Magnetic resonance imaging and spectroscopic changes in brains of patients with cerebrotendinous xanthomatosis

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Summary

Cerebrotendinous xanthomatosis (CTX) is a rare disorder due to an inherited defect in the metabolic pathway of cholesterol. Early diagnosis of the disease is particularly important as patients benefit from therapy with chenodeoxycholic acid. Although the disease is clinically characterized by the concomitant presence of tendon xanthomas, juvenile cataracts and progressive neurological impairment, clinical features may vary greatly. Neuroradiological studies have suggested that the bilateral abnormality of the dentate nuclei could be typical of this disease. However, this finding has been seen inconsistently on conventional MRI. The dynamic of the CNS pathology in CTX is complex, and whether demyelination or axonopathy has primary importance in the pathogenesis of CTX pathology is not known. To clarify both neuroradiological and pathological issues, we performed combined brain MRI and spectroscopy examinations on 12 CTX patients. On conventional MRIs, bilateral hyperintensities of the dentate nuclei were clearly seen in nine out of 12 patients on T2-weighted MRIs, but were evident in all patients using a FLAIR sequence. On proton magnetic resonance (MR) spectroscopy, significant decreases in N-acetylaspartate resonance intensities (P < 0.0001) and increases in lactate MR signals (P < 0.05) were found in the group of CTX patients in large volumes of interest localized above the lateral brain ventricles and in the cerebellar hemispheres. Cerebral values of N-acetylaspartate resonance intensities showed a close correlation with patients’ disability (Spearman rank correlation = –0.78, P < 0.005). These results suggest that MR abnormalities in the dentate nuclei may be evident consistently in patients with CTX. Proton MR spectroscopy data demonstrated widespread axonal damage (as shown by the decrease in N-acetylaspartate) and diffuse brain mitochondrial dysfunction (as shown by the increase in brain parenchymal lactate) in patients with CTX. The close correlation seen between values of the putative axonal marker N-acetylaspartate and patients’ disability scores suggests that proton MR spectroscopy can provide a useful measure of disease outcome in CTX.

Keywords: cerebrotendinous xanthomatosis, magnetic resonance spectroscopy, lactate, N-acetylaspartate

Abbreviations: Cho = choline; Cr = creatine; CTX = cerebrotendinous xanthomatosis; EDSS = Expanded Disability Status Scale; FLAIR = fluid-attenuated inversion recovery; La = lactate; MRS = magnetic resonance spectroscopy; NAA = N-acetylaspartate; SROC = Spearman rank order correlation; TE = echo time; TR = repetition time

Introduction

Cerebrotendinous xanthomatosis (CTX) is a rare inherited disorder due to a systemic defective activity of the mitochondrial enzyme sterol 27-hydroxylase. This enzyme plays an important role in the metabolic pathway of cholesterol by catalysing the oxidation of sterol intermediates. Consequently, patients with sterol 27-hydroxylase deficiency have defective bile acid synthesis (with increases in cholic acid and decreases in chenodeoxycholic acid) and abnormally high levels of cholestanol in plasma, urine, faeces and various tissues (Bjorkhem and Boberg, 1995; Federico and Dotti, 1996).

The abnormal metabolism of cholestanol is considered responsible for the clinical manifestations of CTX. Clinical symptoms may be evident in different organ systems (Cruysberg et al., 1991; Wevers et al., 1992; Berginer et al., 1993a, b; Federico et al., 1993; Federico and Dotti, 1996; Dotti et al., 1998), but are usually dominated by the classical triad of the disease: juvenile cataracts, tendon xanthomas and
progressive neurological impairment (Federico and Dotti, 1996; Verrips et al., 2000). The diagnosis of CTX can be made biochemically [detected by the increased serum level of cholestanol (Berginer et al., 1993a)] and genetically [detected by molecular defects in the sterol 27-hydroxylase gene (Federico and Dotti, 1996; Chen et al., 1998; Verrips et al., 2000)]. Early diagnosis is imperative in patients with CTX, as the pharmacological treatment with chenodeoxycholic acid (or with a combination of chenodeoxycholic acid and HMG-CoA reductase inhibitors) has been shown to slow or even reverse the progression of the disease (Berginer et al., 1984; Pedley et al., 1985; Federico and Dotti, 1994; Verrips et al., 1999a).

The combination of cataract, tendon xanthomas and progressive neurological atrophy is peculiar and strongly suggests the diagnosis of CTX. However, although all classical features of the disease are evident in the majority of CTX patients, these may vary considerably in onset, degree and extent (Berginer et al., 1993a). Moreover, a number of patients may not have tendon xanthomas at the onset of the disease or may never develop them (Siebner et al., 1996; Gilad et al., 1999; Verrips et al., 1999a). Biochemical and genetic tests will often not be performed in patients without xanthomas, even if other clinical manifestations of the disease are present (Siebner et al., 1996). It is therefore very important to find markers that can supplement clinical features in the characterization of the disease, ensuring early diagnosis in cases with atypical clinical manifestation.

Conventional magnetic resonance MRI studies have shown focal or diffuse white matter abnormalities and different degrees of cerebral and cerebellar atrophy in brains of patients with CTX (Swanson and Cromwell, 1986; Bencze et al., 1990; Fiorelli et al., 1990; Hokezu et al., 1992; Berginer et al., 1994; Dotti et al., 1994; Siebner et al., 1996). These MRI findings are non-specific as they can be found in many neurometabolic disorders. However, abnormal MR signals around the dentate nuclei and in the surrounding white matter have been demonstrated in most of the CTX patients reported in the literature and can be suggestive of this disorder (Valk and van der Knaap, 1996).

Conventional MRI detects brain lesions with great sensitivity, but does not provide specific information about the pathology underlying the detected lesions and is often not a good predictor of functional impairment or disability (Rudkin and Arnold, 1999). Proton MR spectroscopy (MRS), by providing a non-invasive biochemical assay of living tissues, can overcome some of these limitations (Arnold and Matthews, 1996). Myelin and axonal integrity, as well as brain oxidative metabolism, can be assessed easily in vivo by this MR technique, and its use in rare metabolic disorders such as CTX may provide a better understanding of the complex dynamics of pathological changes.

We therefore performed combined brain MRI and MRS examinations in a group of 12 patients with CTX with the aim of (i) evaluating in vivo brain metabolic changes occurring in this rare metabolic disorder, (ii) identifying potential neuroradiological markers of the disease, and (iii) providing putative markers of disease outcome.

**Methods**

**Patient population**

Twelve adult patients with CTX from eight families (eight females and four males, age range 32–55 years) were studied. All patients met the clinical criteria for CTX and had a blood level of cholestanol >1 mg/dl (Federico and Dotti, 1996). DNA point mutations or deletions in the sterol 27-hydroxylase gene were detected in all patients (Table 1). A complete clinical evaluation was performed on the day of the MRI examination by an experienced neurologist (M.T.D.), who assessed the patients’ clinical disability using Expanded Disability Status Scale (EDSS) scores (Kurtzke, 1983) (Table 1). At the time of the clinical and MRI examinations, all patients showed the classic triad of the disease. Ten out of 12 CTX patients had been treated with chenodeoxycholic acid for 7–14 years (Table 1), whereas the remaining two patients were not taking any medication (Patients 2 and 10 in Table 1). The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Siena, and informed consent was obtained from all participating patients.

**MR examinations**

Each patient underwent conventional MRI and single-voxel proton MRS examinations in a single session. These were obtained using a Philips Gyroscan NT operating at 1.5 T (Philips Medical Systems, Best, The Netherlands). A sagittal survey image was used to identify the anterior commissure (AC) and posterior commissure (PC). A transverse dual spin-echo sequence [repetition time (TR) = 2300 ms, echo time (TE) = 2090 ms, slice thickness 5 mm) yielding proton density-weighted and T2-weighted images was acquired in the transverse plane parallel to the AC–PC line. Turbo T2-weighted images in the sagittal plane (TR = 3000 ms, TE = 120 ms, slice thickness 5 mm) and fluid-attenuated inversion recovery (FLAIR) images (TR = 9000 ms, TE = 150 ms, slice thickness 5 mm) in the transverse plane were also acquired.

Conventional MRIs were used to position an intracranial volume of interest for spectroscopy. In each MR session, proton MR spectra were acquired from two different volumes of interest. First, a brick-shaped box measuring ~70 mm (anterioposterior) × 50 mm (left–right) × 20 mm (craniocaudal) was positioned just superior to the lateral ventricles (Fig. 1). After the first acquisition, a second volume of interest measuring ~25 mm (anterioposterior) × 50 mm (left–right) × 20 mm (craniocaudal) was positioned in a central cerebellar region (Fig. 2). Brain volumes of interest were positioned to include both grey and white matter of both hemispheres. These included the cerebral and cerebellar MRI.
Fig. 1 Conventional MRI scan of a patient with CTX (Patient 10 in the tables) in sagittal and transverse orientation, illustrating the cerebral volume of interest used for spectroscopy (A) and the proton MR spectrum relative to that volume of interest (B). The proton spectrum of a normal control (originating from a similar volume of interest) is shown for comparison (C). Note the decrease in the NAA/Cr ratio and the increase in La/Cr in the spectra.

Table 1 Demographic and clinical information, molecular defects and clinical scores for the CTX patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years), sex</th>
<th>Molecular defect*</th>
<th>EDSS</th>
<th>Treatment duration (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40, F</td>
<td>A183P, Int7 5 splice site (As)</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>47, F</td>
<td>A183P, Int7 5 splice site (As)</td>
<td>6</td>
<td>Untreated</td>
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</tr>
<tr>
<td>4</td>
<td>39, M</td>
<td>A183Pro</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>54, M</td>
<td>R94Q</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>55, M</td>
<td>R362C</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>46, F</td>
<td>A183P</td>
<td>1</td>
<td>14</td>
</tr>
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</tr>
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<td>45, F</td>
<td>Int7 5 splice site (As)</td>
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<td>Untreated</td>
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<td>38, F</td>
<td>Deletion, Int7 5 splice site (As)</td>
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<tr>
<td>12</td>
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<td>Deletion</td>
<td>1</td>
<td>10</td>
</tr>
</tbody>
</table>

As = aberrant splicing. *For references see Garuti et al., 1996.

lesions, but mostly contained normal-appearing brain (Figs 1 and 2).

Proton spectra were acquired using a 90°–180°–180° (PRESS) sequence for volume selection (Orldige et al., 1987) (TR = 2000 ms, TE = 272 ms, 128 averages). Magnetic field homogeneity was optimized to a line width of ~5 Hz over the volume of interest using the proton signal from water. Water suppression was achieved by placing frequency-selective excitation pulses at the beginning of the MRS sequence (Haase et al., 1985). Post-processing of the raw data was done on a SUN/SPARC system using XUNspec1 software (Philips Medical Systems) as previously described (De Stefano et al., 1998). The residual water signal was removed by applying the linear HSVD (Hankel singular valve decomposition procedure) fitting method (de Beer et al., 1992). A mild exponential filter, Fourier transformation and phase correction were applied prior to the quantification of metabolites. These were determined by integration of peak areas between automatically determined frequency bounds relative to a polynomial baseline. Long echo time (TE = 272 ms) MRS data allows the quantification of four main resonance intensities (Arnold and Matthews, 1996): (i)
choline (Cho) at 3.2 p.p.m., mainly from choline-containing phospholipids (an indicator of cell membrane integrity); (ii) N-acetyl groups at 2.0 p.p.m., mainly N-acetylaspartate (NAA, a marker of axonal integrity); (iii) lactate (La), a doublet at 1.3 p.p.m. divided by a characteristic splitting of 7 Hz, accumulating in pathological conditions such as oxidative metabolism impairment and acute inflammation, and barely distinguishable from the noise in single-voxel MRS experiments in normal controls (Matthews et al., 1993; De Stefano et al., 1995b); and (iv) creatine (Cr) at 3.0 p.p.m., expressing signal from both creatine and phosphocreatine. Metabolite resonance intensity values were expressed as ratios with respect to Cr, which tends to be resistant to changes. Chemical shifts were calculated relative to NAA at 2.0 p.p.m.

Results

Conventional MRI data are summarized in Table 2. Cerebral atrophy was evident at visual examination in nine out of 12 CTX patients and cerebellar atrophy was seen in eight patients. On both T2-weighted and FLAIR images, focal or diffuse white matter lesions were evident in both cerebral and cerebellar hemispheres in the whole group of patients (Fig. 3). An abnormal MRI signal was clearly detected in the dentate nuclei and surrounding white matter in nine out of 12 CTX patients on T2-weighted MRI, but this was clearly evident in all CTX patients on FLAIR images (Fig. 4).

Proton MRS results are summarized in Table 3. In the group of CTX patients, we found significant decreases in brain NAA/Cr (cerebral NAA/Cr = 2.43 ± 0.27 in CTX patients and 2.96 ± 0.19 in normal controls, P < 0.0001; cerebellar NAA/Cr = 1.47 ± 0.13 in CTX patients and 1.85 ± 0.10 in normal controls, P < 0.0001) (Table 3 and Figs 1 and 2). Significant increases in La/Cr ratio were also found in both brain volumes of interest (cerebral La/Cr = 0.50 ± 0.17 in CTX patients and 0.32 ± 0.08 in normal controls, P < 0.001; cerebellar La/Cr = 0.27 ± 0.10 in CTX patients and 0.18 ± 0.04 in normal controls, P < 0.03) (Table 3 and Figs 1 and 2). Interestingly, the two patients who were not under pharmacological treatment showed the highest La/Cr values (Tables 1 and 3).

Patient values of Cho/Cr were within the normal limits in both brain regions (Table 3 and Figs 1 and 2).

In order to assess in vivo putative markers of disease

Statistical analysis

Single-voxel MRS data relative to the patient group were compared with those of normal adult subjects (age range 22–56 years, 23 subjects for cerebral volume of interest and 13 subjects for cerebellar volume of interest) using the non-parametric Kruskal–Wallis test of variance. Values of NAA/Cr relative to the patient group were correlated with their corresponding EDSS scores using the non-parametric Spearman rank order correlation (SROC). Significance of the data was established at P < 0.05.
Table 2 Conventional MRI changes in the CTX patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>White matter</th>
<th>Dentate nuclei</th>
<th>Cerebral atrophy</th>
<th>Cerebellar atrophy</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>–</td>
</tr>
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<td>+++</td>
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<td>+</td>
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<td>*</td>
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<td>–</td>
</tr>
<tr>
<td>12</td>
<td>+ focal</td>
<td>*</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

+ = mild; ++ = moderate; +++ = severe; ++++ = very severe. *Abnormalities not clearly visible in T2-weighted images but evident in FLAIR.

Discussion

Conventional MRI examinations showed a non-homogeneous, hyperintense MR signal in dentate nuclei and surrounding cerebellar white matter in all CTX patients. Although this neuroradiological sign has been proposed recently as a characteristic feature of the disease (Valk and van der Knaap, 1996), it has been reported inconsistently in most of the recent MR studies on patients with CTX (Hokezu et al., 1992; Dotti et al., 1994; Siebner et al., 1996; Verrips et al., 1999a, 2000). In the present study, bilateral abnormalities in the dentate nuclei were clearly detected only in nine out of 12 patients using T2-weighted MR images, but they were evident in all patients on FLAIR MRI (Fig. 4). FLAIR sequences are increasingly used for clinical diagnosis as they have been shown to increase the sensitivity of MRI in detecting brain lesions in several white matter disorders (De Coene et al., 1992; Tourbah et al., 1996; Ashikaga et al., 1997; Kato et al., 1997; Kimura et al., 1997; Abe et al., 1998). The results of our study indicate that abnormalities in the dentate nuclei can be better revealed by FLAIR sequences and suggest that they might be present constantly in patients with CTX.

Previous post-mortem studies on CTX brains have demonstrated that CTX lesions such as those seen in the dentate nuclei consist of a combination of crystalline clefts embedded in a dense, fibrous tissue and lipid and haemosiderin deposition (Soffer et al., 1995; Verrips et al., 1999a). However, the dynamics of the CNS pathology in CTX is complex and not well known. Several studies have suggested the primary importance of demyelination in the pathogenesis of CTX pathology (Philippart and Van Bogaert, 1969; Elleder et al., 1989), whereas others have hypothesized a primary axonopathy with secondary myelin loss (Pop et al., 1984; Soffer et al., 1995). In the present study, proton MRS showed a widespread decrease in NAA in the brains of patients with CTX, whereas values of brain Cho resonance intensities were not different from those of the normal control group. Changes in Cho resonance intensities are usually related to changes in levels of phosphocholine and glycerol phosphocholine, probably reflecting alterations in cell membrane integrity. These changes are seen during the early process of myelin breakdown and indicate active demyelination (Arnold and Matthews, 1996), whereas chronic and slowly progressive demyelinating processes usually do not show changes in Cho resonance intensities (Bruhn et al., 1992; van der Knaap et al., 1992; Kruse et al., 1993; Johannik et al., 1994). Thus, while we cannot exclude the presence of a chronic demyelinating process in brains of patients with CTX, the widespread decreases in NAA found in our study strongly support the hypothesis that the basic enzymatic defect of this disorder leads to accumulation of brain metabolites that can be neurotoxic and may cause a primary neuroaxonal pathology (Soffer et al., 1995).

As immunohistochemical studies have found NAA exclusively in neurones and neuronal processes in the mature brain (Moffett et al., 1991; Simmons et al., 1991), decreases in NAA have been interpreted as the expression of neuronal or axonal damage. The fact that O2A progenitor cells (Urenjak et al., 1993) and mature oligodendroglial cells in culture (Bhakoo and Pearce, 2000) can be induced to express NAA in vivo has raised some concerns about the specificity of NAA changes in vivo. It is not clear whether these in vivo conditions are relevant to the situation in vivo. However, future studies need to reconcile the data obtained from the use of antibodies with those obtained from the HPLC- and NMR-based analyses. As for the results presented here, oligodendrocyte density appears not to be reduced in normal-appearing white matter or chronic white matter lesions (Wolswijk, 1998). Thus, the potential of NAA expression in oligodendrocytes to confound our results appears to be minimal.

In the present study, significant increases in La in the cerebral and cerebellar regions of patients with CTX were found. The resonance intensity of La detected by in vivo MRS originates from intracellular and extracellular tissue.
Fig. 3 FLAIR images in transverse orientation showing mild, diffuse abnormalities in the cerebral white matter (A, Patient 10 in the tables), and a bilateral hyperintensity of the dentate nuclei and the surrounding cerebellar white matter (B, Patient 2 in the tables).

(Prichard, 1991; Arnold and Matthews, 1996). Thus, increased resonance intensities of La can reflect primary or secondary impairment of mitochondrial metabolism or infiltration of macrophages and inflammatory cells (Prichard, 1991). In the latter case, however, La resonance intensities increase transiently in pathologically active brain regions and are often limited to the lesion and the surrounding area (Arnold et al., 1992; De Stefano et al., 1995a). In contrast, an extensive and diffuse pathological increase in brain La is probably indicative of cerebral mitochondrial dysfunction (Matthews et al., 1993; De Stefano et al., 1995b). Recently, morphological and biochemical evidence of mitochondrial dysfunction (probably secondary to the toxic effect of high cholestanol and/or bile alcohol levels) have been reported in patients with CTX (Federico et al., 1991; Dotti et al., 1995). Thus, the results of the present study add to these previous data in suggesting the presence of a diffuse impairment of mitochondrial oxidative metabolism in CTX patients. Finally,
Fig. 4 Conventional T2-weighted (A) and FLAIR (B) images (Patient 10 in the tables) in transverse orientation, showing the dentate nuclei. A mild hyperintensity of the dentate nuclei was clearly detectable on FLAIR images only.

Table 3 Single voxel MR spectroscopy values of patients with CTX

<table>
<thead>
<tr>
<th>Patient</th>
<th>Supraventricular volume of interest</th>
<th>Cerebellar volume of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cho/Cr</td>
<td>NAA/Cr</td>
</tr>
<tr>
<td>1</td>
<td>1.28</td>
<td>2.41</td>
</tr>
<tr>
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</tr>
<tr>
<td>12</td>
<td>1.17</td>
<td>2.70</td>
</tr>
</tbody>
</table>

Patient mean 1.32 2.43 † 0.50 * 1.27 1.47 † 0.27 *
Standard deviation 0.14 0.27 0.17 0.18 0.13 0.10
Control mean 1.27 2.96 0.32 1.21 1.85 0.18
Standard deviation 0.14 0.19 0.08 0.07 0.10 0.04

Data are from large brain volumes positioned above the lateral ventricles and in the cerebellum. NA = not available. *P < 0.05; †P < 0.0001.
it is interesting to note that the two patients who were not under pharmacological treatment showed the highest La/Cr values, indirectly suggesting that an appropriate therapy does improve the brain metabolism in patients affected by CTX.

In the present study, we did not attempt absolute quantification of our MRS data, and they were expressed as ratios with respect to Cr, assuming that this was present at a constant level. Although the resonance intensity of Cr has been widely used as an internal standard in in vivo MRS studies (Arnold and Matthews, 1996), changes in apparent brain Cr concentrations have been reported in patients with several white matter disorders in recent MRS studies attempting absolute quantification (Davie et al., 1995; Frahm and Hanefeld, 1996; Sarchielli et al., 1999). However, Cr appears to be refractory to changes in normal brains (Arnold and Matthews, 1996) and a study using high-resolution in vitro proton NMR spectroscopy (which does not suffer from the same limitations as in vivo quantification) has shown that Cr levels are unchanged in the normal-appearing brain of patients with multiple sclerosis (Davies et al., 1995). As the normal-appearing brain comprised the greatest portion of the brain volume of interest used for our MRS studies, we believe that significant changes in Cr resonance intensities were unlikely. Consistent with this, ratios of Cho/Cr resonance intensities in the group of CTX patients did not differ from those of normal controls.

With the relatively long echo time (TE = 272 ms) used for our MRS acquisitions, the differences in NAA/Cr values found between normal controls and CTX patients could have been influenced by changes in the T2 relaxation properties in the pathological brains. However, it would require very large decreases in T2 to explain the whole reduction in NAA/Cr observed in this study. Recent MRS studies have reported either no changes in the relaxation proprieties of cerebral metabolites or a trend for prolonged T2 of NAA in pathological brains (Wilkinson et al., 1994; Christiansen et al., 1995; van der Toorn et al., 1995; Cady, 1996; Fujimori et al., 1998; Sarchielli et al., 1999). If T2 for NAA was also prolonged in CTX, our measurements would have overestimated NAA and thus underestimated the differences with respect to control subjects. In addition, it should be mentioned that the relatively long echo time does not allow accurate estimation of the lipid peaks in the brain volumes of interest. These are detected in positions 0.9 and 1.2 p.p.m. at this TE only with major accumulation (Arnold and Matthews, 1996; Narayana et al., 1998). Thus, although contamination by lipids of the La signal cannot be excluded, the absence of a visible resonance intensity signal at 0.9 p.p.m. and the presence of the characteristic doublet of the La methyl resonance at 1.3 p.p.m. suggest that most of the signal is originating from brain La and that the amount of MR-visible lipids is not very significant in CTX patients.

An important finding of the study was the close relationship seen between disability scores and cerebral NAA/Cr values. Recent spectroscopic studies have demonstrated highly significant correlations between decreasing NAA and increasing clinical disability in patients with several neurological disorders (Davie et al., 1995; De Stefano et al., 1995a, 1998, 2000; Federico et al., 1998). Thus, the results of the present study add to these previous studies in other neurological disorders in suggesting that the measure of axonal loss provided by MRS can be a reliable surrogate marker of disease outcome.

In conclusion, our study suggests that abnormalities in the dentate nuclei can be revealed by FLAIR sequences with great sensitivity. On the basis of the present results, the bilateral hyperintensity of the dentate nuclei and surrounding white matter can be considered a neuradiological feature suggestive of CTX and could become an important diagnostic marker in patients with incomplete or peculiar clinical manifestations of the disease. The decrease in NAA and increase in La seen by MRS in the brains of patients with CTX indicate the presence of widespread axonal damage and mitochondrial dysfunction and may help to improve understanding of the dynamics of pathological changes occurring in this rare metabolic disorder. The strong correlation seen between the patients’ clinical disability and the putative axonal marker NAA suggests that the marker provided by MRS could be useful in longitudinal studies monitoring response to therapy in CTX patients.

Acknowledgements
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Fig. 5 Data illustrating the relationship between clinical disability (EDSS) and NAA/Cr in the cerebral volume of interest for patients with CTX (SROC = -0.78, P < 0.005).


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