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The Hyperlipoproteinemia - An Approach to Diagnosis and Classification

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Hyperlipoproteinemia contributes both to kidney disease progression and the development of atherosclerosis. Heart disease from atherosclerosis and coronary artery disease is the leading cause of death. Elevated high density lipoprotein cholesterol and apolipoprotein A-I (apoA-I) serum levels are independent factors protective against the atherosclerotic process. Hyperlipoproteinemia refers to a group of acquired and inherited disorders whose common denominator is excessive levels of lipids (fats) in the blood, caused by a metabolic disorder. It is also referred to as hyperlipidemia. Hyperlipoproteinemia and the prevalence and incidence of ischemic heart disease has been established [1,2]. Some genetic conditions can cause high or low cholesterol and high or low levels of HDLs. Primary hyperlipoproteinemia is a genetically inherited disorder of metabolism of fats that causes high blood lipoprotein levels. Secondary disorders are associated with a disease or condition that causes the disorder. Persons with this genetic predisposition to high blood lipoproteins are at increased risk for early heart disease and stroke.

There is no longer any doubt that dietary manipulation or the administration of drugs may lower the levels of these lipids. From a therapeutic viewpoint then, the vital questions concern how the rate of development of atherosclerosis will be altered by these manoeuvres.

The classification of lipoprotein disorders is useful as a guide to accurate diagnosis and effective treatment. Lipoproteins offer more information than analysis of plasma lipids (most of the plasma lipids being bound to various proteins). Hyperlipoproteinemia very seldom occurs without hyperlipidemia and consequently, hyperlipidemia may be used to detect hyperlipoproteinemia; a classification based on lipoproteins offers more information than one based on lipids alone. The Frederickson and Levy Classification (Table 1) based on the type of lipoprotein that is elevated [3]. It is now replaced by classification based on the understanding of the molecular etiology & pathophysiology of lipoprotein disorders (Table 2) [4].

Type I is a rare disorder characterized by severe elevations in chylomicrons and extremely elevated triglycerides, It is caused by mutations of either the lipoprotein lipase gene (LPL), which is critical for the metabolism of chylomicrons as hydrolysis of triglycerides in chylomicrons requires action of LPL in tissue capillary beds & apo C-II is a required cofactor for the activation of LPL, or of the gene's cofactor, apolipoprotein (apo) C-II. Mutations either in the LPL gene or the apo C-II gene results in functional deficiency of LPL and as well inability to hydrolyze triglycerides in chylomicrons and consequent massive hyperchlylomicronemia. The disorder is autosomal recessive, meaning that both alleles of the LPL or apo C-II gene must be affected [5,6].

The diagnosis of familial hyperchylomicronemia is usually made based on clinical presentation and laboratory tests. The plasma is often lactescent and after overnight refrigeration a layer of chylomicrons forms on the surface. The triglycerides always reach well above 1000 mg/dL and not infrequently rising as high as 10,000 mg/dL or more. Chylomicrons contain far less cholesterol than other triglyceride-rich lipoproteins do, when serum triglyceride levels are severely elevated, cholesterol levels can also be quite high. Lipoprotein electrophoresis demonstrates markedly elevated chylomicrons at the origin. The diagnosis of LPL deficiency can be confirmed by measurement of LPL activity in plasma. Defective or absent apo C-II must be determined at a lipid center that performs 1 of the 3 following assays: (1) gel electrophoresis, (2) radioimmunoassay, or (3) confirmation that LPL added to the patient's plasma is not active.

Type IIb is the classic mixed hyperlipidemia (high cholesterol and triglyceride levels), caused by elevations in LDL and VLDL. It is caused by mutation in the receptor-binding domain of Apolipoprotein B-100 which is a major component of LDL and VLDL resulting in reduced clearance of these lipoproteins [7].

These Patients almost always have significantly elevated plasma apo B. The levels of apo B are disproportionately high relative to plasma LDL-C due to the presence of small dense LDL particles, which are characteristic of this syndrome and are highly atherogenic. Elevated LDL, cholesterol and triglycerides is due to dysregulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), the rate-controlling enzyme in cholesterol biosynthesis.

Type III is known as dysbetalipoproteinemia, remnant removal disease, or broad-beta disease. Typically, patients with this condition have elevated total cholesterol and triglyceride levels and are easily confused with patients with type IIb hyperlipidemia. Patients with type III hyperlipidemia have elevations in intermediate-density lipoprotein (IDL), a VLDL remnant, and a significant risk for developing coronary artery disease. Familial dysbetalipoproteinemia is caused by mutations in the gene for apolipoprotein E (apo E). Apo E is present in chylomicrons and VLDL remnants, and mediates their removal from the plasma by binding to receptors in the liver. Defective apo E is impaired in its ability to bind to these receptors, resulting in accumulation of chylomicrons & VLDL remnants in the plasma. Homozygosity for the E2 allele (E2/E2 genotype) is the most common cause of familial dysbetalipoproteinemia [8].

The diagnosis is usually made based on combination of clinical and laboratory parameters. Elevated triglycerides & cholesterol are determined by direct laboratory analysis of serum or plasma after a 10- to 12-hour fast. There are no simple diagnostic tests for dysbetalipoproteinemia. Diagnostic tests are based either on the demonstration of remnant accumulation or characterization of apoE. Electrophoretic techniques include serum agarose gel electrophoresis, but a broad β band is found in less than one half of patients [9]. Ultracentrifugation is required to demonstrate β-migrating VLDL.

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Type	Synonym	Defect	Serum abnormality	Clinical features	Serum apperance
Type - I	Familial hyperchylomicronemia	Low LDL, Altered Apo C- II	Chylomicron↑	Pancreatitis, Lipemia, retinalis,Skin eruptions, xanthoma, hepatosplenomegaly	Creamy top layer
Type - IIa	Familial hypercholesterolemia	↓LDL receptor	LDL↑	Xanthelasma, Arcus senillis, Tendon xanthomas	Clear
Type- IIb	Familial combined hypercholesterolemia	↓LDL receptor & ↑Apo B	LDL & VLDL↑		Clear
Type - III	Familial dysbetalipoproteinemia	Apo E2 synthesis defect	IDL↑	Tubo-eruptive xanthomas, palmar xanthoma	Turbid
Type – IV	Familial hyperprebetalipoproteinemia	↑VLDL production, ↓Elimination	VLDL↑		
Type – V	Endogenous hypertriglyceridemia	↑VLDL production, ↓LPL	VLDL & Chylomicron↑		Creamy top layer & turbid bottom.

***LDL (low-density lipoprotein)**
****VLDL (very low-density lipoprotein)**
*****IDL (intermediate-density lipoprotein)**

Table 1: Fredrickson classification of Hyperlipidemias.

Name	Molecular defect	Lipoprotein elevated	Phenotype	Clinical findings	Genetic transmission
Familial Chylomicronemia	LPL – deficiency, apo C- II deficiency	Chylomicrons	Type- I	Eruptive xanthomas, hepatosplenomegaly	Autosomal recessive
Familial hypertriglyceridemia	Unknown	VLDL occasionally Chylomicrons	Type IV occassionally V	Usually None	Autosomal dominant
Familial dysbetalipoproteinemia	Abnormal Apo- E	VLDL and Chylomicrons remnants	Type III	tuberoruptive xanthomas, premature atherosclerosis	Autosomal recessive or dominant.
Familial combined hyperlipidemia	Unknown	VLDL and LDL	Type II b, sometimes IIa or IV, rarely V	premature atherosclerosis	Autosomal dominant
Familial hepatic lipase deficiency	Hepatic lipase	VLDL remnants	Type III deficiency	premature atherosclerosis	Autosomal recessive
Familial hyper cholesterolemia	LDL- receptor	LDL	Type II	Tendon xanthomas, premature atherosclerosis	Autosomal codominant
Familial defective apo B- 100	Abnormal apo B- 100	LDL	Type IIa	Tendon xanthomas, premature atherosclerosis	Autosomal codominant
Autosomal recessive hyper cholesterolemia	ARH gene	LDL	Type IIa	Tendon xanthomas, premature atherosclerosis	Autosomal recessive
Autosomal dominant hyper cholesterolemia	PCSK9 gene	LDL	Type IIa	Tendon xanthomas, premature atherosclerosis	Autosomal recessive

Table 2: Primary Hyperlipoproteinemias.

Type IV is characterized by abnormal elevations of VLDL, and triglyceride levels are almost always less than 1000 mg/dL. Serum cholesterol levels are normal. Type IV disease is characterized by a turbid serum indicating hypertriglyceridemia and a normal or only slightly elevated serum cholesterol level. It probably represents a complicated interplay of genetic and environmental factors analogous to the maturity onset form of diabetes mellitus. Hyperlipoproteinemia can be primary, resulting from inherited characteristics, or secondary, caused by poorly controlled diabetes, alcoholism, nephrotic syndrome, chronic renal failure, and dysgammaglobulinemia.

The Type IV lipoprotein phenotype (endogenous hypertriglyceridemia, hyperprebetalipoproteinemia), Endogenous hypertriglyceridemia represents a group of heterogeneous disease entities with different etiologies and a varied degree of associated risk for atherosclerosis [10] Two major hereditary disease entities harbouring a Type IV phenotype may be considered, one with an associated elevation of LDL- apo B levels and believed to represent familial combined hyperlipidemia (FCHL) which is a multiple lipoprotein-phenotype disease; the other, familial hypertriglyceridemia (FHTG), in which LDL-apo B levels are normal [11].

The major metabolic defect ascribed to FHTG is increased hepatic synthesis of triglycerides with the accumulation of triglyceride-rich VLDL in plasma, resulting from an apparent saturation of catabolic processes. In FCHL, there is increased synthesis of apo B with an overproduction of both VLDL- and LDL-apoB [12].

Type V is characterized by elevations of chylomicrons and VLDL. Triglyceride levels are invariably greater than 1000 mg/dL, and total cholesterol levels are always elevated. The LDL cholesterol level is usually low. Given the rarity of type I disease, when triglyceride levels above 1000 mg/dL are noted the most likely cause is type V hyperlipidemia. Triglyceride levels greater than 1000 mg/dL increase the risk of acute pancreatitis, and because triglycerides are so labile, levels of 500 mg/dL or greater must be the primary focus of therapy. If a patient also has a high risk for a cardiovascular event the development of this lipid disorder involves a multitude of metabolic derangements including deficient clearance of triglycerides and/or their increased output aggravated by obesity, diabetes, alcohol intake, or use of some hormones. Some studies have suggested that the apolipoprotein E4 phenotype is involved in this dyslipoproteinemia [13].

The three disorders commonly associated with premature atherosclerotic vascular disease are Type II (hyperbetalipoproteinemia), Type III ("broad beta" or "floating beta" disease) and Type IV (hyperprebetalipoproteinemia or, endogenous hypertriglyceridemia). The diagnosis of each of these three disorders can be suggested by the fasting serum cholesterol level and the appearance of the fasting serum after it has remained overnight in a refrigerator. Type II disease

is characterized by a clear serum and a pronounced to moderate hypercholesterolemia.

Chylomicron Determination

- If the triglyceride levels are greater than 1000 mg/dL and the presence of chylomicrons must be confirmed, the simplest and most cost-effective test involves overnight refrigeration of an upright tube of plasma or serum.
- If a creamy supernatant is seen the next day, chylomicrons are present.
- If the infranatant is cloudy, high levels of VLDL are present (type V hyperlipidemia).
- If the infranatant is clear, the VLDL content is normal and type I hypercholesterolemia (elevated chylomicrons only) should be suspected.

This can provide distinction between hypertriglyceridemia due to fasting chylomicronaemia and that due to an increase in VLDL without the necessity to perform electrophoresis. Lipoprotein electrophoresis (Agarose gel gives the best separation).

In general, total cholesterol and triglyceride determinations should be carried out. Electrophoretic pattern can be used for LDL/HDL ratio which can be used as risk index. Ultra-centrifugation gives the precise nature of the density value of lipoprotein affected. Procedure is possible only where ultra centrifuge is available and is also time consuming.

Specialized Laboratory Tests

Apolipoproteins

Recent investigation has resulted in characterization of the protein components (apoproteins) and even determination of their primary structure. Immunological methods are in vogue for determination of apolipoproteins. Each apoprotein is designated by nomenclature based on C-terminal amino acid.

Important amongst these are:

Apo-A: better discriminator for HDL cholesterol.

Apo-B: discriminator for LDL, cholesterol.

Apo-C

Apo-E: discriminator for familial dyslipoproteinaemia.

LDL Receptor:

LDL receptor studies are done on fibroblast cultures. These are research procedures done at advanced laboratories and assist in recognition of genetic phenotype and basic mechanism of hyperlipoproteinaemia.

Secondary or nonfamilial hyperlipoproteinemias must be ruled out before a diagnosis of the primary type can be made. Such conditions as nephrotic syndrome, liver disease, dysproteinemias, and others may give rise to secondary hyperlipoproteinemia.

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