Low LDL Syndromes

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A form of familial hypobetalipoproteinemia not due to a mutation in the apolipoprotein B gene

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Low LDL Syndromes: Outline

• Definition

• Pathogenesis

• Inherited Causes

• Acquired Causes

• Intentional Causes
Definition

- LDL cholesterol level below some predefined threshold, usually the 5° percentile.

- NHANES and VLDL2 cohorts both report 50-55 mg/dl as 5° percentile.

- A search of the Vanderbilt Synthetic Derivative revealed 5554 subjects with at least one LDL cholesterol value below 50 mg/dl.
Pathogenesis

- Reduced production.
- Increased clearance.
Production

Liver

ApoB100

CE + TG

MTP

Endoplasmic reticulum

MTP inhibitor

VLDL

Intestine

Apo B48

MTP

PL + TG

Endoplasmic reticulum

IRE1β

SAR1B

Chylomicron
Clearance
Inherited Low LDL Syndromes

- ApoB mutations leading to truncated protein and reduced VLDL output. Known as Familial hypobetalipoproteinemia (FHBL), transmitted co-dominantly.

- MTP mutations altering transfer of lipid droplets to apoB and leading to reduced VLDL output. Known as Abetalipoproteinemia (ABL), transmitted recessively.

- PCSK9 mutations leading to accelerated LDL clearance.

- SAR1B mutations altering trafficking of chylomicrons in the intestine. Known as Anderson's disease or chylomicron retention disease (CRD), transmitted recessively.

- ANGPTL3 mutations leading to accelerated lipolysis of plasma lipoproteins. Known as Familial Combined Hypolipidemia, transmitted co-dominantly.
Familial Hypobetalipoproteinemia

- Always caused by apoB mutations. Most lead to the formation of a truncated apoB with a consequent loss of capacity to form lipoproteins in the liver and intestine.

- Missense mutations can also alter apoB trafficking or interaction with MTP and lead to decreased VLDL secretion.

- Homozygous subjects have extremely low cholesterol levels and clinical features similar to those of Abetalipoproteinemia patients.

- Heterozygotes are usually healthy and enjoy longevity.
Abetalipoproteinemia

- Autosomal recessive disorder with a frequency of <1 in 100,000.

- Low levels of cholesterol and absence of plasma apoB-containing lipoproteins: chylomicrons, VLDL, remnants, and LDL.

- First reported in 1950 and found to be associated with acanthocytosis, retinitis pigmentosa and ataxia.

- Mutations in MTP do not allow transfer of the lipid droplet to the forming VLDL. To date, about 50 cases of ABL due to MTP mutations have been reported, including frame-shift, nonsense, and splice mutations predicted to encode truncated forms of MTP. A few missense mutations have also been described.
Chylomicron Retention Disease

- Only about 40 cases described.

- Mutations in the *SARA2* gene, encoding for the protein SAR1B. Enterocytes with mutant SAR1B assemble chylomicrons but fail to transport them through the secretory pathway, causing intestinal lipid droplet accumulation.

- The symptoms appear in the first few months of life and include failure to thrive, diarrhea, steatorrhea, hypovitaminosis A and E, and hypocholesterolemia. Later in life, neurological symptoms become evident.
PCSK9 mutations

- Proprotein convertase subtilin/kexin type 9 (PCSK9) is the third gene responsible for autosomal dominant hypercholesterolemia. This is due to gain of function mutations.

- PCSK9 loss of function mutations are instead associated with low LDL and vascular health. As an example, 2.5% of African Americans carry nonsense variants causing 30-40% reduction in plasma LDL-C and 88% reduction in prevalence of CHD.

- Three cases have been reported with an extreme reduction in LDL (<20 mg/dl) and no PCSK9 protein in the circulation. No comorbidities were noted. Fertility was normal. Longevity and absence of CVD were reported.
Familial Combined Hypolipidemia

- Familial combined hypolipidemia is an inherited disorder of lipid metabolism defined by very low levels of plasma apolipoprotein B and LDL (less than fifth percentile), HDL and triglycerides and attributed to mutations in angiopoietin-like 3 (ANGPTL3).

- The prevalence of ANGPTL3 mutations in a cohort of individuals with primary hypobetalipoproteinemia was recently estimated to be around 10%.

- The ANGPTL3 gene encodes for a protein, ANGPTL3, which is mainly expressed and secreted by the liver and known to be involved in suppression of lipoprotein lipase (LPL) and endothelial lipase.
Familial Combined Hypolipidemia

- A mutation in Angptl3 in a strain of obese mice was discovered to cause a severe recessive hypolipidemia.

- Whole-exome sequencing in two siblings with a clinical syndrome of combined hypolipidemia revealed two independent nonsense mutations in ANGPTL3, S17X and E129X.

- A genetic analysis of subjects with very low levels of LDL and apoB in a small Italian town revealed the presence of three ANGPTL3 mutations, the nonsense S17X and two new frame-shift mutations.

- Homozygous carriers showed a significant reduction of all plasma lipoproteins while heterozygotes only had low cholesterol and HDL. No association with hepatic steatosis was reported.
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Mutations in the ANGPTL3 gene and familial combined hypolipidemia: a clinical and biochemical characterization.


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Clinical Correlates of Low LDL Syndromes

- Acanthocytosis with anemia
- Malabsorption of fat and fat-soluble vitamins (E and A)
- Diarrhea, steatorrhea, failure to thrive
- Elevated transaminases with hepatomegaly due to hepatic steatosis
- Neurological involvement with demyelination
- Myositis
- Retinal degeneration
Acquired Low LDL Syndromes

- Anorexia
- Advanced, non-cholestatic liver disease
- Acute infections, neutropenia
- Cancer
- Anemias
- Hyperthyroidism
- Some medications
A Case

• 83-yo wm with diabetes, hypertension, family history of early CAD, personal history of late CAD with CABG.

• On a long list of medications.

• Recent lipid panel typical of the last 20 years: TC 117, LDL 48, HDL 55, TG 68

• My suspicion is that this is a secondary hypocholesterolemia, and the cause is ?
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- Atorvastatin 10 mg
A Case

LDL-C (click-drag-release on graph to expand)
Hypocholesterolemia

- LDL cholesterol level below some predefined threshold, usually the 5° percentile.

- NHANES and VLDL2 cohorts both report 50-55 mg/dl as 5° percentile.

- A search of the Vanderbilt Synthetic Derivative revealed 5554 subjects with at least one LDL cholesterol value below 50 mg/dl.

- Of these 3356 were statin takers.

- The majority of subjects taking PCSK9 antibodies goes below the 50 mg/dl mark, and 60% of heterozygous FH subjects get to <70 mg/dl.
Iatrogenic Low LDL

The effect of lowering LDL cholesterol with statin therapy was evaluated with a meta-analysis of data from 170,000 individuals in 26 randomized trials.

The size of the proportional reduction in major vascular events was directly proportional to the absolute LDL reduction even in those whose LDL cholesterol was already lower than 75 mg/dl at the start of study.

There was no significant evidence that further lowering of LDL cholesterol produced more frequent or unique adverse effects.
Conclusions

• Low LDL cholesterol is not rare and will become ever more common with more widespread use of effective LDL lowering therapies.

• Genetic causes are relative easy to identify and diagnose, even without genetic support, and may be accompanied by other problems requiring aggressive intervention.

• Secondary hypocholesterolemia may serve as clue for diagnosing underlying diseases.

• Use of statins and arrival of potent medications such as PCSK9 antagonists will explain most cases of low LDL cholesterol.

• At present, no complications are expected from long-term reduction of LDL levels into the hypocholesterolemia range.