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Spinal xanthomatosis: a variant of cerebrotendinous xanthomatosis

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Summary

We describe seven Dutch patients from six families with a slowly progressive, mainly spinal cord syndrome that remained for many years the sole expression of cerebrotendinous xanthomatosis (CTX). MRI demonstrated white matter abnormalities in the lateral and dorsal columns of the spinal cord. Post-mortem examination of one of the patients showed extensive myelin loss in these columns. An array of genotypes was found in these patients. We conclude that 'spinal xanthomatosis' is a clinical and radiological separate entity of CTX that should be included in the differential diagnosis of 'chronic myelopathy'.

Keywords: cerebrotendinous xanthomatosis; myelopathy; MRI; pathology

Abbreviations: CDCA = chenodeoxycholic acid; CTX = cerebrotendinous xanthomatosis; CYP 27 = sterol 27-hydroxylase; LFB-HE = luxol fast blue and haematoxylin and eosin; MNF = monoclonal anti-neurofilament antibody; SSCP = single strand conformation polymorphism

Introduction

Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive disease, due to a deficiency of sterol 27-hydroxylase (CYP 27), a key enzyme in the synthesis of chenodeoxycholic acid (CDCA), a primary bile acid. In CTX, deficiency of CYP 27 and thus a lack of CDCA leads to the storage of cholestanol and cholesterol in many tissues, especially the eye lens, the CNS and tendons (Björkhem and Boberg, 1995). Typical disease onset consists of bilateral cataracts and diarrhoea in childhood (Cruysberg *et al*., 1991), followed by progressive cerebellar and pyramidal signs, mental retardation, seizures and the development of tendon xanthomas in late adolescence and early adulthood (Cruysberg *et al*., 1995). MRI in CTX patients often reveals symmetrical lesions in the cerebellar white matter (Fig. 1A; Hokezu *et al*., 1992). Additional multimodal electrophysiological examinations (somatosensory, brainstem auditory and visual evoked potentials) may detect subclinical involvement of the central and peripheral nervous systems in CTX (Tokimura *et al*., 1992).

In this paper we describe patients with a predominantly spinal form of CTX, which has a distinct clinical and radiological pattern.

Methods

Patients

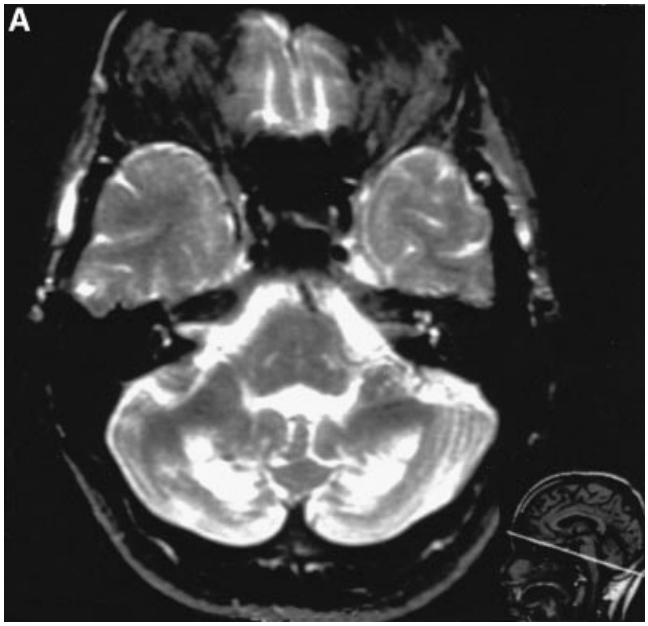
We identified seven adult patients presenting with a predominant spinal cord syndrome from six families out of a population of 22 families in which there were 44 patients with biochemically and genetically proven CTX. Patients B1 and B2 are siblings; the others are patients each of a different family.

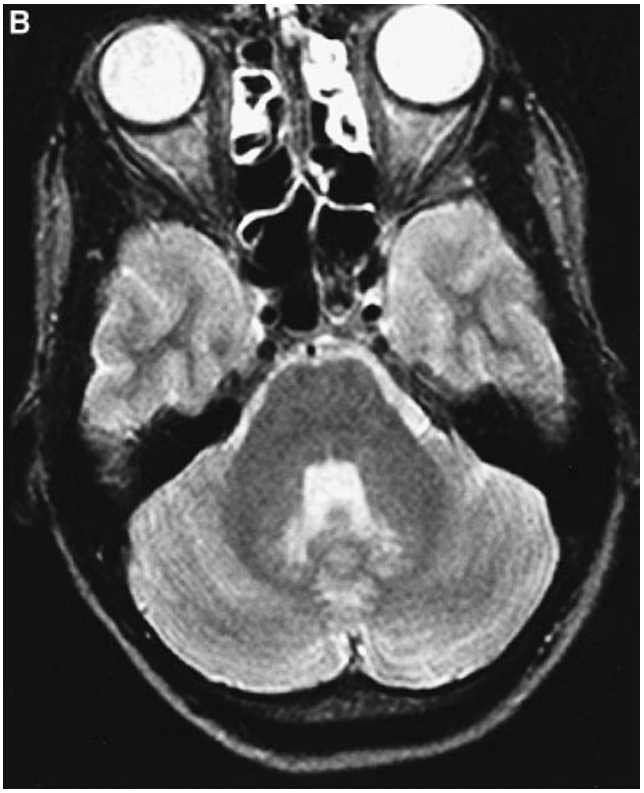
Biochemistry

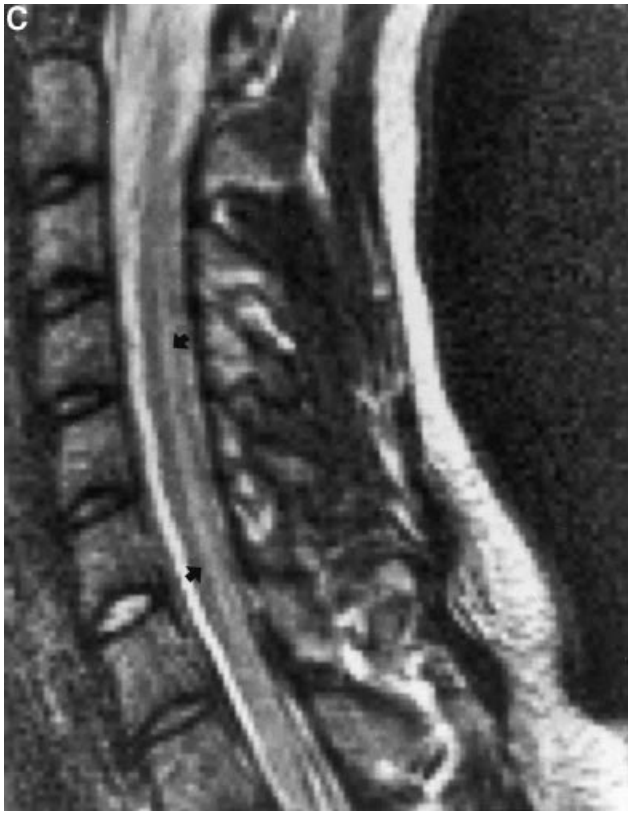
The cholestanol and cholesterol in serum, and bile alcohols in urine were measured according to established procedures (Wolthers *et al*., 1983; Koopman *et al*., 1984). The clinical and biochemical data of the seven patients are summarized in Table 1.

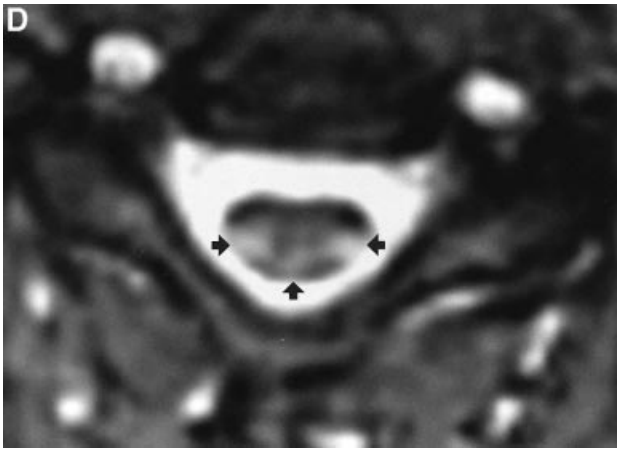
Molecular biology

The CYP 27 gene was amplified in four fragments (exons 1 and 2, exons 3–5 and exons 6–9) by the polymerase









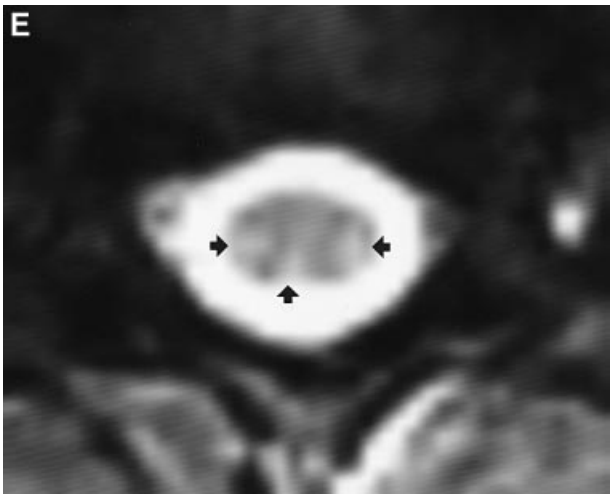


Fig. 1 (**A**) T_2-weighted cerebral MRI of a 39-year-old male with the classic type of CTX: symmetrical lesions in the cerebellar white matter. (**B**) Patient A: T_2-weighted cerebral MRI showing very small symmetrical hyperintensities in the cerebellum. (**C**) Patient A: sagittal T_2-weighted spin-echo MRI of the cervical spinal cord, showing a band of high signal intensity (arrows). (**D**) Patient A: axial T_2-weighted gradient echo MRI, at level C3: abnormal signal intensity in the lateral corticospinal tracts and gracile tracts (arrows). (**E**) Patient B2: axial T_2-weighted gradient echo MRI, at level C5: both the lateral corticospinal tracts and gracile tracts show areas of increased signal intensity (arrows).

Table 1 *Clinical, biochemical, genetical and MRI data*

Patient	A	B1	B2	C	D	E	F
	Female	Female	Male	Male	Female	Female	Female
Age at presentation of the spinal cord syndrome (years)	20	35	30	35	35	28	28
Age at diagnosis of CTX (years)	24	45 (†)	33	43	37	41	36
Systemic signs							
Cataract	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Diarrhoea	Yes	Yes	No	No	No	Yes	Yes
Xanthomas	No	No	Yes	No	No	No	No
Presenting neurological signs							
Pyramidal signs	++++	++++	+++	+++	++++	+++	+++
Dorsal column signs	+++	+++	+++	+++	+++	+++	+++
Other neurological signs at diagnosis							
Seizures	+	−	−	−	−	−	−
Dysarthria	−	+	−	+	−	−	−
Dementia	−	−	−	−	−	−	±
Cerebellar signs	−	+	−	+	−	−	−
Polyneuropathy	−	−	−	±	−	±	−
Biochemical features							
Serum cholestanol (3.3–12.5 mol/l)	61	19	NA	NA	46	63	100
Serum cholesterol (4.7–6.5 mmol/l)	2.7	5.2	NA	NA	3.9	NA	4.6
Excessive urinary bile alcohols	Yes	Yes	Yes	Yes	Yes	Yes	Yes
MRI findings							
Cerebellar white matter lesions	+	NA	+	+	+	−	+
Spinal cord atrophy	−	NA	−	−	NA	−	−
Spinal cord white matter lesions							
Lateral columns	++++	NA	++++	++++	NA	+++	+++
Dorsal columns	+++	NA	++++	+++	NA	++	++

− = absent; ± = dubious; + to ++++ = mild to severe; NA = not available; † = deceased.

chain reaction (PCR) from genomic DNA of leukocytes. Exons 3–9 with their intron boundaries were subsequently amplified separately, with the two PCR fragments 3–5 and 6–9 as a template (Luyten *et al*., 1995). The amplimers thus obtained were subjected to single strand conformation polymorphism (SSCP) analysis, followed by sequencing and restriction analysis according to established procedures (Verrips *et al*., 1996).

MRI

MRI of brain and spinal cord was performed at 1.0 Tesla, immediately after administration of 20 cc gadolinium-DTPA.

MRI of the brain consisted of proton density (PD) and T_2-weighted conventional spin echo (SE) [2300/45/90/1 (TR/TE/TE/excitations)], and T_1-weighted conventional SE (600/15/2). Twenty-one axial slices with an in-plane resolution of ~1 mm, a slice thickness of 5 mm and an interslice gap of 0.5 mm were obtained.

MRI of the spinal cord was performed using a spinal phased array coil. Sagittal slices (3 mm slice thickness, 0.3 mm interslice gap) were acquired using cardiac triggered conventional PD and T_2-weighted SE (2200/20/80/1), and T_1-weighted conventional SE (550/15/2). Field of view (FOV) was 240 × 480 mm and imaging matrix was 256 × 512 mm, yielding pixels of 0.94 mm^2. Furthermore, eight axial slices (5 mm thick) of the spinal cord were acquired at levels C1–T1, using T_2-weighted gradient echo [620/20/20/4 (TR/TE/flip angle/excitations)]. In-plane resolution was 0.90 mm for this sequence.

Total MRI acquisition time was approximately 1 h. MRIs were analysed by two independent neuroradiologists, who were both unaware of the clinical findings.

Pathology

Brain and spinal cord of patient B1 were available for pathological examination. These tissues were examined after staining with luxol fast blue and haematoxylin and eosin (LFB-HE), and after staining with monoclonal anti-neurofilament antibody (MNF; dilution 1 : 10).

Results

Patients

All patients presented with symptoms and signs related to involvement of the corticospinal tracts and the dorsal columns of the spinal cord. None of them had cerebellar signs, dementia or peripheral neuropathy at the moment of presentation of the spinal cord syndrome and, except for patient B2, none of them had tendon xanthomas (Table 1).

Initial diagnoses of this spinal cord involvement were: multiple sclerosis (patients A, D and F), hereditary spastic

Table 2 *Mutations*

Patient	Exon/Intron	Mutation	Homozygous/ heterozygous	Amino acid replacement	Reference
A	Exon 5	1037 C → T	Homozygous	Thr 306 Met	(Reshef *et al*., 1994)
B1 and B2	Exon 5	1037 C → T	Homozygous	Thr 306 Met	(Reshef et al., 1994)
	Exon 6	1204 C → T	–	Arg 362 Cys	(Cali *et al*., 1991*a*)
C	Exon 2	400 C → T	–	Arg 94 Trp	This study
	Exon 5	1037 C → T	Heterozygous	Thr 306 Met	(Reshef *et al*., 1994)
D	Exon 5	1037 C → T	Homozygous	Thr 306 Met	(Reshef *et al*., 1994)
E	Exon 5	1037 C → T	Heterozygous	Thr 306 Met	(Reshef *et al*., 1994)
	Intron 7	1284 + 1 G → A	–	Skipping of exon 7	(Garuti *et al*., 1996)
F	Exon 6	1204 C → T	Heterozygous	Arg 362 Cys	(Cali *et al*., 1991*b*)
	Intron 4	865 + 1 G → A	–	Skipping of exon 4	(Verrips *et al*., 1997)

The cDNA sequence and the amino acids are numbered according to Cali and Russell (Cali and Russell, 1991*a*).

paraparesis (patient C), cervical myelopathy due to a disc herniation C5–C6 (patient B1) and 'slowly progressive pyramidal syndrome with sensory disturbances of unknown cause' (patients B2 and E).

Biochemistry

All patients had an elevated serum cholestanol level and excessive amounts of bile alcohols in urine (Table 1). These levels do not differ from those found in classic CTX.

Genetic findings

The genotypes of all patients are listed in Table 2. A novel missense mutation was found in exon 2 of patient C: a C → T transition at cDNA position 400, resulting in the replacement of arginine by tryptophan in codon 94. No other mutation was found in the other exons or splice sites of the same allele. In 100 alleles of 50 controls this mutation was not found by SSCP screening. The genotype was established in all patients, except in patient B1. We may assume that she had the same genotype as her brother, patient B2.

MRI findings

A spinal cord MRI was carried out in five patients (Table 1). In these patients PD and T_2-weighted MRIs showed increased signal intensity along the entire spinal cord. Axial images revealed increased signal intensity localized in both lateral corticospinal tracts and in the gracile tracts (Fig. 1C–E). The spinal cord was not atrophic. In the six patients in which MRI of the brain could be performed, very small symmetrical hyperintensities next to the dentate nuclei were found, except in patient E (Fig. 1B).

Pathology

The white matter of the spinal cord of patient B1 showed extensive, symmetric loss of myelin, especially in the lateral corticospinal tracts and the gracile tracts in the LFB-HE staining. Severe axonal loss in essentially the same distribution was seen in the MNF staining (Fig. 2A and B, arrows). In these areas gliosis and occasional perivascular accumulation of macrophages were present (Fig. 2C, arrows). Similar changes were found in both pyramids, the basis pontis, the superior cerebellar peduncles, the cerebral peduncles and the cerebellar hemispheres. These changes were accompanied by many lipid crystal clefts and extensive infiltration of macrophages in the base of the pons (somewhat more pronounced in the longitudinal than in the transversal tracts) and in the cerebellum. The supratentorial part of the CNS and the spinal nerve roots were normal.

Discussion

A predominant involvement of the spinal cord was found in the seven CTX patients. In only two patients (B1 and C) did the classical CTX symptomatology become manifest 5 and 8 years, respectively, after the onset of the myelopathy. Because of this atypical presentation and mild clinical course, six patients were not initially diagnosed as having CTX. All patients had juvenile bilateral cataract and four of them had a history of chronic diarrhoea, a symptom that is frequently found in children with CTX (Cruysberg *et al*., 1991), but rarely reported in adult CTX patients (Verrips *et al*., 1997).

This spinal variant of CTX, which we would like to name spinal xanthomatosis, has a relatively mild clinical course compared with the classic form of CTX, which shows cerebellar involvement, dementia, tendon xanthoma formation and peripheral neuropathy early in the disease process. Although the neurological symptoms in CTX are often highly variable (Kuriyama *et al*., 1991), most patients have cerebellar signs and mental retardation from the age of 20 years onwards (Björkhem and Boberg, 1995).

Despite the frequent occurrence of pyramidal symptoms in CTX, no abnormalities in the spinal section of the pyramidal tracts have previously been described using MRI (Restuccia *et al*., 1992; Dotti *et al*., 1994), apart from a slight atrophy of the cervical spinal cord in one patient (Bencze *et al*., 1990). As we used phased-array coils with proven sensitivity for intrinsic spinal cord abnormalities (Lycklama à Nijeholt *et al*., 1996), five of our patients showed extensive

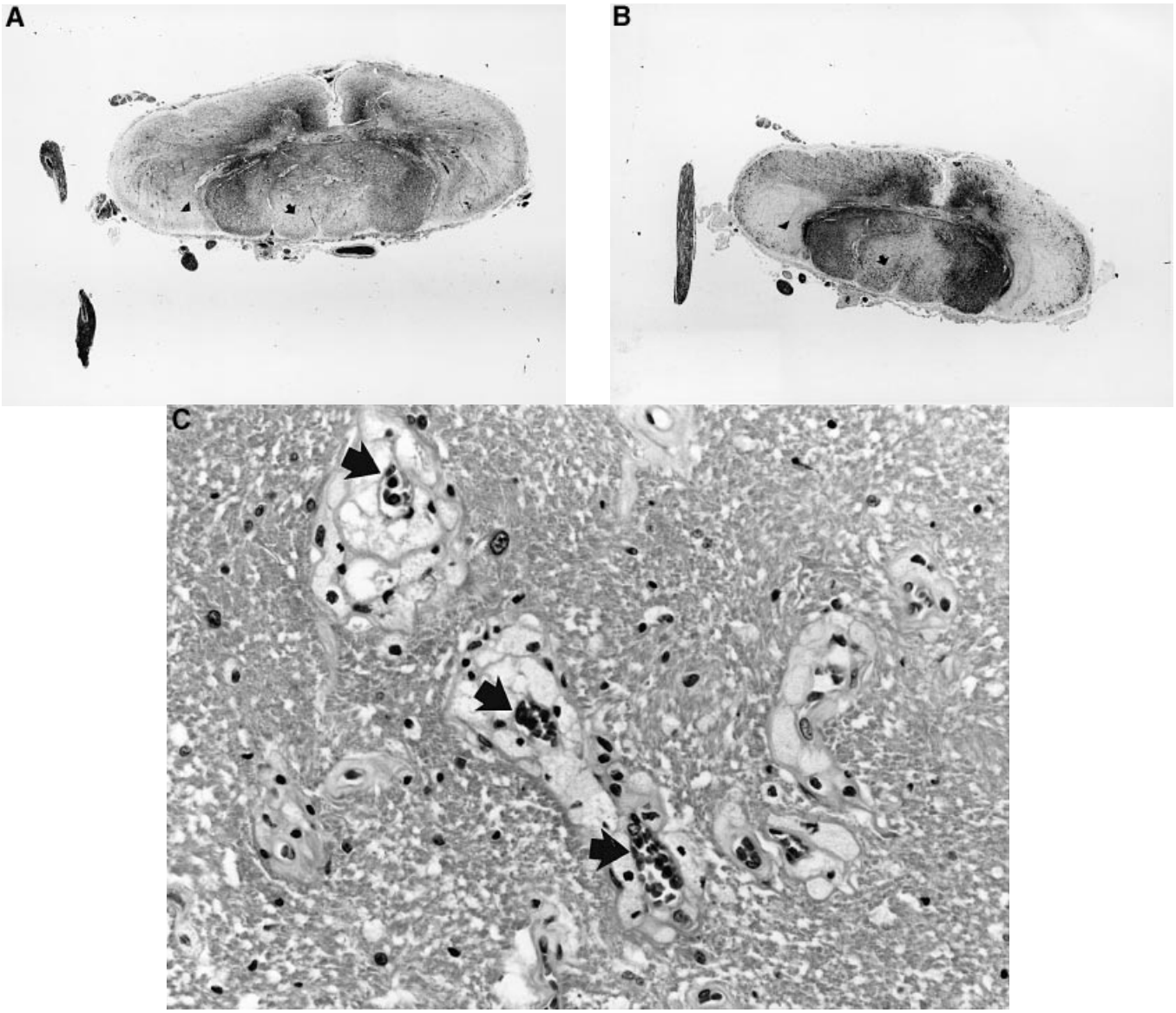


Fig. 2 Thoracic spinal cord of patient B1. (**A**) Myelin stained with LFB-HE (original magnification ×1). (**B**) Axons stained with MNF (original magnification ×1). (**A** and **B**) Severe loss of myelin and axons in the lateral corticospinal tracts (arrowhead), the gracile tracts (arrow) and dispersed loss in the anterior corticospinal tracts; the cuneate tracts are relatively spared. (**C**) LFB-HE staining of corticospinal tract (original magnification ×200). Higher magnification of the cross section of corticospinal tract: perivascular accumulation of macrophages and complete lack of LFB-positive myelin cylinders. Arrows indicate capillaries with erythrocytes.

white matter lesions in the lateral corticospinal tracts and in the gracile tracts (Fig. 1C–E). Our finding of signal increase in the lateral and posterior white matter columns of the spinal cord correlate well with the clinical findings in our patients and with the histopathological findings in patient B1.

Pathological examination of patient B1 showed diffuse involvement of the long tracts in the spinal cord as well as in the brainstem. Our findings are consistent with previous reports on spinal cord abnormalities in four other CTX patients (Van Bogaert *et al*., 1937; Guillain *et al*., 1942; Pop *et al*., 1984; Soffer *et al*., 1995). This spinal cord pathology is different from that seen in multiple sclerosis, where a patchy, irregularly distributed rather than a symmetrical involvement of the white matter is found. Histologically, recent multiple sclerosis lesions show myelin destruction with infiltration of macrophages, a variable lymphoplasmocellular infiltrate, and relative sparing of axons, while old lesions are characterized by myelin loss and gliosis. Other (metabolic) white matter disorders, such as metachromatic leucodystrophy (MLD) and X-linked adrenoleucodystrophy (X-ALD), generally show prominent cerebral involvement. However, in adrenomyeloneuropathy (AMN), a milder subtype of X-ALD manifesting in adulthood, the lumbar corticospinal tracts and the cervical gracile tracts and spinocerebellar tracts may be worst affected (Lake, 1997). Microscopically, MLD and X-ALD/AMN lesions show myelin loss with relative sparing of axons and infiltration of periodic acid Schiff (PAS) positive macrophages, in MLD the latter cells

exhibiting metachromasia in frozen sections. The lesions of the cerebellum in CTX consist of a combination of xanthomatous lesions, fibrosis, lipid crystal clefts and haemosiderin deposition, especially in the area around the dentate nucleus, and are pathognomonic for this disease. The pathogenesis of the CNS pathology is, until now, hypothetical. Several authors suggest demyelination as the primary pathological lesion (Van Bogaert *et al*., 1937; Guillain *et al*., 1942; Schimschock *et al*., 1968; Philippart and Van Bogaert, 1969; Diedrich and Ropte, 1989; Elleder *et al*., 1989), whereas others suggest primary neuroaxonal pathology with secondary myelin loss (Pop *et al*., 1984; Soffer *et al*., 1995). The spinal cord lesions in our patient show severe loss of both myelin and axons, and thus do not clarify this issue.

Mutation analysis in our seven patients revealed missense mutations predominantly in exons 5 and 6 of the gene. All mutations present in these patients are also found in the classical form of CTX. A genotype specific for the spinal variant of CTX is not found.

In the literature, a 35-year-old woman was briefly described in 1942 (Thiébaut, 1942). She had a spastic paraparesis, chronic diarrhoea and tendon xanthomas. This was probably the first description of a patient with the spinal form of CTX. Spinal cord abnormalities resembling CTX can also be found in other conditions. In 1965, a 46-year-old woman was described with a spastic paraparesis, hypercholesterolaemia, hepatosplenomegaly and cutaneous xanthomas. Autopsy showed a circumscript cholesterol accumulation in the cervical spinal cord in the segments C2–C4 within pyramidal tracts and the dorsal columns, resembling the findings in patient B1 (Van Bogaert, 1965).

Up to now in the literature, only seven adult CTX patients have been reported with predominant pyramidal signs, and the absence of both cerebellar signs and mental retardation (Stein and Czuczwar, 1959; Schreiner *et al*., 1975; Swartz *et al*., 1982; Kuriyama *et al*., 1991; Restuccia *et al*., 1992; Dotti *et al*., 1994). Unfortunately, it cannot be deduced from these articles whether the dorsal columns were involved as well. These patients may also have suffered from the spinal variant of CTX. Among the patients with this spinal form there is a female preponderance (10 women, four men), but this finding may be coincidental. There is no sex difference in the severity of the clinical course.

Spinal xanthomatosis can be the first presentation of CTX, which should therefore be included in the differential diagnosis of chronic myelopathy. Particularly, when myelopathy is preceded by bilateral cataracts and diarrhoea, the diagnosis of CTX should be considered. In that case, determination of cholestanol in serum and of bile alcohols in urine could confirm the diagnosis. As a therapy is available, the early recognition of this myelopathy as a variant of CTX is important. Since 1975 CDCA has commonly been used as a therapy for CTX (Salen *et al*., 1975), and has proved to be effective (Berginer *et al*., 1984). With CDCA therapy, there is a considerable decrease in the serum cholestanol level and a sharp decline in the excretion of bile alcohols in the urine (Wolthers *et al*., 1983; Batta *et al*., 1985). Perhaps the most effective inhibitor of cholestanol production is a combination of CDCA with a β-HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitor. In seven of our patients the combination of CDCA and simvastatin resulted in further lowering of an already normal serum cholestanol level, facilitating the long-term wash-out of cholestanol from the CNS (Verrips *et al*., 1999).

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