Inherited metabolic disorders and dyslipidaemia

Raashda A Sulaiman

Department of Medical Genetics, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

Correspondence to
Dr Raashda A Sulaiman, King Faisal Specialist Hospital and Research Center, Riyadh 11211, Saudi Arabia; rsulaiman@kfshrc.edu.sa

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ABSTRACT

Monogenic dyslipidaemia is a diverse group of multisystem disorders. Patients may present to various specialities from early childhood to late in adult life, and it usually takes longer before the diagnosis is established. Increased awareness of these disorders among clinicians is imperative for early diagnosis. This best practice review provides an overview of primary dyslipidaemias, highlighting their clinical presentation, relevant biochemical and molecular tests. It also addresses the emerging role of genetics in the early diagnosis and prevention of these disorders.

INTRODUCTION

Primary dyslipidaemia due to single gene defect is seen in a variety of inherited metabolic disorders (IMDs). These patients may first present with disturbed plasma lipids, mainly total cholesterol (TC), triglycerides and lipoprotein concentrations before the diagnosis of their respective IMD is established. In the absence of secondary causes of dyslipidaemia like diabetes mellitus, renal, hepatic, thyroid disease or use of drugs such as beta-blocker, retinoids and steroids, genetic causes of lipid disorders should be considered. These disorders are mostly due to the defects in the lipoprotein metabolism, however, disruption of intracellular cholesterol trafficking as seen in certain lysosomal storage diseases, also results in dyslipidaemia which may be the initial presenting feature of these disorders. Monogenic dyslipidaemia is often multisystem disorder; therefore, a patient may initially present to different medical specialities. Improved awareness among clinicians regarding the association of dyslipidaemia with various IMDs would, therefore, expedite the process of making early diagnosis and initiation of appropriate management to prevent or delay deleterious multisystem complications.

Monogenic lipid disorders are classified according to the primary lipid or lipoprotein disturbance such as hypertriglyceridaemia, high or low concentrations of high-density lipoprotein cholesterol (HDL-C) or low-density lipoprotein cholesterol (LDL-C) (table 1). This best practice review summarises these disorders, highlighting the clinical features with which patient could present to any specialty as a multisystem disorder.

Disorders associated with primary hypertriglyceridaemia

Familial chylomicronaemia syndrome (type I hyperlipidaemia; OMIM: 238600)

This rare disorder with prevalence of 1–2 per million people, is due to deficiency of the endothelial lipoprotein lipase (LPL) or its activating cofactor apolipoprotein (apo) C-II, its transporter or lipase maturation factor or the presence of LPL inhibitor, resulting in reduced clearance of chylomicron and severe hypertriglyceridaemia (figure 1).[1 2] Patients mostly present in childhood or early adult life with recurrent abdominal pain, nausea, eruptive or tuberous xanthoma and lipemia retinalis.[1–3] Fasting plasma triglycerides are usually >10 mmol/L while LDL-C and HDL-C concentrations are normal or low. Diagnosis is confirmed by molecular testing (table 1). There is a high risk of recurrent acute pancreatitis, which may lead to chronic pancreatitis and diabetes. Management includes a strict low-fat diet, the use of fibrates and omega-3 fatty acids. LPL gene therapy approved earlier, is no longer available. Possible new therapies include volanesorsen, an antisense oligonucleotide which inhibits the production of the apo C-III that blocks LPL and interferes with triglycerides clearance; evinacumab, a monoclonal antibody against angiopoietin-like protein 3; pemafibrate, a selective peroxisome proliferator-activated receptor alpha modulator, and pradigastat, a diacylglycerol acyltransferase-1 inhibitor.[4 5]

Familial hypertriglyceridaemia (type IV hyperlipidaemia; OMIM: 145750)

This is a relatively common disorder with a prevalence of 1 in 500.[6] It is characterised by hepatic overproduction of large very low-density lipoprotein (VLDL) particles with high triglyceride and normal apo-B content. These are not hydrolysed at a regular rate by LPL.[7] Most cases are polygenic rather than monogenic in origin. There is moderate hypertriglyceridaemia (3.5–9.9 mmol/L), normal LDL-C, apo-B concentrations and low HDL-C (<1.0 mmol/L).[6–9] When associated with obesity, pregnancy, type 2 diabetes or alcohol consumption, VLDL concentrations may increase excessively leading to hypercholesterolaemia and severe hypertriglyceridaemia (>11.0 mmol/L).[9] There is a risk of premature cardiovascular disease (CVD) and pancreatitis. Low-fat diet and drugs such as fibrates and omega-3 fatty acid are useful in lowering triglyceride levels.[10]

Familial dysbetalipoproteinaemia (type III hyperlipidaemia; remnant hyperlipidaemia, OMIM: 617347)

Familial dysbetalipoproteinaemia (FD) is characterised by the accumulation of intermediate-density lipoprotein (IDL), due to dysfunctional or absent apo-E which mediates its removal by binding to the hepatic LDL receptor (figure 1). Its prevalence in the general population is 0.1%–0.4%.[11] Patients have a homozygous variant in *ApoE2* with variable penetrance, however, 10% of patients show heterozygous

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Table 1 Dyslipidaemia in various inherited metabolic disorders

Lipid or lipoprotein abnormality	Metabolic pathway	Inherited metabolic disorder (mode of inheritance)	Affected gene
Hypertriglyceridaemia	Disorder of exogenous lipoprotein metabolism	Familial chylomicronaemia syndrome (AR)	*LPL, APOC2, APOA5, LMF5, GPIHBP1*
	Disorder of endogenous lipoprotein metabolism	Familial hypertriglyceridaemia (AD) Dysbetalipoproteinaemia (AR)	*APOA5, LIPI* *APOE*
	Other disorders	Glycogen storage disease (AR) Hereditary lipodystrophy (AR) Hyperglycerolaemia (X-linked recessive)	*G6PC* *AGPAT2, BSCL2, LMNA* *GK*
Low HDL-C	Disorders of reverse cholesterol transport	Apolipoprotein A-1 deficiency (AR) Tangier disease (AR) Familial LCAT deficiency (AR) (FLD and FED)	*APOA1* *ABCA1* LCAT
	Disorders of intracellular cholesterol trafficking (LSD)	Lysosomal acid lipase deficiency (AR) Gaucher disease type 1 (AR) Niemann-Pick type C (AR) Niemann-Pick type B (AR)	*LIPA* *GBA* *NPC1, NPC2* *SMPD1*
High HDL-C	Disorder of reverse cholesterol transport	Cholesterol ester transfer protein Deficiency (AD) Scavenger receptor B1 deficiency	*CETP* *SCARB1*
Low LDL-C	Disorder of apo-B or CM synthesis	Abetalipoproteinaemia (AR) Familial hypobetalipoproteinaemia (AD) Chylomicron retention disease (AR)	*MTTP* *APOB* *SAR1B*
High LDL-C	Disorders of LDL removal	Familial hypercholesterolaemia (AD) AR—hypercholesterolaemia	*LDLR, APOB, PCSK9* *LDLRAP1*
	Defect in sterol transport	Sitosterolemia (AR)	*ABCG5, ABCG8*

AD, autosomal dominant; apo-B, apolipoprotein B; AR, autosomal recessive; CM, chylomicron; FED, fish eye disease; FLD, familial LCAT deficiency;HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LSD, lysosomal storage disease.

mutation.[12] Of *E2/E2* homozygotes, only 15% develop hyperlipidaemia in the adult life, in the presence of secondary risk factors like obesity, diabetes, alcohol or hypothyroidism.[11 13] Patients present with various xanthomas. Palmer crease xanthoma, pathognomonic of FD is present in ~20% cases.[13–15] There is a high risk of premature CVD, and peripheral vascular disease.[11 13] Accumulating remnant lipoprotein with high cholesterol and triglyceride content result in raised TC (6–11 mmol/L), triglycerides (3–10 mmol/L) and TC/TG molar ratio is ~2:1.[11 13] These patients have low LDL-C and low apo-B concentrations. A useful screening test for FD is the low apo-B (g/L)/TC (mmol/L) ratio of <0.15 (sensitivity 89% and specificity 97%) which differentiates FD from other mixed hyperlipidaemias where the ratio is up to 0.33.[16] A broad β-band on serum lipoprotein electrophoresis demonstrates high IDL concentration. *ApoE* genotyping confirms the disease. Patients are generally very responsive to a low-fat diet, lifestyle changes such as exercise, weight reduction, reduce alcohol consumption, treatment of diabetes and a combination of fibrate and statin therapy is often needed.[17 18]

Hereditary lipodystrophies

This group of rare monogenic disorders is characterised by selective loss of adipose tissue. Patients present with deficient subcutaneous tissue, prominent muscularity, severe insulin resistance and early diabetes. They often have voracious appetite due to leptin deficiency. Hypertriglyceridaemia results from either increased hepatic VLDL synthesis or reduced clearance of VLDL and chylomicron due to progressive LPL deficiency or both.[19 20] Cardiomyopathy and arrhythmias have been described in congenital generalised lipodystrophy.[21]

Glycogen storage disease (GSD type1a; OMIM: 232200)

It has an estimated incidence of 1 in 100 000 newborns.[22] Deficiency of enzyme glucose-6-phosphatase leads to glucose-6-phosphate accumulation, increased production of acetyl Co-A, thereby increasing hepatic VLDL production and hypertriglyceridaemia (>4.0 mmol/L).[23] It presents in early life as hypoglycemia and hepatomegaly. Hypertriglyceridaemia predisposes to pancreatitis. Patients with plasma triglycerides >5.6 mmol/L are more prone to develop hepatic adenoma.[24] However, there is no increased risk of early atherosclerosis. Management includes better metabolic control and use of fibrate and statin.

Hyperglycerolaemia (OMIM: 307030)

This is a rare disorder of glycerol metabolism where deficiency of glycerol kinase causes elevated plasma and urine glycerol concentrations. Clinical presentation varies from life-threatening childhood form with metabolic crisis (hypoglycaemia and hyperketonaemia) to an asymptomatic adult form, discovered by the presence of pseudo-hypertriglyceridaemia, due to glycerol interference with triglyceride measurement in assays that measure total glycerol.[25 26] In such cases, plasma is transparent and not lactescent as seen in severe hypertriglyceridaemia.

Disorders associated with severe HDL-C deficiency

Familial apolipoprotein A-1 deficiency (familial hypoalphalipoproteinaemia; OMIM: 604091)

The prevalence of this disorder is <1:1 000 000.[27] Deficiency of apo-A1, the major HDL lipoprotein (figure 1) results in low to absent plasma HDL-C (<0.1 mmol/L), undetectable apo-A1 (<0.1 g/L) and normal LDL-C in homozygotes. Heterozygotes have half normal HDL-C. Homozygotes present with xanthomata, xanthelasma, corneal opacity, retinal lipid deposition, cerebellar ataxia and often premature CVD.[28] *ApoA1* mutations can also cause hereditary amyloidosis affecting kidneys, heart and liver.[29] Currently, there is no specific therapy; management includes reduction of cardiovascular risk and treatment of amyloidosis. Gene-based therapy and apo-A1 infusion therapy are developing.[30 31]

Tangier disease (OMIM: 205400)

Its estimated global prevalence is 1 in 640 000[32] and is caused by a deficiency of ATP-binding cassette transporter A1 (ABCA1) that facilitates the efflux of cellular cholesterol to the nascent

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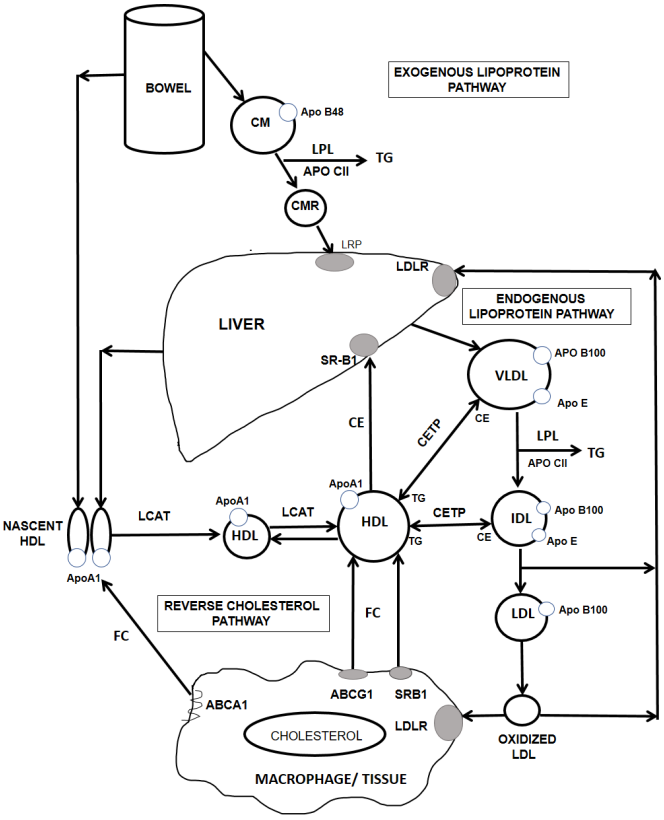

Figure 1 Lipoprotein metabolism: exogenous (intestinal) and endogenous (hepatic) lipoprotein pathways and reverse cholesterol transport pathway. ABCA1, ATP-binding cassette protein A1; ABCG1, ATP-binding cassette protein G1; Apo, apolipoprotein; CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; CM, chylomicron; CMR, chylomicron remnant; FC, free cholesterol; HDL, high-densitylipoprotein; IDL, intermediate-density lipoprotein; LCAT, lecithin:cholesterol acyltransferase; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; LPL, lipoprotein lipase; LRP, low-density lipoprotein-like receptor; SRB1, scavenger class B type receptor; TG, triglyceride; VLDL, very low-density lipoprotein.

HDL particles (figure 1). This results in reduced HDL formation and cholesterol accumulation in macrophages and peripheral tissue.[27] Patients present with orange hyperplastic tonsils. Peripheral neuropathy is common. There may be corneal opacity, hepatosplenomegaly, haemolytic anaemia, thrombocytopaenia. They are predisposed to premature CVD. Lipid profile shows extremely low HDL-C (<0.1 mmol/L), apo-A (<0.1 g/L), low LDL-C and mildly raised triglycerides.[27 33] Diagnosis is confirmed by *ABCA1* mutation analysis. There is no specific treatment. Monitoring for cardiovascular risk factors and use of statin to reduce LDL-C:HDL-C ratio is beneficial.[33]

Familial LCAT deficiency and fish eye disease (FLD, OMIM: 245900; FED, OMIM 136120)

These rare disorders with prevalence of <1:1 000 000, are caused by the deficiency of lecithin:cholesterol acyltransferase (LCAT), a plasma enzyme, which esterifies free cholesterol in HDL, facilitating its transformation into a mature globular HDL particle (figure 1).[27 34] FLD is characterised by complete lack of LCAT activity as both α and β LCAT isoforms are reduced. There is an accumulation of free cholesterol in various tissues. In fish eye disease (FED), only α LCAT activity is reduced. Corneal opacity is the common presenting feature in both FLD and FED while haemolytic anaemia and renal disease progressing to renal failure are seen only in FLD.[34 35] Lipid profile in both FLD and FED shows low HDL-C (<0.2 mmol/L) and apo-A (<0.2 g/L), while LDL-C concentration is relatively low in FLD (2.6 mmol /L) as compared with FED (3.2 mmol/L).[36] Premature CVD is more often seen in FED than in FLD.[36] Management includes monitoring of renal function and corneal opacity. Enzyme replacement therapy (ERT) with recombinant human LCAT is being developed.[37]

Lysosomal storage disorders associated with low HDL-C

Lysosomal acid lipase deficiency (LAL-D; OMIM: 278000)

This disorder has estimated prevalence of 3–5 per million Caucasian population.[38] Lysosomal acid lipase (LAL) hydrolyses cholesterol esters (CE) and triglycerides in the lysosomes. Its deficiency leads to intracellular accumulation of CE and triglycerides in various organs, especially the liver and spleen. Reduced intracellular free cholesterol and oxysterols impair liver X-receptor (LXR) activation and reduce ABCA1 activity, thereby decreasing the transfer of cholesterol to apoA-1. This results in reduced HDL formation and hypoalphalipoproteinaemia.[39 40] The severe neonatal form (Wolman disease) due to absent enzyme activity, presents in early infancy with failure to thrive, malabsorption, diarrhoea, vomiting, progressive abdominal distension, hepatosplenomegaly and adrenal calcification.[41] The late-onset form (cholesteryl ester storage disease) with residual enzyme activity, presents with disturbed liver function, hepatosplenomegaly, low plasma HDL-C (<1.0 mmol/L), high LDL-C (>5.0 mmol/L) and mild hypertriglyceridaemia (~2.2 mmol/L).[42 43] Progressive liver failure and accelerated atherosclerosis contribute to early mortality.[38–44] It should be suspected when a patient presents with elevated hepatic transaminases, low HDL-C and elevated LDL-C in the absence of metabolic syndrome risk profile. Diagnosis is confirmed by measuring enzyme activity in the dried blood spot and sequencing for *the LIPA* gene. Enzyme replacement therapy (ERT; sebelipase alfa) is the standard treatment.[45] Although liver transplantation may be required for liver failure, it is not sufficient to prevent disease progression or recurrence of liver disease.

Niemann-Pick disease

Niemann-Pick type C (NP-C1, OMIM: 257220; NP-C2, OMIM: 607625) has an incidence of 1/19 000–1/36 000 for late-onset forms.[46] Deficiency of intracellular cholesterol transporters NP-C1 and NP-C2, which export free cholesterol from lysosomes to other cell sites, results in cholesterol and glycosphingolipids accumulation in the lysosomes with disruption of LXR and decreased ABCA1 activity leading to impaired lipid mobilisation for HDL formation.[47] Clinical presentation is heterogeneous with ataxia, seizures, hepatosplenomegaly, supranuclear gaze palsy and psychiatric problems. Plasma HDL-C is mostly <0.5 mmol/L, apo-A1 <0.5 g/L, triglycerides <4.0 mmol/L and normal apo-B concentrations.[48] Diagnosis is confirmed by molecular testing.[46] Patients may respond to substrate reduction therapy with miglustat. A deficiency of lysosomal acid sphingomyelinase causes Niemann-Pick type B (OMIM: 607616). Sphingomyelin impairs the binding of LCAT to HDL leading to markedly reduced HDL-C concentrations. Patients present with arthralgia, fatigue, hepatosplenomegaly, lung disorder and thrombocytopenia.[49 50]

Gaucher disease type 1 (OMIM: 230800)

Its incidence is 1/40 000 to 1/60 000 births, increasing to 1/800 in Ashkenazi Jews.[51] Deficiency of lysosomal glucocerebrosidase,

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leads to the accumulation of glucosylceramide in the macrophages. These macrophages (Gaucher cells) may have a pathological role in lipoprotein metabolism, causing a significant reduction in HDL-C (~0.6 mmol/L) with correspondingly low apo-A1 concentrations. TC and LDL-C concentrations are also reduced, ~3.6 and 2.1 mmol/L, respectively, while triglycerides concentrations are variable 1.7–5.6 mmol/L.[52 53] Patients show marked phenotype heterogeneity. They may be asymptomatic with dyslipidaemia discovered incidentally or present with anaemia, thrombocytopenia, hepatosplenomegaly, skeletal abnormalities. HDL-C concentration correlates negatively with the severity of the disease and the magnitude of hepatosplenomegaly.[52] HDL-C and apo-A1 concentrations rise rapidly following ERT. HDL-C may therefore, serve as a biomarker for disease activity.[52 53] These patients do not develop premature atherosclerosis, however, cholesterol gall stones are fairly common. This may reflect presumably increased reverse cholesterol transport.[53–55]

Disorders associated with high HDL-C levels

CETP deficiency (hyperalphalipoproteinaemia; HALP; OMIM: 143470)

It is caused by the reduced activity of cholesteryl ester transfer protein (CETP) in the plasma which transfers CE from HDL to apo-B containing lipoproteins (VLDL, IDL, chylomicrons, LDL) in exchange for triglycerides (figure 1). Patients are generally asymptomatic. Lipid profile shows very high HDL-C (4.0±1.0 mmol/L) with large HDL particles, high apo A-1 (2.45±0.59 g/L) and low LDL-C (1.3±0.3 mmol/L) concentration.[56 57] It is seen mainly in the Japanese population. Interestingly, there is an inconsistent relationship between CETP deficiency and premature CAD.[56]

Scavenger receptor B1 deficiency (OMIM: 610762)

Scavenger receptor B1 (SR-B1) is HDL-receptor, which facilitates efflux of cholesterol from peripheral tissues back to the liver (figure 1). Heterozygous mutation in *SCARB1* causes impaired cholesterol efflux from macrophages and reduced HDL-C uptake by the liver and steroidogenic tissues. There is an increase in size and amount of HDL-C. It may be associated with accelerated atherosclerosis and adrenal glucocorticoid insufficiency.[58–60]

Disorders associated with LDL-C deficiency

Abetalipoproteinaemia (ABL; OMIM: 200100)

This disorder is characterised by markedly reduced synthesis of apo-B containing lipoproteins (chylomicron, VLDL) with a subsequent reduction in their metabolites (CM remnants, IDL-C, LDL-C). Its prevalence is <1:1 000 000.[61] Patients present in childhood with malabsorption, steatorrhoea, failure to thrive and vitamin E deficiency. Later they may develop cerebellar ataxia, myopathy and retinopathy. Lipid profile shows TC around 1.0 mmol/L with undetectable LDL-C, triglycerides and apo-B concentrations.[62–64] Patients are managed with the low-fat diet (5–20 g/day), restricted in long-chain fatty acids and vitamin E, K and A supplements.

Familial hypobetalipoproteinaemia (OMIM: 615558)

Its prevalence is 1:1000-1:3000.[61] Patients are generally asymptomatic. They may develop hepatic steatosis. Homozygous subjects present with a phenotype similar to abetalipoproteinaemia [64]

Chylomicron retention disease (OMIM: 246700)

To date, ~50 patients have been reported.[65] It is caused by defective Sar1b protein, which is essential for chylomicron formation. This leads to the accumulation of lipids in the enterocytes. Infants present with fat malabsorption, steatorrhoea, vomiting, abdominal distension and deficiency of fat-soluble vitamins. Lipid profile shows half of the normal value of TC, LDL-C, apo-B, HDL-C and normal triglycerides.[65 66] Diagnosis is often delayed due to non-specific symptoms and hypocholesterolaemia is attributed to malnutrition. Late complications include sensory neuropathy, ataxia and myopathy. Symptoms improve with a low-fat diet and fat-soluble vitamin supplements. Molecular testing distinguishes this disease from other congenital causes of fat malabsorption.

Disorders associated with markedly high LDL-C

Familial hypercholesterolaemia (OMIM: 606945)

Monogenic autosomal dominant familial hypercholesterolaemia (FH) is not a rare disease.[67] It will not be discussed here. Homozygous familial hypercholesterolaemia (HoFH) due to a biallelic mutation in *LDLR, ApoB* or *PCSK9* is rare with an incidence of 1 in 160 000–250 000 people. It presents in childhood with extensive xanthomata, premature CVD and aortic valve stenosis.[68] If untreated it causes death before the age of 30 years. Lipid profile shows LDL-C of >13 mmol/L. Both parents are obligatory heterozygotes. Management includes use of statin, plasma apheresis and liver transplantation. New drugs such as lomitapide (MTP inhibitor), mipomersen (antisense apo-B inhibitor), evolocumab (PCSK9 inhibitor), gene and stem cell-based therapy are in development.[69–72]

Autosomal recessive hypercholesterolaemia (OMIM: 603813)

Deficiency of LDL receptor adaptor protein 1, which promotes LDL receptor internalisation, leads to failure of LDLR internalisation into the cell and severe hypercholesterolaemia. Its incidence is 1:1 000 000 except in Sardinia (Italy) where it is 1:40 000.[73] Clinical presentation is similar to but less severe than HoFH with xanthomata, valvular disease and premature CVD. Management includes therapy with statin, ezetimibe, lomitapide and plasma apheresis.[73]

Sitosterolaemia (OMIM: 210250)

This rare disorder is caused by defective sterol efflux transporter proteins ABCG5 (sterolin1) or ABCG8 (sterolin 2) which results in increased absorption and accumulation of sterol in the body.[74] The global prevalence is 1 in 2.6 million for *ABCG5*, and 1 in 360 000 for *ABCG8* mutation.[75] Clinical manifestations often mimic FH with tendon xanthoma, macrothrombocytopenia, premature CVD in childhood.[74–77] There is hypercholesterolaemia and extremely high plasma sterol levels. Diagnosis is confirmed by genetic testing.[75] Management includes fat and plants sterol restricted diet and ezetimibe.[75]

CLINICAL EVALUATION

Genetic dyslipidaemia is suspected when there is a personal or family history of premature CVD, pancreatitis or neurological disease. However, autosomal recessive disorders due to homozygous or compound heterozygous mutations may not be evident in each generation, thereby reducing the suspicion of genetic disease. On the contrary, diseases due to autosomal dominant inheritance, appear in every generation except when the penetrance is low, and the disorder is not expressed or it is due to de-novo mutation.

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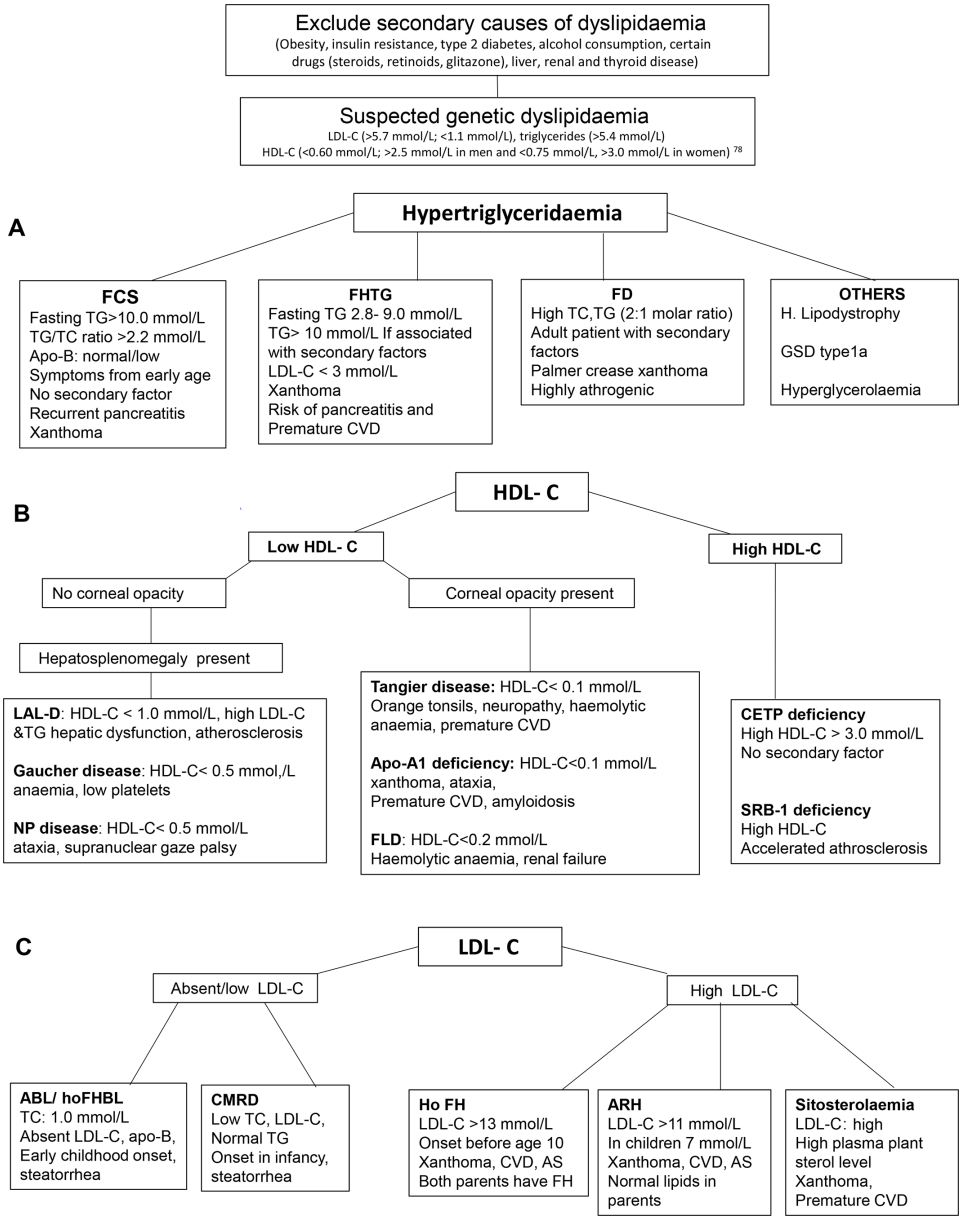

Figure2 Algorithm of evaluation for genetic dyslipidaemias. ABL, abetalipoproteinaemia; ARH, autosomal recessive hypercholesterolaemia; CETP, cholesterylester transfer protein; CMRD, chylomicron retention disease; FCS, familial chylomicronaemia syndrome; FD, familial dysbetalipoproteinaemia; FHTG, familial hypertriglyceridaemia; FLD, familial LCAT deficiency; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolaemia; hoFHBL, homozygous familial hypobetalipoproteinaemia; LAL-D, lysosomal acid lipase deficiency; LDL-C, low-density lipoprotein cholesterol; NP disease, Niemann-Pick disease; SRB1, scavenger class B type receptor; TC, total cholesterol; TG, triglyceride.

Systemic evaluation of these patients should exclude secondary causes of dyslipidaemia (figure 2). Nevertheless, certain genetic disorders such as FD, manifest clinically on exposure to these secondary factors. Physical examination includes assessment for tendon, tuberous, eruptive or palmer xanthoma, premature corneal arcus (<45 years), corneal opacity, lipaemia retinalis and presence of bruit in the carotids, abdominal aorta and femoral arteries.

Baseline laboratory tests include a fasting lipid profile (TC, triglycerides, HDL-C, directly measured or calculated LDL-C unless triglycerides are >4.5 mmol/L), haemoglobin A1c, liver, renal function and thyroid-stimulating hormone. Fasting values above the 99th percentile in the population, for LDL-C, triglycerides, and below the first percentile for LDL-C and HDL-C can be associated with monogenic dyslipidaemia (figure 2).[78] Additional tests such as apo-A or apo-B measurement and lipoprotein electrophoresis are useful in further delineation.

Primary hypertriglyceridaemia is a group of heterogeneous disorders that vary significantly in their age of expression, clinical presentation and severity (figure 2A). Severe HDL-C deficiency (<0.6 mmol/L) in the absence of triglycerides of >5.5 mmol/L is rare. Absence of secondary causes including acute illness or occult malignancy and its association with xanthomata, corneal clouding, hepatosplenomegaly or ataxia often suggest the diagnosis (figure 2B). Plasma apo-A concentrations are required for further characterisation of hypoalphalipoproteinaemia.

Presentation in early childhood with failure to thrive, steatorrhea, severe hypocholesterolaemia, and absent or low apo-B levels suggest ABL and familial hypobetalipoproteinaemia (FHBL) (figure 2C). Conversely, severe hypercholesterolemia,

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very high LDL-C with extensive xanthomata, and premature CVD in childhood are due to HoFH, autosomal recessive hypercholesterolaemia or very rarely sitosterolaemia (figure 2C).

Role of genetics

Recent advances in the genetic testing such as next-generation sequencing (NGS) which includes multiple gene panels, whole-exome sequencing (WES) and whole-genome sequencing (WGS), have revolutionised the whole diagnostic process of hereditary diseases. A multigene panel including all the known genetic mutations causing monogenic dyslipidaemia would be a useful tool for early diagnosis of these rare disorders.[79] It is particularly helpful in providing the definitive diagnosis when a mutation in different genes can cause clinically identical disorder such as FH or familial chylomicronaemia syndrome. Better insight into molecular biology and knowledge of the precise site of the defect in the metabolic pathway helps in planning specific treatment such as ERT for LAL-D, PCSK9 inhibitor in FH, ezetimibe for sitosterolaemia. Early diagnosis and appropriate management of specific disorder may prevent long-term complications like premature CVD, hepatic complications in LAL-D, neurological complications in ABL, FHBL and multisystem complications in Gaucher disease. Cascade family screening by lipid and genetic testing, therefore, helps in planning preventive strategies during the preclinical stage. Currently, no guidelines are available for genetic testing in monogenic dyslipidaemias other than FH. The decision for genetic testing is based on family history, abnormal clinical and laboratory findings or when genetic diagnosis might change the disease management. Genetic counselling should be available at all stages of testing. It also provides an opportunity for making decisions regarding choice of preventive reproductive options such as prenatal diagnosis and preimplantation genetic diagnosis.

At present, the major barrier to the easy availability of genetic testing is its high cost. Nonetheless, with rapidly declining cost, these tests would be soon more readily available. There are, however, certain limitations of NGS testing, such as WES and WGS are disclosing a large number of variants of unknown significance which are challenging to interpret. This may lead to the wrong diagnosis with severe consequences related to wrong clinical decisions. Moreover, incidental findings unrelated to the disease of interest, such as identifying cancer-related genes, may raise serious ethical issues.

CONCLUSION

Primary dyslipidaemia may be the presenting feature of a wide variety of IMDs. Increased awareness among clinicians of these rare disorders is crucial for early diagnosis and better prognosis. Genetics has an evolving role in expediting the diagnostic process, instituting preventive strategies and in the development of new interventions to improve the clinical outcome of these patients.

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ORCID iD

Raashda A Sulaiman http://orcid.org/0000-0002-6868-9823

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