F.H. (Familial Hypercholesterolemia)

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Clinical Diagnosis and Treatment

Case:

- 48 y/o female with a strong family hx of premature CVD.- No other risk factors and BMI 26.
- LDL-C 220 mg/dL/ lifelong LDL-C >95th -
- Recommended diet/ exercise only
- Deceased from ACS/MI
- Judgement for plantiff >2 million.

Familial Hypercholesterolemia (FH)

A good model for the cholesterol theory

Cholesterol Theory

- Lifelong exposure to elevated cholesterol has a log linear curve with cardiovascular disease. (De Castro,I. Application of Clinical Genetics. 2010;353-54.)
- PCSK-9...loss of function mutation- lifelong low cholesterol with no atherosclerosis.

FH:

- FH is a condition of very elevated T.Chol. and LDL-C.
- Typically heterozygotes have TC of >290 and LDL-C > 190 (TC of 290-550)
- Homozygotes typically >650-1000mg/dL
- Goldberg,A. JCL (Journal Clinical Lipidology) :Vol 5, No.3., June 2011

FH: Common

- One of the most common genetic disorders
- Considered to be the most common serious genetic d/o.
- Over 10 million worldwide
- over 620,000 in US
- Only approx. 20% diagnosed!
- Bambauer R. Therapeutic Apheresis. 2003;7(4):382-390.

FH: Heterozygotes and Homozygotes:

- Heterozygotes: This is a co-dominantly inherited disease: homozygotes inherit one defective allele in the gene coding for the LDL-receptor on the liver.
- Therefore, these patients have essentially 1/2 the number of LDL-receptors
- Thus, chol. is approx. double “normal”- 20X CVD risk... presents in early 40’s - *Log linear with CVD.*
- Common- 1:300-500 Most common inherited genetic disorder

Goldstein,J. Familial Hypercholesterolemia. McGraw-Hill; 2001:2863-2913

F.H.-Homozygotes cont…

- Homozygotes are exceptionally rare and have TC and LDL 3-5X ‘normal’-chol>1000mg/dL.
- Inherited this gene defect from both parents.
- Typically 1 in a million... is homozygous
- Rapidly accelerated atherosclerosis

- Hopkins PN. Familial Hypercholesterolemias: J. Clinical Lipidology. 2011;5(3 suppl):S9-17

Homozygotes cont…

- Homozygotes (compound heterozygotes as well) have severe atherosclerosis and manifest CVD during childhood and adolescence.
- HoFH pt's die by age 30- Many by age 20.
- Initiation of drug therapy early in life, but still require apheresis and for some liver transplant.
- Some work with gene therapy.

- Fahed,A Journal Nutr Metab. 2011;8.

FH- typically referring to heterozygotes

- Quite common- 1:300-500
- >620,000 in America at least
- More common in founder effect populations ie: French Canadians/Dutch Africaners, certain Jewish populations.../Christian Lebanese and Amish...
- *Only 20% pts Dx'd and even less treated.*
- *Manifest CVD by early 40's/ 50's for females-*

Diagnosis of FH:

- Age: <20 yrs- LDL >160
- 20-29 yrs and up- LDL-190 and greater
- +Family history of very high chol. and premature CVD (men <55, women<65) Dx is probable
- Typically triglycerides are normal...but not always.

- Willard,K. Lipid Spin. 2013 p5-17.

Physical Exam Findings:

- Not typically found in all with FH, but can be sensitive and specific:
- Tendon Xanthomas: (Achilles, finger extensor tendons, patellar and triceps)
- Arcus Cornae (age <45)
- Tuberous Xanthomas or Xanthelasma age under 25...
- Various Scoring sytems: MEDPED/ SBRG in Europe
- Khachadurian AK:The American Journal of Medicine 1964,37:402-7.

Genetic Testing in FH:

- Available... but generally not needed
- FH we are discussing is a phenotype (cholesterol levels/ physical findings)
- Remember- over 1600 gene mutations for the LDL-receptor. Defective ***apoB*** and gain of function mutations in ***PCSK9.*** will all take on FH phenotype. Abifadel,M. Gene in Cholesterol Met and Disease. Human Mutation 2009.

Universal Screening:

- Screen all adolescents between 9-11 yrs of age.
- Begin screening by age two if strong family history of premature CVD in parents/ grandparents etc...aunts and uncles
- Cascade screening and reverse cascade screening important... Goldberg,A. Jour Clin Lipidology (2011) 5,133-140

Cascade Screening

- Testing lipid levels in all 1st degree relatives of diagnosed FH patients
- This will elucidate newly identified FH cases and provide additional relatives who should be screened
- Cascade screening is most cost-effective for cost per year of life saved.

Need to Diagnose

- MEDPED model: (make early diagnosis and prevent early death).
- A common disease process that causes accelerated atherosclerosis and early morbidity/ mortality. Identification and treatment with statins has been shown to be effective in preventing and delaying disease.

Treatment

- Remember, these patients may not follow the typical rules:
- The typical 10 year CHD risk models/ CT calcium scoring etc will not adequately predict disease burden. - 10 year risk assessment in not recommended in these pt’s
- Begin Rx

Treatment recommendations:

- Diet/ exercise and weight loss...***along with***
- -Moderate to high dose statin
- -Ok to add Niaspan/ Welchol/Zetia
- -Many will need Apheresis

Statin Therapy:

- How statins work:
- Inhibit HMGCo-A
- This causes reduced intracellular sterol level in hepatocytes, thus
- Gene upregulation and trascription for production of proteins..-producing LDL-receptors on liver. - but this is the defect in FH.

Treatment goals:

- Both adult and children with LDL-C >190 require drug therapy
- The initial goal is to reduce LDL-C by 50% in those without manifest CVD
- Statins are the initial choice
- Pt’s with CVD/very high risk may need intensification of therapy to get LDL-C under 100 or 130mg/dL etc.

Treatment in children

- Statins should be started by age 8 or older
- Homozygous children need to be treated earlier-apheresis.
- Safe and effective in children in studies
- Pediatric patients goal: reduce LDL-C by 50% or LDL-C under 130mg/dL

Homozygous FH Rx:

- Max dose statins/combo Rx- may be effective but many will need LDL-apheresis.
- Liver transplantation-some institutions-can be curative
- Ileal bypass-rare
- New drugs- Mipomersen/ PCSK-9/MTP inhibitors... currently available products with REMS training.

Women of Childbearing Age

- Pre-pregnancy counseling
- Not to use statin/ zetia/niacin for at least 4 weeks prior to IUP.
- Not to be used with lactation
- Welchol (bile acid sequestrant)to be considered
- Apheresis can be considered (pregnant) if advanced disease or HoFH.

Apheresis

- FDA approved therapy
- A process by which blood is passed through a machine to eliminate athrogenic lipoproteins- Lp(a) as well- 50%
- Five different technologies: -Cascade filtration/Immunoabsorption/Heparin precipitation/ dextran sulfate liposorber/Dali- polyacrylate beads…(Bambauer,R. LDL-Apheresis. Scientic World Journal; 2013.)

Apheresis

- Typically weekly or bi-weekly
- Indices average out over time and oral meds needed
- Lowers LDL-C by 55-83 %
- Observational data (many children) show lowering LDL-C from 400-200mg/dL can double life
- No placebo driven survival trial due to ethical
- reasons… (Bambauer,R. LDL-Apheresis. Scientific World Journal.2012;)

Candidates for Apheresis

- US FDA approved medical therapy
- If after 6 months of max tolerated drug treatment and not to LDL goal, apheresis
- HoFh and LDL-C >300mg/dL
- Compound HeFH and LDL-C >200 and > 2 RF's including Lp(a)>50 mg/dL
- HeFH-LDL>160 and manifest CVD-cocoCommon

Apheresis referrals

- A list of sites available on website of the National Lipid Association
- www.lipid.org

- Contact a lipid specialist in your area (contact www.lipid.org)

Future Treatments: Already Here!

- Apheresis Rx until better options come.

- Juxtapid-MTP inhibitor
- Mipomersen- Antisense technology
- PCSK9 inhibitors
- Summary and Questions...?