Cerebrotendinous xanthomatosis in a Saudi Arabian family-genotyping and long-term follow-up

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ABSTRACT

A Saudi Arabian family is described in which there were 2 siblings with typical features of cerebral xanthomatosis (CTX) including premature cataracts, xanthomata of the Achilles tendons, neuro-psychiatric disturbances, and atherosclerosis. The 2 patients were homozygous for a point mutation in the mitochondrial 27-hydroxylase gene (CYP27A1, OMIM 606530) located in the splice site of intron 6, where G was exchanged for A (IVS6+1G>A). Their parents were cousins, 5 siblings were healthy, 2 were heterozygous for the mutation, and one showed the wild-type genotype. The father was heterozygous for the mutation, while the other family members were not tested. The progress of the 2 CTX patients over 14 years is described; firstly when they were receiving treatment with chenodeoxycholic acid; when this medication was not available, and later when it was restored. A hereditary hyperlipidemia was also present in this family. It is suggested that when this occurs with CTX, a more serious illness results that merits more aggressive dual therapy.

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The objective of this article is to call attention to cerebrotendinous xanthomatosis (CTX). It is important to recognize this disease because it can be successfully treated. This disorder is due to a disturbance of sterol metabolism with a classical picture of neuropsychiatric symptoms and signs, bilateral premature cataracts, osteoporosis, tendon xanthomata, and atherosclerosis. It was first described in 1937,[1] and is a Mendelian autosomal recessive disorder.[2] Cholestanol concentrations are increased in the central nervous system,[3] and also in most other tissues, as well as in the plasma. The content of chenodeoxycholic acid is markedly reduced in the bile, while incomplete oxidation of the C27 in the cholesterol side-chain causes enhanced excretion of large amounts of C27 bile alcohols.[4,5] A liver biopsy from a CTX patient showed an almost complete lack of mitochondrial 27-hydroxylase (CYP27).[6] When the structure of the gene was determined, mutations were identified as the cause of the disease in CTX patients.[7-9] Replacement therapy with chenodeoxycholic acid (CDCA) has an inhibiting effect on cholesterol and cholestanol synthesis in these patients, producing an improvement in the clinical condition.[10] We describe the genetic mutation in, and clinical features of, CTX in a Saudi Arabian family.

Case Report. *Patients.* The proposita was an unmarried female born in 1969. Her parents were first cousins. She was referred to DAPE at the Riyadh Military Hospital on 17 September 1991 by a consultant orthopedic surgeon to whom she had been sent because of swellings in her Achilles tendons, which were increasing in size, and were sometimes painful. On the consultation slip was written: "Has had premature cataracts and now has swellings in the Achilles tendons. Is this a syndrome?" The patient had unexplained persistent chronic diarrhea during childhood, but had otherwise been well until the age of 10 years. Then she started to be aggressive in school, fighting with other girls, and her behavior at home changed. She became mentally slow and had to stop attending school. At this time she developed cataracts, which were surgically removed when she was 15 years of age. Her behavior was very abnormal, especially in the evenings. She would stay awake most of the

night walking from one room to another. During the day, she would become aggressive, and she was liable to hit anyone that annoyed her. The physical examination revealed a mentally dull young woman wearing spectacles, weighing 38 kg with large sausage–shaped swellings in both Achilles tendons. Examination of her respiratory, cardiovascular, abdominal, and nervous systems were normal. There was no abnormality in the mouth, spine, loins, joints or lymph glands. Her blood pressure was 130/90 mm Hg.

This patient had 7 siblings, ranging in age from 4 to 30 years old at the time of the initial consultation, as shown in **Figure 1**. Six of her siblings were considered to be healthy. Her oldest sibling was a brother aged 30 years (IV.1) whose school performance deteriorated after the sixth grade. Bilateral cataracts were removed at 18 years of age. He had a simple job feeding numerical data into a computer, but this job was in danger because of his odd behavior. However he was not aggressive. He was ataxic, particularly when arising from the sitting position, and he also had sausage shaped swellings of his Achilles tendons.

Biochemical analyses. A surgical biopsy was taken under local anesthesia from the left Achilles tendon of the proposita, and stored frozen. Serum and tendon cholestanol analyses were performed by standard methods at St. Thomas Hospital Medical School, London, United Kingdom. The urinary 7-hydroxylated bile acids analyses were performed at the Central Laboratory for Clinical Biochemistry, University Hospital, Groningen, Netherlands (via Bioscientia, Germany).

Genomic DNA analysis. Standard reagents, isotopes, and oligonucleotides were obtained as described.[11] Reagents for polymerase chain reaction (PCR) were purchased from Perkin-Elmer Corp, Foster City, California, United States of America. Restriction endonucleases were obtained from Boehringer Mannheim, Mannheim, Germany. Genomic DNA was prepared from peripheral white blood cells utilizing Quiagen Blood and Cell Culture DNA Midi Kit (Quiagen GMbH, Hilden, Germany). In exons 2 through 9, the reversed primer in each oligonucleotide pair was biotinylated. Sequence analysis of the amplified fragments was carried out manually by established procedures on single strands, using dideoxy sequencing method (Sequenase version 2.0 Sequencing Kit; Amersham Life Science, Buckinghamshire, United Kingdom). To obtain single strands from the PCR fragments, streptavidin-coated magnetic particles (M20 Streptavidin Dynabeads, Dynal A.S, Oslo, Norway) were used according to the manufacturer's instructions.

Neuroradiology. The male patient (**Figure 1** [IV.1]) had an MRI of brain with T1, and T2 weighted images plus an axial FLAIR sequence using a Magneton Symphony 1.5 Tesla instrument with a superconductive magnet. It was not possible to obtain an MRI on the proposita.

Gene sequencing in the propositi. Sequence analysis of exons 2 through 9 in the proposita (**Figure 1** [IV.4]) showed a point mutation in the splice donor site of intron 6, where the first base G was replaced by A (**Figure 2**). In the other exons or adjacent intron

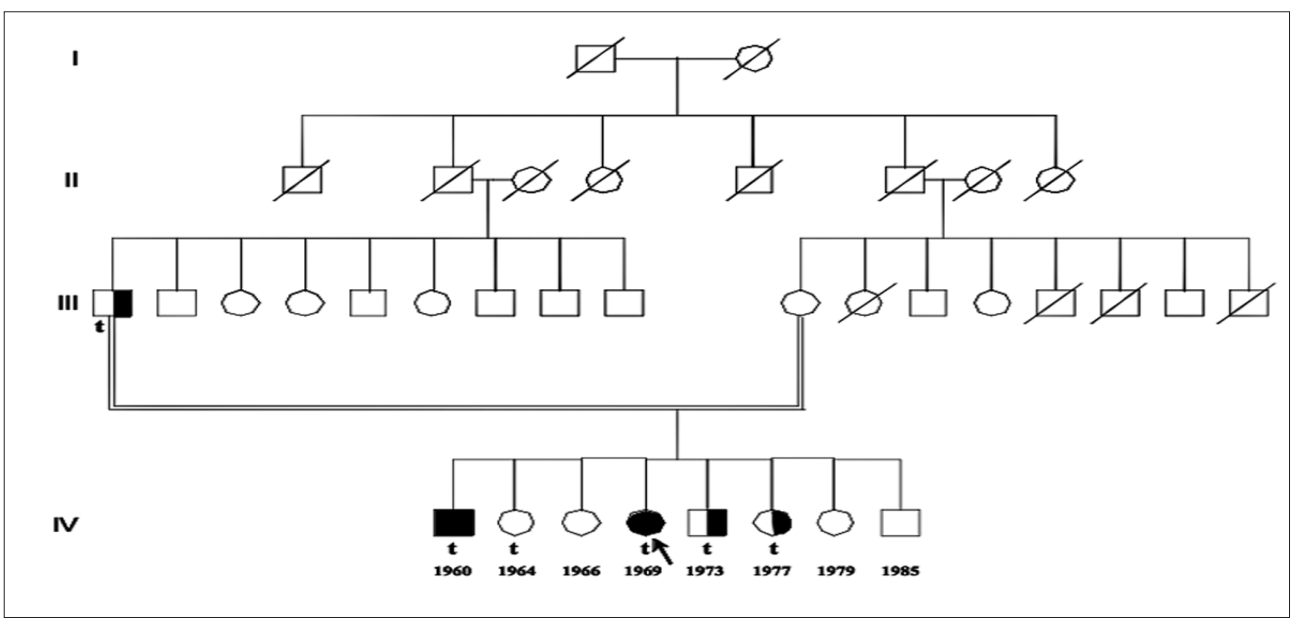

Figure 1 - A Saudi Arabian family showing 2 patients with cerebrotendinous xanthomatosis and 3 heterozygotes. The numbers beneath the individuals in generation IV are their years of birth. The proposita is indicated by the arrow. Note: t=tested.

regions, no other mutations were found that would affect the amino acid sequence or the splicing process. One polymorphism was detected in exon 6, where the A in the codon for the residue Gly in position 122 was exchanged for a C.

Genetic investigation of the family members. Genomic DNA could be obtained from 4 of the patient's siblings (**Figure 1**, [IV.1, IV.2, IV.5, IV.6]) and from the father (**Figure 1**, [III.1]). Blood could not be obtained from the mother (**Figure 1**, [III.10]) because she lived 958 km from the laboratory where the blood samples were collected, and she was reticent. For rapid identification of the mutation the amplified fragment 6a-9a (991bp) was subjected to digestion by the restriction enzyme AciI which would cleave the wild type in position 210, generating 2 fragments of 210 and 530 bp, but would not cleave the mutated DNA, where a fragment of 740 bp was obtained. In addition, 2 other fragments of 137 and 114 bp were obtained in all samples, independent of whether the individual had the present mutation or not. Both homozygotes and heterozygotes could easily be identified by analyzing the digestion pattern on an agarose gel. In this way, individuals IV.5 and IV.6 in **Figure 1**, and the father (**Figure 1**, [III.1]) were found to be heterozygous for the mutation, while individual IV.1 in **Figure 1** was homozygous, and individual IV.2 in **Figure 1** showed the wild type. These results were verified by sequence analysis.

Analyses for sterols and bile acids. The serum cholestanol levels, and the urinary 23,25 pentol, 24,25 pentol were substantially raised above normal in both CTX patients. There was a slight elevation of serum campesterol concentration at 1.12 mg/DL (reference range 0.2-0.8 mg/DL) in the proposita only, and there was a slight elevation of the urinary 27-nor,25 pentol in both patients. These values are typical for cerebrotendinous xanthomatosis. A biopsy from the Achilles tendon of the proposita showed a cholestanol concentration of 63.9 mg per g wet weight of tissue.

Neuroradiology. The MRI of the brain obtained on the male patient (**Figure 1**, [IV.1]) when he was 44 years old showed areas of abnormal hyperintensity in the dentate nuclei, and there was axonal loss with dilatation of the fourth ventricle (**Figure 3**). These appearances were most clearly visible in the T2 weighted images, which was the experience of some previous workers,[12] but not of others,[13] who found the abnormal hyperintensity of the dentate nucleus in all of their 12 CTX patients only by using a FLAIR sequence. An MRA carried out at the same time showed attenuated distal portions of the middle cerebral arteries, especially on the left side.

Clinical response of the 2 patients to treatment. The proposita was given an oral dose of 250 mg chenodeoxycholic acid (CDCA) 3 times daily. After 5 months of treatment her behavior was markedly improved, for example, she was much less aggressive, and after 20 months she was getting along well with her relatives, had lens implants, went back to school and obtained good marks. She developed an interest in reading. After 4 years of treatment her father reported that she could understand jokes, which she was unable to do previously. This improvement was maintained up to 8 years after the initiation of therapy. In 1997, CDCA became unavailable, a fact commented upon by others.[14] After 8 months without CDCA, the behavior of the proposita completely changed. She became very depressed and aggressive. She would go to the bathroom frequently for no reason, and refuse to drink liquids (which are necessary in the hot climate). She did not want to talk to anyone and did not want to go outside

	Exon 6	Intron 6
		↓
Patients	GGAGACTCTGCG	ATAGGACA
Normal	GGAGACTCTGCG	GTAGGACA

Figure 2 - The mutation found in the 2 cerebral xanthomatosis patients.

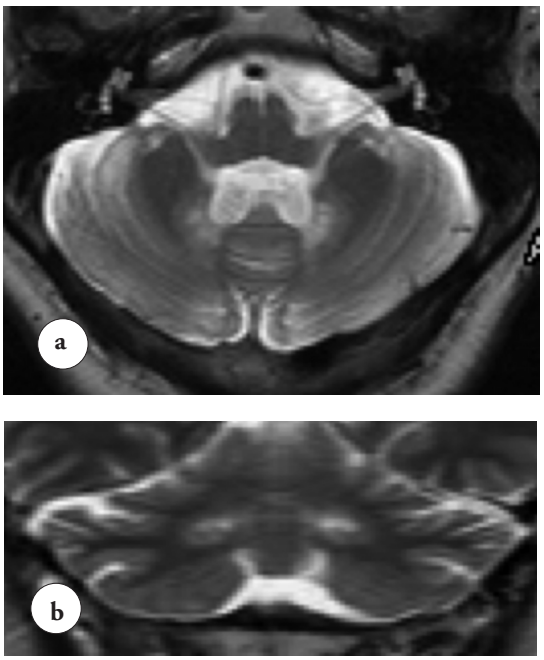

Figure 3 - T2 weighted images of the cerebellum of subjects IV.1 in Figure 1. a) Transverse view. b) Coronal view. The lesions in the dentate nuclei on both sides are clearly visible as hyperintense blobs.

the home with her family because she could not walk well or go downstairs. When CDCA became available again in April 2004 and her treatment was restored, she improved over a period of 2 months. She became talkative again (sometimes excessively so), and frequently requested visits to restaurants. Her movements became normal, and she was able to ascend and descend stairs without difficulty. She can now efficiently perform most household tasks. However, she is still somewhat aggressive, especially towards children.

As regards, the male homozygote (**Figure 1**, [IV.1]) following CDCA treatment (although he was erratic in taking it) he lost his ataxia, and his behavior became more normal. Consequently, he was able to keep his job. In 1999 he developed angina and then had a myocardial infarction, for which he had a coronary artery bypass graft implanted. When CDCA became unavailable, his condition deteriorated over 8 months, as shown by example, difficulty in walking, and in speaking. After restoration of the CDCA treatment his deterioration was arrested. However, he still complains of pain on walking and his ataxia is more noticeable than previously. Sometimes he falls when he is walking. His speech is improved and his intellect has improved, but his ataxia remains the same. The improvement after the restoration of the CDCA was less and was slower than the improvement observed in his sister. In addition to the CDCA he is receiving atorvastatin and anti-hypertensive therapy.

Serum lipid results of the family members. The serum lipid results of the family members are particularly relevant to the clinical course of individual IV.1 in **Figure 1**. The parents were both found to have elevated cholesterol levels, which have responded to dietary and statin therapy, and the father has had 2 coronary bypass operations. Four of their offspring were found to have fasting cholesterol levels above the National Cholesterol Education Program guideline of 5.20 mmol/L (IV.1 - 5.5, IV.2 - 6.5, IV.4 - 6.4, IV.5 - 5.3). Two individuals had values below the guideline (IV.6 - 3.6, and IV.7 - 3.9). Two individuals could not be tested (IV.3 and IV.7).

Discussion. There have been 2 previous reports of CTX in Arabs. An Arab boy from Kuwait had the phenotypic features of CTX but was not genotyped.[15] An Israeli Druze Arab family, in which CTX occurred has been described.[16] It is not clear why so few CTX patients have been reported from Arab populations. Perhaps the condition is not being recognized, or the responsible mutations are rare in Arabs. Another possible explanation is that amongst uneducated people, any neurological affliction or mental deficiency is considered shameful, so the parents may hide such offspring at home and prevent them from being exposed to the public, and do not take them for medical attention. Paralleling the Arab experience is the statement that CTX is "exceptionally rare in the Indian population."[17] On the other hand, a number of CTX patients have been described originating from relatively small populations, for example, those due to 3 mutations in Jews of North African origin.[18] The splice site mutation in intron 6, which was found in our patients has been described previously in Italians,[19] and in a "Caucasian."[20] Numerous other mutations have been described,[21-30] which produce the typical picture of CTX in the homozygote, usually becoming apparent at around 6-10 years of age.

The clinical features in our 2 patients were standard. However, as more mutations have been found, and more individuals and families have been investigated, it has become clear that the clinical manifestations in homozygotes can be varied, and may not follow the standard pattern. For example, childhood diarrhea (which occurred in our proposita) has only recently been recognized. The deposition of cholestanol and cholesterol in the nervous system is correlated to dysfunction. Post-mortem histopathological studies showed lipid crystal clefts, perivascular macrophages, neuronal loss, demyelination, fibrosis, and astrocytosis in the dentate nuclei, globus pallidus, substantia nigra, and inferior olives.[12] On the other hand, serial observations were described in 3 CTX siblings treated with CDCA for 7 years.[31] The EEG improved dramatically whereas the MRI of brain showed only slight changes. There is more insight into the way in which the atherosclerotic process is enhanced in CTX. High levels of sterol 27-hydroxylase occur in macrophages in advanced atherosclerotic lesions. This is particularly true near the shoulder region of atherosclerotic plaques, at the edge of the lipid core. The CYP27 gene is also expressed in the arterial endothelium. When the enzyme is inactivated by mutation, its gene products do not generate sterol intermediates (mostly bile acids) for transport to the liver. Absence of these mechanisms probably accounts for the accelerated atherosclerosis that occurs in CTX.[32,33]

Individual III.1 has suffered serious atherosclerotic disease. A similar patient with severe coronary artery disease has been described,[35] and a similar family to ours with CTX genes and genes for hyperlipidemia not co-segregating has also been described.[36] Whilst there is convincing evidence that only CDCA is required to treat CTX alone,[37] the presence of other deleterious genes, causing hypercholesterolemia, makes a case for the addition of other therapeutic measures such as a low cholesterol diet and statins. It seems likely that the beneficial effects of CDCA therapy are greater the

earlier in life the treatment is started, and furthermore it must be continued without interruption. Our 2 patients were unable to obtain CDCA for 6 years and 8 months. This was also the experience of others,[13] who, discussing the treatment of CTX described CDCA as "an essential drug for this disorder that is no longer available." The effects of stopping the CDCA treatment in our 2 patients were serious, as noted above. Now CDCA is marketed by 20 companies, their details can be found by entering "chenodeoxycholic acid suppliers" in a search engine (for example, Yahoo) and select URL: http//www.chemexper.com/chemicals/suppliers/cas474-25-9html.

It was not possible, in the family described, to use a DNA-based presymptomatic detection of the homozygous state, but its importance as an indication to initiate early treatment with CDCA has been emphasized.[38] The ability to identify heterozygotes unequivocally with genotypic methods offers the possibility of providing genetic counseling for members of affected families. This is of particular importance in populations in which cousin marriages are common.

OMIM,[2] lists 65 conditions which are associated with premature cataracts. One of them is CTX. Routine screening of these patients for CTX could be performed by visual inspection of the Achilles tendons, or measurement of serum cholestanol or urinary bile acids. Genotyping would probably be too expensive in view of the large number of alleles, which could be responsible.

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