In vivo Proton MR Spectroscopy Findings specific for Adenylosuccinate Lyase Deficiency

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Introduction:

Adenylosuccinate lyase (ADSL) deficiency (OMIM #103050) is a rare autosomal recessive inborn error of purine metabolism [1]. The broad clinical spectrum ranges from fatal neonatal encephalopathy to mild psychomotor retardation and autistic features. On brain MRI some patients present with white matter (WM) signal changes [2-4]. Biochemically, ADSL deficiency is characterized by the accumulation of succinylaminoimidazolecarboxamide riboside (SAICAr) and succinyladenosine (S-Ado) in cerebrospinal fluid (CSF), urine, and plasma [5]. Concentrations of SAICAr and S-Ado can be determined by high resolution *in vitro* proton MRS [6]. To date, 56 cases have been reported exhibiting about 40 different disease causing mutations in the *ADSL* gene [4]. Here we report a conclusive finding in localized *in vivo* proton MRS in three patients with biochemically and genetically proven ADSL deficiency.

Patients:

Three boys (pat. 1-3, age 4-9 yrs) presented with muscular hypotonia, psychomotor delay, behavioral abnormalities, and WM changes on brain MRI (**Fig. 1A-C**). Two of them had seizures. Screening for inborn errors of metabolism included *in vitro* high resolution proton MRS. It revealed an ADSL deficiency that was confirmed genetically.

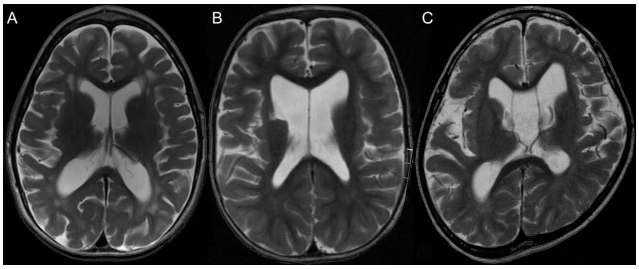

Fig. 1: Patient 1 Patient 2 Patient 3
Note the different appearance of WM changes

Methods:

For pat. 1 and 2, 3T MRI systems (Magnetom Trio, Magnetom Tim Trio, Siemens, Germany) were used. Pat. 3 was studied with a 1.5T MRI system (Magnetom Vision, Siemens, Germany). For localization STEAM [7] (pat. 1: TR/TE/TM 6000/20/10 msec, Volume of interest (VOI) 4.1ml; pat. 3: TR/TE/TM 6000/20/30 msec, VOI 8ml) or PRESS (pat. 2: TR/TE 6000/30 msec, VOI 4.1ml; pat. 3: TR/TE 2000/136 msec, VOI 8ml) were applied. VOI was placed in abnormal and normal appearing frontal and parieto-occipital WM and basal ganglia (BG).

Major detectable metabolites include *N*-acetylaspartate and *N*-acetylaspartylglutamate (tNAA), creatine and phosphocreatine (tCr), choline-containing compounds (Cho), and *myo*-inositol (Ins). The absolute concentrations were determined by LCModel and compared to age-matched controls [8,9]. To increase SNR spectra from BG and frontal WM of pat. 1 were summed using LC-Model. The spectral parts between 4 and 9ppm of pat. 1-3 were compared to spectra of healthy controls (n=17, age 8.2 ± 1.6 years (mean ± SD)).

Results and Discussion:

An additional resonance at 8.3ppm was detected in all patients in all brain regions investigated independent of the used localization sequences, measurement parameters, and field strengths (**Fig. 2A-C**). This signal is not present in the normal human brain (**Fig. 2D**).

In vitro MRS of CSF of ADSL deficiency patients showed at pH 7.4 singlets at 8.27 and 8.29ppm and a doublet 6.08ppm corresponding to elevated concentrations of S-Ado as well as a singlet at 7.48ppm and a doublet at 5.66ppm corresponding to SAICAr [6]. Given the lower spatial resolution of *in vivo* MRS, the 8.3 ppm peak represents the merged singlets at 8.27 and 8.29ppm of S-Ado. The *in vitro* MRS S-Ado resonances originate from a single proton [6]. The resonances at 8.27 and 8.29ppm overlap in *in vivo* MRS, thus increasing the signal height above noise level whereas the split resonance at 6.08ppm remains undetectable. S-Ado resonances were of comparable prominence in spectra from 1.5 and 3T. This might be due to the larger VOI of the 1.5T spectrum and the use of PRESS. Semiquantitative assessment of the 8.3ppm peak was accomplished by comparing the amplitudes to the tCr singlet (3.03ppm) and correcting for number of protons. Assuming an imperfect overlay of the singlets a range of concentrations is given (0.4-1mM). There were no additional signals that may be ascribed to accumulated SAICAr. Quantitative analyses of the major metabolites revealed increased Ins and tCr in WM, probably reflecting unspecific astrocytic proliferation.

In summary, the additional signal at 8.3ppm originating from accumulated S-Ado in ADSL deficiency represents an unambiguous *in vivo* proton MRS feature in a neurometabolic disorder.

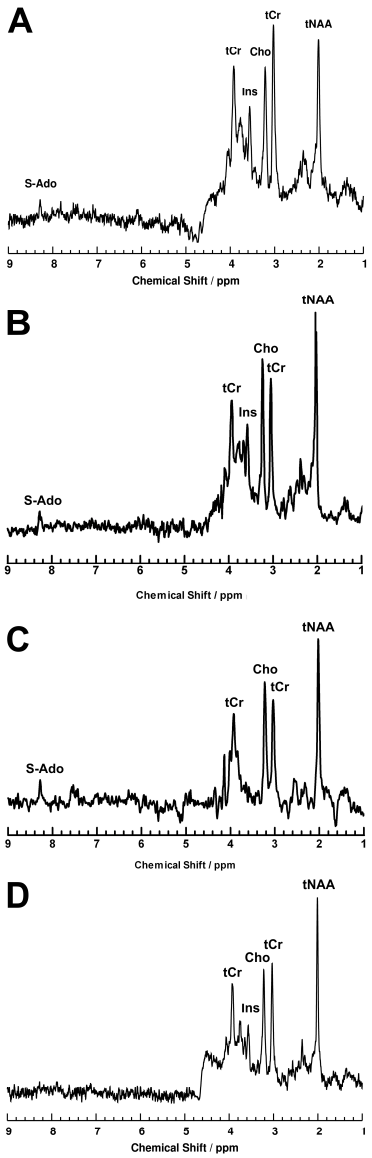

Fig. 2: (*A*): pat. 1: sum of WM and BG spectrum (3T, TE 20ms). (*B*): pat. 2: WM spectrum (3T, TE 30ms). (*C*): pat. 3: WM spectrum (1.5 T, TE 135ms). (*D*): control WM spectrum (3T, TE 20ms).

References:

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