MONOGENIC DISORDERS ALTERING HDL LEVELS

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ABSTRACT

Very low HDL-C levels (<20mg/dL) may be due to severe elevations in triglycerides, very poorly controlled diabetes, inflammation, infections, malignancy, liver disease, and certain medications such as anabolic steroids. Additionally, variants in multiple genes that each have a small effect but cumulatively lead to a decrease in HDL-C can result in very low HDL-C levels. Finally, rare monogenic disorders such as familial hypoalphalipoproteinemia, Tangier disease, and lecithin acyltransferase (LCAT) deficiency can lead to very low HDL-C levels. In this chapter we discuss the lipid abnormalities and clinical features of these monogenic disorders causing very low HDL-C levels. An elevated concentration of apo A-I and apo A-II is called hyperalphalipoproteinemia (HALP). HALP is classified as moderate (HDL-C levels between 80 and 100 mg/dL) or severe (HDL-C levels > 100 mg/dL). HALP is a heterogeneous condition caused by a variety of genetic and secondary conditions (for example ethanol abuse, primary biliary cirrhosis, multiple lipomatosis, emphysema, exercise, and certain drugs such as estrogens). In many individuals HALP has a polygenic origin. Monogenic HALP includes CETP deficiency, hepatic lipase deficiency, endothelial lipase deficiency, and loss of function mutations in SRB1. In this chapter we discuss the lipid abnormalities and clinical features of these monogenic disorders causing HALP.

LOW HDL CONDITIONS

The inverse relationship between HDL-C and ASCVD risk is well established but it should be recognized that while this association is consistently observed recent genetic and cardiovascular outcome studies suggest that this association is not causal (1). However, as discussed below major reductions in HDL-C induced by specific monogenic disorders may increase the risk of ASCVD.

Isolated low HDL-C levels can occur; however, it is more commonly found in association with hypertriglyceridemia and/or elevated apo B levels, typically as part of the obesity/metabolic syndrome (2). Patients with very low HDL-C (<20 mg/dL) in the absence of severe hypertriglyceridemia, very poorly controlled diabetes, inflammation, infections, malignancy, liver disease, anabolic steroids, or a paradoxical response to PPAR agonists are very rare (<1% of the population) (3,4). These individuals may have a very rare monogenic disorder associated with marked HDL deficiency, including familial hypoalphalipoproteinemia, Tangier disease, and

lecithin acyltransferase (LCAT) deficiency. Table 1 summarizes the genetic, lipid, and clinical features of these monogenic low HDL conditions. Inheritance is autosomal co-dominant with heterozygotes having decreases in HDL-C levels approximately midway between normal and homozygotes (3). In some individuals the decrease in HDL-C can be polygenic i.e., variants in multiple genes that each have a small effect but cumulatively lead to a decrease in HDL-C (5).

Table 1. Characteristics of Monogenic Low HDL Syndromes

	Effected genes	Lipids	Clinical features
Familial hypoalpha-lipoproteinemia	apo A-I/apo C-III/ apo A-IV apo A-I/apo C-III apo A-I	Apo AI undetectable, marked deficiency in HDL-C, low – normal triglycerides, normal LDL-C	Xanthomas Premature ASCVD Corneal manifestations
Tangier disease	ABCA1	HDL species exclusively preß-1, HDL-C <5 mg/dL LDL-C low (half normal)	Hepatosplenomegaly Enlarged tonsils Neuropathy ASCVD (6-7th decade)
LCAT deficiency	LCAT	HDL-C <10 mg/dL apo A-I 20-30 mg/dL <36% cholesteryl esters Low LDL-C Presence of Lp-X particles	FLD develop corneal opacities (“fish eye”), normochromic anemia and proteinuric end stage renal disease FED only develop corneal opacities

Inheritance is autosomal co-dominant with heterozygotes having decreases in HDL-C levels approximately midway between normal and homozygotes (3). FLD- Familial Lecithin: Cholesteryl Ester Acyltransferase Deficiency; FED- Fish Eye Disease

Familial Hypoalphalipoproteinemia

Familial hypoalphalipoproteinemia is a heterogeneous group of apolipoprotein A-I (apo A-I) deficiency states. This disorder is the rarest cause of monogenic severe HDL deficiency (6). These various conditions are characterized by the specific apolipoprotein genes that are affected on the apo A-I/C-III/A-IV gene cluster (3). The genes for these 3 apolipoproteins (apo A-I, apo C-III, and apo A-IV) are grouped together in a cluster on human chromosome 11. In patients with apo A-I/C-III/A-IV deficiency, apoA-1 is undetectable in the plasma and is associated with marked deficiency in HDL-C, low triglyceride levels (due to apo C-III deficiency), and normal LDL-C levels (3). Heterozygotes have plasma HDL-C, apo A-I, apo A-IV, and apo C-III levels that are about 50% of normal (3). This condition is associated with aggressive, premature ASCVD. Additionally, there is evidence of mild fat malabsorption due to deficiency of apo A-IV. Patients with apo A-I/C-III deficiency have undetectable apo A-I and a similar lipid profile as those with apo A-I/C-III/A-IV deficiency (3). This condition is also

associated with premature ASCVD. It is distinguished from the former by presence of planar xanthomas and absence of fat malabsorption (since apo A-IV is present). Familial apo A-I deficiency is itself a heterogeneous group of disorders associated with numerous Apo A-I mutations (3). Common manifestations include undetectable plasma Apo A-I, marked HDL deficiency with normal LDL-C and triglyceride levels, xanthomas (planar, tendon, and/or tubero-eruptive depending on the specific gene mutation), and premature ASCVD. Some forms of the disease are also associated with corneal manifestations, including corneal arcus and corneal opacification. One of the interesting manifestations of familial apo A-I deficiency is that levels of apo A-IV and apo E containing HDL particles are only modestly reduced, with preserved electrophoretic mobility and particle size (7).

It is notable that familial hypoalphalipoproteinemia is associated with an increased risk of premature ASCVD presumably due to the marked deficiency in Apo A-I and HDL. Given the increased ASCVD risk associated with Apo A-I deficiency, treatment is directed towards aggressive reduction of LDL-C and non-HDL-C levels and reducing other cardiovascular risk factors.

Some mutations in Apo A-I are associated with low HDL-C levels and hereditary amyloidosis and are the second most frequent cause of familial amyloidosis (6,8). Note that HDL-C levels are not always decreased in patients with familial amyloidosis secondary to Apo A-I mutations. The N-terminal fragment of the mutated protein is found in the amyloid fragments.

Tangier Disease

Tangier disease is due to mutations in the gene that codes for ATP-Binding Cassette transporter A1 (ABCA1) and is inherited in an autosomal co-dominant manner (9,10). Fredrickson first reported this condition in two patients who hailed from Tangier Island in the Chesapeake Bay, for which the disorder is named. ABCA1 facilitates efflux of intracellular cholesterol from peripheral cells to lipid poor A1, the key first step of reverse cholesterol transport (11). As such, this disorder is characterized by severe deficiency of HDL-C (HDL-C <5 mg/dL) and the presence of only the preß-1 HDL fraction of HDL (10). The poorly lipidated Apo A-I is rapidly catabolized by the kidney. These patients also demonstrate moderate hypertriglyceridemia and low LDL-C levels (10). The decrease in LDL-C is likely due to absence of the transfer of cholesterol from HDL to LDL. Studies have also suggested that an increase in LDL uptake by the liver also occurs (12). The increase in triglycerides may be due to the failure of HDL to provide co-factors that increase lipoprotein lipase activity. Additionally, ABCA1 deficiency in the liver increases triglyceride secretion and hepatic angiopoietin-like protein 3 secretion which could inhibit lipoprotein lipase activity leading to an increase in triglycerides (12,13).

Since ABCA1 deficiency impairs free cholesterol efflux from cells, there is accumulation of cholesterol esters in many tissues throughout the body (10). Classically, patients present with hepatosplenomegaly and enlarged yellow-orange hyperplastic tonsils, however, a wide spectrum of phenotypic manifestations is now appreciated with considerable variability in terms of clinical severity and organ involvement (9,10). Peripheral neuropathies are also a common complication and may be relapsing-remitting or chronic progressive (9,10). Tangier disease patients appear to have an increased risk of premature ASCVD, though not as pronounced as those with familial hypoalphalipoproteinemia (3,9,14). When the non-HDL-C levels are greater than 70mg/dL patients with Tangier disease are at higher risk of ASCVD whereas when the non-HDL-C levels are less than 70mg/dL ASCVD is low (9). Less common complications include corneal opacities and

hematological manifestations such as thrombocytopenia and hemolytic anemia (9,10).

Individuals who are heterozygous for ABCA1 mutations have HDL-C levels that are variable but approximately 50% of normal with normal levels of preß-1 HDL but a deficiency of large α-1 and α-2 HDL particles (10). Cholesterol efflux capacity in heterozygotes has been reported as ~50% of normal. A mutation in one ABCA1 allele has been associated with increased risk of ASCVD in some studies and with no increase in ASCVD risk in other studies (15-20). Different mutations in ABCA1 result in varying HDL-C levels and phenotypes, which might explain the difference in ASCVD risk (21).

While Tangier patients manifest characteristically low HDL-C and Apo A-I, this lipid/lipoprotein phenotype is not adequate to make the diagnosis. ABCA1 gene sequence analysis is the preferred test to make the diagnosis of Tangier disease (10). Alternatively, non-denaturing two-dimensional electrophoresis followed by anti-apo A-I immunoblotting demonstrates only preβ1-HDL.

Currently, there is no specific treatment for Tangier disease (10). In fact, HDL-C raising therapies such as niacin and fibrates have proven ineffective in patients with this condition (22). Even HDL infusion was not beneficial (23). The major clinical issue in Tangier patients is disabling neuropathy; however, there is no effective intervention to manage this complication (10). Aggressive LDL-C lowering and treatment of other risk factors for atherosclerosis is recommended (10).

LCAT Deficiency

LCAT is an enzyme that is bound primarily to HDL, with some also found on LDL (24,25). It facilitates cholesterol esterification by transferring a fatty acid from phosphatidyl choline to cholesterol (24,25). The hydrophobic cholesteryl esters are then sequestered in the core of the lipoprotein particles. LCAT is critical in the maturation of HDL particles. LCAT deficiency is an autosomal co-dominant disorder that manifests as either familial LCAT deficiency (FLD) or fish-eye disease in homozygotes (FED) (24,25). In FLD, mutations in LCAT lead to the inability of LCAT to esterify cholesterol in both HDL and LDL, whereas in FED, mutations in LCAT lead to the inability of LCAT to esterify cholesterol in HDL but the ability of LCAT to esterify cholesterol in LDL is preserved (24,25). Patients with FLD have virtually no cholesterol esters in the circulation while patients with FED have subnormal levels of cholesterol esters carried in apo B containing lipoproteins (24,25). Heterozygotes having decreases in HDL-C levels approximately midway between normal and homozygotes.

Individuals with FLD develop corneal opacities (“fish eye”), normochromic hemolytic anemia (due to cholesterol enrichment of red blood cell membranes), mild thrombocytopenia, and proteinuric end stage renal disease, which is the major cause of morbidity and mortality (24,25). The corneal opacities begin early in life and some patients may need corneal transplants. The rate of development of renal disease is variable but in a large cohort renal failure occurred at a median age of 46 years (26). Patients with FED generally only manifest corneal opacities (24,25).

The lipid and lipoprotein profile in patients with FLD usually demonstrates low HDL-C levels (frequently <10 mg/dL) (24,27). In one cohort patients with FED tend to have higher HDL-C levels but in a large systematic review HDL-C levels were similar in patients with FLD and FED (24,27). LDL-C levels tend to be low in FLD and FED while triglyceride levels are increased (24,27). Lipoprotein X (Lp-X) particles are present in patients with FLD but not in patients with FED (24). Lp-X is a multilamellar vesicle with an aqueous core. It is primarily composed of free cholesterol and phospholipid with very little protein (albumin in the core and apolipoprotein C on the surface) and cholesteryl ester.

Given the association of Lp-X and kidney disease only with FLD (and not FED) and animal studies demonstrating the nephrotoxicity of Lp-X, it is likely that increased levels of Lp-X results in renal dysfunction in patients with FLD (25,28). Lp-X particles accumulate in the mesangial cells in the glomerulus and are thought to induce inflammation and breakdown of the basement membrane leading to proteinuria. It is notable that after renal transplantation in patients with FLD there is recurrence of renal damage in the transplanted kidney (26).

It is unclear as to whether LCAT deficiency is associated with an increased risk of ASCVD (25,29). Atherosclerosis imaging studies have yielded divergent data and the number of patients with FLD or FED studied is limited (25,29). In one study carriers of FLD mutations (i.e., heterozygotes) had a decrease in ASCVD while carriers of FED mutations had an increase in ASCVD (30). This may have been due to higher LDL-C levels in the carriers of FED mutations (30).

Current management of FLD focuses on managing the renal dysfunction. The associated kidney disease is traditionally managed with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and a low-fat diet (25). Whether lipid lowering drugs are beneficial is unknown. Possible future therapies include enzyme replacement therapy with recombinant human LCAT, liver-directed LCAT gene therapy, small peptide or molecule activators of LCAT, and HDL mimetics (31,32). Infusions of recombinant human LCAT has improved the anemia and most parameters of renal function in a patient with FLD (33). Administration of CER-001, an apolipoprotein A1 (apoA-1)–containing HDL mimetic, has been shown to have beneficial effects on kidney and eye disease in a patient with LCAT deficiency (34).

Approach to the Patient with Low HDL-C Levels

When encountering a patient with very low HDL-C levels it is important to first determine if this is a new abnormality or has been present for a long time. If prior HDL-C levels are normal, this excludes a primary monogenic etiology. If the decrease in HDL-C is new, one should consider the possibility of very poorly controlled diabetes, inflammation, infections, malignancy, liver disease, paraproteinemia, anabolic steroids, or a paradoxical response to PPAR agonists. Marked hypertriglyceridemia can also lead to very low HDL-C levels.

In a patient with long-standing very low HDL-C levels without an identifiable secondary cause, one should consider a monogenic etiology. To evaluate potential monogenic causes, a detailed family history, with attention to HDL-C levels, is important. Obtaining lipid levels from relatives is very helpful. A focused physical examination, with particular attention to the skin, eyes, tonsils, and spleen may point to a specific monogenic disorder. Plasma apo A-I levels should be obtained. Individuals with familial hypoalphalipoproteinemia deficiency have undetectable plasma apo A-I. Patients with Tangier disease demonstrate very low apo A-I levels (<5 mg/dL). LCAT deficiency is associated with apo A-I levels that are low but substantially higher than the other monogenic etiologies. Patients with LCAT deficiency also have a higher ratio of free: total cholesterol in plasma and measurement of plasma free (unesterified) cholesterol can be helpful. Two-dimensional gel electrophoresis of plasma followed by immunoblotting with antibodies specific for apo A-I separates lipid-poor preß-HDL from lipid-rich–HDL and can be helpful in differentiating these disorders. Genetic analysis is indicated when a monogenic disorder is suspected.

HIGH HDL-C CONDITIONS (HYPERALPHALIPOPROTEINEMIA)

An elevated concentration of apo A-I and apo A-II is called hyperalphalipoproteinemia (HALP). HALP is classified as moderate (HDL-C levels between 80 and 100 mg/dL) or severe (HDL-C levels > 100 mg/dL). While it is well recognized that high HDL-C levels are associated with a decrease in ASCVD it should be noted that very high HDL-C levels are paradoxically associated with an increase in ASCVD (35,36).

HALP is a heterogeneous condition caused by a variety of genetic and secondary conditions (for example ethanol abuse, primary biliary cirrhosis, multiple lipomatosis, emphysema, exercise, and certain drugs such as estrogens). In many individuals, the very high HDL-C levels have a polygenic origin (5,37). Given the focus of this chapter, monogenic causes of HALP will be reviewed. Monogenic HALP includes CETP deficiency, hepatic lipase deficiency, endothelial lipase deficiency, and loss of function mutations in SRB1. Despite epidemiology that demonstrates an inverse relationship between HDL-C and ASCVD risk, some forms of familial HALP are paradoxically associated with increased cardiovascular risk.

HALP is generally identified incidentally after routine assessment of a lipid profile as it is not usually associated with any signs or symptoms. Generally, patients are asymptomatic and no medical therapy is required.

Cholesterol Ester Transfer Protein (CETP) Deficiency

CETP transfers cholesteryl esters from HDL particles to triglyceride rich lipoproteins and LDL in exchange for triglycerides (11). Individuals who are homozygous for CETP variants have very high HDL-C levels (>100mg/dL) while heterozygotes have moderately increased HDL-C levels (38-41). LDL-C and apo B levels may be normal or modestly decreased. The increase in HDL cholesterol are largely due to the accumulation of cholesterol esters (39). The decrease in LDL-C is due to the failure of cholesterol ester transport from HDL to apo B containing lipoproteins. There is a predominance of small LDL particles. Individuals who are heterozygotes for CETP mutations show modestly elevated HDL-C levels (38,39). In Japanese individuals with HDL-C levels > 100mg/dL 67% were demonstrated to have CETP gene mutations (42). CETP deficiency is the most important and frequent cause of HALP in Japan. CETP deficiency is common in other Asian populations but is relatively rare in other ethnic groups (39). Despite extensive studies the effect of CETP variants on the risk of ASCVD is uncertain (38-40,43). A variety of studies have indicated that a decrease in LDL-C and non-HDL-C levels (i.e. pro-atherogenic lipoproteins) rather than an increase in HDL-C induced by CETP variants underlies a potential beneficial effect on ASCVD (44).

Endothelial Lipase (EL) Deficiency

Endothelial lipase (EL) is encoded by the LIPG gene and hydrolyzes phospholipids on HDL resulting in smaller HDL particles that are more rapidly metabolized (11). Genetic variants in LIPG have been identified Iin individuals with elevated HDL-C levels (38,39). As one would predict large HDL particles enriched in phospholipids are observed in individuals deficient in EL (39). Whether variants in LIPG leading to decreased EL activity and increased HDL-C levels reduces ASCVD risk is uncertain (38-40).

Hepatic Lipase (HL) Deficiency

Hepatic lipase (HL) is encoded by the LIPC gene and mediates the hydrolysis of triglycerides and phospholipids in intermediate density lipoproteins

(IDL) and LDL leading to smaller particles (IDL is converted to LDL; LDL is converted from large LDL to small LDL) (11). It also mediates the hydrolysis of triglycerides and phospholipids in HDL resulting in smaller HDL particles (11). Several case reports of families with elevated HDL-C levels (HALP) caused by a genetically defined HL deficiency have been described (39,40). HL deficiency may also be associated with elevated triglycerides and cholesterol with increased intermediate density lipoproteins (IDL) (40,45). Several HL deficient individuals had premature ASCVD likely due to increased levels of apo B containing lipoproteins (40,45). Heterozygotes do not appear to have discrete lipoprotein abnormalities (45).

Scavenger Receptor Class B Type I (SR-BI)

Scavenger receptor class B type I (SR-BI) is encoded by the SCARB1 gene and facilitates the selective uptake of the cholesterol esters from HDL into the liver, adrenal, ovary, and testes (11). In macrophages and other cells, SR-B1 facilitates the efflux of cholesterol from the cell to HDL particles (11). SR-B1 deficient mice have an increase in atherosclerosis despite elevated HDL-C levels (46). Mutations in SCARB1 associated with decreased SR-B1 have been observed in individuals with high HDL-C levels (47-49). Heterozygotes have intermediate elevations of HDL-C between wild-type and homozygous individuals. Studies have suggested that some but not all mutations in SCARB1 result in an increased risk of ASCVD despite increased HDL-C levels (40,49). A decrease in adrenal function has been reported in some individuals with SCARB1 mutations likely due to a reduced ability of SR-B1 to facilitate cholesterol uptake into the adrenal glands (48,50). Abnormalities in platelet function have also been observed in some patients (50).

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