Some inherited lipid disorders can be recognized by the deposition of cholesterol and other lipids in lesions on the body termed xanthomas. Lipid deposition can occur in cutaneous and subcutaneous structures, including tendons, with the pattern of deposition characteristic of the underlying genetic disorder. Tuberous xanthomas are nodules frequently localized to the extensor surfaces of elbows, knees, knuckles, and buttocks. Tendon xanthomas are subcutaneous nodules found in fascia, ligaments, and tendons, which can occur particularly in the Achilles tendon and extensor tendons of the hands. (See Figure 1) The focus of this article is to highlight less common genetic disorders that cause tuberous and tendon xanthomas to promote better diagnosis of these disorders.

The most common hyperlipidemia underlying tuberous and tendon xanthomas is familial hypercholesterolemia (FH), caused by defects in the genes encoding the low-density lipoprotein (LDL) receptor, apolipoprotein B (apoB)-100, PCSK9, and LDLRAP1, although a number of other genetic disorders can cause these types of xanthoma. (See Table 1) Tuberous xanthomas also can occur in type III hyperlipidemia (familial dysbetalipoproteinemia) and sitosterolemia (phytosterolemia). Tendon xanthomas can occur in sitosterolemia and cerebrotendinous xanthomatosis (CTX).

Outside of xanthomas in children with Alagille syndrome, finding xanthomas in children is extremely suggestive of homozygous familial hypercholesterolemia, sitosterolemia or CTX. For CTX especially, the appearance of xanthomas often occurs early in the course of disease and prompt diagnosis and early treatment is crucial in preventing disease progression and development of severe neurological disease.

Sitosterolemia (along with autosomal recessive FH because of mutations in LDL receptor adaptor protein 1 [LDLRAP1] and ARH) should be considered as the underlying cause of xanthomas when hypercholesterolemia is present and in the absence of a family history of FH.

CTX should be considered as the underlying cause of xanthomas in the absence of marked hypercholesterolemia.
Table 1. Genetic disorders that can cause tuberous and tendon xanthomas.

**Disorder:** heterozygous familial hypercholesterolemia (FH), homozygous FH.

**Types of xanthoma:** Tuberous, tendinous and xanthelasma (additional types of xanthoma may be formed, particularly in homozygous FH).

**Genotype:** Defects in LDL receptor gene, in apoB-100 gene (specifically LDL receptor-binding domain), proprotein convertase subtilisin kexin type 9 (PCSK9) and LDL receptor adaptor protein 1 (LRAD1). The latter condition is transmitted as a recessive trait and in its homozygous form is known as autosomal recessive hypercholesterolemia (ARH). FH is the most common disorder with an estimated prevalence of 1 in 200-300 individuals affected; approximately 1% of families with premature coronary heart disease (CHD) have heterozygous FH.

**Phenotype:** The disorder is characterized by significant risk of coronary atherosclerosis and for homozygous FH development of CHD and aortic stenosis prior to age 20 years. Biochemically, plasma low-density lipoprotein cholesterol (LDL-C) is elevated (>190 mg/dL is suggestive of heterozygous FH and >450-500 mg/dL homozygous FH, although there may be considerable overlap between the LDL-C concentrations in heterozygous and homozygous FH). Familial defective apoB-100 and PCSK9 gain of function mutations cannot be clinically distinguished from classical FH, although the elevation in LDL-C is less severe.

**Treatment:** A diet low in cholesterol and saturated fat, statins, ezetimibe, anion exchange resins, and niacin. Two anti-PCSK9 monoclonal antibody therapies, alirocumab and evolocumab, are efficacious to lower LDL-C, with evolocumab approved by the U.S. Food and Drug Administration (FDA) for treatment of mild homozygous FH. Treatment for homozygous FH also can include high-dose statins, ezetimibe, niacin, bile acid sequestrants, mipomersen (an antisense therapeutic for apoB), lomitapide, evolocumab, and low-density lipoprotein (LDL) apheresis. Historically, ileal bypass and liver transplantation have also been used to treat this condition.

**Disorder:** type III hyperlipidemia (familial dysbeta lipoproteinemia).

**Types of xanthoma:** Tuberous xanthomas may be present, tubero eruptive xanthomas normally are observed, xanthomas striatum palmaris is a characteristic cutaneous feature (although their absence does not rule out this disorder).

**Genotype:** Apolipoprotein E2/2 (apoE2/2) occasionally apoE deficiency or hepatic lipase deficiency.

**Phenotype:** The disorder is defined by accumulation of chylomicron remnants and very low-density-lipoprotein (VLDL) remnants, premature CHD, other vascular disease, gout, and diabetes. Biochemically, elevated plasma total cholesterol and triglycerides are observed (both in the range 250-500 mg/dL), non-high-density lipoprotein cholesterol (non-HDL-C) (total cholesterol-HDL cholesterol) is elevated (>200 mg/dL), LDL-C is decreased and HDL-C is normal (with apoE deficiency, HDL cholesterol may be elevated). E2/E2 homozygosity only causes type III hyperlipidemia when overproduction of VLDL also is present (e.g. hypothyroid, diabetes, alcohol excess, hormonal changes). The abnormal genotype is necessary, but not sufficient to cause this condition.

**Treatment:** Regular exercise and weight loss (if overweight), a diet low in cholesterol, saturated fat and sugar, as well as treatment with fibric acid derivatives, statins, niacin, and fish oil. Treatment of the underlying “second hit” or cause of VLDL overproduction is necessary to correct the lipid disorder. Treatment often leads to regression of xanthomas.

**Disorder:** sitosterolemia (phytosterolemia).

**Types of xanthoma:** Tuberous and tendinous.

**Genotype:** Defects in ATP binding cassette sub-family G members 5 (ABCG5) and 8 (ABCG8) transporter genes.

**Phenotype:** The disorder is characterized by premature CHD and normal hematologic findings may be present (hemolytic anemia, abnormally shaped erythrocytes and large platelets). Biochemically, LDL-C may be normal to elevated with plant sterols, such as -sitosterol and campesterol, markedly elevated (for typical plasma sitosterol concentrations see Table 2). Phytosterols and free cholesterol are absorbed by the Niemann-Pick C1-Like 1 protein expressed on enterocytes. Phytosterols are then normally excreted back into the intestinal lumen by the ABCG5/8 transporter. Sitosterolemia occurs when this transporter is defective leading to pathologic absorption of high levels of phytosterols.

**Treatment:** A diet low in shellfish sterols, plant sterols (avoidance of vegetable oils, margarine, nuts, seeds, avocados, chocolate, and shellfish) and cholesterol, along with ezetimibe treatment can lower plant sterols by 10 to 50% and stabilize xanthomas. Bile acid sequestrants such as cholestyramine may be useful.

**Disorder:** cerebrotendinous xanthomatosis (CTX).

**Types of xanthoma:** Tendinous.

**Genotype:** Defects in CYP27A1 gene that encodes sterol 27-hydroxylase enzyme.

**Phenotype:** The disorder is characterized by recurrent diarrhea in infancy and childhood, juvenile cataracts, xanthomas, and development of neurological disease (cerebellar ataxia, cognitive decline, and dementia). Biochemically, plasma cholesterol is only modestly elevated (for typical plasma concentrations see Table 2). Synthesis of chenodeoxycholic acid is blocked in this disorder, leading to pathological induction of the bile acid pathway and production of excessive cholesterol.

**Treatment:** In adults, 250 mg TID/day oral chenodeoxycholic acid (weight-based dosing is used in children) to normalize bile acid synthesis and cholesterol production. Statin treatment may be useful. It can take up to six months for cholestanol to return to normal levels. Treatment normally stabilizes xanthomas.
and when persistent diarrhea, juvenile cataracts, and cognitive impairment may be present.

Biochemical diagnosis of sitosterolemia and CTX cannot be accomplished using standard laboratory methods of cholesterol measurement. Specialized analyses of cholestanol and plant sterols are required, typically using gas chromatography mass spectrometry (GC-MS). In sitosterolemia concentrations of the plant sterol sitosterol can be as high as 10-65 mg/dL. Typical plant sterol concentrations in healthy individuals are 100-fold lower than cholesterol (for sitosterol 0.21 ± 0.7 mg/dL; see also Table 2). A plasma sitosterol concentration > 1 mg/dL is considered diagnostic for sitosterolemia. Identification of pathogenic mutations in \(ABCG5\) and \(ABCG8\) by molecular genetic testing also can be useful to confirm sitosterolemia. In untreated CTX patients, concentrations of cholestanol can range from 0.84 mg/dL to 6.6 mg/dL. The range of the mean cholestanol concentration in healthy individuals is around 0.13 mg/dL. (See Table 2) A plasma cholestanol concentration > 1 mg/dL is considered diagnostic for CTX. Because cholestanol can be elevated in liver disease and concentrations of up to 0.7 and 1.1 mg/dL have been reported in healthy individuals, a diagnostic threshold of 1 mg/dL helps avoid false positive results. Bile acid intermediates that accumulate in CTX also may be useful for biochemical diagnosis of this disorder. Identification of pathogenic mutations in \(CYP27A1\) by molecular genetic testing also can be useful in confirming CTX. The plasma concentration ranges for sitosterol and cholestanol in unaffected and affected individuals as historically determined by the Oregon Health and Science University (OHSU) Sterol Analysis Laboratory are provided in Table 2.

Sitosterolemia and CTX should not be overlooked when evaluating the cause of tuberous and tendon xanthomas, because correct diagnosis and appropriate treatment of these rare underlying genetic disorders are critical to ensure the best outcome for patients affected by these disorders.

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References are listed on page 35.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Total Cholesterol (mg/dL)</th>
<th>Cholestanol (mg/dL)</th>
<th>Sitosterol (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unaffected individuals (n=180)</td>
<td>150 ± 51.7 [52.8-459]</td>
<td>0.237 ± 0.226 [0.065-0.794]</td>
<td>0.273 ± 0.203 [0.015-0.719]</td>
</tr>
<tr>
<td>CTX-affected untreated (n=6)</td>
<td>185 ± 26.2 [154-231]</td>
<td>2.29 ± 1.50 [0.839-5.52]</td>
<td>0.353 ± 0.154 [0.053-0.480]</td>
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<tr>
<td>CTX-affected treated longer than 6 months (n=40 samples from n=7 individuals)</td>
<td>162 ± 34.6 [95.2-242]</td>
<td>0.338 ± 0.186 [0.076-0.874]</td>
<td>0.267 ± 0.127 [0.067-0.589]</td>
</tr>
<tr>
<td>Sitosterolemia-affected+ (n=2 samples from one individual)</td>
<td>130, 185</td>
<td>0.781, 1.24</td>
<td>10.6, 9.33</td>
</tr>
</tbody>
</table>

Table 2: Concentrations of plasma total cholesterol, cholestanol and sitosterol in CTX and sitosterolemia measured by gas chromatography mass spectrometry (GC-MS)*.

The mean concentration ± S.D. and [range of results] are given.

+ Treatment status unknown.

Samples are analyzed for the same patients at least annually for therapeutic monitoring.

*Historical data from samples submitted for biochemical CTX and sitosterolemia diagnosis to the Sterol Analysis Laboratory, OHSU. This is one of only a few laboratories in the U.S. that performs biochemical testing for CTX and sitosterolemia. For questions regarding obtaining testing please email Dr. DeBarber at debarber@ohsu.edu.