Clinical features of familial hypercholesterolemia

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Mona Lisa (Leonardo da Vinci, 1056) => signifying the first case of familial hypercholesterolemia

1) a yellow irregular leather-like spot at the inner end of the left eyelid (xanthelasma)

2) a well-defined swelling on the right hand beneath the index finger (lipoma)
Familial Hypercholesterolemia (FH)
Overview of FH (1)

- FH is *almost always* inherited as an autosomal dominant disorder with a very rare autosomal recessive form\(^1,2\)
- LDL-cholesterol level generally exceeds the 95th percentile during childhood in patients with FH\(^2,3\)
- LDL-cholesterol concentrations are generally
  - 2- to 3-fold higher in people with heterozygous FH (HeFH)
  - 3- to 6-fold higher in people with homozygous FH (HoFH) than normal\(^4\)
- Patients with FH have heightened risk of cardiovascular disease (CVD) due to life-long exposure to elevated cholesterol\(^5,6\)

Overview of FH (2)

- If left untreated, individuals with HoFH often develop symptomatic CVD before age 25.
- Those with untreated HeFH often experience CVD by age 55.¹
- A small fraction of treated FH patients have
  - no CVD but persistently elevated LDL-C levels >300 mg/dL (7.75 mmol/L)
  - CVD and persistently elevated LDL-C levels >200 mg/dL (5.17 mmol/L) despite maximally tolerated lipid-lowering therapy.
- Severe FH patients are currently eligible for LDL apheresis.

References:
FH can be caused by mutations in 4 genes

FH is typically caused by mutations in LDLR, ApoB, PCSK9, LDLRAP1 or other as yet other unidentified genes\(^1\)

- LDL Particle
- Circulation
- Liver cell
- LDL Receptor on hepatocyte, binds to Apo B on LDL particle, inducing endocytosis of LDL
- Apo B acts as ligand, binding LDL particle to receptor
- PCSK9 Enzyme degrades LDL receptors
- LDLRAP1 (ARH) mediates internalization via clathrin coated pits


The atherosclerotic burden of FH reflects the lifelong accumulation of LDL and ApoB-containing lipoproteins.

Adapted from Robinson JG. *J Am Coll Cardiol.* 2010;55(1):42-44.
Familial Hypercholesterolemia

CLINICAL PRESENTATION
Clinical presentation of HoFH

- Cutaneous xanthomas at birth or by early childhood\(^1\)
- Planar xanthomas (on hands, elbows, buttocks, or knees), which are diagnostic for the homozygous state\(^1\)
- Tuberous xanthomas (on hands, elbows, or knees)\(^1\)
- Cardiac murmur due to aortic stenosis may be heard\(^{1,2}\)

*Six-year-old girl with HoFH. Bumps on skin are deposits of cholesterol derived from LDL.*

Physical exam findings in FH

Tuberous xanthomas

- Seen mostly in HoFH, and not as often in HeFH


Planar xanthomases

- Seen mostly in HoFH (on hands, elbows, buttocks, or knees), and not as often in HeFH
- are diagnostic for the homozygous state


Clinical outcomes of HoFH

- Severe vascular disease at an early age.
- Numerous case reports of CABG or death before age 10.
- Severe aortic stenosis is common.
- Untreated, usually results in death before age 30.
- Almost all HoFH patients require LDL apheresis.
- But even with maximal medical therapy there is disease progression.
Xanthelasma

Xanthelasmas around the eyes in an untreated adult patient with FH


Corneal arcus

- Common in older individuals (even non-FH)
- Definitive of FH in younger individuals.


30%-50% of the HeFH population have tendon xanthomas. Especially on extensor tendons of hands or Achilles tendon.
Achilles tendon xanthomas

Physical exam findings in FH

Normal (left) versus xanthomatous Achilles tendons (right) and their radiological assessment

Distribution of LDL-cholesterol in Untreated Patients With Definite FH

Median = 6.95 mmol/L (268.76 mg/dL)
Mean = 7.22 mmol/L (279.2 mg/dL)

3 Most Common Physical Signs in FH

Absence of physical signs does not exclude the possibility of FH.

Clinical course in HeFH

- 20-fold increased risk of CVD
- If untreated:
  - Men have 50% risk of CVD by age 50
  - Women have 30% risk of CVD by age 60
- Many HeFH patients present with established CVD (angina, MI)
## Characteristics of HoFH and HeFH

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>HoFH</th>
<th>HeFH</th>
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<tbody>
<tr>
<td>Untreated LDL-C (mg/dL)</td>
<td>Generally &gt;465 mg/dL&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Average &gt;220 mg/dL</td>
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<tr>
<td>Treated LDL-C</td>
<td>&gt;300 mg/dL after max tolerated drug therapy&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Mean 135 +/- 38 mg/dL after treatment with high dose statins</td>
</tr>
</tbody>
</table>
| Cutaneous features       | Tendon xanthomas  
                            | Xanthelasma  
                            | Tuberous xanthomas  
                            | Planar xanthomas |
| Corneal arcus            | Possible before age 20 | Common after age 40 |
| Symptomatic Atherosclerosis | Within 2nd decade | Within 4th-5th decade |


Familial Hypercholesterolemia

ADDITIONAL RISK FACTORS TO CONSIDER
Additional CVD risk factors to consider in HeFH

- Lipoprotein(a) [Lp(a)] ≥50 mg/dL<sup>1,3,4</sup>
- Tendon xanthomas
- Cigarette smoking: active smokers<sup>1</sup>
- Family history of premature CVD<sup>1</sup>
  - in male first-degree relative <55 y
  - or in female first-degree relative <65 y
- HDL-C <40 mg/dL (1.0 mmol/L)<sup>1</sup>
- High Blood pressure: >140/90 mmHg<sup>1</sup>
- Diabetes mellitus<sup>1</sup>

- Independent CVD risk factors
- In FH, independent CVD risk factors could potentially interact with lifelong high LDL-C levels to aggravate risk

2 risk factors in FH independent of LDL-C

Tendon xanthomas
- Tendon xanthomas in FH are associated with CV risk independently of the LDLR gene mutation
- Approximately 30%-50% of HeFH patients with genetic diagnosis have tendon xanthomas

Lipoprotein(a)
- Lp(a) is an independent risk factor for CVD in HeFH
- Elevated serum Lp(a) concentrations may be regarded as a component of the clinical syndrome of FH
- In homozygous or heterozygous FH, mutations in the LDLR show clear gene-dose effect on plasma Lp(a) levels
- Potential interactions between high Lp(a) level and additional risk factors for CVD may potentiate the very high CVD risk of FH patients

Lp(a) elevations are more frequent in FH

- Lp(a) levels in FH increased 3 times higher than controls
- Across Lp(a) ranges, LMW forms are greater in FH than controls

Significant difference in intima-media thickness (IMT) between children with FH and unaffected siblings \((P = 0.002)\) by age of 12

Carotid IMT in FH vs non-FH patients

Summary: FH

• FH is an inherited disorder that is characterized by high levels of LDL from early childhood.
• Patients with FH have a high risk of CVD related to elevated LDL levels.
• The diagnosis of FH is based primarily on:
  ◦ Extreme hypercholesterolemia early in life (untreated LDL-C ≥ 190 mg/dL in early adulthood)\(^3\)
  ◦ Clinical evidence of premature CVD and/or family history of hyperlipidemia.
• FH is an autosomal dominant condition, so once a family member with FH is identified, ‘cascade’ screening in the rest of the family is mandatory.

Despite current lipid-lowering therapy, all HoFH patients and a significant proportion of HeFH patients remain far from desired LDL-cholesterol goals.

Advances in lipid-lowering treatment

- alter their disease spectrum from a fatal CVD in childhood
- delay CV events and prolong survival in HoFH patients

Candidate emerging therapies for FH are

- PCSK9 inhibitors
- ApoB inhibitors
- MTP inhibitors

Take home messages

- FH is a common cause of high cholesterol and early heart disease, including heart attacks.
- Parents, brothers, sisters, and children of individuals with FH have a 50% chance to also have FH.
- FH is different than other types of high cholesterol and needs to be treated differently.
- FH is manageable! Patients with FH need to take their medications, NEVER SMOKE, eat a healthy diet, and exercise.
Thank you for your attention