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Proton magnetic resonance spectroscopy reflects metabolic decompensation in maple syrup urine disease

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Abstract. Using localized proton magnetic resonance spectroscopy (^{1}H-MRS), accumulation of branched-chain amino acids (BCAA) and their corresponding 2-oxo acids (BCOA) could be non-invasively demonstrated in the brain of a 9-year-old girl suffering from classical maple syrup urine disease. During acute metabolic decompensation, the compounds caused a signal at a chemical shift of 0.9 ppm which was assigned by in vitro experiments. The brain tissue concentration of the sum of BCAA and BCOA could be estimated as 0.9 mmol/l. Localized ^{1}H-MRS of the brain appears to be suitable for examining patients suffering from maple syrup urine disease in different metabolic states.

Localized proton magnetic resonance spectroscopy (^{1}H-MRS) of the brain allows the non-invasive study of metabolic disorders in vivo [1–3]. Maple syrup urine disease (MSUD; McKusick 24860) is characterized by acute and chronic brain dysfunction due to accumulation of branched-chain amino acids (BCAA) and their 2-oxo acids (BCOA) caused by a defect of the oxidative decarboxylation of leucine, isoleucine, and valine [4, 5].

In this study, we present the results of an MRS examination of the brain of a 9-year-old girl suffering from classic MSUD, during an acute metabolic decompensation. The accumulation of the pathologic metabolites within cerebral tissue was demonstrated non-invasively. The concentration of the sum of BCAA and BCOA could be estimated using in vivo ^{1}H-MR spectroscopy.

Patients and methods

The plasma concentrations of BCAA were determined by automated amino acid analysis, and of BCOA as quinoxalinole derivatives by a high-performance liquid chromatography (HPLC) method [6]. Image-guided volume-selective ^{1}H-MRS measurements were performed using a clinical 1.5-T whole-body MR system (Gyroscan S 15, Philips, Best, The Netherlands) operating at 63.86 MHz for protons. ^{1}H imaging preceded spectroscopy to define the volume of interest. The spectrum was taken from a $3 \times 3 \times 7$ cm^3 volume located in the parieto-occipital region of the patient's brain (see Fig. 1).

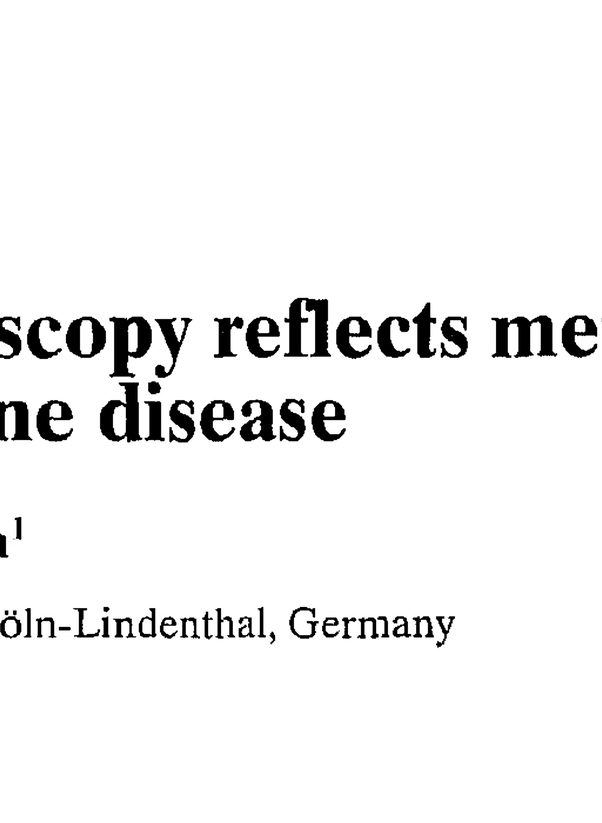

Fig. 1. T2-weighted axial MR image from a 9-year-old girl suffering from classic MSUD. The *rectangle* indicates the volume selected for localized ^{1}H-MR spectroscopy

Volume-selective ^{1}H spectra were achieved using a spatially selective 90°–180°–180° spin-echo sequence [7, 8] with water suppression by selective inversion. The applied spin-echo times (TE) of 136 ms resulted in inversion of doublets with spin-spin couplings of about 7.35 Hz (e.g. lactate and amino acids as leucine, isoleucine, valine, and the related 2-oxo derivatives). A repetition time (TR) of 2 s resulted in a total acquisition time of 8 min 32 s for 256 scans.

Spectra were evaluated quantitatively after Lorentzian broadening of 2 Hz and phase correction by comparing peak areas, which were calculated using the product of peak height and full line width at half maximum, assuming Lorentzian line shape.

Spectra from six additional children of between 4.5 and 14.5 years of age, without known metabolic disorders, taken under the same conditions were available for comparison.

Results

The 9-year-old patient presented with high fever, vomiting and moderate ataxia during acute metabolic decompensation of known classic MSUD, diagnosed in the

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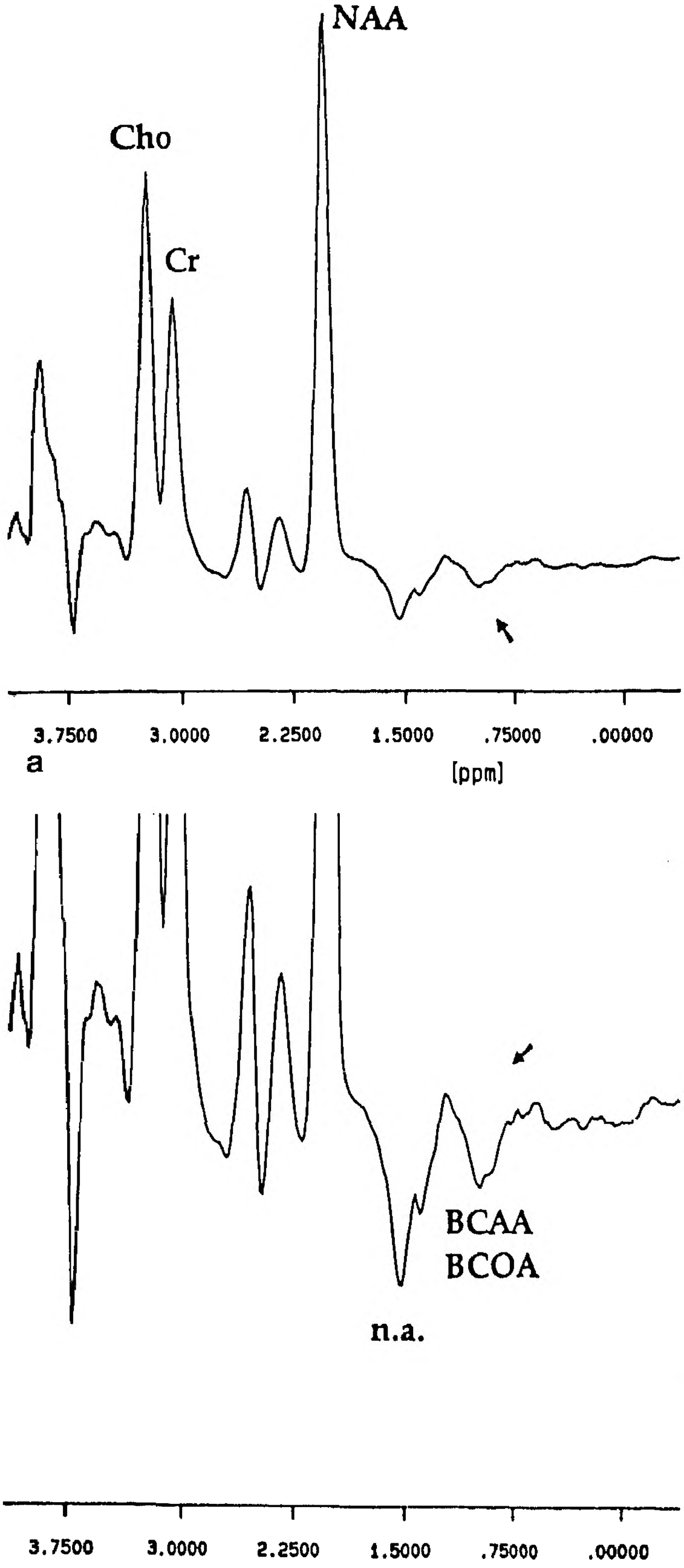

Fig. 2a. Proton MR spectrum from a 9-year-old girl with classic MSUD. Spectrum of predominantly white matter from a 63-ml volume indicated in Fig. 1; **b** the same spectrum after magnification of the intensity axis by a factor of 3

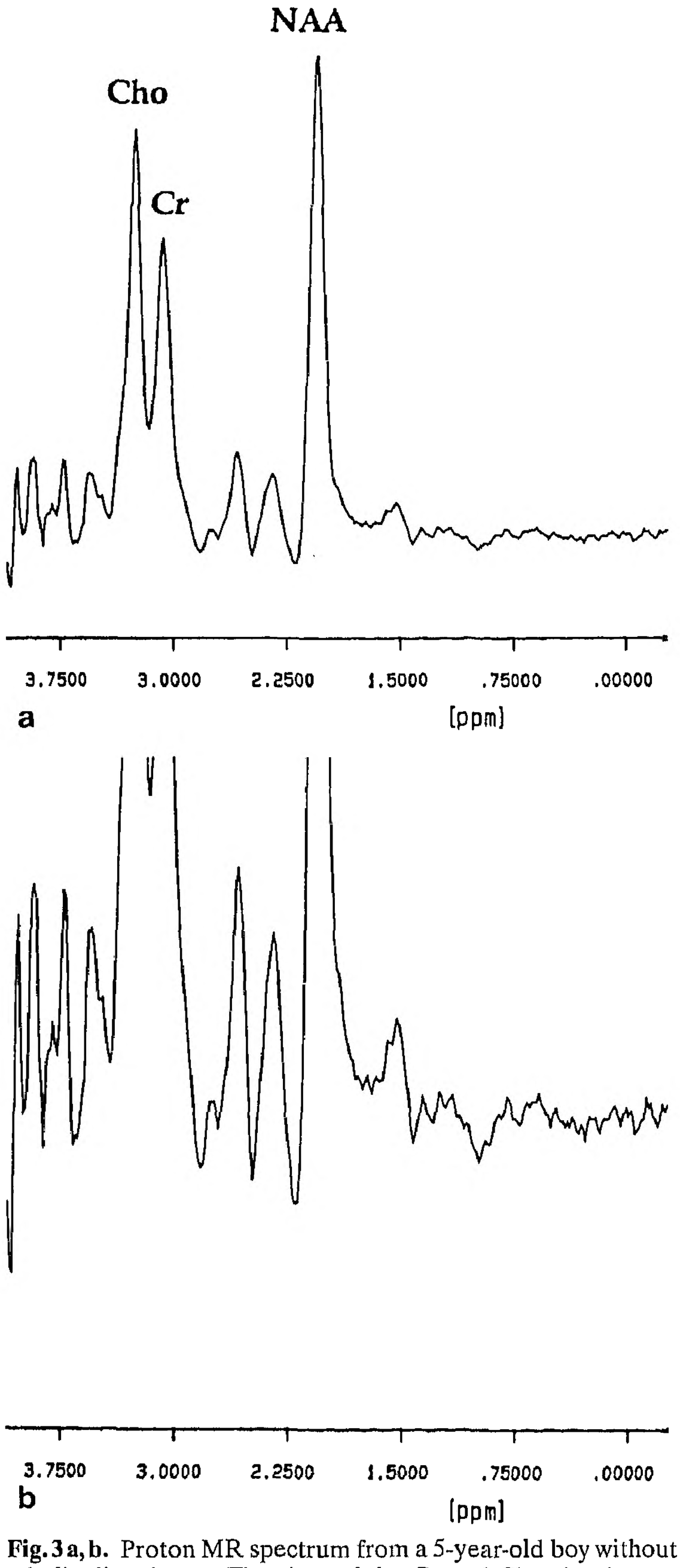

Fig. 3a, b. Proton MR spectrum from a 5-year-old boy without metabolic disorders. **a** The sizes of the Cr and Cho signals are matched to the corresponding signals in Fig. 2; **b** the same spectrum after magnification of the intensity axis by a factor of 3. The signal at 0.9 ppm is significantly smaller than in the spectrum from the patient suffering from MSUD

neonatal period when she sufferend from metabolic coma. At the time of admission, the plasma concentrations of BCAA were found to be elevated: Leu, 1023 μmol/l; Val, 692 μmol/l; Ile, 290 μmol/l, compared with normal concentration ranges: Leu, 77–173 μmol/l; Val, 167–265 μmol/l; Ile, 30–71 μmol/l [9]. Oral feeding was stopped, and high-caloric parenteral nutritition was started immediately. During the following days, oral feeding was reintroduced, using a diet extremely reduced in leucine.

Seven days after admission, ^{1}H-MRS of the brain was performed. At that time the patient showed only mild ataxia and she was being fed completely orally. The plas-

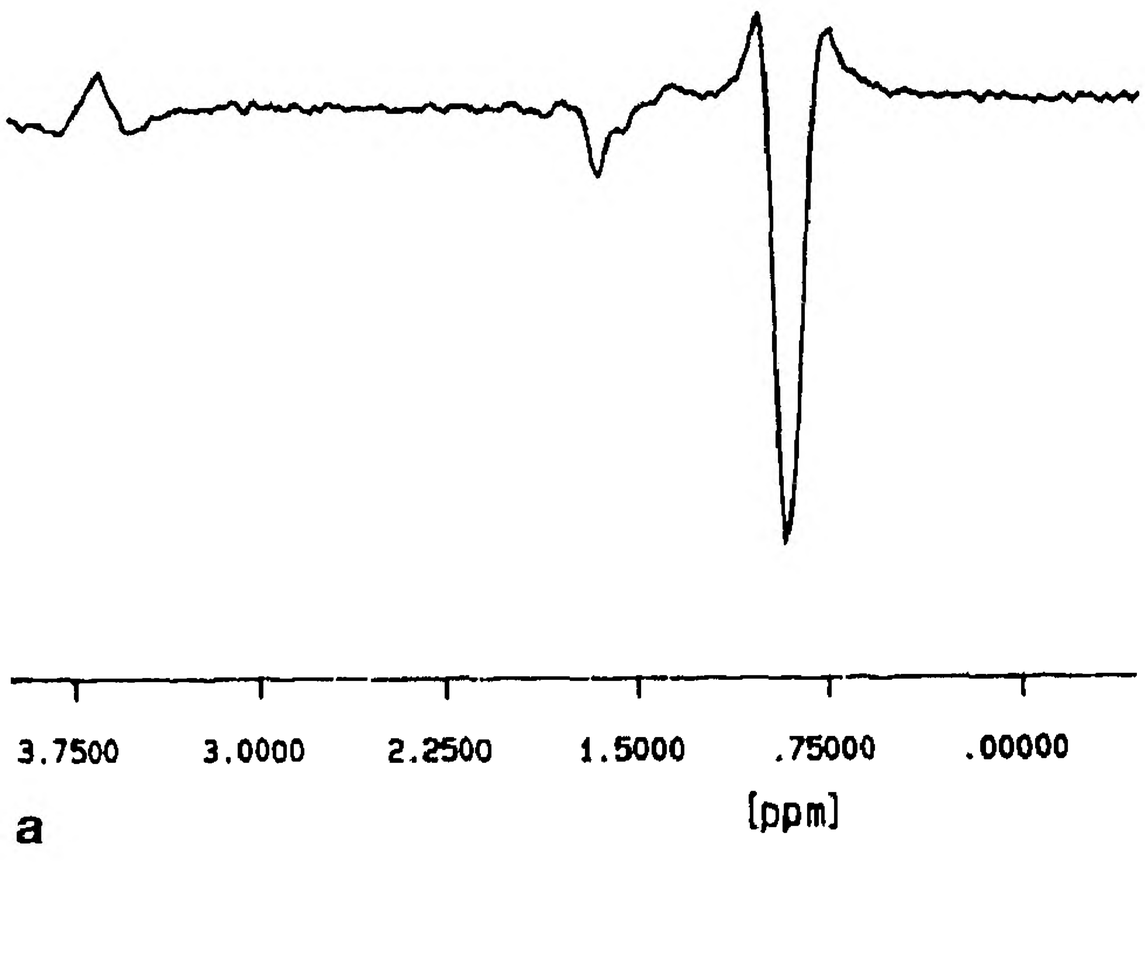

Fig. 4 a, b. Proton MR spectra of aqueous solutions of **a** leucine and **b** 2-oxo-isocaproic acid, obtained with an echo time of TE = 136 ms and phased according to the spectrum shown in Fig. 2

ma concentrations of BCAA and their corresponding BCOA were still high: Leu, 1143 μmol/l; 2-oxo-isocaproic acid, 497 μmol/l; Val, 487 μmol/l; 2-oxo-isovaleric acid, 49 μmol/l; Ile, 259 μmol/l; 2-oxo-3-methylvaleric acid, 101 μmol/l. Normal plasma concentrations of BCOA are: 2-oxo-isocaproic acid, 42 μmol/l; 2-oxo-isovaleric acid, 15 μmol/l; 2-oxo-3-methylvaleric acid, 20 μmol/l [10].

MR imaging showed normal intracerebral structures, and no abnormalities of cerebral white and grey matter could be detected.

Fig. 1 shows a representative T2-weighted axial image, which was used to select a rectangular volume comprising predominantly occipital white matter for spectroscopy. The proton spectrum of this patient (Fig. 2 a) shows relative signal intensities of *N*-acetyl-aspartate (NAA), choline (Cho) and creatine (Cr) quite comparable to findings in normal subjects (Fig. 3). The ratios are NAA/Cho = 1.37, NAA/Cr = 1.98, Cr/Cho = 0.70. In addition, the spectrum exhibited a small but distinct inverted signal at a chemical shift of 0.9 ppm, which becomes evident after magnification (Fig. 2 b). This signal was assigned to the methyl residues of BCAA and BCOA, based on its chemical shift and the fact that the signal was inverted at the echo time of 136 ms, which indicates a spin-spin coupling of about 7 Hz. To confirm the assignment, pure 2-oxo-isocaproic acid as well as pure leucine, which contribute the largest amount to the signal in question, were dissolved in demineralized water and adjusted to neutral pH. In vitro spectra of the solutions were obtained using the same volume-selection method and echo time (Fig. 4).

A signal intensity ratio (BCAA + BCOA)/Cr of 0.20 was calculated for the patient. In spectra of healthy children this signal was found only in low intensities ((BCAA + BCOA)/Cr < 0.1, Fig. 3).

A further inverted signal at 1.6 ppm in the patient's spectrum could not be assigned.

Discussion

In MSUD, acute metabolic decompensation leads to accumulation of BCAA and their BCOA in brain tissue, resulting in both short-term and long-lasting cerebral impairment. MRI studies report on dysmyelination of the white matter and abnormalities of grey matter, particularly the globi pallidi [11].

In the child presented here, morphological changes could not be observed. However, ^{1}H-MRS provided information on increased concentrations of BCAA and BCOA in the brain in a non-invasive manner. Similar results have recently been reported by another group [12]. However, in contrast to the spectra of the patient described by Felber et al. [12], in the brain tissue of our patient no signal of lactic acid was found by ^{1}H-MRS, possibly reflecting the lower degree of metabolic disturbances.

The concentration of BCAA and BCOA in the brain tissue may be estimated from the intensity of their methyl residue resonance.

Using creatine as an internal concentration standard with an assumed brain tissue concentration of 9 mmol/l [13], the concentration for the sum of BCAA and BCOA can be calculated as 0.9 mmol/l. This value accounts for the fact that six protons contribute to the signal instead of three as in the case of creatine. A correction for relaxation and saturation effects is not feasible, as T1 and T2 values are not known for BCAA in brain tissue. We assume that the relaxation times of BCAA and creatine are comparable, as the sizes of the molecules are in the same order, so that the error from this source would be minor. The concentration may be underestimated, however, owing to incomplete spectral visibility and incomplete refocusing of methyl residue doublets. In the brain tissue, the true JJ coupling constants may not match exactly the 7.3 Hz of lactate, for which the standard spectroscopic measurement protocol is optimized.

In comparison, in the spectrum of a subject without metabolic disorders given in Fig. 3, the resonance at 0.9 ppm indicates an amount of spectroscopically visible BCAA of less than 0.4 mmol/l in brain tissue.

The measured signals represent metabolite content of brain tissue, while only plasma values are available from biochemical assays. As has been shown for glycine, brain tissue concentrations of amino acids are usually in the same order of magnitude as plasma concentrations [3]. In the child without metabolic disorders, the sum of normal plasma concentrations of BCAA and BCOA, as assumed to be present in this case, range from 350 to 590 μmol/l. This is an accordance with the brain tissue concentration of less than 0.4 mmol/l estimated from the MR spectrum. The plasma concentration of the patient was 2536 μmol/l on the day of the MR examination. The brain tissue concentration of 0.9 mmol/l estimated from the spectrum is well below this value. This may reflect incomplete visibility of the amino acids or underestimation due to a systematic error. The increase over normal values is clearly detectable, however.

In conclusion, localized ^{1}H-MRS of the brain serves as a non-invasive tool to obtain information on BCAA and BCOA concentrations in the brain tissue in different metabolic states. Our preliminary data indicate that ^{1}H-MRS may be useful in evaluating the state of disease in MSUD and response to therapy.

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