diagnosed in childhood. "Globally, one baby is born with FH every minute" (Wiegman et al., 2015, p. 2425). Individuals with familial hypercholesterolemia can have a normal life expectancy if diagnosed and treated early in childhood. This independent study aims to improve awareness of the need for early detection of FH children through the implementation of universal screening.

Cascade screening, also known as selective screening, based on family history is currently being used in clinical practice to identify affected individuals, but many with FH are undiagnosed during childhood by relying on this strategy (Ferranti, 2015). Recent American guidelines have been released recommending that selective screening "in the presence of a positive family history of elevated cholesterol or premature cardiovascular disease beginning at age 2 years AND universal screening at age 9-11 years, with repetition of the process at age 17-20 years" (Sullivan, Freeman, Molloy, & Williams, 2015, p. 3). Identifying FH early and subsequently lowering LDL-C over the lifespan reduces the collective LDL-C burden to potentially prevent the complications that are associated with FH. The purpose of this independent study is to provide an agenda for further progress in screening for familial hypercholesterolemia, building on the foundation provided by recent guidelines. Increased awareness and early identification of FH is critical to improve the lifespan for children and adolescents with FH.

Keywords: familial hypercholesterolemia, cascade screening, universal screening

Universal screening for hypercholesterolemia in primary care

Background

"Familial hypercholesterolemia (FH) is an autosomal dominant disorder of low-density lipoprotein (LDL) metabolism leading to high LDL cholesterol (LDL-C) and accelerated atherosclerosis" (Ferranti, 2015, p. S11). There is a rare homozygous form of familial hypercholesterolemia that is correlated with coronary heart disease and abnormal assessment findings during childhood. The more common heterozygous form (hetFH) is "asymptomatic until adulthood" (Ferranti, 2015, p. S11). Familial hypercholesterolemia is diagnosed either on phenotypic criteria or positive genetic testing. Phenotypic criteria includes, "an elevated low-density lipoprotein cholesterol (LDL-C) level plus a family history of elevated LDL-C, premature coronary artery disease and/or genetic diagnosis" (Wiegman et al., 2015, p. 2426). Screening is crucial in order to identify affected individuals due to the high prevalence rate. FH is one of the most common genetic disorders, affecting 1 in 200 to 500 people in the European population; thus making familial hypercholesterolemia more common than Down syndrome (Safeer, 2015).

Cascade screening, also known as selective screening, is "a strategy in which the diagnosis is confirmed in an index case, after which it is sought in close family members in a cascade fashion" (Sullivan, Freeman, Molloy, & Williams, 2015, p. 4). In familial hypercholesterolemia, a vertical pattern of inheritance produces a 50% chance of inheritance in first-degree relatives and a 25 % chance of inheritance in second-degree relatives. Universal screening refers to, "a case detection strategy in which the diagnosis in question has been sought in every individual in the population" (Sullivan et al., 2015, p. 2). Universal screening promotes

reverse cascade screening. By identifying children with total cholesterol levels > 200 mg/dL through universal screening, providers will consequently identify many parents at risk who may never have been previously evaluated for hypercholesterolemia (Benuck, 2015).

Cascade screening is currently being performed in clinical practice based on a patient's family history. Although this can identify affected individuals, many people with hetFH go undiagnosed when relying on cascade screening alone. "Overall, estimates are that fewer than 25% of persons with FH are diagnosed" (Ned & Sijbrands, 2011, p. 1). Individuals with untreated FH are 100-times more likely to develop cardiovascular disease and atherosclerosis as young adults when compared to individuals without FH (Boyles, 2015). By screening the entire population at a specified interval, consistent diagnoses can be made to appropriately treat those affected individuals and prevent future complications. Early detection and treatment of familial hypercholesterolemia bids one of the "most effective interventions for further reduction in the incidence of premature coronary disease, stroke, and peripheral vascular disease" (Sullivan et al., 2015, p. 1). The benefits of implementing universal lipid screening will not only appropriately identify children and families that are heFH, but will also detect those with abnormal lipid patterns, which has been noted to be roughly 20% of the pediatric population (Benuck, 2015).

Case Report

History of Presenting Illness

A 24-year-old male presents to the clinic requesting that his cholesterol be checked related to family history. The patient's father recently died at the age of 46 while shoveling snow; therefore, the patient is requesting further screening. His brother has been on pharmacological medications for high cholesterol for roughly one year. There are no other first degree relatives that the patient is aware of with a medical history of hyperlipidemia.

Past Medical History/Surgical History

No significant past medical history is noted. He has a past medical history of allergic rhinitis and a surgical history to include tonsillectomy and adenoidectomy at four years of age. Patient's medication regimen limited to a Zyrtec as needed. He is up to date with all immunizations. He is allergic to pollen. He has no known drug allergies.

Family History

As noted in the history of presenting illness, the patient's father recently passed away of cardiac complications at the age of 46 and had hyperlipidemia. The patient's brother is currently being treated for hypercholesterolemia. There are no other first degree relatives that the patient is aware of with a medical history of hyperlipidemia.

Social History

The patient is a college student that refrains from tobacco use and recreational drugs. He denies any exposure to secondhand smoke. He admits to drinking one to two alcoholic beverages several nights out of the week and drinks one to two caffeinated beverages per day. He exercises for at least 30 minutes per day five days per week. He denies any overwhelming life stressors and feels as if he copes with daily stress well.

Review of Systems

The patient denies any constitutional symptoms such as fever, sleep disturbance, weakness, fatigue, or unexplained weight loss or gain. He denies any changes in vision, upper respiratory symptoms, or headaches. He denies symptoms of shortness of breath, chest pain, palpitations, edema, irregular heartbeat, or murmur. He denies experiencing loss of balance, dizziness, or numbness to any of his extremities. He denies any changes in bowel or bladder

such as dysuria, urinary frequency, hematuria, or hematochezia. He denies any dermatologic concerns such as rashes, wounds, or lesions.

Physical Examination

Patient is 6'1" and 200 lbs. with a Body Mass Index of 26.4. Vitals signs are as follows: BP 110/54; HR 62; Temperature 37.1 degrees Celsius. Patient is alert, oriented, cooperative, and appears to be in no acute distress. He makes appropriate eye contact and is able to verbalize in a clear and understandable manner. A steady gait is noted while in the examination room. The thyroid gland was palpated with no evidence of nodules or enlargement on examination. His pupils are equal, round, and reactive to light. His lung sounds are clear throughout all lung fields with no wheezing, cough, or shortness of breath noted on examination. His heart sounds are regular with S1 S2 noted upon auscultation. Heart sounds are free of murmur, ectopy, or irregularity. There are no carotid bruits present on auscultation. His bowel sounds are active in all four quadrants of the abdomen. There is appropriate dullness and tympany noted with percussion of the various anatomical structures of the abdomen. There is no tenderness of the abdomen upon light and deep palpation of all four quadrants of the abdomen. There is no hepatosplenomegaly or CVA tenderness noted. His peripheral pulses are strong, regular, and intact. There is no evidence of peripheral edema noted. His skin is warm and dry with no areas of concern present on examination.

Laboratory Findings

Based upon the patient's family history of hyperlipidemia, a fasting lipid panel as well as a comprehensive metabolic panel was obtained with the results as follows:

COMPREHENSIVE METABOLIC PANEL	REFERENCE RANGE	PATIENT RESULT

SERUM BUN	7-22 mg/dL	18
SODIUM	136-145 mmol/L	139
POTASSIUM	3.6-5.5 mmol/L	3.9
CHLORIDE	98-109 mmol/L	102
SERUM GLUCOSE	70-99 mg/dL	86
SERUM CREATININE	06-1.3 mg/dl	1.1
CALCIUM	8.8-10.5 mg/dL	9.8
ANION GAP	5-13 mmol/L	9.7
GFR CALCULATED	ML/MIN/1.73 SQUARE M	>60
SERUM ALBUMIN	3.4-4.7 g/dL	4.00
ALKALINE PHOSPHATASE	50-136 U/L	88
TOTAL PROTEIN	5.97.6 g/dL	7.4
TOTAL BILIRUBIN	0.2-1.2 mg/dl	0.4
AST	5-34 U/L	20
ALT	7-55 U/L	22

FASTING LIPID PROFILE	PATIENT RESULT
CHOLESTEROL	310
TRIGLYCERIDES	140
HDL	60
LDL	209

Assessment/Plan

Based on the patient's fasting lipid profile and significant family history of hyperlipidemia, the patient was diagnosed with familial hyperlipidemia. He was initiated on simvastatin 40 mg daily. He was informed to re-check his liver function tests in one month for drug safety monitoring. He will have a follow-up visit in three months with a fasting lipid profile and a comprehensive metabolic panel completed prior to that three month appointment. A detailed discussion was conducted in regards to his current alcohol consumption while taking the simvastatin due to the risk of liver toxicity. Education was provided on stress management and exercise as this may assist in improving his overall health. Education was also provided on promoting a diet low in saturated fats. Educational handouts were provided and the patient is in agreement to visit with a nutritionist. A referral was placed for the patient to schedule this at his convenience.

Search Strategies

The University of North Dakota's Harley French Library website was utilized for gathering literature. The focal point for this literature search was primarily centered on familial hypercholesterolemia and cascade screening. PubMed was the first avenue utilized for the literature search as this is noted to be "comprised of over 24 million citations for biomedical literature from MEDLINE, life science journals, and online books" (National Center for Biotechnology Information [NCBI], n.d., para. 1). This database specializes in "reviews of clinical effectiveness research, with easy-to-read summaries for consumers as well as full technical reports" (UND Harley French Library of the Health Sciences website, 2011, p. 1). PubMed is free for users and is successfully managed by the National Center for Biotechnology Information that is located at the National Institutes of Health (NCBI, n.d., para. 2). The first medical subject heading, MeSH, terminology utilized in this search focused on "familial

hypercholesterolemia" AND "cascade screening". This yielded 117 results. The English filter was added, resulting in 110 results. The search was then refined to include articles within the last 5 years, resulting in 71 results. The focus of this literature search is universal screening; however, there has not been many publications on this specific screening as new recommendations were implemented in 2015. By incorporating cascade screening in the MeSH terminology, research comparing cascade screening and universal screening was noted and applicable to the research topic. It was noted through many attempts that this was the best route to search the question at hand. After selecting the articles and filtering many were eliminated due to either redundancy or to insignificant applicability to the present topic. Therefore, a total of 15 articles via the PubMed database as well as one outside article were utilized in this literature review.

Literature Review

Familial hypercholesterolemia (FH) is an autosomal-dominant genetic disease that is present in all racial and ethnic groups that is correlated with premature atherosclerotic coronary heart disease. The heterozygous FH has the highest prevalence of genetic defects; thus causing significant premature mortality (American Heart Association, Inc., 2015). Extensive research has been completed on genetic testing, implications of acquiring familial hypercholesterolemia, and treatment modalities. Despite these advances in research, "FH remains underdiagnosed and undertreated worldwide" (American Heart Association, Inc., 2015, p. 2167). According to the American Heart Association (2015), a majority of patients receive treatment in primary care settings without knowing the implications of the genetic disease itself. Dr. Stephen Daniels, a pediatric cardiologist, noted in a recent article that children in the United States are often not being screened for familial hypercholesterolemia (Boyles, 2015). Dr. Stephen Daniels stated, "We have

this epidemic of childhood obesity, so the focus seems to be on screening children who are overweight, but the truth is that most kids who have genetic dyslipidemias are not overweight" (Boyles, 2015, p. 2). Guidelines have been published to improve the awareness of familial hypercholesterolemia. Improved identification of individuals with FH at a young age has become a priority due to the correlation between lifelong exposure to elevated LDL-C levels and ischemic heart disease (American Heart Association, 2015).

Similar to the case report depicted in this independent study, many people seek medical advice for cholesterol monitoring once a first-degree relative has been diagnosed with hypercholesterolemia or deceased from a complication of hypercholesterolemia. In the case of the 24-year-old male with the positive family history his total cholesterol was noted to be 310 with an LDL of 209, placing him at significant risk of future cardiovascular events if left untreated. This patient willingly came in requesting to have his cholesterol levels checked after the passing of his father at the age of 46. Based on the new guidelines recommending that universal screening be completed at age 9-11 years with repetition of the process at age 17-20 years, this particular 24-year-old patient may have already been diagnosed and treated for familial hypercholesterolemia; thus, preventing the cumulative LDL burden that has perpetuated up until the age of 24. Furthermore, had the universal screening been implemented in this patient during childhood, his deceased father may have been diagnosed or perhaps more aggressively treated through the concept of reverse cascade screening. A review of the literature acquired will be presented throughout this section illustrating the advantages and disadvantages between cascade and universal screening. There are fewer studies available in regards to universal screening in younger children merely due to the fact that recent guidelines advocating for universal screening were

released in 2015. The research does; however, provide evidence that favors universal screening due to the prevention of people going undiagnosed as seen in cascade screening.

Evidence supports the concept that familial hypercholesterolemia causes pathological changes to the cardiovascular system at an early age. Thus, the recommendations were released for "selective screening in the presence of a positive family history of elevated cholesterol or premature cardiovascular disease beginning at age 2 years AND universal screening at age 9-11 years, with repetition of the process at age 17-20 years" (Sullivan et al., 2015, p. 3). Both the USPSTF and the American Academy of Family Physicians indicated that there is insufficient evidence to screen asymptomatic children and adolescents for FH; however, these new recommendations based on expert opinion and the National Heart, Lung, and Blood Institute (NHLBI) suggest universal screening. The American Academy of Pediatrics has also adopted these recommendations (Safeer, 2015). The time frame of 9-11 years recognizes that detection of FH by measurement of LDL or total cholesterol is optimum between these years. Re-evaluation in late adolescence/young adulthood between the ages of 17-20 years reflects the need to avoid, "the confounding effect of variable age of onset of puberty whilst maintaining the opportunity to detect and address risk factors before adult patterns become established" (Sullivan et al., 2015, p. 3). There are currently numerous tests performed in the process of universal screening; therefore, a reliable and inexpensive method is required when screening for familial hypercholesterolemia. LDL-C and total cholesterol are relatively inexpensive and meet these requirements. Genetic screening; however, is unsuitable for universal screening due to the complexity and high associated cost. Testing for genetic mutations is more noted in populations in which a founder gene effect is present. According to Sullivan et al. (2015), more research is needed for universal screening in order to convince providers to initiate it into clinical practice. "Its implementation is likely to

require extensive education and appropriate allocation of resources" (Sullivan et al., 2015, p. 3). Universal screening requires wide-ranging awareness in order to promote participation and success. If implemented in childhood, universal screening for FH offers the opportunity to, "intervene before atherosclerosis and adverse lifestyle factors become entrenched, but a convincing argument must be mounted to win the support of the vast majority of the population" (Sullivan et al., 2015, p. 5). Cascade screening may be difficult to prolong and sustain as it does not guarantee prevention of premature CVD due to FH. However, universal screening requires extensive implementation. According to Sullivan et al. (2015), family cascade screening may offer an acceleration of case detection once universal screening has been established; thus, working synergistically.

One study conducted by Santos, Frauches, & Chacra (2015) discussed how cascade screening does present the risk of leaving people undiagnosed; thus, increasing evidence exists favoring a general population screening due to the low detection rates of cascade screening. Unfortunately, prior to the date of the publication no countries had reported on a universal screening program being implemented. The two most cited concerns regarding the universal screening would be cost and utilizations of resources during the implementation process. However, the cost could possibly be justified with the prevention of costly treatments of associated cardiovascular complications. The economic health cost of universal screening as well as early intervention costs that include follow-up and counseling disease management have not been well studied and these health economic questions need to be addressed with future research (Benuck, 2015). Benuck (2015) discussed how "potentially significant risk factors leading to coronary artery disease may not be evident by either taking a careful medical and family history or performing a physical examination" (p. S99).

McNeal, Toth, & Wilson (2015) address the issue of cost-effectiveness as it relates to universal screening by noting that this factor may be offset as this screening modality has the potential to detect FH in the parents of the affected youth through reverse cascade screening. Universal screening with reverse cascade screening may be the best tactic to identify the highest number of individuals with FH (McNeal et al., 2015). According to Pang et al. (2015), FH is quite prevalent among patients with a history of early-onset coronary artery disease in the coronary care unit (CCU). Due to the increased prevalence rates, genetic testing for FH is being completed in CCUs after severe complications have ensued. Recommendations from this study are to initiate screening tactics for FH to reduce the high costs associated with future complications of coronary artery disease as currently individuals are being diagnosed with FH while receiving critical care treatment that may have potentially been prevented.

According to Hartgers, Ray, & Hovingh (2015), when LDL particles accumulate in the arterial wall, the endothelial tissue becomes damaged and atherosclerotic plaques form. This process begins at a young age with endothelial function already impaired in a study of asymptomatic HeFH patients at the age of 9 to 18 years of age. The extent of atherosclerosis is enhanced by other risk factors such as diet and exercise, acknowledging the fact that childhood obesity is rapidly increasing. To date, universal screening has only recently been introduced in Slovenia for children at the age of 5. As previously noted by similar research, universal screening has been proposed in the U.S. at 9 and 11 years, perhaps at the same time as scheduled immunizations, and again in later adolescence/young adulthood. "Ideally, this screening strategy would be integrated with cascade screening afterwards, to maximize the detection rate" (Hartgers et al., 2015, p. 4).

A recent study by Klancar et al. (2015) conducted on 279 Slovenian children between 1989 and 2009 proves to be the only study completed to evaluate genetic identification of FH by a national universal screening for hypercholesterolemia. Altogether, 272 unrelated participants born between 1989 and 2009 had measurements of fasting serum triglycerides (TC) drawn during routine examination of 5-year old children by primary pediatricians. Children with TC > 6 mmol/l or > 5 mmol/l plus a family history positive for premature cardiovascular complications identified in this universal screening were genotyped for genetic variants. Of the referred children, 57.0% carried disease-causing variants for FH. These findings note that family history alone may not suffice for appropriate identification of patients through the use of cascade screening. The findings support the latest recommendations; however, the U.S. recommendations are more specific on the age of the child during screening. Universal screening coupled with cascade screening for family members could be a "powerful approach for FH detection and prevention of cardiovascular complications" (Klancar et al., 2015, p. 1256). This study was limited due to the small sample size; therefore, additional studies are recommended to confirm these results. Based on this study, pediatric cardiologist Dr. Stephen Daniels stated, "The finding of genetic variants in a large percentage of referred children without a family history of early CVD, supports the concept that the family history is not a reliable indicator of pediatric patients with FH" (Boyles, 2015, p. 3). Dr. Stephen Daniels went on to discuss that he supports the universal approach to screening for individuals with FH (Boyles, 2015).

Familial hypercholesterolemia is a serious disease that needs to be screened and treated as such. Krogh, Mundal, Holven, & Retterstol (2015) conducted a study that assessed cardiovascular disease at the time of death in patients with familial hypercholesterolemia. They found that the mean age at first CVD event was 44 years of age with the mean age at the time of death being 60

years of age. Of the 4,688 people that were studied, 50% of the deaths were due to cardiovascular disease. These staggering statistics illustrate that immediate action is needed to promote early diagnosis and treatment for individuals with familial hypercholesterolemia.

Learning Points

The review of literature from this independent study illustrated the severity of familial hypercholesterolemia and the dire need for a consistent screening regimen. Challenges to advancing familial hypercholesterolemia screening practices do exist in regards to integrating universal screening strategies into practice versus continuing to utilize cascade screening. Even with these challenges, it is crucial to recognize the most important reason to initiate universal screening in the first place, which is to identify those children with FH in order to improve their lifespan. Patients with heterozygous FH are at an increased risk of myocardial infarction due to the lifetime exposure of elevated LDL-C. These myocardial infarctions in individuals with FH have occurred as early as the third decade of life. "Unfortunately, the first clinical sign of disease in untreated heterozygous FH may be a myocardial infarction or sudden death" (Daniels, 2015, p. 1). Universal screening with appropriate guidelines for follow-up is relatively new and will take time for most practices to implement into their standard of care (Benuck, 2015, p. S99). Integrating the universal screening policy into practice remains one of the biggest challenges due to the wide-spread education that would be necessary for proper implementation. To conclude this independent study, the following bullet points are listed highlighting the important concepts to promote positive change as it relates to screening for familial hypercholesterolemia.

- Cascade screening is currently being utilized as the predominant screening method for familial hypercholesterolemia. Based on the literature review, this screening method

exhibits voids in effectiveness due to the large number of individuals with familial hypercholesterolemia remaining undiagnosed.

- Universal screening may be a necessary process that needs to be implemented into clinical practice in order to consistently identify individuals with familial hypercholesterolemia. Implementing universal screening into clinical practice may lead to necessary surveillance and treatment of these individuals in order to improve and lengthen the overall lifespan.
- Universal screening coupled with reverse cascade screening for family members could be a superior tactic to appropriately detect familial hypercholesterolemia; thus, averting complications.
- Cost-effectiveness and implementation are both barriers that need to be overcome in order to successfully promote and integrate universal screening into clinical practice. The first universal screening research study completed in Slovenia as well as the release of the new guidelines and recommendations for universal screening to detect individuals with familial hypercholesterolemia will help force the issue to the public in order for further research to be conducted. Future studies regarding the cost-effectiveness and positive outcomes of initiating universal screening, especially in the young, are necessary to drive policy change.

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