Multi-slide proton MRSI and clinical outcome in children with late infantile Metachromatic Leukodystrophy (MLD)

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Introduction

Metachromatic Leukodystrophy (MLD) is a rare autosomal recessive disease caused by deficient arylsulfatase A, resulting in an accumulation of galactosyl sulfatides (cerebroside sulfate), a major constituent of myelin. The accumulation of galactosyl sulfatides leads to a progressive degeneration of white matter in the central nervous system (CNS), and the peripheral nervous system (PNS), which is accompanied by neuropsychological and neurological symptoms. MLD is caused by mutations in the *ARSA* gene. The incidence has been estimated to be about 1 per 40.000. The disease has three forms: The late infantile form, which is usually diagnosed in the second year of life, the juvenile form (with onset at 4-16 years), and the adult form (with onset after 16 years of age). The late infantile form has an early, rapidly progressive, debilitating course with sensory-motor dysfunctions, and it is fatal before the age of 10 years. Until now, there is no approved treatment for the late infantile form, but many different approaches are currently being investigated [1 2 3 4 5]. MR spectroscopy has been used to describe and quantify metabolic variation in brains with white matter disease, but spectroscopy studies in patients with MLD are few. Two studies conducted at short echo time showed a reduction of N-acetyl-aspartate (NAA) in grey and white matter, elevated lactate, and increased levels of brain myo-inositol, when compared to age matched controls.[6] In this study, thirteen children with late infantile MLD were examined by multi-slice spectroscopic imaging. Drastic spectral changes at long echo time and pronounced brain-area specific variations were found. The relative concentrations of N-acetyl aspartate (NAA), total Choline (Cho) and total Creatine (Cr) were determined in selected areas. [7]

Material and methods

Eight girls and 5 boys with an age range from 25 – 59 months, were enrolled as part of an enzyme replacement therapy study.. The diagnosis was confirmed by genotyping and measurement of the arylsulfatase A activity in leukocytes (2.2 – 9.4 nmol/h/mg). The inclusion criteria required a residual motor function and a symptom debut before the age of 4 years. The scan, the Gross Motor Function Measure-88 (GMFM), and the Mullen's Scale of Early Learning were done in the same week. [8 9] Echo-planar spectroscopic imaging was performed on a 1.5T Siemens Vision [10] with the following parameters: 8 axial slices covering most of the cerebrum, matrix 32x32, isotropic $(1cm)^3$ resolution, TE/TR=144/4300 ms. Lipid suppression was achieved via inversion (TI=165ms). A water-reference acquisition provided voxelwise frequency correction and phasing. The spectroscopic measurement duration was 20 minutes. Spectra were evaluated for individual voxels and for regions of interest (ROIs), using software developed in house. Metabolite measures were corrected for global coil loading and are given as institutional units and ratios based on voxelwise regression. Corresponding T2-weighted anatomical images with high in-plane resolution (matrix 256x256) were measured with a spin echo sequence with echo train length 11, TE/TR=99/5400ms. Brain regions were selected on these based on the known evolution of abnormalities in the early MLD brain with special focus in the white matter regions.

Results

All thirteen children had low ASA enzyme activities, debut symptoms before the age of 4, and a genotype confirming the diagnosis of late infantile MLD.

The metabolite measures from a ROI in Semiovale and the calculated ratios are presented from all subjects in the table. The spectroscopic images show an almost complete loss of NAA signal, but less so in children with the least pronounced symptoms (subject 1, 3, 13). The NAA signal vanishes as the disease progresses. The results from the motor function (GMFM) varied in raw score from 180, where the child is still able to walk, to 13, where the child can move the head in a lying position. Three children were ambulatory, three were able to sit alone, and seven children had no trunk control. The cognitive function (Mullen's test) showed severe impairment in all children, except in the ones who could still walk. We found a significant correlation between decreasing NAA spectra in the deep white matter and decreasing cognitive and motor function, figure 1 and 2.

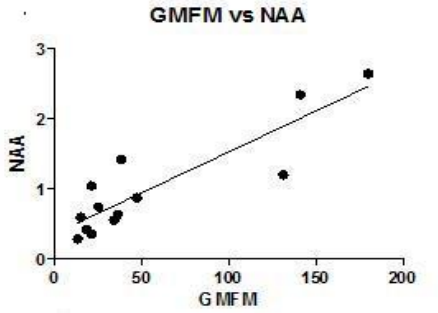

Fig 1 The NAA plotted against GMFM (R^2 0.7860).

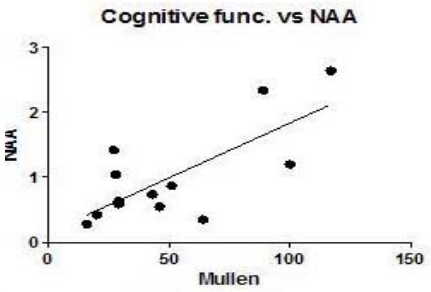

Fig. 2 The NAA plotted against the Mullens test (R^2 = 0.5490)

Subjects	Age	NAA signals (Semiovale)		
Number	**Months**	**NAA**	**Cho**	**Cr**
1	25	2,34	3,8	2,46
2	26	0,87	2,46	1,59
3	30	2,64	4,14	2,59
4	31	0,28	2,17	1,23
5	34	1,04	3,91	2,07
6	34	0,59	2,03	1,11
7	36	0,35	1,75	0,92
8	37	0,55	2,73	1,55
9	40	0,42	2,44	1,49
10	41	1,2	3,31	1,9
11	44	0,74	2,56	1,54
12	50	0,63	2,77	1,5
13	59	1,42	2,67	1,36

Discussion.

We examined NAA spectra from Semiovale (deep white matter) in children with late infantile MLD. In this region, the contaminations from the grey matter and CSF are minimal. NAA serve as a marker of neural and axonal integrity. The brain of a normal child has low NAA at birth, increasing rapidly in the first year of life. We found very low NAA values in most of the children and a significant correlation of decreasing signal of NAA with the scores of cognitive and motor function. This finding could indicate that MRSI can be an important parameter when evaluating MLD disease progression in future studies of possible MLD therapies.

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