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LIPIDS AND CARDIOVASCULAR DISEASE

Update on the diagnosis, treatment and management of rare genetic lipid disorders

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Summary

Rare genetic lipid disorders affect the levels of cholesterol and/or triglyceride in the circulation and, if untreated, can often lead to severe multisystem complications. The field of rare lipid disorders is evolving and increasing awareness of these conditions, along with the systematic integration of recent advances or knowledge into clinical practice, is crucial to improve patient outcomes. The aim of this review is to provide an overview of selected rare genetic lipid disorders, focusing on the recommended diagnostic strategies and contemporary treatment and management options.

Key words: Rare genetic lipid disorders; rare diseases; patient and clinical registries; genetic testing; novel therapies.

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INTRODUCTION

Rare diseases are defined as affecting less than 1 in 2,000 people and, whilst individually scarce, they are estimated to collectively affect ~8% of the Australian population.[1] Rare genetic lipid disorders affect the normal levels of cholesterol (C) and/or triglyceride (TG) in the circulation. Figure 1 shows the pathophysiology of selected rare genetic lipid disorders. Some conditions may manifest from an early age as failure to thrive, but due to the wide variety of manifestations (Table 1), patients with these rare conditions may present later in life to a general practitioner, gastroenterologist, cardiologist, endocrinologist, ophthalmologist, or dermatologist depending on the clinical context.

Pathology laboratories have a crucial role in the diagnosis and monitoring of these rare genetic lipid disorders. If left untreated, they often lead to significant multisystem complications, and therefore a timely diagnosis and effective management are paramount. Thus, increasing awareness about these conditions, facilitating translational research and integrating new knowledge into clinical practice are priorities in this field; patient registries will assist in this endeavour.[2] This review of selected rare lipid disorders outlines the current understanding of these conditions, including recommended diagnostic strategies and contemporary management options.

LOW LDL-CHOLESTEROL

Abetalipoproteinaemia and homozygous familial hypobetalipoproteinaemia

Abetalipoproteinaemia (ABL) and homozygous familial hypobetalipoproteinaemia (hoFHBL) are characterised by the inability to produce triglyceride-rich lipoproteins, namely chylomicrons (CM) from the intestine and very low density lipoprotein (VLDL) from the liver, resulting in the absence or extremely low levels of these lipoproteins and their metabolites [CM-remnants and intermediate density lipoprotein (IDL), respectively] and low density lipoprotein (LDL). ABL and hoFHBL generally present in childhood with failure to thrive, fat malabsorption, and steatorrhoea.[3] Gastrointestinal symptoms such as vomiting, diarrhoea and hepatomegaly are variably present and, if left untreated, progressive and debilitating neurological and ophthalmic complications such as spinocerebellar ataxia, dysarthria, and retinitis pigmentosa may occur related to deficiencies of fat-soluble vitamins.[4,5]

ABL (OMIM #200100) is an autosomal recessive disorder caused by mutations in the *MTTP* gene, which encodes the microsomal triglyceride transfer protein, essential in the lipidation and production of apolipoprotein (apo) B. In contrast, hoFHBL (OMIM #615558) is an autosomal co-dominant disorder, caused by mutations in the *APOB* gene, affecting the production, structure and/or stability of apoB.[6]

A diagnosis of ABL or hoFHBL is based on a characteristic lipid profile [total cholesterol (TC) ~1.0 mmol/L, LDL-C <0.1 mmol/L; TG <0.2 mmol/L; apoB <0.1 g/L) and symptoms as mentioned above.[3,4] Family screening is useful in differentiating ABL from hoFHBL, as obligate heterozygote parents of hoFHBL patients have LDL-C and apoB levels approximately one-third of normal [see heterozygous FHBL (heFHBL)], whilst obligate heterozygote parents of ABL patients have normal lipid profiles.[3] Molecular testing can confirm the diagnosis.[4,7,8]

Management of ABL and hoFHBL includes a low-fat diet (<30% of total calories) and restricting long-chain fatty acid consumption is recommended, while maintaining intake of essential fatty acids.[3,4] High-dose oral vitamin E and vitamin

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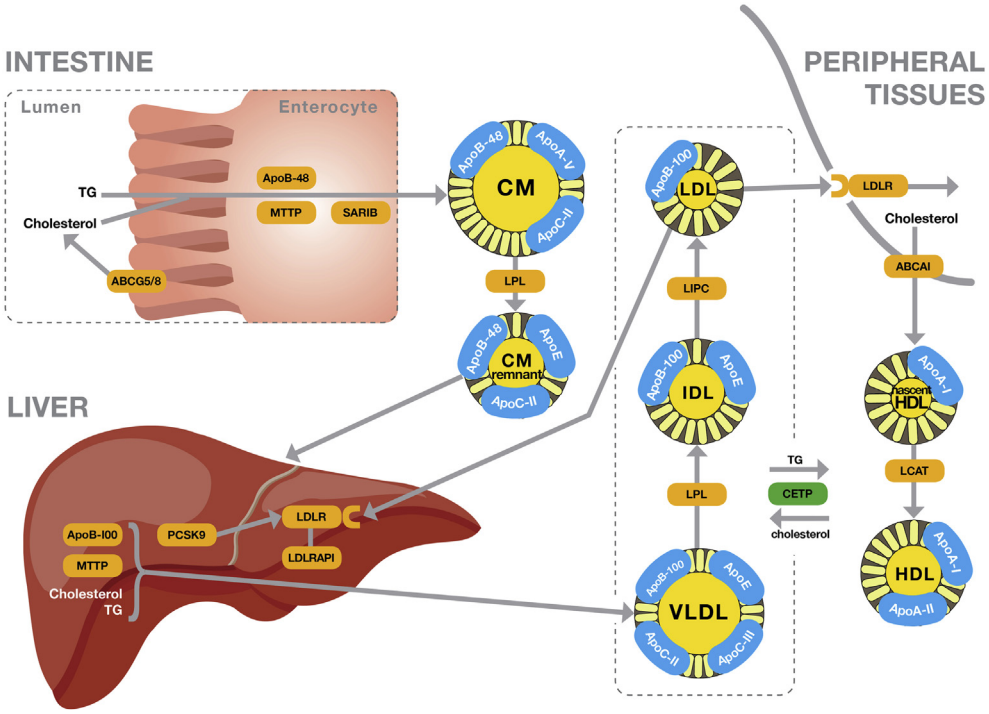

Fig. 1 Pathophysiology of selected rare genetic lipid disorders. Lipids are transported through circulation in various complexes with the assistance of apolipoproteins, enzymes and cofactors. Monogenic variants in specific genes implicated in these lipid pathways may result in rare lipid disorders. ABCA1, ATP-binding cassette subfamily A member 1; ABCG5/8, ATP-binding cassette transporter G5/G8; Apo, apolipoprotein; CETP, cholesteryl ester transfer protein; CM, chylomicron; HDL, high density lipoprotein; IDL, intermediate density lipoprotein; LCAT, lecithin:cholesterol acyltransferase; LDLRAP1, low density lipoprotein receptor adaptor protein 1; LIPC, hepatic lipase; LPL, lipoprotein lipase; MTTP, microsomal triglyceride transfer protein; PCSK9, proprotein convertase subtilisin/kexin type 9; TG, triglyceride; VLDL, very low density lipoprotein.

A supplementation is advised for prevention of neurological and ophthalmic complications, respectively.[4] Vitamin D and vitamin K supplementation is also recommended.[4] Follow-up should include assessment of growth in children and monitoring for potential complications with annual clinical and laboratory investigations and periodic investigations for hepatic, neurological, ophthalmic and cardiac function.[4]

Heterozygous familial hypobetalipoproteinaemia

FHBL patients with a single *APOB* variant have reduced levels of apoB-containing lipoproteins, but are typically asymptomatic.[4] Heterozygous FHBL is estimated to affect at least 1 in 3,000 people.[9] Biochemically, FHBL heterozygotes have LDL-C and apoB levels that are one-quarter to one-third of normal, and often have elevated liver transaminases.[3] Patients may develop hepatic steatosis due to decreased triglyceride export from the liver, on average having three times the hepatic fat content of control subjects.[5] Progression to steatohepatitis, fibrosis, cirrhosis and hepatocellular carcinoma have been reported in FHBL, and thus monitoring of liver enzymes is suggested with hepatic imaging if indicated.[5] FHBL has been associated with cardiovascular protection, presumably due to the lower lifetime exposure to LDL-C.[10]

Chylomicron retention disease

Chylomicron retention disease (CMRD) (OMIM #246700) is a recessive condition characterised by the selective absence of CMs due to variants in the *SAR1B* gene. *SAR1B* encodes for *Saccharomyces cerevisiae* homology 1B protein, which enables the transport of CMs through cellular secretory pathways; its absence results in the failure of CM formation, leading to accumulation of lipid droplets within enterocytes.[3,11]

CMRD usually presents in infancy with non-specific symptoms such as failure to thrive, diarrhoea, steatorrhoea, malabsorption of fat-soluble vitamins (A, D, E and K), vomiting, abdominal distension, and occasionally hepatomegaly.[12] If untreated, CMRD may lead to cardiomyopathy, skeletal myopathy, neurological complications such as ataxia and decreased reflexes, and visual abnormalities and retinopathy.[3,12] Endoscopy reveals white duodenal mucosa and histology displays multi-vacuolated enterocytes in intestinal villi of normal architecture.[12]

There is currently no specific treatment for CMRD, with the current recommendations mirroring therapeutic regimens for ABL, i.e., a low-fat diet with essential fatty acid supplementation to improve digestive symptoms, and fat-soluble vitamin supplementation to prevent complications.[3,12] Annual follow-up during childhood should focus on growth and nutrition with monitoring for neurological, gastrointestinal and hepatic complications. Over 10 years of age, neurological and ophthalmological review and bone densitometry scans are recommended every three years, with the addition of an echocardiogram once adulthood is reached.[12]

HIGH TRIGLYCERIDE

Familial chylomicronaemia syndrome

Familial chylomicronaemia syndrome (FCS; also known as hyperlipoproteinaemia type 1 or monogenic chylomicronaemia) (OMIM #238600) is an autosomal recessive disorder

Table 1 Genetic, clinical and biochemical features of rare genetic lipid disorders

Disorder	Gene	Inheritance	Clinical phenotype	Biochemical phenotype				
				Features	TC	HDL-C	LDL-C	TG
Abetalipoproteinaemia	*MTTP*	Recessive	Failure to thrive, non-specific GI symptoms, steatorrhoea, progressive neurological and ophthalmic abnormalities, easy bruising and bleeding, osteopenia	Absence of LDL-C, VLDL-C, chylomicrons and apoB, low total cholesterol and triglycerides, very low to absent vitamins A, D and E, prolonged INR	↓↓↓	↓	↓↓↓	↓↓↓
Homozygous familial hypobetalipoproteinaemia	*APOB*	Codominant	As for abetalipoproteinaemia	As for abetalipoproteinaemia	↓↓↓	↓	↓↓↓	↓↓↓
Heterozygous familial hypobetalipoproteinaemia	*APOB*	Codominant	Asymptomatic; hepatic steatosis	Less than one-third normal LDL-C, low vitamin E	↓	n	↓↓	↓
Chylomicron retention disease	*SAR1B*	Recessive	Failure to thrive, non-specific GI symptoms, steatorrhoea, hepatomegaly, neurological, muscular and ophthalmic complications	Absence of chylomicrons, LDL-C <50% levels of normal for age and sex	↓↓	↓↓	↓↓	n
Familial chylomicronaemia syndrome	*LPL* *APOC2* *APOA5* *GPIHBP1* *LMF1*	Recessive	Failure to thrive, non-specific GI symptoms, hepatosplenomegaly, lipaemia retinalis, eruptive xanthomas, pancreatitis	Severe hypertriglyceridaemia (>10 mmol/L); fasting chylomicronemia	↑↑	↓↓	n-↓	↑↑↑
Hepatic lipase deficiency	*LIPC*	Recessive	Asymptomatic, xanthomas, atherosclerosis	High HDL-C, hypertriglyceridaemia, abnormally large TG-rich HDL and LDL particles	↑	↑	n-↓	↑
Tangier disease	*ABCA1*	Recessive	Hyperplastic orange tonsils, peripheral neuropathy, hepatosplenomegaly, rectal mucosa changes, corneal opacities, haematological abnormalities, premature CAD	Very reduced HDL-C and apoA-I, hypertriglyceridaemia	↓	↓↓↓	n-↓	↑
Familial apoA-I deficiency	*APOA1*	Codominant	Premature CAD, xanthomas (cutaneous, tendinous, tubero-eruptive), retinal lipid deposition, corneal opacification, neurological abnormalities, amyloidogenesis	Very low (homozygotes) or half-normal HDL-C (heterozygotes), low apoA-I	↓	↓↓	n-↓	n
Familial LCAT deficiency (complete)	*LCAT*	Recessive	Corneal opacification, kidney disease, haemolytic anaemia, splenomegaly	Very low HDL-C and apoA-I, increased plasma FC/CE ratio, very low cholesterol esterification rate, presence of LpX	↑	↓↓	n-↓	n-↑
Fish eye disease	*LCAT*	Recessive	Severe corneal opacification, premature CAD	Very low HDL-C and apoA-I levels	↑	↓↓	n-↓	n-↑
Homozygous familial hypercholesterolaemia	*LDLR* *PCSK9* *APOB*	Codominant	Extensive xanthomas, arcus cornealis, premature CAD, valvular heart disease	Extreme LDL-C elevation	↑↑↑	↓	↑↑↑	n
Autosomal recessive hypercholesterolaemia	*LDLRAP1*	Recessive	Extensive xanthomas, arcus cornealis, premature CAD, valvular heart disease	Extreme LDL-C elevation	↑↑↑	↓-n	↑↑↑	n
Sitosterolaemia	*ABCG5* *ABCG8*	Recessive	Xanthomas, arthralgia, haemolytic anaemia, macrothrombocytopaenia, splenomegaly, premature CAD	High plant sterols, hypercholesterolaemia	↑ (infant ↑↑↑)	↓-n	↑ (infant ↑↑↑)	n
Familial dysbetalipoproteinaemia	*APOE*	Other	Requires trigger by secondary cause; xanthomas (palmar crease, tuberous, eruptive, tendinous), hepatosplenomegaly, premature CAD	Raised TC and TG (approx. 2:1 ratio), significantly increased IDL (↑↑↑)	↑↑	↓	↓ (IDL) ↑↑↑	↑↑
Lysosomal acid lipase deficiency	*LIPA*	Recessive	Severity varies; failure to thrive, hepatosplenomegaly, steatorrhoea, thrombocytopenia, liver disease, non-specific GI symptoms, premature CAD	Reduced lysosomal acid lipase activity, raised TC and TG, elevated serum transaminases	n-↑	↓	↑	↑

↓, decreased; ↑, increased; n, normal.

CAD, coronary artery disease; FC/CE, free cholesterol/cholesterol ester; HDL-C, high density lipoprotein-cholesterol; IDL, intermediate density lipoprotein; INR, international normalised ratio; LCAT, lecithin:cholesterol acyltransferase; LDL-C low density lipoprotein-cholesterol; TC, total cholesterol; TG, triglycerides; VLDL-C, very-low density lipoprotein.

estimated to affect 1–2 per 1,000,000 persons.[2,13] It is characterised by severe fasting hypertriglyceridaemia due to defective hydrolysis of the triglyceride content of CMs in circulation by lipoprotein lipase (LPL), leading to the accumulation of triglyceride-rich lipoproteins; levels of VLDL, LDL and HDL are often normal or even low in this condition.[14] FCS is predominantly caused by variants in the *LPL* gene encoding LPL, causing LPL deficiency, but can also be due to variants in the genes encoding apoC-II (*APOC2*), apoA-V (*APOA5*), glycosylphosphatidinositol-anchored high density lipoprotein binding protein 1 (*GPIHBP1*), and lipase maturation factor 1 (*LMF1*).[13–15]

FCS typically presents in childhood or early adulthood and clinical features include failure to thrive, hepatosplenomegaly, lipaemia retinalis and eruptive xanthomas.[14,16] Patients may also complain of mild to severe abdominal pain, nausea and vomiting, which may correlate with dietary fat intake. The development of acute pancreatitis is the most serious complication of FCS, with very high risk once TG >20 mmol/L.[13,17,18] Recurrent episodes of pancreatitis may lead to long-term consequences such as chronic pancreatitis, pancreatic insufficiency, secondary diabetes and pancreatic pseudocysts.

The diagnosis of FCS should be suspected in younger patients with primarily elevated fasting TG >10 mmol/L, especially in the presence of the clinical features listed above.[13,19] DNA sequencing for bi-allelic variants in *LPL*, *APOC2*, *APOA5*, *GPIHBP1* and *LMF1* genes can confirm the clinical diagnosis.

The cornerstone of treatment involves strict adherence to a specialised low-fat diet (15–20 g/day) and sufficient essential fatty acid and fat-soluble vitamin intake, with supplementation if necessary.[14,20] Secondary contributors to hypertriglyceridaemia, such as obesity, diabetes, insulin resistance and hypothyroidism, should also be managed; alcohol should be avoided.[13]

Potential future therapies for FCS include an antisense *APOC3* inhibitor (volanesorsen),[21,22] and angiopoietin-like protein (ANGPTL3) inhibitors. Clinical trials of volanesorsen demonstrated significant reductions in triglyceride levels and pancreatitis events in FCS patients, although adverse events included platelet count reductions (which recovered after volanesorsen was ceased).[21,22] Evinacumab, a monoclonal antibody for ANGPTL3, reduces TG and LDL-C levels but this compound is yet to be evaluated in FCS patients.[23,24]

Hepatic lipase deficiency

Hepatic lipase (HL) deficiency (OMIM #614025) is an extremely rare autosomal recessive disorder caused by mutations in the *LIPC* gene.[2] *LIPC* encodes HL, which is involved in the hydrolysis of TGs and phospholipids. *LIPC* variants result in a loss of circulating HL activity and impaired plasma TG regulation.[25]

HL deficiency should be suspected in a patient with elevated HDL-C, hypertriglyceridaemia and abnormally large, triglyceride-rich HDL and LDL particles.[26,27] HL deficiency has been associated with premature coronary artery disease (CAD), although there is conflicting evidence in the literature.[25,28,29]

There are no guidelines for the treatment of HL deficiency. Management includes reduction of cardiovascular disease risk, and would include the use of lipid-lowering medication, with limited case reports documenting the use of statins and fibrates that resulted in reductions in TC and TG in this condition.[27,30,31]

LOW HDL-CHOLESTEROL

Tangier disease

Tangier disease (OMIM #205400) is an autosomal recessive disorder characterised by profound HDL-C deficiency caused by variants in the *ABCA1* gene. ATP-binding cassette subfamily A member 1 (ABCA1) facilitates the efflux of cellular cholesterol to form nascent HDL-C, and loss-of-function variants in *ABCA1* result in severely reduced levels of HDL-C and accumulation of cholesteryl esters in tissues.[32,33] Tangier disease is estimated to affect at least 1 in 640,000 people globally.[33]

Tangier disease often presents with hyperplastic yellow-orange coloured tonsils as a direct consequence of cholesterol ester accumulation and, when combined with severe HDL-C deficiency, is considered pathognomonic for the disease.[32] Other clinical features may include peripheral neuropathy, hepatosplenomegaly, and corneal opacities.[33–35] Haematological abnormalities such as thrombocytopenia, reticulocytosis, stomatocytes and haemolytic anaemia may also be present.[33] Tangier disease is associated with increased risk for heart disease, with approximately one-third of cases linked to premature CAD.[36–38]

Biochemically, Tangier disease is characterised by severely reduced HDL-C (<0.1 mmol/L) and apoA-I (<0.1 g/L) concentrations and mildly elevated TGs.[32,35,39] Genetic testing of the *ABCA1* gene can confirm the diagnosis. Heterozygous *ABCA1* mutation carriers are asymptomatic, but display isolated HDL-C deficiency at approximately half of normal levels, with an increased risk of coronary events.[32,35]

As there is no specific treatment for Tangier disease, management is largely based on controlling symptoms and complications. Ongoing monitoring and treatment of cardiovascular risk factors, serial assessment of atherosclerotic plaque burden and decreasing LDL-C with statins are recommended.[32,40] Annual neurological and ophthalmological examinations are recommended.[33] Tonsillectomy may be indicated if hyperplastic tonsils cause airway obstruction or other mass-related symptoms, whilst corneal transplant may be considered in cases of significant corneal opacification.[32] A very low fat diet has also been suggested to reduce the potential to develop fatty liver.[35]

Familial apoA-I deficiency

Familial apoA-I deficiency (also known as familial hypoalphalipoproteinaemia, FHA) (OMIM #604091) is caused by co-dominant mutations in *APOA1*, which encodes apoA-I, the major structural protein in HDL.[41]

Patients with FHA display markedly reduced HDL-C (<0.2 mmol/L in homozygotes, usually half-normal in heterozygotes) and apoA-I levels (<0.2 g/L), and is often associated with an increased risk of premature CAD.[39–43] Clinical features in homozygotes may include cutaneous, tendinous and tubero-eruptive xanthomata, xanthelasmata, retinal lipid deposition, corneal opacification and a range of

neurological abnormalities including mild cerebellar ataxia.[44] Approximately one-third of cases are associated with amyloidogenesis which may result in variable degrees of organ dysfunction in the kidneys, liver, heart and other organs.[45]

There is no specific therapy for FHA and current practice involves the prevention of cardiovascular disease (CVD), monitoring for ophthalmic and neurological signs, and treatment of amyloidosis.[41] Cardiovascular risk factors should be regularly assessed and managed, including the use of statins.[41] *APOA1* gene replacement therapy and apoA-I peptide infusions are in pre-clinical development.[46]

Familial LCAT deficiency and fish eye disease

Lecithin:cholesterol acyltransferase (LCAT) is a key enzyme in cholesterol metabolism, which catalyses the formation of CE from free cholesterol (FC) in plasma, primarily on HDL (α-LCAT activity) and on VLDL-C and LDL-C (β-LCAT activity), and is important in HDL maturation.[47] Mutations in *LCAT* may result in one of two autosomal recessive disorders: familial LCAT deficiency (FLD) or fish eye disease (FED).

FLD (OMIM #245900) is caused by *LCAT* mutations resulting in a lack of both α- and β-LCAT activity, leading to the accumulation of FC in body tissues and severely reducing plasma HDL-C levels.[47] In contrast, FED (OMIM #136120) is caused by *LCAT* variants that result in only partial LCAT deficiency, with impaired α- but preserved β-LCAT activity.[47]

The clinical features of FLD include corneal opacification, renal disease with proteinuria and progression to end-stage kidney disease, haemolytic anaemia and splenomegaly.[47–49] Biochemically, FLD and FED patients exhibit significantly reduced HDL-C (<0.2 mmol/L) and apoA-I (<0.2 g/L), increased FC and plasma FC/CE ratio, a very low cholesterol esterification rate, and the accumulation of lipoprotein X (an abnormal cholesterol-rich lipid fraction) in FLD.[39,47–49] Patients variably display hypertriglyceridaemia and decreased TC, LDL-C and VLDL-C, and a peripheral blood smear will often show the presence of target cells.[47,48] A renal biopsy may help to support the diagnosis.[48] Although FLD patients have severely reduced HDL-C levels, they are not necessarily at higher cardiovascular risk.[47,48,50,51] In contrast, FED patients develop severe corneal opacification but no renal disease or anaemia, although are at increased risk of premature CAD.[47,49,51]

Management includes global cardiovascular risk reduction by addressing lifestyle factors and the use of statins if required. Monitoring visual acuity and corneal opacities is recommended, with corneal transplant if indicated.[48] Regular assessment of renal function in FLD should be carried out and risk factors for renal insufficiency controlled. Implementation of a low-fat diet and angiotensin receptor blocker may inhibit progression or improve renal function;[47,48,52] alternatively, the use of corticosteroids, ACE inhibitors or a nicotinic acid/fenofibrate combination has been reported to good effect.[53,54] More recently, enzyme replacement therapy using recombinant human LCAT (rhLCAT) appears promising; early studies show rhLCAT is well-tolerated and increases HDL-C levels with a shift towards the formation of mature HDL-C, increased CE production, stabilisation of renal function and improvement of anaemia.[55–57]

HIGH LDL-CHOLESTEROL

Homozygous familial hypercholesterolaemia

Homozygous familial hypercholesterolaemia (hoFH) is characterised by extremely high LDL-C levels resulting in premature CVD, aortic valve disease and xanthomata. It is predominantly caused by mutations in both alleles of the LDL-receptor gene (*LDLR*; OMIM #606945), or rarely *APOB* or *PCSK9*, leading to an inability to clear LDL particles from the circulation via the LDLR pathway and manifesting as extreme hypercholesterolaemia.[58]

HoFH differs from heterozygous FH (heFH) in prevalence and severity. Heterozygous FH, affecting between 1 in 200 to 1 in 500 individuals, is not classed as a rare disease and will not be discussed further in this review. HoFH affects between 1 in 160,000–250,000 people and typical manifestations include extensive xanthomas, arcus cornealis, premature atherosclerotic CVD, valvular heart disease and occasionally supravalvular stenosis.[58–60] Xanthomas appear during childhood and are often the presenting complaint.[61] Exposure to markedly elevated LDL-C levels from birth, if untreated, typically leads to CAD before 20 years and death before 30 years of age.[60] Family history is important in the assessment of FH, given that both parents should be obligate heterozygotes and thus will have elevated LDL-C levels together with a strong family history of premature CVD; therefore, cascade screening is recommended once the diagnosis is made.[58–60,62] The criteria for the diagnosis of hoFH is LDL-C >13 mmol/L (untreated) or LDL-C ≥8 mmol/L (treated), together with either cutaneous or tendon xanthomas before age 10 years or untreated elevated LDL-C levels consistent with heFH in both parents (although lower LDL-C levels, especially in children or treated patients, does not exclude hoFH).[60] Alternatively, the diagnosis may be confirmed by genetic testing.

The primary goals of management are the prevention of atherosclerotic CVD by controlling hypercholesterolaemia and the early detection and control of complications.[60] Regular imaging to monitor for cardiovascular complications, such as echocardiogram, CT angiogram and cardiac catheterisation, should be carried out as recommended.[63] Within Australia, the National FH Registry captures hoFH patient data and is useful for assessing treatment response and monitoring disease progression.[2] Pharmacological lipid-lowering therapy should be initiated as early as possible with ambitious LDL-C targets of <2.5 mmol/L (<3.5 mmol/L in children; <1.8 mmol/L in adults with clinical CVD).[60] The use of a statin is recommended and the addition of ezetimibe further decreases LDL-C levels, although concomitant use of other cholesterol-lowering medications such as bile-acid sequestrants, niacin and fibrates may also be considered.[60] Lipoprotein apheresis should be considered as it is cost-effective, improves xanthomas, can induce plaque regression and/or stabilisation and improves prognosis.[60,61] Liver and/or heart transplantation is an alternative treatment approach.[60]

Newer agents, such as lomitapide (oral MTP inhibitor) and mipomersen (antisense apoB inhibitor), are both approved for use in the US and are effective at reducing LDL-C, although adverse effects including hepatic fat accumulation may limit their use and further studies investigating their long-term efficacy and safety are required.[60,64–67] Evolocumab (the

injectable monoclonal antibody PCSK9 inhibitor) is a newer therapy approved for use in Australia that is well-tolerated and effective at reducing LDL-C.[68–70]

Autosomal recessive hypercholesterolaemia

Autosomal recessive hypercholesterolaemia (ARH; OMIM #603813) is caused by mutations in the *LDLRAP1* gene. *LDLRAP1* encodes LDL receptor adaptor protein 1 (LDLRAP1), which normally plays a critical role in the internalisation of the LDL-receptor; loss-of-function mutations in LDLRAP1 result in the accumulation of LDL-receptors at the cell surface and hypercholesterolaemia.[71] ARH is extremely rare worldwide with less than 1 in 1,000,000 affected, except for Sardinia, Italy, where ARH affects 1 in 40,000 and 1 in 143 are carriers.[72,73]

Patients with ARH have very high levels of LDL-C (adult >11 mmol/L; child >7 mmol/L), often have extensive xanthomas, arcus cornealis and may develop aortic stenosis and premature atherosclerotic CVD with poor cardiovascular prognosis.[39,71,74] These findings, in addition to a history of consanguinity and normal lipid profiles in parents, may assist in the diagnosis. Whilst the ARH phenotype is clinically similar to hoFH, it is generally less severe, has lower rates of premature CAD and better response to lipid-lowering therapies.[73,75]

Specific treatment is similar to hoFH but generally with a better response to lipid-lowering therapy and includes the use of a statin in combination with ezetimibe, with or without apheresis.[76–79] The addition of PCSK9 inhibitors, lomitapide or mipomersen may be considered to further improve LDL-C levels.[67,69,80–83]

Sitosterolaemia

Sitosterolaemia (OMIM #210250), also known as phytosterolaemia, is an autosomal recessive disorder characterised by elevated plasma concentrations of plant sterols (i.e., sitosterol, campesterol, and stigmasterol). The *ABCG5* and *ABCG8* genes together encode sterolin, a transporter protein found in the intestines and liver, which is responsible for regulating and eliminating dietary sterols. Homozygous loss-of-function mutations in either gene ultimately result in the hyperabsorption, decreased biliary excretion and accumulation of plant sterols in the body.[84]

Sitosterolaemia shows extreme phenotypic heterogeneity and clinical manifestations include increased plasma plant sterols, hypercholesterolaemia, xanthomas, premature atherosclerotic CVD and arthralgia.[84,85] Haematological abnormalities such as macrothrombocytopenia, haemolytic anaemia, stomatocytes and splenomegaly are often present and awareness of these characteristic findings is important, given asymptomatic patients may be at risk of misdiagnosis and inappropriate therapy.[85,86] Infants with sitosterolaemia can present with extreme hypercholesterolaemia (with levels often higher than those observed in hoFH) and xanthomas; breast milk contains sitosterol and can exacerbate hypercholesterolaemia.[87] Diagnosis is based on genetic testing or high levels of plant sterols in plasma, typically increased between 30 to 100 times normal, which is considered pathognomonic for sitosterolaemia.[84–86,88]

Recommended treatment involves dietary restriction of cholesterol and plant sterols, which includes vegetable oils, margarine, nuts, seeds, avocado and chocolate, in addition to avoiding algae-derived plant sterols from shellfish and seaweed.[84–86,89] In infants, weaning from breastfeeding is recommended.[87] Ezetimibe is very effective and has become the mainstay of therapy, leading to regression of xanthomas, atherosclerotic CVD and most haematological abnormalities.[84,89–92]

HIGH IDL-CHOLESTEROL

Familial dysbetalipoproteinaemia

Familial dysbetalipoproteinaemia (also known as type III hyperlipoproteinaemia, remnant hyperlipidaemia, or broad beta disease) (OMIM #617347) is associated with *APOE* gene variants and affects less than 1 in 2,000 people. The majority of cases are homozygous for the ε2 allele, although rarer autosomal dominant variants have been reported.[93] Dysbetalipoproteinaemia is characterised by hypercholesterolaemia and hypertriglyceridaemia due to the impaired removal of triglyceride-rich lipoproteins and the accumulation of remnant lipoproteins (primarily IDL) as a result of dysfunctional or absent apoE.[94]

Unlike other inherited lipid disorders, dysbetalipoproteinaemia does not usually manifest a lipid phenotype unless triggered by a secondary cause, such as hypothyroidism, alcohol, obesity, hormone use or diabetes.[95] Patients present throughout adulthood, with more men than women demonstrating the lipid phenotype, and women often not presenting until after menopause. Typical findings in dysbetalipoproteinaemia include xanthomas in various forms and particularly of the palmar crease, which is pathognomonic.[95,96] Due to the extremely atherogenic nature of lipoprotein remnants, patients with dysbetalipoproteinaemia are at significantly increased risk of atherosclerosis and are prone to developing premature CAD and peripheral vascular disease.[94,97]

An abnormal fasting lipid profile of increased TC and TG (approximately a 2:1 molar ratio) is characteristic of dysbetalipoproteinaemia.[98] *APOE* genotyping can be performed to confirm the diagnosis.

Dysbetalipoproteinaemia patients generally respond well to a diet low in cholesterol and saturated fat, lifestyle changes such as exercise and reducing alcohol intake, and managing secondary factors such as hypothyroidism, obesity and diabetes.[95] The use of lipid-lowering medication is similarly proven to be effective and combination therapy using a fibrate and statin is often required.[99,100]

OTHER DYSLIPIDAEMIAS

Lysosomal acid lipase deficiency

Lysosomal acid lipase deficiency (LALD; OMIM #278000) is an autosomal recessive condition caused by mutations in the *LIPA* gene, resulting in markedly reduced lysosomal acid lipase (LAL) activity. LALD may be classified into two types: the severe, infantile-onset form (previously known as Wolman disease) characterised by a complete absence of LAL activity, or the less severe, later-onset forms (previously known as cholesteryl ester storage disease) which retain partial LAL activity. LAL is responsible for the lysosomal degradation of CEs and TGs, producing FC and free fatty acids which then suppress HMG-CoA reductase activity and *LDLR* gene transcription, resulting in decreased cellular cholesterol synthesis and reduced intracellular LDL uptake, respectively.[101] LALD thus causes the accumulation of CE

and TG in bodily tissues (especially the liver) and increases endogenous cholesterol synthesis, resulting in hyperlipidaemia. LALD is estimated to affect 1 in 40,000–300,000 people.[102]

In its more severe, infantile-onset form, LALD presents with failure to thrive (malnutrition), hepatosplenomegaly, vomiting, diarrhoea, steatorrhoea and abdominal distension.[101] Progression to liver failure and adrenal cortical insufficiency may occur. Prognosis is poor and infants do not usually survive beyond one year, with a median age of death at 3.7 months.[102] In contrast, the later-onset forms, caused by variants that retain partial LAL activity, have a wider phenotypic spectrum of disease, and may present later in childhood with symptoms similar to the infantile-onset form or in adulthood either asymptomatically on routine screening (with incidental liver enzyme and/or lipid abnormalities) or may present with hepatic dysfunction, hepatosplenomegaly, non-specific gastrointestinal symptoms, thrombocytopenia or xanthelasmata.[101,103] LALD has been associated with premature atherosclerosis and cases of CAD and stroke at a young age have been reported.[101,104] Hepatic complications include fibrosis, portal hypertension, oesophageal varices, cirrhosis, hepatocellular carcinoma and liver failure.[104]

Diagnosis of LALD is suspected with the above clinical findings and an abnormal lipid profile showing increased TC, LDL-C, TG and decreased HDL-C.[101] Other blood test abnormalities (such as liver enzymes and coagulation tests) may be secondary to liver disease, splenomegaly or malabsorption. Characteristic findings and immunohistochemistry on liver biopsy is useful and assists in differentiating LALD from non-alcoholic fatty liver disease, non-alcoholic steatohepatitis or cryptogenic cirrhosis.[105,106] The diagnosis may be confirmed by measuring LAL enzyme activity or *LIPA* sequencing.[101]

Supportive care to treat and prevent complications in LALD may include liver transplantation should the patient progress to liver failure, the use of statins and corticosteroid replacement therapy.[101,107] Haematopoietic stem cell transplantation in LALD has been performed with variable success, but is associated with serious complications.[108–110] More recently, enzyme replacement therapy to target the underlying cause of LALD using sebelipase alfa, a recombinant human LAL (rhLAL), has displayed encouraging results and is approved for use in Australia, the US and the EU. Sebelipase alfa is well-tolerated and a phase 3 trial showed reduction in hepatic fat content and improvement in dyslipidaemia and liver transaminases.[111] Further, its use in LALD patients displayed survival benefits and improvements in symptoms and growth parameters.[112]

CONCLUSION

Rare genetic lipid disorders may lead to severe multisystem complications if left untreated and therefore early and appropriate intervention is paramount. Although challenges persist in our understanding of rare genetic lipid disorders, diagnostic and management strategies are available and effective; pathology laboratories have an important role in this process. Patient registries will assist with increasing the awareness of and providing further insight into these rare lipid disorders, the development of novel therapies, and the integration of new knowledge to optimise clinical best practice and ultimately improve patient outcomes.

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