DISORDERS OF LIPID METABOLISM

By
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Classification of hyperlipidaemias

Hyperlipidemias may basically be classified as either familial (also called primary) caused by specific genetic abnormalities, or acquired (also called secondary) when resulting from another underlying disorder that leads to alterations in plasma lipid and lipoprotein metabolism

The study of hyperlipidaemias is of considerable importance, mainly because of the involvement of lipids in cardiovascular disease.

Fredrickson, Levy and Lees first defined the hyperlipidaemias in a classification system based on which plasma lipoprotein concentrations were increased (Table below). Although this so-called Fredrickson's classification helped to put lipidology on the clinical map, it was not a diagnostic classification. It gives little clue as to the aetiology of the disorder; indeed, all of the phenotypes can be either primary or secondary. Furthermore, the Fredrickson type can change as a result of dietary or drug intervention.

Fredrickson classification of hyperlipidemias

Hyperlipo-proteinemia		OMIM	Synonyms	Defect	Increased lipoprotein	Main symptoms	Treatment	Serum appearance	Estimated prevalence
Type I	a	238600 (https://omim.org/entry/238600)	Buerger-Gruetz syndrome or familial hyperchylomicronemia	Decreased lipoprotein lipase (LPL)	Chylomicrons	Acute pancreatitis, lipemia retinalis, eruptive skin xanthomas, hepatosplenomegaly	Diet control	Creamy top layer	One in 1,000,000[9]
	b	207750 (https://omim.org/entry/207750)	Familial apoprotein CII deficiency	Altered ApoC2					
	c	118830 (https://omim.org/entry/118830)		LPL inhibitor in blood					
Type II	a	143890 (https://omim.org/entry/143890)	Familial hypercholesterolemia	LDL receptor deficiency	LDL	Xanthelasma, arcus senilis, tendon xanthomas	Bile acid sequestrants, statins, niacin	Clear	One in 500 for heterozygotes
	b	144250 (https://omim.org/entry/144250)	Familial combined hyperlipidemia	Decreased LDL receptor and increased ApoB	LDL and VLDL		Statins, niacin, fibrate	Turbid	One in 100
Type III		107741 (https://omim.org/entry/107741)	Familial dysbetalipoproteinemia	Defect in Apo E 2 synthesis	IDL	Tuberoeruptive xanthomas and palmar xanthomas	Fibrate, statins	Turbid	One in 10,000[10]
Type IV		144600 (https://omim.org/entry/144600)	Familial hypertriglyceridemia	Increased VLDL production and decreased elimination	VLDL	Can cause pancreatitis at high triglyceride levels	Fibrate, niacin, statins	Turbid	One in 100
Type V		144650 (https://omim.org/entry/144650)		Increased VLDL production and decreased LPL	VLDL and chylomicrons		Niacin, fibrate	Creamy top layer and turbid bottom	

Primary hyperlipidaemias

1- Chylomicron syndrome

This can be due to familial lipoprotein lipase deficiency, an autosomal recessive disorder affecting about 1 in 1 000 000 people. Lipoprotein lipase is involved in the exogenous lipoprotein pathway by hydrolysing chylomicrons to form chylomicron remnants, and also in the endogenous pathway by converting VLDL to IDL particles.
Gross elevation of plasma triglycerides due to the accumulation of uncleared chylomicron particles occurs.
Lipid stigmata include eruptive xanthomata, hepatosplenomegaly and lipaemia retinalis (Figure).

Other variants of the chylomicron syndrome include circulating inhibitors of Lipoprotein Lipase and deficiency of its physiological activator Apolipoprotein C2.

To confirm the diagnosis of familial lipoprotein lipase deficiency, plasma lipoprotein lipase can be assayed after the intravenous administration of heparin, which Releases the enzyme from endothelial sites.

2- Familial hypercholesterolaemia

This condition is occurred when there is mutation in the LDL receptor resulting in impaired LDL catabolism and hypercholesterolaemia.

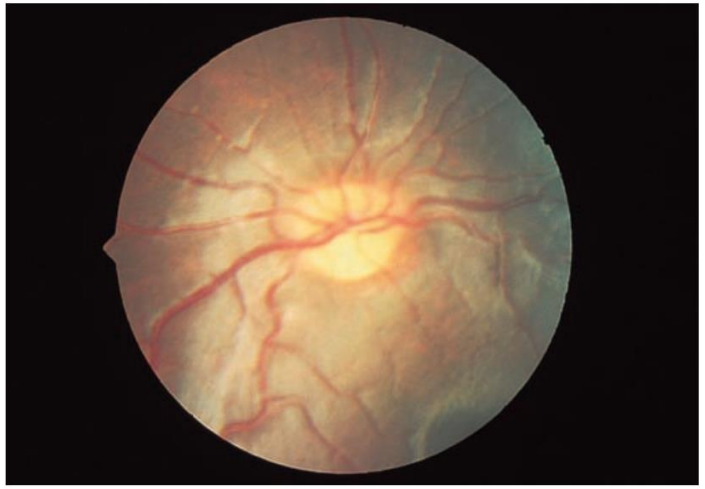

Figure [redacted] Lipaemia retinalis in a patient with lipoprotein lipase deficiency. Reproduced with kind permission from Nyhan WL and Barshop BA. *Atlas of Inherited Metabolic Diseases*, 3rd edition. London: Hodder Arnold, 2012.

Familial hypercholesterolaemia (FH) is defined as a plasma cholesterol concentration of more than 7.5 mmol/L in an adult (more than 6.7 mmol/L in children under 16 years) or a plasma LDL cholesterol concentration of more than 4.9 mmol/L in an adult in the presence of tendon xanthoma.

Typically, patients manifest severe hypercholesterolaemia, with a relatively normal plasma triglyceride concentration in conjunction with xanthomata, which can affect the back of the hands, elbows, Achilles tendons or the insertion of the patellar tendon into the pretibial tuberosity (Fig. 13.11). Premature cardiovascular disease is often observed, along with premature corneal arci (Fig. 13.12).

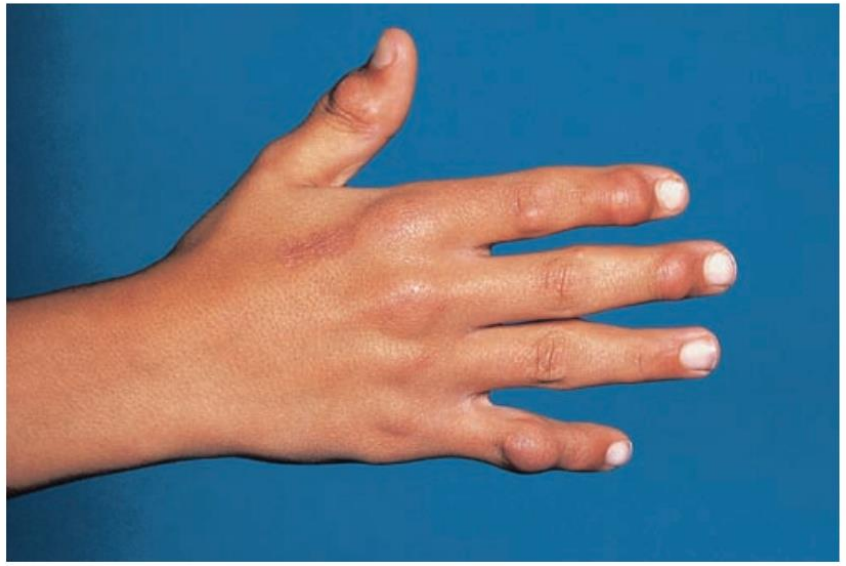

Figure 13.11 Tendinous xanthomas in familial hypercholesterolaemia. Reproduced with kind permission from Nyhan WL and Barshop BA. *Atlas of Inherited Metabolic Diseases*, 3rd edition. London: Hodder Arnold, 2012.

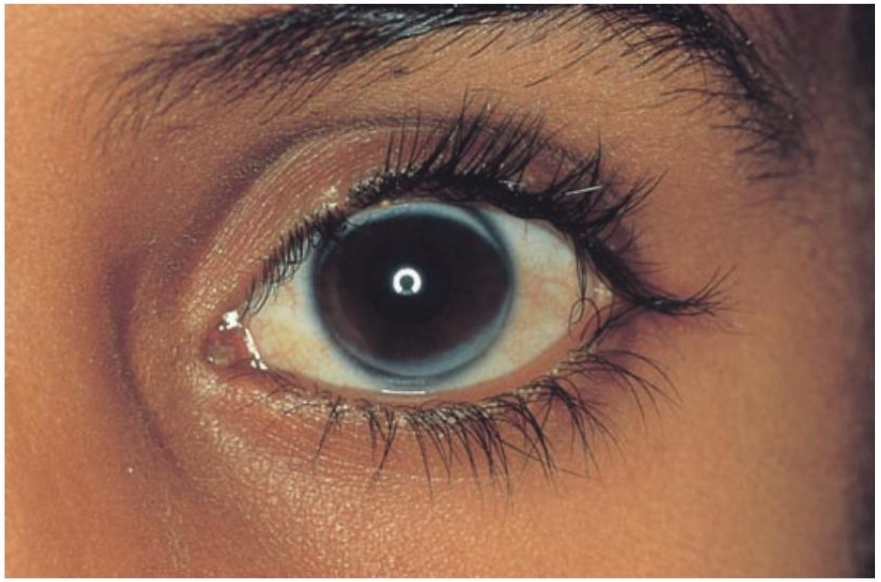

Figure 13.12 Corneal arcus in familial hypercholesterolaemia. Reproduced with kind permission from Nyhan WL and Barshop BA. *Atlas of Inherited Metabolic Diseases*, 3rd edition. London: Hodder Arnold, 2012.

The diagnosis of FH is usually obvious from the markedly elevated plasma cholesterol concentration and the presence of tendon xanthomata in the patient or first-degree relation. The diagnosis may not be so clear cut in patients without the lipid stigmata. A functional assay of the LDL receptors has recently been described using cultured lymphocytes, but this has not yet gained wide routine acceptance, and deoxyribonucleic acid (DNA) screening is now important. The response to a lipid-lowering diet is often disappointing and the treatment is usually with the HMG-CoA reductase inhibitors, that is, the statins.

3- Familial defective apoB3500

This condition is due to a mutation in the apoB gene. Apolipoprotein B is the ligand upon the LDL particle for the LDL receptor. It may be indistinguishable clinically from FH and is also associated with hypercholesterolaemia and premature coronary artery disease.

4- Familial combined hyperlipidaemia

In familial combined hyperlipidaemia (FCH), the plasma lipids may elevated, plasma cholesterol concentrations often being between 6 mmol/L and 9 mmol/L and plasma triglyceride between 2 mmol/L and 6 mmol/L. Familial combined hyperlipidaemia may be inherited as an autosomal dominant trait About 0.5 per cent of the European population is affected, and there is an increased incidence of coronary artery disease in family members. The metabolic defect is unclear, although plasma apoB is often elevated due to increased synthesis; LDL and VLDL apoB concentration is increased. The synthesis of VLDL triglyceride is increased in FCH and there may also be a relationship with insulin resistance.

5- Familial hypertriglyceridaemia

Familial hypertriglyceridaemia is often observed with low HDL cholesterol concentration. The condition usually develops after puberty and is rare in childhood. The exact metabolic defect is unclear, although overproduction of VLDL or a decrease in VLDL conversion to LDL is likely. There may be an increased risk of cardiovascular disease. Acute pancreatitis may also occur, and is more likely when the concentration of plasma triglycerides is more than 10 mmol/L. Some patients show hyperinsulinaemia and insulin resistance.

6- Type III hyperlipoproteinaemia

The underlying biochemical defect is one of a reduced clearance of chylomicron and VLDL remnants.

7- Polygenic hypercholesterolaemia

This is one of the most common causes of a raised plasma cholesterol concentration. There is usually either an increase in LDL production or a decrease in LDL catabolism.

8- Hyperalphalipoproteinaemia

Hyperalphalipoproteinaemia results in elevated plasma HDL cholesterol concentration and can be inherited as an autosomal dominant condition or, in some cases, may show polygenic features. The total plasma cholesterol concentration can be elevated, with normal LDL cholesterol concentration. There is no increased prevalence of cardiovascular disease in this condition; in fact, the contrary probably applies, with some individuals showing longevity. Plasma HDL concentration is thought to be cardioprotective, and individuals displaying this should be reassured. Box 13.1 gives the causes of raised plasma HDL cholesterol concentrations.

Box 13.1 Some causes of raised plasma high-density lipoprotein (HDL) cholesterol

Primary

Hyperalphalipoproteinaemia
Cholesterol ester transfer protein deficiency

Secondary

High ethanol intake
Exercise
Certain drugs, e.g. estrogens, fibrates, nicotinic acid, statins, phenytoin, rifampicin

Secondary hyperlipidaemias

One should not forget that there are many secondary causes of hyperlipidaemia. These may present alone or sometimes concomitantly with a primary hyperlipidaemia. Some of the causes of secondary hyperlipidaemia are listed in Box 13.2. Secondary causes of hyperlipidaemia include obesity, type 2 diabetes mellitus, hypothyroidism, chronic kidney disease, cholestasis and certain drugs. The reader should refer to the other chapters in this book for details of the relevant diseases.

Box 13.2 Some important causes of secondary hyperlipidaemia

Predominant hypercholesterolaemia

Hypothyroidism
Nephrotic syndrome
Cholestasis, e.g. primary biliary cirrhosis
Acute intermittent porphyria
Anorexia nervosa/bulimia
Certain drugs or toxins, e.g. ciclosporin and chlorinated hydrocarbons

Predominant hypertriglyceridaemia

Alcohol excess
Obesity
Diabetes mellitus and metabolic syndrome
Certain drugs, e.g. estrogens, β-blockers (without intrinsic sympathomimetic activity), thiazide diuretics, acitretin, protease inhibitors, some neuroleptics and glucocorticoids
Chronic kidney disease
Some glycogen storage diseases, e.g. von Gierke's type I
Systemic lupus erythematosus
Paraproteinaemia

Thank you for your attention

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