Coronary Heart Disease: Family History of Father with Early CHD

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Key Points

- Both genetic and environmental factors contribute to risk of coronary heart disease (CHD).
- Inherited lipid disorders account for approximately 20% of early-onset CHD.
- Interventions directed at modifiable risk factors for CHD are effective in reducing morbidity and mortality from CHD.

Learning Objectives

Participants will be able to:

- Use family history to identify people at increased risk for CHD;
- Identify family history information suggestive of inherited causes of CHD;
- Identify strategies for CHD prevention in people at increased risk.

Family History Issues

Premature CHD is defined as CHD or sudden death occurring before age 55 years in a male or before age 65 years in a female.

A history of premature CHD in a first-degree relative (i.e., parent, sibling, child) confers an approximately twofold increased risk of CHD.

If the family history includes two or more relatives with premature CHD, an inherited condition causing high lifetime risk of CHD may be present.

Red Flags 

Clinical presentations that indicate a possible inherited predisposition to CHD include:

- Symptoms of CHD occurring before age 55 years in a male or before age 65 years in a female.
- Physical examination findings of xanthomas (raised, waxy-appearing, frequently yellowish-colored skin lesions) and xanthelasma (yellow plaques usually

occurring on the upper eyelid); both are skin findings associated with hypercholesterolemia (see MedlinePlus: Familial hypercholesterolemia).

Case 4. A Healthy Young Man whose Father Died of CHD at Age 50

A medical student wants to know if she should check a cholesterol level on a 25-year-old man who is establishing care. The patient is a vegetarian who exercises regularly and does not smoke. His blood pressure is 110/70, and his body mass index (BMI) is 20 (see BMI calculator). He has no medical complaints, but is concerned about his family history of coronary heart disease; his father died of a heart attack at age 50. He notes that his father had high cholesterol, which he attributes to his father being overweight, eating a high-fat diet, and never exercising. The patient seeks reassurance that his healthy lifestyle will protect him from also having a heart attack at a young age.

Clinical Care Issues

Prevention of CHD is focused on management of modifiable risk factors. These include:

- Hypertension
- Hyperlipidemia
- Cigarette smoking
- Diabetes mellitus
- Obesity
- Sedentary lifestyle

The patient already has normal blood pressure and BMI, and is pursuing a healthy lifestyle. Given his family history, further assessment of his risk is warranted.

Risk Assessment

Family history

The patient's father had premature CHD according to the National Cholesterol Education Program (NCEP) Guidelines, which define premature CHD as CHD or sudden death occurring in a female before age 65 years or in a male before age 55 years. A family history of premature CHD in a first-degree relative (for example, a parent or sibling) increases personal risk by about twofold.

The NCEP definition of positive family history is intended to identify increased genetic

risk for hyperlipidemia and serve as a guide to lipid management. It has the advantage of providing a simple rule for stratifying risk for patients. However, family history is a complex measure that reflects both lifestyle and genetics. Further exploration of family history is of value in this patient.

A history of early CHD in a parent may reflect a genetic predisposition, non-genetic risk factors such as diet and smoking, or both. In general, the likelihood of genetic risk increases with an increasing number of biological relatives with premature CHD. However, family structure needs to be taken into account in assessing family history. For example, a strong family history on the mother's side may be more evident in her male relatives than in her own medical history, due to the later onset of disease in females; if she has few male relatives, family history may be uninformative. In addition, medical treatment may modify family history: for example, effective early prevention may result in a parent with a history of medically treated hypercholesterolemia rather than myocardial infarction. Family history information should be evaluated with these considerations in mind.

For this patient, more information about CHD among his father's relatives would help. If other paternal relatives, such as paternal uncles or grandparents, had premature CHD, an inherited risk could be present.

Hypercholesterolemia

Epidemiologic, observational, and interventional studies identify hypercholesterolemia as a risk factor for CHD. The risk of CHD increases as total serum cholesterol concentration increases above 200 mg/dL. Cholesterol serum concentrations of 200 mg/dL to 239 mg/dL are considered "borderline high," and serum concentrations of 240 mg/dL and above are considered "high." Twenty percent of adult Americans have a serum cholesterol concentration greater than 240 mg/dL, which in a middle-aged man indicates a 9-12% risk of developing symptomatic coronary artery disease within seven to nine years. In the lipid profile, elevated LDL cholesterol and low HDL cholesterol are associated with higher risk for coronary events.

Because of the association between high serum cholesterol concentration and increased CHD risk, routine screening of adults for hypercholesterolemia is recommended by many advisory groups. Evaluation of the full lipid profile (total cholesterol, HDL cholesterol, LDL cholesterol, and trigylcerides) is recommended when serum cholesterol concentration is elevated above 200 mg/dL. However, screening recommendations vary. The **US Preventive Services Task Force** (USPSTF) and **American College of Physicians** (ACP) recommend routine screening for hypercholesterolemia in men age 35-65 years and in women age 45-65 years. Earlier screening is recommended for individuals with a family history of hypercholesterolemia or at least two other cardiac risk factors [American College of Physicians 1996, Berg et al 2002]. In assessment of family history, ACP and USPSTF recommendations use the same definition of premature CHD as NCEP. The **NCEP Adult Treatment Panel III**

guidelines take a more aggressive approach to screening, recommending that all adults undergo lipid screening starting at age 20 years. By all screening approaches, this patient is a reasonable candidate for lipid screening, because of the history of premature CHD in his father.

Genetic Counseling and Testing

The goal of care for this patient is to identify and treat any modifiable risk factors. By the patient's report, his father's early heart attack was associated with elevated cholesterol. His father's elevated cholesterol, and therefore his risk for CHD, could have been due to lifestyle factors such as diet, excess weight, and lack of exercise, or to polygenic factors contributing to increased cholesterol level, or to a combination of these factors.

Inherited causes of premature CHD

An inherited hyperlipidemia is also a consideration when early CHD occurs. In particular, two genetic conditions associated with lipid abnormalities confer high risk of CHD: familial hypercholesterolemia (FH) and familial combined hyperlipidemia (FCH). Although the prevalence of FH is under 1%, it accounts for about 5% of premature CHD; FCH accounts for about 15% of premature CHD (Table 1).

Table 1. Common Inherited Conditions Associated with a High Risk of CHD

Condition	Prevalence	Mode of Inheritance	Underlying Deficit	Lipid Profile
Familial hypercholesterolemia (FH)	~1/500	Autosomal dominant	LDL receptor defect	Elevated cholesterol: typically >300 mg/dL; level may be >600 mg/dL
Familial combined hyperlipidemia (FCH)	~1/100	Autosomal dominant	Unknown	Variable • Elevated cholesterol, LDL/VLDL, and/or trigylcerides • Decreased or normal HDL • Elevated apolipoprotein B100 (serum concentration >125 mg/dL)

In addition to markedly elevated serum cholesterol concentration, FH is associated with lipid deposits observable on skin examination. These are waxy, yellowish skin lesions commonly found on the extensor tendons of the hand or as thickening (>7 mm) of the Achilles tendon (tendinous xanthomas) or on the eyelid (xanthelasma). Such lesions are rare in FCH.

Genetic counseling

If FH or FCH is diagnosed, further evaluation of family members is warranted. Siblings and children of a person with FH or FCH have a 50% risk of inheriting the condition and may benefit from early detection and aggressive management of lipids and other modifiable cardiac risk factors, with diet, exercise, cholesterol-lowering drugs, and other management as indicated by assessment of cardiac risk profile. Genetic counselors can assist families by providing information about the inheritance of these genetic conditions, determining which family members are at risk, and organizing testing for at-risk family members.

Genetic testing

FH and FCH are diagnosed by a combination of lipid testing and evaluation of family history. DNA-based testing, to identify mutations in the gene encoding the LDL receptor, is available in some international laboratories, and is sometimes used to detect family members with FH. More commonly, detection of affected relatives is accomplished by measurement of serum cholesterol and other lipid measures (Table 1).

Interventions

Whether cardiac risk results from genetic or non-genetic factors, the general approach to risk management is the same: Identification of all modifiable risk factors, and the use of lifestyle measures and medications to improve the risk profile.

Lifestyle modification is beneficial for all patients with cardiac risk factors, even if drug treatment is also required. Measures include regular exercise; low-fat diet; and smoking cessation (see sections below on physical activity and diet).

Drug treatment is an important component of the management of hypertension, hyperlipidemia, and diabetes mellitus.

Current NCEP guidelines for lipid management use the patient's risk status to determine the LDL cholesterol (LDL-C) threshold at which drug therapy should be initiated. For patients at the highest risk — i.e., those who already have CHD or a CHD equivalent such as diabetes mellitus or carotid artery disease — NCEP recommends consideration of drug therapy when LDL-C is ≥130 mg/dL, and identifies drug therapy

as an option when the patient's baseline LDL-C is ≥100 mg/dL; at the other end of risk spectrum, for patients without disease and with one or fewer cardiac risk factors, NCEP recommends consideration of drug therapy when LDL-C is ≥190 mg/dL. (Further discussion of lipid management can be found at the NCEP Web site.)

Increasing physical activity. Physical Activity and Health: A Report of the Surgeon General summarizes current findings and recommendations related to physical activity. This report notes that:

- People who are usually inactive can improve their health and well-being by becoming even moderately active on a regular basis.
- Physical activity need not be strenuous to achieve health benefits.
- Greater health benefits can be achieved by increasing the amount (duration, frequency, or intensity) of physical activity.

Many different kinds of physical activities can provide a health benefit, with a longer duration recommended for less intense activities. Exercise should occur on a daily basis if possible. The Surgeon General's Report includes the following examples of daily exercise (from less to more intense; see report for additional examples):

- Washing windows or floors for 45-60 minutes
- Gardening for 30-45 minutes
- Walking 1 3/4 miles in 35 minutes (20 min/mile)
- Pushing a stroller 1 1/2 miles in 30 minutes
- Raking leaves for 30 minutes
- Walking 2 miles in 30 minutes (15 min/mile)
- Swimming laps for 20 minutes
- Jumping rope for 15 minutes
- Running 1 1/2 miles in 15 minutes (10 min/mile)
- Shoveling snow for 15 minutes
- Stairwalking for 15 minutes

In addition, the report notes that "cardiorespiratory fitness gains are similar when physical activity occurs in several short sessions (e.g., 10 minutes) as when the same total amount and intensity of activity occurs in one longer session (e.g., 30 minutes), and for people who are unable to set aside 30 minutes for physical activity, shorter episodes are clearly better than none."

Diet. NCEP guidelines include the following essential features for a diet to reduce CHD risk:

- Reduced intake of saturated fats (to <7% of total calories), cholesterol (to <200 mg per day) and total fat (to 25-35% of total calories).
- Inclusion of plant stanols & sterols (found naturally in fruits, vegetables, nuts, seeds, cereals, legumes, and vegetable oils, particularly soybean oil).

- Inclusion of 20-30 g per day of fiber, including 10-25 g per day of viscous (soluble) fiber (found naturally in oats, barley, soybeans, dried beans and peas, and citrus fruit).
- Balance of energy intake and expenditure to maintain desirable body weight.

Ethical/Legal/Social/Cultural Issues

Does knowledge of genetic risk lead to fatalism?

One might expect that knowledge of increased risk would motivate behavioral change, but the evidence for motivation is not strong. For example, several studies indicate that compliance with recommendations for lifestyle modification is not significantly increased based on knowledge of one's cholesterol level [Robertson et al 1992, Elton et al 1994, Hanlon et al 1995, Strychar et al 1998]. When the risk factor is perceived as inherited, the motivation to change could be even more problematic.

For example, in a pilot study of the parents of 24 children who were found to have FH based on neonatal screening, the parents responded differently depending on their perception of the underlying cause of this risk. When they perceived the test as detecting raised cholesterol, their child's condition was seen as "familiar, dietary in origin, controllable and less threatening." When it was viewed as a genetic problem, it was seen as "uncontrollable and, hence, more threatening" [Senior et al 1999]. These results suggest the need to present information about genetic risk factors for CHD in a context that emphasizes the options for improving risk through lifestyle modification and drug treatment.

Resources

- **American Heart Association**
- **NIH National Cholesterol Education Program**
- **Familial Hypercholesterolemia**
- **Familial Combined Hyperlipidemia**
- **Physical Activity and Health: A Report of the Surgeon General**
- **GeneTests Online Medical Genetics Information Resource**

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