Familial Hypercholesterolemia Case Studies

Paul Ziajka MD, PhD, FNLA
Director, The Florida Lipid Institute
Past President, SELA
Paul Ziajka - Disclosures

• Research Support:
  – Merck, Genzyme, Regeneron, Kowa, Catabase, Aegerion

• Speakers Bureau / Consultant:
  – AZ, Abbott, Merck, Lupin, Kowa, Aegerion, GSK, Amarin, Hunter Heart Lab, Genzyme
FH Case Presentations

• All patients presented are “real” and are being treating at my facility

• All lipid values are in mg/dL
  – Lp(a) values where reported are in CMUs

• All drugs are presented with their generic / chemical name
Presentation Outline

• Classic HoFH
• Atypical HoFH
• HoFH and his HeFH Family
Classic HoFH - RS

- 40 yo WM referred by cardiology with ↑↑↑ cholesterol
- PMHx:
  - s/p MI at age 18
  - CABG x 5 at age 28
  - HTN
- Social Hx:
  - (-) smoker; (+) social EtOH, (-) exercise
  - married with no children
  - works full time as a CPA in a large firm
Classic HoFH - RS

• FHx:
  – No siblings
  – Mother with CAD at ~40 yo; father with CAD age 35 yo
  – ↑↑ TC on both sides of his family but actual values unknown
  – NIDDM on maternal side

• ROS: (-)
Classic HoFH - RS

• Meds at presentation:
  – Niacin ER 2 gm/d, EZ 10 mg qD
  – Hx statin intolerance: true rhabdo on A & S

• PE: unremarkable except for corneal arcus

• By history TC > 600 mg/dL when on no Rx

• At presentation on EZ10 and N2000
  – TC = 295; LDL = 227, trigs and HDL wnl
  – Lp(a) = 13 CMUs
Classic HoFH – RS- Rx

- Recommended referral for apheresis
  - due to employment considerations not possible
- Checked vitamin D level (=48), TSH wnl
  - started CoQ10 200 mg qD and after 2 weeks re-challenged with pitavastatin 1 mg qD
  - recurrent rhabdo Sx’s and ↑↑ CPK with 1 week
- Discussed options for lomitapide vs. mipomersen
  - opted for lomitapide
Classic HoFH – RS - Rx

• Saw the dietitian for a very low fat diet
• Then started on lomitapide:
  – 5 mg qD: LDL 227 → 170
  – 10 mg qD: LDL 170 → 153
  – 20 mg qD: LDL 153 → 124
• Now on lomitapide 40 mg qD with f/u labs pending
• Well tolerated unless there’s a “dietary indiscretion”
Atypical HoFH - MS

• 44 yo WM referred by PCP with ↑↑ cholesterol

• PMHx: (-)
  – no CAD, PVD, CVD…..

• Soc Hx:
  – (-) smoker, (+) social EtOH, (+) regular PA
  – married with no children
Atypical HoFH - MS

• FHx:
  – (+) CAD on both sides, but onset after 4th – 5th decade of life
  – (+) high cholesterol on both sides but specific #’s not available
  – both father and mother still alive
  – one sibling with “high” cholesterol controlled with a statin

• ROS: (-)
Atypical HoFH - MS

• Meds: none on presentation
  – despite baseline LDL>400 he has never been on a cholesterol lowering medication

• PE: wnl
  – no arcus, xanthomas, xanthasamas

• Baseline labs:
  – TC=465; LDL=415

• Dx’d probable HeFH
  – WHO score: 8 (“probable” HeFH)
**Atypical HoFH - MS**

### Clinical Study Protocol

#### Appendix 2: WHO Criteria (Dutch Lipid Network Clinical Criteria) for Diagnosis of Heterozygous Familial Hypercholesterolemia

<table>
<thead>
<tr>
<th>Diagnostic Scoring for Heterozygous Familial Hypercholesterolemia</th>
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<tbody>
<tr>
<td><strong>Family History</strong></td>
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<tr>
<td>a. First degree relative with known premature CHD (&lt;55 yrs; women: &lt;60 yrs) coronary and cerebrovascular disease.</td>
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<tr>
<td>b. First degree relative with known LDL cholesterol &gt;250% percentile for age and sex.</td>
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<tr>
<td>and/or</td>
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<tr>
<td>c. First degree relative with tendon xanthomas and/or xanthomas.</td>
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<tr>
<td>d. Child/teen, age &lt;15 yrs., with LDL-cholesterol &gt;150% percentile for age and sex.</td>
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<table>
<thead>
<tr>
<th><strong>Clinical History</strong></th>
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<tbody>
<tr>
<td>a. Patient has premature CHD (&lt;55 yrs; women: &lt;60 yrs) coronary artery disease.</td>
</tr>
<tr>
<td>b. Patient has premature CHD (&lt;55 yrs; women: &lt;60 yrs) cerebrovascular or peripheral vascular disease.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Physical examination</strong></th>
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<tbody>
<tr>
<td>a. Tendon xanthomas</td>
</tr>
<tr>
<td>b. Accessory vessels before age of 45 yrs.</td>
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</table>

<table>
<thead>
<tr>
<th><strong>Laboratory analysis</strong></th>
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<tbody>
<tr>
<td>LDL cholesterol</td>
</tr>
<tr>
<td>a. LDL cholesterol</td>
</tr>
<tr>
<td>b. LDL cholesterol</td>
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<tr>
<td>c. LDL cholesterol</td>
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<tr>
<td>d. LDL cholesterol</td>
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<table>
<thead>
<tr>
<th><strong>DNA sample</strong></th>
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<tbody>
<tr>
<td>a. Familial mutation low-density Lp(a) receptor gene present.</td>
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### Diagnosis of HoFH

<table>
<thead>
<tr>
<th>Category/Genotype</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>10</td>
</tr>
<tr>
<td>Probable</td>
<td>8-9</td>
</tr>
<tr>
<td>Possible</td>
<td>3-5</td>
</tr>
</tbody>
</table>
Atypical HoFH – MS - Rx

- Referred to the dietitian and started simvastatin 20 mg qD
  - LDL 415 → 299
- Changed simva to rosuva 20 plus EZ 10
  - LDL 299 → 146
- Added colesevelam oral suspension 3.75 gm/d
  - LDL 146 → 124
Atypical HoFH – MS - Aside

• My clinic was involved in an HoFH clinical trial that had very poor recruitment
  – ♀ excluded & all my other HoFH patients were fairly well controlled on lomitapide or mipomersen

• Study sponsor agreed to pay sites to screen anyone with a baseline LDL>400

• Conventional wisdom: HoFH have an LDL>300 on max. medical Rx
  – MS had an LDL=124 on Rx
Atypical HoFH – MS - Aside

• The study protocol called for genetic testing

• My perspective on genetic testing:
  – cost
  – false negative rate
Atypical HoFH – MS - Aside

Dear Colleague,

below is the result of the DNA analysis or genotyping you requested:

patient details:
name/ID: 0477 00001
date of birth: 01-01-1980
gender: male
address:

referral details:
requested by: Paul Ziaka
hospital/origin: clinical trial via PPP
analysis details:
entry date: 07-08-2013
DNA number: S4076
Indication: mutation detected after sequence and MLPA analysis of the low-density lipoprotein receptor gene
finding: mutation detected after sequence and MLPA analysis of the low-density lipoprotein receptor gene
mutation/gene type 1: LDLR: 2263delG, exon 15
mutation/gene type 2: LDLR: 6 kb deletion of exon 35 [PH-Tonami]-[ESPO]
mutation types: deficient (null) and defective (non-null)
conclusion: Familial Hypercholesterolemia, compound heterozygous form, is confirmed

Sincerely yours,

Dr. Ir. J.J.C. Deviloo, molecular biologist
Molecular Diagnostics Laboratory, Dept. of Vascular Medicine, Academic Medical Centre, G3-115

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HeFH

• 3 male siblings referred by their pediatrician for very high cholesterol
  – TS age 12 yo: TC=292 with LDL=240
  – ZS age 10 yo: TC=230 with LDL=195
  – JS age 8 yo: TC=315 with LDL=260

• PMHx, PE, ROS all (-) or wnl
HeFH

- FHx:
  - both paternal grandparents with premature CAD and “high cholesterol”
  - father with TC>600 at baseline; s/p MI at age 21 yo
  - mother with normal TC and LDL
HeFH

- Father is not my patient
  - He is under the care of a local cardiologist on high dose statin, EZ and niacin ER with a recent LDL=190
- Was never dx’d with FH
- Family screening was never recommended
- Never referred to a dietitian or lipid center
HeFH

- Target LDL for all the boys at 100-130
- All boys started on simva 40 mg qD
  - TS: LDL 240 → 163
  - ZS: LDL 195 → 110
  - JS: LDL 260 → 180

- ZS continued on simva 40
HeFH

• Added EZ to simva 40:
  – TS: LDL 240 → 163 → 141
  – JS: LDL 260 → 180 → 150

• Added colesevalam 3.75 gm/d to simva and EZ:
  – TS: LDL=115
  – JS: LDL=120
HeFH

• Genetic testing never done, but suspect father is a compound heterozygous FH
  – one null allele
  – one partially functioning allele

• Suspect:
  – ZS inherited the partially functioning allele
  – TS and JS inherited the null allele
Conclusions

• HoFH is a devastating genetic disease presenting with very early CVD events
• HoFH is a treatable condition
• Some HoFH patients do not have the extremely high TC and LDL as is classically described
• HeFH is largely under-diagnosed and under-treated