MRS Characteristics of Creatine Deficiency Syndrome

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Introduction

Creatine (Cr) and phosphocreatine (PCr) are essential for the storage and transmission of phosphate-bound energy in muscle and brain. Therefore, Cr deficiency is a severe condition leading to developmental delays. Two siblings were suspected to suffer from Cr deficiency disorder following the clinical phenotype and homozygosity mapping. Both patients presented with mental retardation, speech delays and myopathy. The appearances of their brain MRI examinations were normal. To ascertain the diagnosis of Cr deficiency syndrome non-invasively, MRS of the patients' brain[1] and muscle was performed. The results of brain MRS confirmed the Cr deficiency diagnosis and were in agreement with the severe mutation in a gene encoding the first enzyme, namely L-arginine:glycine amidinotransferase (AGAT), in the Cr biosynthetic pathway[2].

Previous ^{1}H-MRS examinations of Cr deficiency were performed on patients carrying a mutation in the gene encoding of the second enzyme in the Cr synthetic pathway, namely guanidinoacetate methyltransferase (GAMT)[3], or a mutation in the creatine transporter gene (CT1/SLC6A8)[4]. Here we report on the muscle and brain ^{1}H-MRS characteristics of patients with the rare AGAT deficiency.

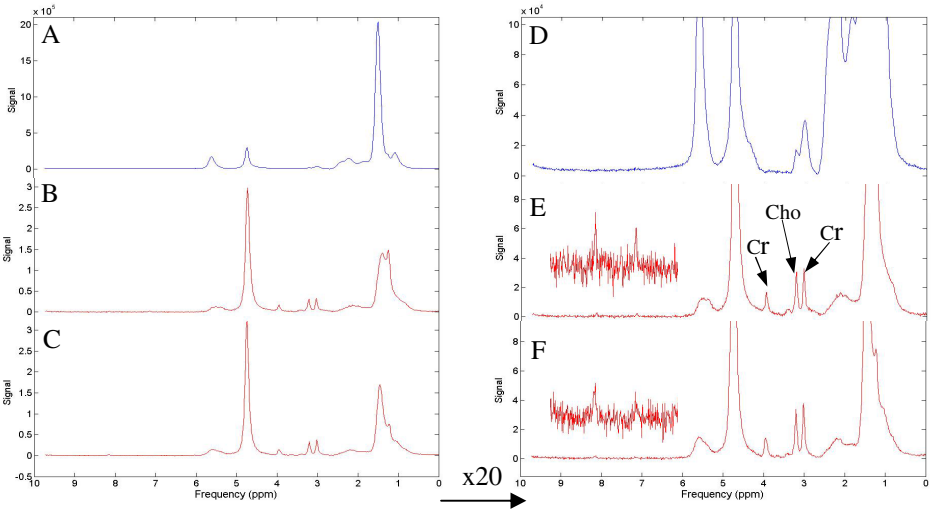
Materials and Methods

Patients: Two siblings, 20 and 14 years old (male and female, respectively). Healthy volunteers: 27, 24, and 25 years old (two men and one woman, respectively). ^{1}H-MRS was carried out using a single voxel PRESS, TE=30 msec, TR=2 s, voxel=8 ml (2x2x2 cm^3) at 3T (Tim Trio, Siemens). For brain spectroscopy, the volume of interest was positioned within the frontal lobe and a 12 channel receive only coil was used for detection of 80 averages. For muscle spectroscopy an 8 channel knee matrix coil was used for collecting 8 averages. Spectral analysis was performed using JMRUI (EU), MATLAB (Natick, MA, USA), and LC-Model (S. Provencher, Canada) [5].

Results

Figures A-C demonstrate the MRS characteristics of the gastrocnemius muscle tissues of healthy subjects (B, C) vs. the adductor muscle of one of the Cr deficiency patients (A). Figures D-F show the same speactra that are shown in A-C (respectively) with a 20 fold enlargment of the vertical scale. The inserts in E and F depict additional signals at 7.2 and 8 PPM which are present in the healthy muscles but appear to be absent in the muscle of the Cr deficiency patient. The 3-3.2 PPM spectral region of the Cr deficiency patient (D) appears different than the in the healthy muscles (E-F): first, the signal at 3.2 PPM (choline) appears at a lower level and second, the peak at 3 PPM appears wider and since it is not accompanied by a peak at 3.9 PPM, can not be attributed to Cr. The lipid region (0.9-2.2 PPM and 5.4-5.6 PPM) shows a much higher lipid content (both saturated and unsaturated) in the Cr deficiency muscle (A and D).

Figure G shows the brain MRS characteristics of the Cr deficiency patient: Cr signals were on the boarder of detection, both choline (Cho) and myo-Inositol (mI) concentrations were lower than normal (e.g. in comparison to one healthy volunteer, Table of LC-Model results below).



Metabolite in mM:	NAA	Cho	Cr	mI
Healthy volunteer	7.2	2.1	5.0	4.2
Cr deficiency (20 y/o)	5.3	1.0	0.5	1.6
Cr deficiency (14 y/o)	7.7	1.0	0.0	2.8

Discussion

^{1}H-MRS of the muscle in healthy volunteers showed metabolite signals that were similar to those observed on previous studies[6-8]. The Cr deficiency syndrome may occur due to two gene mutations, either in AGAT or GAMT. The diagnosis of Cr deficiency that is caused by a mutation in the AGAT enzyme in the two siblings was reinforced by ^{1}H-MRS of their brain and muscle and both started a treatment of Cr supplementation. The patients will be followed clinically and by MRS. The findings in the muscle indicate a range of metabolic abnormalities associated with the lack of Cr production.

References

(1) M. C. Bianchi, et al. *Ann. Neurol.* **2000**, 511-513. (2) C. B. Item, et al. *Am. J. Hum. Genet.* **2001**, *69*, 1127–1133. (3) T. Thiel, et al. *Proc. Intl. Soc. Mag. Reson. Med* **2001**, *9*. (4) G. J. Pyne-Geithman, et al. *Mol. Cell. Biochem.* **2004**, *262*, 35–39.(5) S. W. Provencher, *Magn. Reson. Med.* **1993**, *30*, 672-679. (6) M. A. Thomas, et al. *Magn. Reson. Med.* **2005**, *53*, 495-502. (7) J. Rico-Sanz, et al. *J. Appl. Physiol.* **1999**, *87*, 2068-2072. (8) M. J. Kruiskamp, et al. *NMR Biomed.* **2001**, *14*, 1-4.