Lipoprotein-X and LCAT Deficiency

Thomas Dayspring MD, FACP

Bile lipids are organized into an abnormal type of low density lipoprotein with albumin as the apoprotein. Bile lipoprotein is a precursor for an abnormal form of LDL, identified as **lipoprotein-X (Lp-X)** which can escape into the systemic circulation during cholestasis.

Lp-X is a lamellar particle of 30 to 70 nm in diameter (electron microscopy) which is present in large amounts in individuals suffering from obstructive liver diseases but can also be seen in newborn infants with premature liver function. It exists as a bilayer vesicle of equimolar phospholipids (66%) and unesterified cholesterol (22%) containing small amounts of plasma proteins (mainly albumin) in its internal aqueous compartment together with some apolipoproteins adsorbed on its surface. It separates with LDL on ultracentrifugation. The difference between bile lipoprotein and LP-X is in the protein/lipid ratio causing immunological and electrophoretic differences. LP-X can be divided into three distinct populations: LP-X1, Lp-X2 and Lp-X3 which differ in density and apolipoprotein composition.

Lp-X predominates in the circulation of patients suffering from not only cholestatic liver disease but also ***lecithin-cholesterol acyl transferase*** (**LCAT)** deficiency or. In both cases there is an elevation in the level of circulating free cholesterol and phospholipids. In cholestasis it is albumin and lipids and in the latter it is apoA and lipids. These vague lipoprotein collections are recognized as Lp-X using NMR technology. It is a valuable feature of the NMR LipoProfile, as it can help in making the diagnosis of LCAT deficiency.

ApoA-I normally gathers cholesterol (is lipidated) from peripheral cells, atheromata or the liver. ApoA-I carries an enzyme called lecithin cholesterol acyl transferase (LCAT) which immediately esterifies (attaches fatty acid phospholipids to the #3 position on the cholesterol molecule) transforming the free (unesterified) cholesterol into cholesteryl ester (CE). This nonpolar cholesteryl ester is hydrophobic and moves from the surface of the discoid HDL particle into the core of apoA-I and these accumulations of CE cause the discoid apoA-I to change into a spherical larger HDL particle. If one lacks LCAT, cholesterol cannot be esterified and the apoA-I particle stays very small and discoidal and is subject to rapid renal excretion. Thus persons with LCAT deficiencies have very low apoA-I and HDL-C levels. ApoA-I without cholesteryl ester (contains only a bit of unesterified cholesterol) is chemically and structurally very similar to Lp-X and the NMR picks it up and reports it as elevated Lp-X.

If the HDL-C level is very low, then some degree of LCAT deficiency is likely present. Many of these patients with very low HDL-C (hypoalphalipoproteinemia) are not subject to CHD. However only small numbers of such patients exist and there is not a lot of long term follow up data. The genetics is very complicated and currently the disorder is classified into Class 1, 2, 3 and 4.

Class 1 and 2: Familial LCAT deficiency is associated total loss of LCAT activity in both alpha and beta-lipoproteins and is associated with several impairments such as corneal opacifications, anemia, proteinuria and renal disease, but often not CHD.

Class 3 and 4: Fish eye disease (FED) and are probably missense mutations for LCAT. The LCAT deficiency of FED seems to be in the alpha (HDL) but not beta-lipoproteins (LDL, VLDL). FED patients may or may not be associated with CHD, even though there is severe hypoalphalipoproteinemia and hypertriglyceridemia. There may be corneal opacifications.

CHOLESTATIC LIVER DISEASES: If there is any indication of cholestasis (elevated bilirubin, alkaline phosphatase, etc.) then that is the cause of the detected Lp-X. Bile lipoprotein is a precursor lipoprotein for LP-X and it refluxes into the plasma pool under cholestatic conditions. The cholesterol transported by LP-X is mainly taken up by the cells of the reticuloendothelial system. It increases the activity of hepatic HMG-CoA reductase and suppresses remnant uptake, thus emphasizing a major role of LP-X in cholestatic hypercholesterolemia. Primary biliary cirrhosis and similar disorders may be accompanied by marked hypercholesterolemia that results from an accumulation of lipoprotein-X. Clinical stigmata include xanthomata striata palmare that

may appear when the serum cholesterol concentration is 1400 mg/dL (36 mmol/L) or higher. Xanthomata appear on the extremities as well. Marked elevations in lipoprotein X has been associated with the hyperviscosity syndrome, but no clear association with coronary heart disease (CHD) has been established

References:

1) Review: Molecular pathology of LCAT Deficiency Syndromes Journal of Lipid Research 1997;38:191-205

2) Formation of Lipoprotein-X. Journal of Clinical Invest 1976;57:1248-60

3) Role of Lp-X in Pathogenesis of Cholestatic Hypercholesterolemia
Journal of Clinical Invest 1984;74:867-879

4) Lp-X in Cirrhosis Hepatology 1998;28:1199-1205

5) Human Lecithin:Cholesterol Acyltransferase Deficiency In Vivo Kinetics of Low-Density Lipoprotein and Lipoprotein-X . Arterioscler Thromb Vasc Biol. 2006;26:1370-1375