Prevalence and Linkage of Cerebrotendinous Xanthomatosis and Phytosterolemia in the Boston Heart Diagnostics Database

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INTRODUCTION
Cerebrotendinous xanthomatosis (CTX) is a rare disorder of cholesterol and bile acid metabolism that is characterized by high plasma cholesterol levels (>10 mg/dL), progressive neurologic disease, and often tendinous xanthomas (FIGURE 1). It is caused by defects in the CYP27A1 gene which encodes mitochondrial sterol 27-hydroxylase, a key enzyme in bile acid synthesis from cholesterol.2,3 The result is excess cholesterol formation and the lack of formation of chenodeoxycholate.2 The disease can be effectively treated with oral chenodeoxycholate.4 Phytosterolemia is associated with high plasma β-sitosterol levels (>15 mg/dL), premature coronary heart disease, and often tendinous xanthomas. It is caused by defects in the ATP binding transporters G5 and G8.5

OBJECTIVE
The objectives were (1) to determine the prevalence of CTX and phytosterolemia in a large reference laboratory database of plasma sterol results and (2) to ascertain the degree of overlap between the two disorders.

METHODS

Study Design. Subjects having fasted plasma cholesterol concentrations > 10 mg/dL were identified from 325,543 analyses in the Boston Heart Diagnostics database (52% female; mean age, 58.5 years).

Plasma Sterols. Plasma sterols were assayed by gas chromatography/mass spectrometry after lipid extraction, in blood samples obtained following an overnight fast.7 Absolute levels of lathosterol and desmosterol (biomarkers of cholesterol production) and β-sitosterol, campesterol, and cholestanol (biomarkers of cholesterol absorption) were determined. The concentration of each sterol was also normalized to total cholesterol (TC).

Lipids and Apolipoproteins. Fasting serum TC, triglycerides (TG), LDL-C, small dense LDL cholesterol (sdLDL-C), high density lipoprotein cholesterol (HDL-C), lipoprotein (a) or Lp(a), apolipoprotein (apo) B, and apoA-I were measured by direct, automated standardized assays. Very low density lipoprotein cholesterol (VLDL-C) and non-high density lipoprotein cholesterol (non-HDL-C) were calculated from direct measurements of TC, LDL-C, and HDL-C.

Statistical Analysis. Data are presented as mean (SD) or median (Inter-Quartile Range), as indicated. Spearman correlations were used in the correlation analysis. Significant differences were assessed by two-sample t-tests. P <0.05 was considered significant.

RESULTS
As shown in TABLE 1, the prevalence of CTX and phytosterolemia may be greater than the number of known cases would indicate. Plasma lipid and sterol values indicate an overlap between the two disorders (TABLE 2). Relative to controls, all cases with elevated cholesterol had elevated levels of LDL-C, sdLDL-C, β-sitosterol, campesterol, and, by definition cholesterol (TABLES 3 and 4), all P <0.001. These significant differences persisted after controlling for TC levels. Correlation analysis (TABLE 5) suggests that CTX patients may not only be unable to produce chenodeoxycholate; they may also over-absorb plant sterols and cholesterol.

CONCLUSIONS
Our biochemical analyses indicate a higher prevalence of CTX and phytosterolemia than prior estimates and substantial under-diagnosis in the US population. In patients with LDL-C levels >190 mg/dL, we recommend checking apoE genotype, thyroid and liver function, and plasma sterols, especially in those with tendinous xanthomas and/or neurologic disease so that CTX and phytosterolemia can be identified early. Early diagnosis and treatment can halt the progression of disease.

REFERENCES

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TABLE 1. Plasma sterol and lipoprotein levels in cases with cholestanol > 10 mg/L compared with controls.

TABLE 2. Cases with cholesterol > 10 mg/L by β-sitosterol concentration.

TABLE 3. Plasma lipid and apolipoprotein levels in cases with cholesterol > 10 mg/L and β-sitosterol > 15 mg/L, compared with controls.

TABLE 4. Plasma sterol levels in cases with cholesterol > 10 mg/L and β-sitosterol > 15 mg/L, compared with controls.

TABLE 5. Correlations between plasma sterol levels in CTX cases.

FIGURE. Case presenting with tendinous xanthomas on the Achilles tendon. Therapy for >30 years over-absorbed plant sterols and cholesterol. Treatment with oral ezetimibe is effective.