Presence of Diarrhea and Absence of Tendon Xanthomas in Patients With Cerebrotendinous Xanthomatosis

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Background: Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive disorder of bile acid synthesis. A diagnosis of CTX should be considered in patients with premature bilateral cataracts, intractable diarrhea, neurological signs and symptoms, and tendon xanthomas, especially in the Achilles tendons. The prevalence of these signs and symptoms increases with age.

Objectives: To investigate signs and symptoms, age at onset, and age at diagnosis in 32 patients with biochemically and genetically confirmed CTX, and to compare this clinical spectrum with reports in the literature.

Methods: Retrospective analysis of records of all patients with CTX at our hospital (27 adults and 5 children). After a MEDLINE search in the English, French, and German literature, 181 patients with CTX (165 adults and 16 children) were identified worldwide.

Results: Of our 32 patients with CTX, 31 (97%) had cataracts and neurological signs and symptoms, predominantly pyramidal signs (26 [81%]); 21 (66%) had low intelligence and 18 (56%) had cerebellar signs. Only 13 (41%) had visible or palpable tendon xanthomas at the time of diagnosis. In total, 16 patients (50%) had chronic, intractable diarrhea that started in childhood. These findings were in contrast with the literature, where tendon xanthomas were reported in 89% and diarrhea in only 2 patients.

Conclusions: We believe that CTX is underdiagnosed worldwide. We recommend that the presence of 2 of the 4 clinical hallmarks of CTX prompt thorough metabolic screening, including determination of urine bile alcohol excretion and serum cholestanol level, because CTX is a treatable disease.

Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive disorder of bile acid synthesis first described by Van Bogaert et al in 1937.1 A deficiency of the mitochondrial enzyme sterol 27-hydroxylase results in a virtual absence of chenodeoxycholic acid. This leads to excessive production of cholestanol and cholesterol and accumulation of these sterols in several tissues, particularly the central nervous system. A diagnosis of CTX should be considered in patients with premature bilateral cataracts, intractable diarrhea, neurological signs and symptoms, and tendon xanthomas, especially in the Achilles tendons. Determination of cholestanol level in serum and of levels of bile alcohols in urine can confirm the clinical suspicion. At our laboratory, we have been performing these tests since 1990 on patients with 2 of the 4 above-mentioned clinical hallmarks.

The neurological signs and symptoms consist of progressive cerebellar and pyramidal signs, mental retardation, and seizures. However, it is also possible for CTX to be a slowly progressive, mainly spinal cord syndrome that remains the sole expression of the disorder for many years.2 Tendon xanthomas are seldom seen in patients with CTX younger than 20 years, so if young patients are seen with persistent diarrhea and bilateral cataracts, the diagnosis of CTX should be considered.3,4 Therapy with chenodiol (chenodeoxycholic acid) leads to a considerable decrease in the serum cholestanol level and a sharp decline in the excretion of bile alcohols in the urine.5,7

We describe the clinical signs and symptoms of 32 Dutch patients with CTX from 17 families, which is the largest series reported, to our knowledge. We estimated the delay in diagnosis in the adult patients and compared the clinical spectrum with that reported in the literature.
PATIENTS AND METHODS

PATIENTS

Between September 1, 1983, and August 31, 1998, 27 adults and 5 children with CTX were seen at our hospital. Biochemical screening was performed on patients with at least 2 of the clinical CTX hallmarks (premature bilateral cataracts, intractable diarrhea, neurological signs and symptoms, and tendon xanthomas). A biochemical diagnosis of CTX was made by the detection of bile alcohols in urine, followed by the determination of the serum cholesterol level, and finally by genetic analysis. Clinical characteristics of the patients with and without tendon xanthomas at the time of diagnosis are summarized in Table 1. The prevalence of the general and neurological signs and symptoms present at the time of diagnosis are presented in Figure 1 and Figure 2, according to age group.

GENETIC ANALYSIS

The sterol 27-hydroxylase or CYP27 gene was amplified in 4 fragments (exon 1, exon 2, exons 3-5, and exons 6-9) by the polymerase chain reaction from genomic DNA of leukocytes. Exons 3 through 9 with their intron boundaries were subsequently amplified separately, with the 2 polymerase chain reaction fragments 3 through 5 and 6 through 9 as a template. The oligonucleotides used as primers for polymerase chain reaction amplification and for sequence analysis are those described by Leitersdorf et al. Human genomic DNA from the patients have been screened for mutations in the CYP27 gene by single-strand conformation polymorphism analysis by a polyacrylamide gel electrophoresis instrument (Pharmacia Phast System; Amersham Pharmacia Biotech AB, Uppsala, Sweden), or were subjected to DNA sequencing. Cycle sequencing of the coding and the noncoding strands of all amplimers was carried out by a DNA cycle sequencing kit (TaQ Dye Deoxy Terminator; PE-Biosystems, Foster City, Calif) with the use of a DNA sequencer (ABI 377; PE-Biosystems).

LITERATURE

After a MEDLINE search in the English, French, and German literature, a total of 181 patients were identified: 165 adults and 16 children. The literature was carefully screened for presence and absence of signs and symptoms, taking into account the fact that some literature reports are noninformative for specific signs and symptoms. Publications that included the same patients were skipped to avoid double counting.

STATISTICAL ANALYSIS

Differences in the age at onset, age at diagnosis, and delay in diagnosis between adult patients with and without tendon xanthomas were analyzed with the t test.

RESULTS

CLINICAL FEATURES

Between 1983 and 1998, 32 patients with CTX were diagnosed at our hospital. At the time of diagnosis, 31 (97%) had cataracts and neurological signs and symptoms, predominantly pyramidal signs (26 patients [81%]), low intelligence (21 patients [66%]), cerebellar signs (18 patients [56%]), and polyneuropathy (10 patients [31%]); only 13 (41%) of them had visible or palpable tendon xanthomas (Table 1). In total, 16 patients (50%) had chronic, intractable diarrhea, which had started in childhood. With increasing age, cataracts and neurological signs (especially pyramidal signs) were the most prevalent clinical features (Figures 1 and 2).

The clinical and genetic characteristics of the patients with CTX are summarized in Table 2. In 1 family, no genetic data were available; in all other patients, mutations were found in both alleles. The patients from 6 families were homozygous; in the others, compound heterozygous alleles were found.

The clinical features at the time of diagnosis in the patients described in the literature are summarized in Table 1. In these patients, clinical characteristics differed from those of the 32 patients in the current study.
Apart from tendon xanthomas, consanguinity was more often reported. Less frequently mentioned in the literature were cataracts and diarrhea.

**DELAY AND INITIAL DIAGNOSES**

Age at diagnosis of our 32 patients varied from 7 to 55 years (mean, 35 years). The interval between the first signs and the time of CTX diagnosis varied from 1 to 50 years (mean, 17 years). In the group of 13 patients with tendon xanthomas, the age at diagnosis varied from 33 to 51 years (mean, 40 years). The delay in diagnosis in this subgroup varied from 1 to 29 years (mean, 17 years), compared with 1 to 50 years (mean, 19 years) in the 19 patients without tendon xanthomas. All but 1 of the 32 patients (97%) had bilateral

### Table 2. Clinical and Genetic Characteristics of 32 Patients With Cerebrotendinous Xanthomatosis

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*CAT indicates premature bilateral cataracts; TX, tendon xanthomas; D, diarrhea; LI, low intelligence; PYR, pyramidal signs; CER, cerebellar signs; EPI, epilepsy; PN, polyneuropathy; PARK, parkinsonism; cDNA, complementary DNA; aa, amino acid; and ptc, premature termination codon.

†Nucleotide numbering: the G of the first GCA is number 1.

‡Amino acid numbering: the first methionine of the translated frame is number −33; alanine (number 1) is the first amino acid.

§Not applicable.
cataracts and neurological signs, while 16 of them (50%) had chronic diarrhea.

In our adult CTX group, 14 patients did not have tendon xanthomas. There were no significant differences in age at onset (P = .12), age at diagnosis (P = .33), and delay in diagnosis (P = .34) between the adult patients with CTX without (n = 14) and those with (n = 13) tendon xanthomas. In the patients without tendon xanthomas, various progressive neurological disorders were diagnosed initially, such as probable multiple sclerosis without laboratory support (n = 2), hereditary spastic paraparesis (n = 2), olivopontocerebellar atrophy (n = 2), spinocerebellar degeneration (n = 2), and Sjogren syndrome (n = 1).

In this large series of 32 patients with CTX from 1 hospital, we identified 19 patients (59%) without tendon xanthomas and 16 patients (50%) with chronic diarrhea at the time of diagnosis. In this patient group, tendon xanthomas were detected at the age of 31 years or older. In all the patients, there was a considerable delay in diagnosis (from 1 to 50 years), but this delay was not significantly different between the group of patients with and those without tendon xanthomas. In all of our patients, the primary key to the diagnosis was the combination of premature bilateral cataracts with neurological signs. Predominant neurological signs were a pyramidal syndrome, low intelligence, and cerebellar signs (Figure 2). This combination prompted us to determine serum cholesterol levels and bile alcohol excretion in urine. In all but 1 patient, pathogenic mutations were found in both alleles of the CYP27 gene, confirming the diagnosis of CTX genetically.

Our findings demonstrate that the presence of tendon xanthomas is not obligatory for the diagnosis of CTX and that diarrhea, in adults as well as children, is a key symptom in the diagnosis. The presence of chronic diarrhea in almost half of our adult patients with CTX is remarkable, because in the literature on adult patients with CTX, it was reported only incidentally (Table 1). Many of these patients had undergone repeated gastrointestinal tract investigations, but no underlying gastrointestinal tract disorder was found. In our patients, diarrhea disappeared within a few days after chenodiol therapy was started. The pathogenesis of this symptom is still unknown. The presence of excessive amounts of bile alcohols in the gut may increase intestinal motility, influence fluid and electrolyte transport by the intestinal epithelium, or influence intestinal bacterial equilibrium.

There were several differences between our patient group and those reported in the literature. Bilateral cataracts were present in 97% of our patients, in contrast to 85% of the patients in the literature (Table 1). Consanguinity was found in 3% of our families compared with 53% in the literature. This may relate in part to reporting and recognition biases, as well as to different sociocultural climates and gene frequencies, in the Netherlands compared with other parts of the world. The differences in the presence of xanthomas, cataracts, and diarrhea between our patients and those reported in the literature may have been caused by our particular interest in the combination of neurological signs with cataracts and diarrhea, resulting in screening for CTX. As only a minority of our adult patients with CTX had tendon xanthomas at the time of diagnosis, we conclude that there are probably more undiagnosed patients with CTX without tendon xanthomas. Instead, they may have been diagnosed as having multiple sclerosis without laboratory support, hereditary spastic paraparesis, Sjogren syndrome, low intelligence, and cerebellar signs (Figure 2). This combination prompted us to determine serum cholesterol levels and bile alcohol excretion in urine. In all but 1 patient, pathogenic mutations were found in both alleles of the CYP27 gene, confirming the diagnosis of CTX genetically.

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We recommend that the presence of 2 of the 4 clinical hallmarks of CTX (premature cataracts, intractable diarrhea, progressive neurological signs and symptoms, and tendon xanthomas) should prompt thorough metabolic screening for CTX. The biochemical diagnosis can be established easily and reliably. Because affected relatives may be asymptomatic and an effective treatment is available, we advocate biochemical examination of all siblings of a patient with CTX.

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