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Approach to Familial hypercholesterolemia in children

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Familial hypercholesterolemia in children

Definition

1. DNA-based evidence of mutation in the LDLR, PCSK9, or APOB gene.
2. Clinical characteristics that usually include high LDL-C.

Diagnostic Criteria

1. American Heart Association criteria to the clinical diagnosis of FH: LDL-C > 190 mg/dl and either a first degree relative with LDL-C > 190 mg/dl or with known premature coronary artery disease.

2. Dutch Lipid clinic

3. Simon Broome

Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia

Criteria	Points
1. Family history	
▪ First-degree relative with known premature (men: <55 years; women: <60 years) coronary or vascular disease, or ▪ First-degree relative with known LDL-C above the 95th percentile	1
▪ First-degree relative with tendinous xanthomata and/or arcus cornealis, or ▪ Children <18 years of age with LDL-C above the 95th percentile	2
2. Clinical history	
▪ Patient with premature (men: <55 years; women: <60 years) coronary artery disease	2
▪ Patient with premature (men: <55 years; women: <60 years) cerebral or peripheral vascular disease	1

Simon Broome Familial Hypercholesterolemia Register diagnostic criteria for familial hypercholesterolemia[1-3]

Criteria	Description
a	Total cholesterol concentration above 7.5 mmol/liter (290 mg/dL) in adults or a total cholesterol concentration above 6.7 mmol/liter (259 mg/dL) in children aged less than 16 years, or
	Low-density lipoprotein cholesterol concentration above 4.9 mmol/liter (189 mg/dL) in adults or above 4.0 mmol/liter (155 mg/dL) in children
b	Tendinous xanthomata in the patient or a first-degree relative
c	DNA-based evidence of mutation in the *LDLR, PCSK9,* or *APOB* gene
d	Family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree relative

Genetic Considerations:

Patients with FH usually have a functional mutation of one of three genes.

1. LDLR mutations are the most common (85 to 90 per cent)
2. Gain of function PCSK9 mutations (2 to 4 percent)
3. APOB mutations (1 to 12 percent)
4. STAP1, occurring in < 0.1 percent of cases

Other factors that affect LDL-C Level:

1. Other genetic abnormalities
2. Comorbid diseases (e.g. hypothyroidism, liver disease)
    1. Acute viral illness
    2. Inflammatory state
    3. Post-surgical state

Prevalence

- FH is the most common monogenic, autosomal dominant disorder in humans.
- Heterozygous FH worldwide is about 1 in 300 individuals.
- Homozygous FH prevalence is 1:300,000 - 1:400,000.

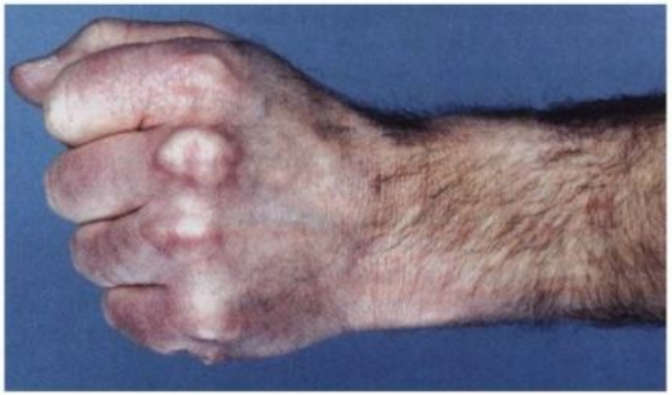
Clinical Suspicion to FH

1. LDL-C ≥ 190 mg/dl
2. Family member with known FH or total cholesterol > 240 mg/dl in either parent.
3. Cholesterol deposits (xanthomas which often occur in tendons, around the cornea, or perioral) in the patient or family members.
4. Premature CAD in the patient or family members.
5. Sudden premature cardiac death in a family member.

Physical examination

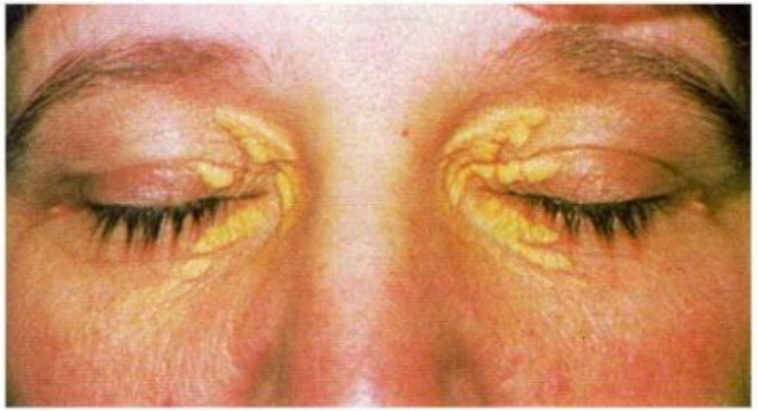
1. Tendon xanthomata are most common in the Achilles tendons and dorsum of the hands.
2. Planar xanthomas in palms and soles and are often painful.
3. Xanthelasmas usually appear on the medial aspects of the eyelids.
4. Corneal arcus.
5. Evidence of vascular obstruction in arteries.

Tendon xanthomata



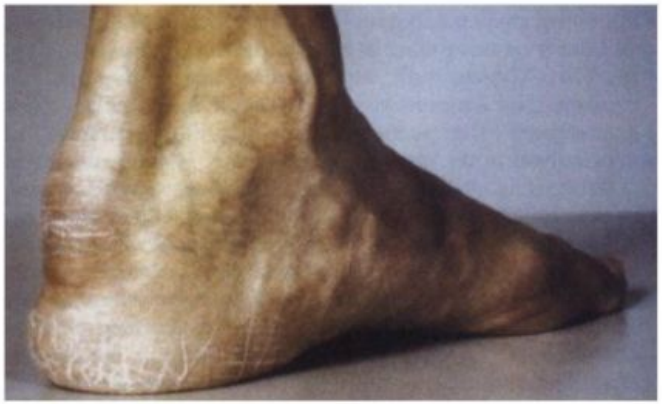
Tendon xanthomata on the dorsum of the hand in a patient with heterozygous familial hypercholesterolemia.

Xanthelasma

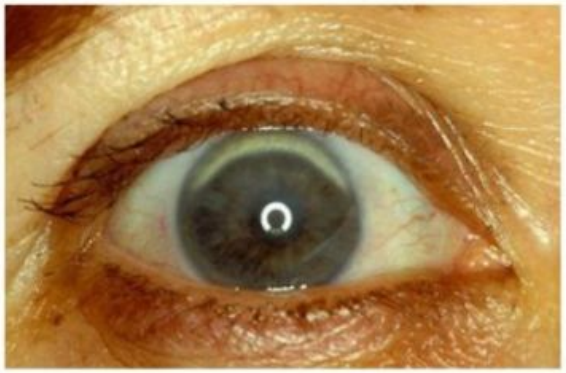


Yellow plaques are present bilaterally.

Achilles tendon xanthoma



Early corneal arcus



Fasting Lipid Profile

In patient with FH, total cholesterol and LDL-C are elevated with normal or low HDL-C and normal TG levels (unless the patient is obese, has diabetes, or other mutations in TG-regulating genes, in which case TG levels may also be elevated)

Genetic Testing

Testing for mutations in the LDL R, APOB, and pcsk9 gens can be performed in individual with clinical diagnoses of homozygous FH. Negative results may not necessarily mean that there is no genetic defect.

Criteria for diagnosis of homozygous FH

1. Untreated LDL-C > 500 mg/dl or treated LDL-C > 300 mg/dl

or

2. Cutaneous or tendon xanthoma before age 10 years.

or

3. Elevated LDL-C levels consistent with heterozygous FH in both parents.

Differential diagnosis

1. Familial combined hyperlipidemia

2. Hyperbetalipoproteinemia

3. Polygenic hypercholesterolemia

4. Familial dysbetalipoproteinemia

Secondary causes of dyslipidemia in adults

- Diabetes mellitus
- Cholestatic liver disease
- Nephrotic syndrome
- Chronic kidney disease
- Hypothyroidism
- Obesity
- Cigarette smoking
- Excessive alcohol consumption
- Medications

Prognosis

Prior to the widespread use of statin therapy for patients with heterozygous familial hypercholesterolemia, the risk of CAD was very high.

In an analysis of Danish registry the mean age at death increased from 50 to 78.

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- At any Level of untreated LDL-C, the prognosis for patients with heterozygous FH is worse than those without.
- Patients with LDL-C ≥ 190 mg/dl compared with those with LDL-C < 130 mg/dl had a 22-fold increased risk for coronary artery disease.
- For homozygous patients, the extent of reduction of serum cholesterol is a major determinant of survival.

Clinical suspicion of FH

- There is a family history of premature ASCVD and the child or adolescent’s LDL-C level is ≥ 160 mg/dl
- In the absence of a family history of premature ASCVD FH should be suspected if the patient's LDL-C level is 190 ≥ mg/dl

Most patients with FH have heterozygous FH, in which LDL-C Levels are typically in the range of 160 to < 400 mg/dl

Homozygous FH is rare and LDL-C levels > 400 mg/dl

Risk stratification for children and adolescents at risk for early cardiovascular disease

High-risk conditions and risk factors	Moderate-risk conditions and risk factors	At-risk conditions and risk factors
▪ Homozygous FH ▪ Diabetes mellitus (type 1 or 2) ▪ End-stage kidney disease ▪ Kawasaki disease with persistent coronary aneurysms ▪ Solid-organ transplant vasculopathy ▪ Childhood cancer survivor following stem cell transplantation ▪ Multiple comorbidities – Any **moderate-risk** condition plus ≥2 additional **moderate-** or **at-risk** factors	▪ Severe obesity (BMI ≥99th percentile or ≥35 kg/m^2) ▪ Confirmed hypertension (BP >95th percentile or ≥130/80 mmHg on 3 separate occasions) ▪ Heterozygous FH ▪ Predialysis chronic kidney disease ▪ Aortic stenosis or coarctation ▪ Childhood cancer survivor with exposure to chest irradiation ▪ Multiple risk factors – ≥3 **at-risk** conditions or risk factors	▪ Obesity that is not severe (BMI ≥95th to <99th percentile) ▪ Insulin resistance with comorbidities (eg, NAFLD, PCOS) ▪ Family history of premature CVD* ▪ Parent with known dyslipidemia (eg, FH) or TC >240 mg/dL (6.2 mmol/L) ▪ Current smoker or significant exposure to second-hand smoke ▪ White-coat hypertension (elevated BP measurements in the office with normal

Treatment

High-risk patients:

In this group who have LDL-C ≥130 mg/dl, both lifestyle changes and statin therapy are suggested. The exception is the patient with type 1 or type 2 diabetes.

The treatment target once on statin therapy is LDL-C < 100 mg/dl.

Moderate-risk patients

In these patients initial management is lifestyle changes for three months. If the LDL-C remains > 160 mg/dl statin therapy is initiated.

The treatment target once on statin therapy is LDL-C < 130 mg/dl.

At-risk patients:

In these patients initial management is lifestyle changes for six months. If the LDL-C remains >160 mg/dl statin therapy is initiated. The treatment goal is LDL-C < 130 mg/dl.

Heart-healthy lifestyle:

1. Dietary modification
2. Physical activity
3. Weight loss
4. Maximizing high-quality sleep
5. Avoidance of nicotine

Dietary modification:

1. Diet high in fiber from fruits, vegetables, and whole grains.
2. High in polyunsaturated and monounsaturated fats.
3. Low in saturated fats.
4. Devoid of trans fats.

Behavior modification and ***motivational interviewing*** techniques may be helpful. Support and lifestyle modification for the whole family is usually necessary for successful change in the child.

Fat comprises 30 percent of total energy intake, and saturated fat is limited to < 10 percent ***if hypercholesterolemia persists*** limiting total fat to 25 to 30 percent of total calories and saturated fat to < 7 percent.

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A diet low in saturated fats and high in fiber modestly lowers LDL-C.

In children with FH diet modification alone is rarely sufficient to reach target levels for LDL-C.

Plant stanol and sterols:

These components are found in fruits, vegetable oils, nuts, and seeds.

Stanols and sterols decrease TG and LDL-C levels.

These compounds decrease absorption of fat-soluble vitamins and beta-carotene, therefore must take a daily multivitamin.

Fiber

Fiber binds with cholesterol within bile acids, thus removing it from the enterohepatic circulation.

Consuming fiber from dietary sources (fruits, vegetables, whole grains) are better than fiber supplements.

Daily dose:

- 2-12 years old: 6 gr
- Older than 12: 12 gr

Ineffective supplements

1. Garlic is not effective

2. Omega 3 fatty acids are not recommended for children with hypercholesterolemia, they may increase LDL-C levels. However, they are sometimes used to treat patients with hypertriglyceridemia.

Weight Loss

For children with obesity and dyslipidemia, weight loss can result in substantial improvement in lipid values.

Physical activity

Daily moderate to vigorous physical activity improves cardiovascular health and reduces the risk of ASCVD.

60 minutes of moderate to vigorous intensity physical daily activity is recommended.

Avoiding nicotine exposure

Nicotine increases LDL-C, and decreases HDL-C level.

Smoking promotes the oxidation of LDL particles.


Thank you