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When are your patients' abnormal lipid levels not their fault?

Lipid-lowering lifestyle behaviors alone will not usually reduce the risk of premature heart attack and stroke when patients have an inherited dyslipidemia such as familial combined hyperlipidemia.

ABSTRACT: Elevated plasma cholesterol and high triglycerides are frequently considered to be primarily the fault of a patient's lifestyle habits. At least 1 in 40 British Columbians, however, is born with an inherited tendency to dyslipidemia that is not related to diet, activity level, or weight. Awareness of when hyperlipidemia is likely inherited rather than the result of lifestyle habits is critical to counseling patients and initiating and maintaining treatment to reduce the risk of premature heart attack, stroke, and mortality. Supporting patients at risk requires knowing the main types and clinical features of inherited dyslipidemias such as familial combined hyperlipidemia; when to suspect an inherited condition based on history, physical examination, and laboratory measurement of lipid levels; and the initial approach to managing these disorders. When necessary, patients can be referred to specialty clinics such as the Healthy Heart Program—Prevention Clinic at St. Paul's Hospital in Vancouver, BC.

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The overall frequency of major inherited dyslipidemias of all kinds in BC and Canada is conservatively estimated to be about 1 in 40 individuals, with a higher incidence found in the French-Canadian population. Among inherited lipid disorders, familial combined hyperlipidemia (FCH) is the most common. FCH presents with high LDL-C and apolipoprotein B100 (apoB), and occurs in up to 1 in 50 individuals.[1]

Familial combined hyperlipidemia and familial hypercholesterolemia

Familial hypercholesterolemia (FH) is less common than FCH with approximately 1 in 500 individuals being heterozygous for this condition. Other inherited conditions to consider include familial dysbetalipoproteinemia and familial forms of hypertriglyceridemia.

Features of FCH or FH can include a family history of premature ischemic cardiovascular disease, defined as onset of ischemic vascular symptoms or a coronary or cerebrovascular event before age 55 in male first-degree relatives (father, brother, son) or before age 65 in female first-degree relatives (mother, sister, daughter). Even without a positive family history, an LDL-C level above 4.5 mmol/L or an apoB level above 1.3 g/L, with or without elevated triglycerides, suggests the presence of either FCH or FH.

The most specific indicator of FH is the presence of tendon xanthomas, particularly of the Achilles tendons (**Figure 1**).[2] Tendon xanthomas, however, are not a strict requirement for a diagnosis of FH.[3] The finding of corneal arcus (**Figure 2**)[4] before age 65 strongly suggests the presence of an inherited dyslipidemia, but is not specific to a particular disorder. Xanthomas around the eyes (**Figure 3**)[5] —referred to as xanthelasma or xanthelasma palpebrarum—are frequently associated with inherited dyslipidemia, but are also not specific to a particular disorder. In addition to premature coronary disease in the family and corneal arcus,[4] other strong indicators of FH are elevated LDL-

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C from a very young age and more marked LDL-C elevation than seen in FCH.[6] The lipid phenotype frequently overlaps in FCH and FH.[7] To date, no specific genetic cause of FCH has been identified and no genetic test is available; genetic testing for the cause of FH is available at a research level, but not yet at a clinical level. It is not critical, however, to make an exact diagnosis of FCH or FH, or to identify the gene mutations causing FH. It is more important to recognize that an inherited lipid disorder is present, that it is not going away, and that it puts the patient at increased risk of premature cardiovascular disease. Treatment of FCH and FH, in any case, is the same.

Familial dysbetalipoproteinemia

Familial dysbetalipoproteinemia, also known as remnant removal disease or type III dyslipidemia, is a less common familial dyslipidemia, occurring in approximately 1 in 5000 individuals, and caused by the apoE2/E2 genotype and overproduction of very low density lipoprotein by the liver. The presence of palmar xanthomas, indicated by orange-brown palmar creases (**Figure 4**),[8] is highly suggestive of this disorder.

Familial forms of hypertriglyceridemia

Inherited cases of isolated high triglycerides without high apoB are less common than FCH or FH, and can be caused by a variety of gene mutations affecting triglyceride metabolism.[9] Specific genetic tests are not available for clinical use, but can be performed in cases of severe refractory hypertriglyceridemia with recurrent pancreatitis, as seen in lipoprotein lipase or apolipoprotein C-II deficiency. Plasma triglyceride levels are more sensitive than cholesterol levels to secondary factors. High

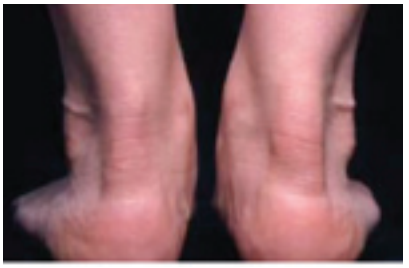

Figure 1. Tendon xanthomas, shown here as thickening and nodularity in the Achilles tendons.

simple carbohydrates or fats in the diet, low exercise level, presence of diabetes or prediabetes, hypothyroidism, alcohol, and drugs, including estrogen and retinoids, can all raise triglyceride levels. Marked elevation of triglycerides (levels higher than 4 to 5 mmol/L), are usually due to an underlying inherited cause of high triglycerides plus one or more secondary factors.[10] In addition to pancreatitis,[10] triglyceride levels higher than 20 mol/L can be associated with eruptive xanthomas (**Figure 5**).[11]

Familial low HDL

Plasma HDL-C below about 0.7 mmol/L is usually indicative of an inherited mutation affecting HDL-C level, especially when combined with a low plasma apolipoprotein A-1 level, and is sometimes, but not always, associated with increased risk of premature coronary heart disease.[12] Genetic testing can be done for specific very low HDL-C disorders such as Tangier disease or LCAT deficiency.

Elevation of lipoprotein(a)

Elevation of lipoprotein(a) or Lp(a) is an independent inherited risk factor for premature myocardial infarction and stroke.[13] Lp(a) levels higher than 500 mg/L (normal being considered below 300 mg/L) was found to occur in 20% of men and women in a large population study.[14] In one study, 17% of patients with coronary artery

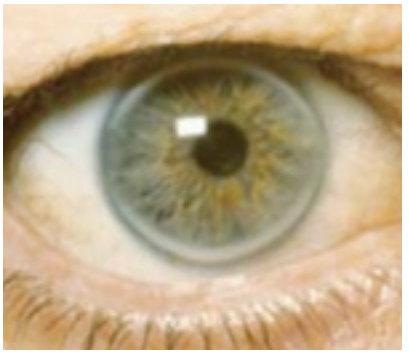

Figure 2. Corneal arcus, indicated by the white ring adjacent to the outer edge of the iris.

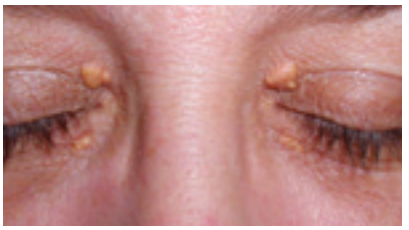

Figure 3. Xanthelasma palpebrarum, indicated by yellowish deposits above and below the eyelids.

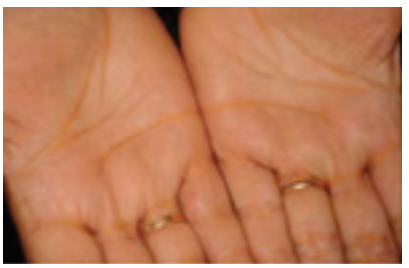

Figure 4. Palmar xanthomas, indicated by the orange-brown coloration of the palm creases.

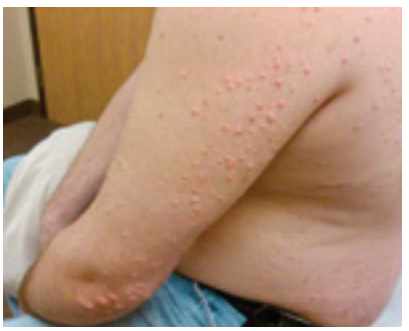

Figure 5. Eruptive xanthomas in severe hypertriglyceridemia.

disease were found to have Lp(a) levels above the 90th percentile for the population.[15] While Lp(a) is not part of the routine lipid profile, it should be measured in patients with a family history or a personal history of premature or recurrent heart attack or stroke, particularly when other obvious risk factors for cardiovascular events are not present in the patient or their family members.[16]

When to suspect an inherited dyslipidemia

In most cases, baseline (untreated) fasting lipid levels can indicate that an inherited lipid disorder is likely. While physical stigmata of hyperlipidemia such as corneal arcus may suggest the presence of a familial lipid disorder and should prompt the measurement of lipid levels, these signs are not required to make a diagnosis of familial dyslipidemia. The following results from a standard lipid profile are all suggestive of inherited dyslipidemia, even when obtained prior to diet and exercise improvements: LDL-C > 4.5 mmol/L, triglycerides > 4.0 mmol/L, HDL-C < 0.7 mmol/L, non-HDL-C > 5.1 mmol/L, apoB > 1.3 g/L. In the absence of inherited disorders of lipid metabolism, high-fat or high-cholesterol diets, lack of exercise, and obesity, whether alone or in combination, cause relatively minor rather than major elevations of LDL-C and triglycerides. An Lp(a) level above 300 mg/L is considered high and is a risk factor for premature heart attack or stroke.

Approach to managing inherited dyslipidemia

Identification and education

Identification of an inherited dyslipidemia is important on multiple levels. Inherited hypercholesterolemia increases the risk of premature cardiovascular disease and death in women as well as men,[6,17,18] and this risk is markedly reduced, down to a level similar to that of the general population, with statin treatment.[18] Once an inherited dyslipidemia is identified, patients should be educated about their risk. After a trial of lifestyle modification, they should be informed that their dyslipidemia is not just the fault of their diet or exercise routines, that it is not going away, and that if treatment is recommended it is meant to be ongoing, possibly lifelong. If medication for inherited dyslipidemia is stopped, lipid levels revert quickly to elevated baseline levels. It is also important to advise patients to discuss their dyslipidemia with family members and to encourage family members to be tested.

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Risk stratification

The Canadian Cardiovascular Society guidelines for managing patients with dyslipidemia, including patients with inherited dyslipidemia, recommend thresholds of LDL-C for initiating lipid-lowering drug treatment at all levels of cardiovascular risk.[19] A family history of premature cardiovascular events in first-degree relatives doubles the score obtained with the Framingham risk calculator, and provides further strong impetus to initiate statin therapy earlier rather than later. Additional tests can be used to further stratify risk where there is uncertainty about the need for drug treatment or reluctance to start treatment. Secondary tests include carotid ultrasound and coronary calcium scan.[19]

Trial of lifestyle measures

A heart-healthy diet, regular physical activity, and quitting smoking all enhance the benefits of drug treatment for dyslipidemia and are recommended for all individuals, regardless of their lipid levels.[19] In patients who are not at high risk, a 3- to 6-month trial of healthy eating and increased activity are important to determine whether the dyslipidemia responds to these measures. Persistent high levels of LDL-C, apoB, or non-HDL-C indicate the presence of an inherited dyslipidemia. These findings confirm the diagnosis, help relieve the guilt patients can feel about their high lipid levels, and reinforce the need to stay on lipid therapy if it is recommended. While patients with remnant removal disease and isolated elevated triglycerides can respond quite well to

improved diet and exercise routines, patients with FCH and FH will usually still have total cholesterol and LDL-C levels well above normal levels despite careful lifestyle habits. In individuals with inherited dyslipidemia who have a high Framingham risk score, initiation of statin therapy is usually recommended at the same time diet and exercise improvements are discussed. In patients with severe hypertriglyceridemia (above 8 to 10 mmol/L) a fibric acid derivative such as fenofibrate, not a statin, should be the first-line treatment to reduce the risk of pancreatitis.[10]

Initiating lipid-lowering treatment

Individuals with a persistent high LDL-C level (above 5 mmol/L) despite lifestyle improvements should be treated for inherited dyslipidemia using a statin even if they have a low Framingham risk score. The optimum time in life to initiate lipid therapy for inherited dyslipidemia remains somewhat controversial, and is dependent on family history, the presence of other major risk factors such as smoking, hypertension, and diabetes, the result of secondary testing in some cases, and individual preferences. Women with inherited dyslipidemia are at high risk; like men with inherited dyslipidemia, they also benefit from statin therapy and should be treated.[18,20] If a premenopausal woman is taking a statin or most other lipid-lowering therapies, she should be advised to use effective contraception and discontinue treatment several months before attempting to conceive, and not to use statins during pregnancy and lactation.

A recent study has shown a marked reduction in cardiovascular events is associated with chronically low LDL-C levels in individuals with loss-of-function mutations in a protein mediating LDL receptor degradation, PCSK9.[21] This finding provides strong evidence that maintaining lower LDL-C levels throughout life has a highly beneficial effect, and that it may be better to initiate statin therapy at younger ages in individuals with inherited hypercholesterolemia. The benefits of statin treatment, particularly in the case of inherited dyslipidemia, far outweigh the potential adverse effects, and this should be conveyed to patients. All patients should be advised to report new onset or worsening of muscle aches, weakness, or other side effects that occur after initiating statin treatment, even if they occur years after starting the medication. When managing inherited dyslipidemia, the recommendation is to initiate a low-dose newer generation statin such as rosuvastatin, and to titrate the dose as needed to achieve at least a 50% reduction in LDL-C levels, which confers an approximate 50% reduction in risk of cardiovascular events.[22] Where statins are not tolerated or are insufficient to achieve at least a 50% reduction of baseline LDL-C levels, additional lipid-lowering agents such as ezetimibe, bile acid-binding resins, or niacin may be required.

When to measure Lp(a)

Lp(a) should be measured in patients with premature or recurrent heart attack or stroke, or when a first-degree family member has experienced a premature cardiovascular event, particularly when it is unclear why the event has occurred. Lp(a) is not lowered by healthy lifestyle behaviors. When elevated Lp(a) (above 300 mg/L) is found in an intermediate-risk or higher-risk patient, a statin should be used to lower LDL-C to target levels. This has been shown to reduce a large part of the risk of high Lp(a), despite the fact that statins themselves do not lower Lp(a).[23] Additional treatment for elevated Lp(a) in individuals with recurrent cardiovascular events despite effective statin treatment can include niacin, the only agent currently available that effectively lowers Lp(a).

Identification and treatment of inherited dyslipidemia is critical, both for patients and their family members, to reduce the risk of premature cardiovascular disease and death in these individuals.

When to refer

Patients can be referred to a specialty clinic for diagnosis of inherited dyslipidemia, dietary and lifestyle counseling, treatment of complicated dyslipidemia, management of statin or other lipid-therapy intolerance, and overall cardiovascular risk reduction. The Healthy Heart Program—

Prevention Clinic (previously known as the Lipid Clinic) at St. Paul's Hospital in Vancouver is the main provincially funded resource in BC for patients with inherited dyslipidemia.[24]

Summary

Inherited dyslipidemia is common. The overall frequency of major inherited dyslipidemias in BC is estimated to be about 1 in 40 people. An even greater number are affected if people with elevated Lp(a) are counted in this estimate. Healthy lifestyle behaviors alone cannot effectively treat inherited lipid disorders. Identification and treatment of these disorders is critical, both for patients and family members. Patient education, risk stratification, lipid-lowering therapy, and referral to a specialty clinic, if necessary, can help reduce the risk of premature cardiovascular disease and death in these individuals.

Competing interests

Dr Hamata has no declared competing interests. Dr Francis is currently a member of the speakers' board for Valeant and an advisory board member to Amgen, Sanofi, and Valeant.

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