NLA Pediatric Session

Cascade Screening for Familial Hypercholesterolemia (FH)

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Cardiovascular Genetics
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Prerequisites for cascade screening for FH

1. Realize the significance of FH
2. Be motivated to prevent early CAD in family members!
3. Be willing to implement family screening
4. Be able to recognize, diagnose FH
5. Know treatment strategies
Definition of FH

- **Autosomal co-dominant high LDL-C**
  - Easiest to recognize when lipids from the entire family are examined.
    - Invite families of suspected probands for screening!
  - Most families have only heterozygotes (HeFH).

- **Gene dosage effect**
  - Homozygotes (HoFH) have much higher LDL-C and much earlier CAD onset than heterozygotes (HeFH)
Genetic basis of FH

- All known genetic causes of autosomal dominant hypercholesterolemia impair LDL receptor activity
  - ½ LDL catabolic rate $\rightarrow$ 2x increase in LDL in HeFH
  - LDLR (85-90+% of cases of clinical HeFH)
    - Over 1600 mutations known (http://www.ucl.ac.uk/ldlr)
  - Apo B (0-12% of cases of clinical HeFH)
    - 3 mutations documented
    - most common Arg3500Gln (northern European origin)
  - PCSK9 (2-4% of cases of clinical HeFH)
    - Only gain of function (GOF) mutations cause HeFH
Molecular mechanisms of genetic hypercholesterolemia

Adapted from Calandra S J Lipid Res 2011 52 1885
Homozygous FH (HoFH)

- Recent new interest with upcoming new therapies
- Historically the first FH syndrome to be recognized
  - “Xanthoma multiplex”
    - Burns FS. Arch Dermatol 1920; 2:415 (cites a 1899 study)
  - Dramatic presentation at a young age
    - more easily recognized than HeFH
  - Completely or severely impaired LDLR activity
  - “Compound heterozygotes” more common than true HoFH
    - different LDLR mutations from each parent.
  - “Double heterozygous” LDLR/APOB, LDLR/PCSK9 now described
    - HoFH phenotype when untreated
    - Better response to therapy than classical HoFH
Various criteria for Dx of HoFH

- Elevated serum total and LDL cholesterol
  - Total-C 500+, 550+, 600+, 650+ mg/dl
  - LDL-C 400+, 500+, “220+ mg/dl with maximal Rx”
  - Triglycerides <600 mg/dl (few criteria require this)
- Xanthomas in the first decade of life
- Both parents have HeFH
  - Total-C 250+, 300+; LDL-C 200+
- LDLR mutation or functional deficit
  - True HoFH, compound HeFH, “double HeFH”
  - <30% normal LDL uptake by cultured fibroblasts

Raal FJ, Santos RD. Atherosclerosis 2012; 223:262
An example of HoFH

12-year old boy from Bhopal, India with chest pain.

serum cholesterol 641 mg/dl
12-year old boy from Bhopal, India (continued)
Homozygous FH (HoFH)

18 y/o female
TC 669 mg/dl

20 y/o female - Utah
27 y/o French Canadian woman with aortic and mitral murmurs
serum cholesterol 660-999 mg/dl
Burns FS. Arch Dermatol 1920; 2:415
Surveys of HoFH to estimate both HoFH and HeFH frequency

  - Serum total cholesterol 508-1,108 mg/dl
  - Japan: 44 cases, population age 0-35 = 64 million
    - Tokyo: 12 cases in 11 million
    - Osaka: 7 cases in 9 million
  - HeFH estimated at 0.17 to 0.2% (1 in 500-588)

- **HoFH in England & Wales** (Slack J. Atheroscler Rev 1979;5:35)
  - 10 HoFH in 16 million age 0-30. HeFH 0.16% (1 in 625)

- **Higher rates in founder populations**
  - Afrikaners, French Canadians, Lebanese, Hokuriku
Physical, lab findings in HeFH

- Untreated plasma LDL-C generally most useful for diagnosis but there is overlap with non-FH
  - LDL-C >160 mg/dl in about 80% of HeFH
  - LDL-C >200 mg/dl in about 60% of HeFH
  - Total-C 500 mg/dl is about the 98-99th percentile for HeFH
- Most commonly, HeFH have NO physical findings!
- In HeFH, tendon xanthomas can be subtle
  - Nearly pathognomonic if present
  - 39.3% of 262 Utah HeFH age 30+ had xanthomas
  - Prevalence of xanthomas is age-dependent
  - Tuberous xanthoma and xanthelasma occasionally seen but not typical of HeFH
- Arcus is generally not useful for diagnosis

Hopkins PN, et al. Am J Cardiol 2001;87:547
Cumulative Probability of Fatal and Non-Fatal CAD in 116 FH Pedigrees

Cumulative Probability of Non-Fatal CAD in Utah FH vs a Random U.S. Population

6-fold higher risk in men versus women among FH subjects

Hopkins PN. Clin Lipidol 2010; 5:339
Recognized FH Diagnostic Criteria

● Best characterized clinical diagnostic tools:
  - US MEDPED Program
  - Simon-Broome Registry Group (UK)
  - Dutch Lipid Clinic Network

● DNA evidence:
  - Only the gold standard in families with a known mutation

1993 “MEDPED” Criteria for Diagnosing Heterozygous FH in U.S. Population

- Cut points chosen for 80% probability that an individual is affected.
- Other criteria were applied to diagnose a newly identified family.

<table>
<thead>
<tr>
<th>Age</th>
<th>First</th>
<th>Second</th>
<th>Third</th>
<th>General</th>
<th>“100%”</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>220 (155)</td>
<td>230 (165)</td>
<td>240 (170)</td>
<td>270 (200)</td>
<td>(240)</td>
</tr>
<tr>
<td>20-29</td>
<td>240 (170)</td>
<td>250 (180)</td>
<td>260 (185)</td>
<td>290 (220)</td>
<td>(260)</td>
</tr>
<tr>
<td>30-39</td>
<td>270 (190)</td>
<td>280 (200)</td>
<td>290 (210)</td>
<td>340 (240)</td>
<td>(280)</td>
</tr>
<tr>
<td>40+</td>
<td>290 (205)</td>
<td>300 (215)</td>
<td>310 (225)</td>
<td>360 (260)</td>
<td>(300)</td>
</tr>
</tbody>
</table>

## Simon Broome Register
### Diagnostic Criteria for HeFH

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>DNA-based diagnosis: mutation in LDLR or any other HeFH-related gene</td>
</tr>
<tr>
<td>B</td>
<td>Tendon xanthomas in the patient or any first- or second-degree relatives</td>
</tr>
<tr>
<td>C</td>
<td>MI by age 50 years in a 2° relative or by 60 years in a 1° relative</td>
</tr>
<tr>
<td>D</td>
<td>Plasma Total-C &gt;290 mg/dL in any first- or second-degree relative</td>
</tr>
<tr>
<td>E</td>
<td>Total-C &gt;290 mg/dL (adult patient) or &gt;259 mg/dL (child aged &lt;16 years)</td>
</tr>
<tr>
<td>F</td>
<td>LDL-C &gt;190 mg/dL (adult patient) or &gt;155 mg/dL (child aged &lt;16 years)</td>
</tr>
</tbody>
</table>

### Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Criteria Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite HeFH</td>
<td>A OR B + (E or F)</td>
</tr>
<tr>
<td>Probable HeFH</td>
<td>C + (E or F) OR D + (E or F)</td>
</tr>
</tbody>
</table>

Y Hamilton-Craig I. *Medicine Today* 2008; 9:39
## Dutch Lipid Clinic Diagnostic Criteria

<table>
<thead>
<tr>
<th>Family history</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-degree relative with premature CVD (M &lt;55, F &lt;60)</td>
<td>1</td>
</tr>
<tr>
<td>First-degree relative with LDL-C &gt;95th percentile</td>
<td>1</td>
</tr>
<tr>
<td>First-degree relative with tendon xanthomas and/or arcus</td>
<td>2</td>
</tr>
<tr>
<td>Children &lt;18 with LDL-C &gt;95th percentile</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Personal history of CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature CHD (men &lt;55 years, women &lt;60 years)</td>
</tr>
<tr>
<td>Cerebral or peripheral vascular disease (M &lt;55, F &lt;60)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tendon xanthomas</td>
</tr>
<tr>
<td>Arcus senilis in patients &lt;45 years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LDL-C level (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;330</td>
</tr>
<tr>
<td>250-329</td>
</tr>
<tr>
<td>190-249</td>
</tr>
<tr>
<td>155-189</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DNA analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional mutation of LDL receptor gene</td>
</tr>
</tbody>
</table>

- **Definite FH** >8 points
- **Probable FH** 6-8 points
- **Possible FH** 3-5 points

### Genetic testing in 408 Danes with clinical FH

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Mutation ID</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Utah MEDPED</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total-C</td>
<td>63.4%</td>
<td>73.4%</td>
<td>53.5%</td>
</tr>
<tr>
<td>LDL-C</td>
<td>70.3%</td>
<td>69.8%</td>
<td>51.6%</td>
</tr>
<tr>
<td><strong>Dutch MEDPED</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>41.5%</td>
<td>87.9%</td>
<td>62.9%</td>
</tr>
<tr>
<td>Probable+</td>
<td>66.7%</td>
<td>64.5%</td>
<td>48.1%</td>
</tr>
<tr>
<td>Possible+</td>
<td>99.3%</td>
<td>5.9%</td>
<td>34.3%</td>
</tr>
<tr>
<td><strong>Simon-Broome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>34.1%</td>
<td>89.4%</td>
<td>61.3%</td>
</tr>
<tr>
<td>Possible</td>
<td>90.4%</td>
<td>28.6%</td>
<td>38.5%</td>
</tr>
</tbody>
</table>

Cascade screening

- Most cost-effective means to find FH
- Infrequently performed in a clinical setting
- High yield!
  - 50% have FH among 1st degree relatives
  - 25% among 2nd degree relatives
  - 0.02% in general population
- Within a known FH pedigree, LDL-C alone is 90-95% sensitive and specific versus genetic testing.
  - Thorsson B, et al. ATVB 2003;23:33
- Find younger FH patients and prevent CAD!
Developing criteria to diagnose FH

mean LDL-C mutation negative: 2.2 mmol/L = 85/mg/dl
mean LDL-C mutation positive: 4.4 mmol/L = 170 mg/dl
Guidelines for screening

- 2 cost-effective means to prevent early CHD deaths in FH ($/year of life gained):
  - Family screening (cascade screening)
    - lowest cost per patient identified
  - General population screening by at least age 16 with early initiation of effective treatment
    - Effective for preventing early deaths and CHD events in FH

- This is a major reason for the recent changes in pediatric guidelines.

Rationale for newer, more aggressive pediatric guidelines

- Evidence that universal screening in childhood for FH is cost-effective in terms of cost/year of life saved.
- Decreased progression of carotid IMT in statin-treated FH
- Good evidence for safety of most statins


Full panel report. Pediatrics 2011:128;S213
Guidelines for pediatric screening and treatment of hyperlipidemia

- Universal screening age 9-11
  - lipids are relatively stable
  - Difference in LDL-C between HeFH and non-FH is most evident
- Screen at age 2+ in FH families
  - Rule out hypothyroidism, nephrotic syndrome, and liver disease
- Start statin at age 10 if LDL stays >190 mg/dl
  - Consider bile acid sequestrant as secondary treatment
  - Goal: LDL-C <130 mg/dl or at least 50% reduction of LDL-C
- Earlier Rx in HoFH

Full panel report. Pediatrics 2011:128;S213
Cascade screening for FH

WILL YOU MAKE A DIFFERENCE?
Aggressive lipid treatment led to net regression of CAD in FH

Mean % stenosis changes:
- Lovastatin, BAS, niacin ($\Delta = -1.53 \pm 4.34, N = 40$)
- Diet & low dose BAS ($\Delta = +0.80 \pm 5.07, N = 32$)

Randomized trial
Initial LDL about 280 mg/dl
On trial LDL-C:
- Lova 172 ± 63
- Diet 243 ± 67

Adapted from Kane JP, et al. JAMA 1990;264:3007
### CAD death rates in FH from the Simon Broome Registry

<table>
<thead>
<tr>
<th>Age attained</th>
<th>Person-years</th>
<th>Observed CAD deaths</th>
<th>Expected CAD deaths</th>
<th>SMR</th>
<th>p-value</th>
<th>Rate per 10,000 person-yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–39</td>
<td>2209</td>
<td>8</td>
<td>0.09</td>
<td>89</td>
<td>&lt;0.001</td>
<td>36.2</td>
</tr>
<tr>
<td>40–59</td>
<td>3197</td>
<td>17</td>
<td>3.92</td>
<td>4.3</td>
<td>&lt;0.001</td>
<td>53.2</td>
</tr>
<tr>
<td>60–79</td>
<td>1225</td>
<td>12</td>
<td>6.87</td>
<td>1.7</td>
<td>0.02</td>
<td>98.0</td>
</tr>
</tbody>
</table>

#### 1 January 1992 to 31 December 2006 (after statins)

<table>
<thead>
<tr>
<th>Age attained</th>
<th>Person-years</th>
<th>Observed CAD deaths</th>
<th>Expected CAD deaths</th>
<th>SMR</th>
<th>p-value</th>
<th>Rate per 10,000 person-yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–39</td>
<td>8456</td>
<td>4</td>
<td>0.26</td>
<td>15.4</td>
<td>&lt;0.001</td>
<td>4.7</td>
</tr>
<tr>
<td>40–59</td>
<td>16542</td>
<td>47</td>
<td>13.02</td>
<td>3.6</td>
<td>&lt;0.001</td>
<td>28.4</td>
</tr>
<tr>
<td>60–79</td>
<td>12728</td>
<td>102</td>
<td>58.34</td>
<td>1.7</td>
<td>&lt;0.001</td>
<td>80.1</td>
</tr>
</tbody>
</table>

Primary and secondary cases combined

CAD event-free survival in 1950 Dutch FH patients by statin Rx

CAD event-free survival in 261 FH patients age >55*

*matching the age of the Rotterdam study