Extreme xanthomatosis in patients with both familial hypercholesterolemia and cerebrotendinous xanthomatosis


Two unrelated individuals were referred to Lipid Clinics in The Netherlands and Chile with extreme xanthomatosis and hypercholesterolemia. Both were diagnosed with heterozygous familial hypercholesterolemia (heFH) after molecular genetic analysis of the low-density lipoprotein (LDL) receptor gene. Since heFH by itself could not account for the massive xanthomas, the presence of an additional hereditary lipid or lipoprotein disorder was suspected. Further genetic analysis revealed homozygozity for mutations in the sterol 27-hydroxylase gene, confirming the diagnosis of cerebrotendinous xanthomatosis (CTX). Markedly, the typical neurological manifestations of CTX were absent, suggestive of a protective role of LDL-receptor deficiency against the severe neurological consequences of CTX.

Conflict of interest
None reported for this article.

Case 1
A 27-year-old Dutch male was referred with tendon xanthomas and hypercholesterolemia to the outpatient Lipid Clinic of the Academic Medical Center, Amsterdam, The Netherlands. The patient had experienced neither cardiovascular nor neurological complaints. He had successfully completed his university education. His mother had been diagnosed with severe hypercholesterolemia and his uncle from mother’s side had died from an acute myocardial infarction at the age of 35.

On physical examination, extreme xanthomatosis was noted on the extensor tendons of both elbows (circumference 24 cm), several digits of the hands (largest circumference of the fourth digit 17 cm),
Extreme xanthomatosis in patients with FH and CTX

**Case 1**

A 40-year-old female patient presented at the Lipid Unit of Clinica Las Condes, Santiago, Chile, with extreme, progressive xanthomatosis. Personal history showed neither cardiovascular nor neurological abnormalities. Family history revealed hypercholesterolemia as well as premature cardiovascular disease. Extreme xanthomas of the extensor tendons of hands, elbows, knees and Achilles tendons were observed during physical examination (Fig. 1). Plasma levels of total and LDL cholesterol were increased (Table 1). DNA analysis revealed mutations in the sterol 27-hydroxylase gene (CYP27A1; Table 1), resulting in the diagnoses of heFH and CTX (4, 6) and in a B-mode ultrasound of intima-media thickness of the carotid arteries (cIMT) MRI-scan of the brain showed no abnormalities. Carotid atherosclerosis as assessed by cIMT was more pronounced in the patient compared to 29 age-matched males with heFH: mean cIMT of the three segments on both sides was 0.94 vs 0.64 ± 0.12 mm; p = 0.018 (5). Upon CTX diagnosis, 250 mg chenodeoxycholic acid td was added to 20 mg atorvastatin od therapy. However, after 11 months of this combination therapy the patient discontinued the use of all medications because he held the treatment responsible for complaints of recurrent infections. At his last medical evaluation at the age of 33, he had not experienced neurological or cardiovascular problems, but the width of his Achilles tendons, i.e. 55 mm on the left and 71 mm on the right side, had not decreased compared to that at original presentation. He had not restarted treatment at that time.

**Case 2**

A 22-year-old Chilean male was presented at the Lipid Unit of Clinica Las Condes, Santiago, Chile, with extreme, progressive xanthomatosis. Personal history showed neither cardiovascular nor neurological abnormalities. Family history revealed hypercholesterolemia as well as premature cardiovascular disease. Extreme xanthomas of the extensor tendons of hands, elbows, knees and Achilles tendons were observed during physical examination (Fig. 2). Plasma levels of total and LDL cholesterol were increased (Table 1). DNA analysis showed mutations in the sterol 27-hydroxylase gene (CYP27A1; Table 1), resulting in the diagnoses of heFH and CTX (4, 6) and in a B-mode ultrasound of intima-media thickness of the carotid arteries (cIMT) MRI-scan of the brain showed no abnormalities. Carotid atherosclerosis as assessed by cIMT was more pronounced in the patient compared to 29 age-matched males with heFH: mean cIMT of the three segments on both sides was 0.94 vs 0.64 ± 0.12 mm; p = 0.018 (5). Upon CTX diagnosis, 250 mg chenodeoxycholic acid td was added to 20 mg atorvastatin od therapy. However, after 11 months of this combination therapy the patient discontinued the use of all medications because he held the treatment responsible for complaints of recurrent infections. At his last medical evaluation at the age of 33, he had not experienced neurological or cardiovascular problems, but the width of his Achilles tendons, i.e. 55 mm on the left and 71 mm on the right side, had not decreased compared to that at original presentation. He had not restarted treatment at that time.

**Table 1.** Genetic defects and sterols and stanols before and after treatment

<table>
<thead>
<tr>
<th>Molecular defects</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDLR mutation</td>
<td>Duplication</td>
<td>p.Cys95Gly</td>
</tr>
<tr>
<td>Sterols and stanols</td>
<td>Untreated</td>
<td>Untreated</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>376</td>
<td>270</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>299</td>
<td>184</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>50</td>
<td>47</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>139</td>
<td>189</td>
</tr>
<tr>
<td>Cholestanol (μg/dl)</td>
<td>1205</td>
<td>4091</td>
</tr>
<tr>
<td>7-lathosterol (μmol/l)</td>
<td>30.3</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

HDL, high-density lipoprotein; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor.

Stable treatment with 250 mg chenodeoxycholic acid td and 40 mg simvastatin od.

Reference range for cholestanol in laboratory of Academic Medical Center: 129–488 μg/dl.

Reference range for 7-lathosterol in laboratory of Academic Medical Center: 0–15.0 μmol/l.

Not measured in the untreated plasma sample.
a treatment regimen, which consisted of 40 mg simvastatin od and 250 mg chenodeoxycholic acid td after
the diagnoses. This resulted in normalization of cholesterol and cholestanol levels (Table 1). After 3 years of
treatment, the patient underwent surgical removal of xanthomas on the hands and under treatment his tendon
size did not further increase. He had not experienced neurological or cardiovascular problems at his last med-
cal evaluation, at the age of 25.

Familial hypercholesterolemia

FH (OMIM 143890) is an autosomal dominant disorder of lipoprotein metabolism, characterized by elevated
levels of plasma LDL cholesterol and in approximately 20% of the patients by the presence of tendon xan-
thomas (2, 7). Premature atherosclerosis is a hallmark in untreated patients FH (2). The genetic basis of FH
comprises more than 1000 point mutations and/or large gene rearrangements in LDLR (OMIM 606945) (8).
The LDLR mutations identified in the two cases have been described as pathogenic mutations before (1, 6, 8).
The duplication of exon 7 is a pathogenic mutation that prevents the synthesis of LDLR protein (9).
The p.Cys95Gly mutation is a receptor defective mutation (6). The prevalence of heFH is about 1 in 500
individuals in most Western countries and the diagno-
sis is usually made on the basis of clinical signs (2).
Stringent use of statins in FH patients has resulted in a profound reduction in cardiovascular event rate (10).

Cerebrotendinous xanthomatosis

CTX (OMIM 21700) is a rare autosomal recessively
inherited inborn error of metabolism (4). Prevalence is
estimated at 1:50,000 individuals (4, 11). A dysfunc-
tional sterol 27-hydroxylase leads to impaired oxidation
of the cholesterol side chain, reduced synthesis of cholic
acid and markedly diminished chenodeoxycholic acid
formation. As a result, intermediates such as cholestanol
and 27-carbon bile alcohols accumulate leading to the
deposition of these products in body tissues. These
depositions give rise to clinical symptoms such as
tendon xanthomas, cataract, diarrhea, atherosclerosis
and neurological dysfunction (4, 12–14). Neurological
symptoms are considered to be a hallmark in CTX (14).
Whereas neurological dysfunction is present in more
than 95% of cases (15), the severity of symptoms varies
widely, ranging from low intelligence to ataxia, demen-
tia, cerebellar and pyramidal signs, multiple sclerosis
and epilepsy (14). Mutations in the gene for sterol
27-hydroxylase (CYP27A1) underlie CTX. To date,
more than 50 mutations in the CYP27A1 gene have
been reported (11, 13, 14). In our cases, the muta-
tions p.Leu142Pro, p.Arg395Cys and p.Arg405Trp were
found in the CYP27A1 gene, of which the latter two
mutations have been characterized as pathogenic (13).
The amino acid leucine on position 142 is a highly con-
served region and in silico analyses for the p.Leu142Pro
mutation suggest that this mutation is pathogenic:
according to SIFT it is deleterious and according to POLYPHEN it is probably damaging. In addition, the
functional relevance of the p.Leu142Pro mutation is
highlighted by the markedly increased cholestanol and
bile alcohols, combined with characteristic clinical
symptoms.

Oral supplementation with chenodeoxycholic acid
has been shown to be effective in CTX (16). It has
been reported to correct biochemical abnormalities
and possibly reverse neurological manifestations of
CTX (16, 17). Some studies have also reported a
reduction in xanthoma size following chenodeoxycholic
acid (17). Combination of chenodeoxycholic acid with
statins has also been studied in CTX. This regimen was
reported to correct both plasma cholestanol and LDL
cholesterol levels and significantly reduce xanthoma
size in one study (18), although xanthoma regression
was not statistically significant in another (19).

Discussion

This is the first report of patients with heFH in combina-
tion with CTX. Since LDLR and CYP227A1 are located
on different chromosomes, inheritance is independent
with an estimated incidence of the combined disorders
of 1:25 million individuals (approximately 275 persons
worldwide). Both cases share several striking features.
On one hand, the combination of heFH and CTX results
in a progression of xanthomatosis and atherosclerosis that appears to be more severe compared to subjects affected with only one of these conditions. On the other hand, the characteristic neurological manifestations of CTX are hitherto absent. The absence of neurological symptoms suggests a protective effect exerted by the condition of heFH. Several scenarios can be envisioned: the production of cholestanol may be diminished due to a decreased uptake of cholesterol esters by the LDL receptor in hepatocytes and LDL-receptor activity may directly influence lipid and sterol transport over the blood–brain barrier.

Regarding the first option, the absence of negative feedback of chenodeoxycholic acid on 7α-hydroxylase in CTX leads to an increased flux of cholesterol through the 27α-hydroxylase pathway in hepatocytes. As a consequence, cholestanol and other metabolites accumulate in many tissues (14, 20). The LDLR will be up regulated in CTX, because hepatic cholesterol is the substrate for the bile acid synthesis and this pool is depleted in CTX (2, 21). We postulate that impaired LDL-receptor activity due to a mutation in LDLR may be associated with a reduced cholesterol pool in hepatocytes, which leads to decreased production of cholestanol in subjects with both FH and CTX. In support, the more pathogenic LDLR defect in case 1 was associated with higher LDL cholesterol and lower cholestanol levels compared to case 2. In line, cholesterol synthesis, reflected by lathosterol level, was much higher in case 1 compared to untreated individuals with heterozygous FH (22), implying a maximally stimulated hepatic cholesterol synthesis. In this scenario, de novo synthesis of cholesterol is the rate-limiting step for cholestanol production.

Regarding the second option, increased levels of cholestanol as well as apolipoprotein B have been documented in the cerebrospinal fluid of CTX patients (20). Since neither of these substances is synthesized in the brain, their presence suggests that the blood–brain barrier is not functioning properly in CTX (20). In our patients with both heFH and CTX, the marked discrepancy between peripheral accumulation (extreme xanthomatosis, increased carotid atherosclerosis), without any evidence for central accumulation could imply that the transport of cholestanol and cholesterol across the blood–brain barrier is reduced compared to patients with isolated CTX. Further research on the mechanism of transport of apolipoprotein B and cholestanol over the blood–brain barrier in CTX is warranted.

However, it cannot be ruled out that it is just a coincidence that both cases have not developed neurological manifestations of CTX yet or that defects could have been detected if both cases would have been examined on neurological functions more thoroughly.

In conclusion, the patients presented here have a rare combination of heFH and CTX, which manifests itself with extreme xanthomatosis and possibly more accelerated atherogenesis than in patients with heFH alone. The lack of neurological symptoms – a hallmark in CTX patients – implies a role for LDL-receptor activity in modulating the cholestanol levels and/or its accumulation in the central nervous system.

Acknowledgements

The authors thank both cases for their collaboration to publish about their impressive features.

References

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