Leukoencephalopathy with Brain Stem and Spinal Cord Involvement and Elevated White Matter Lactate (LBSL). Serial Proton MRS and DTI of a Child over a Period of 6 Years

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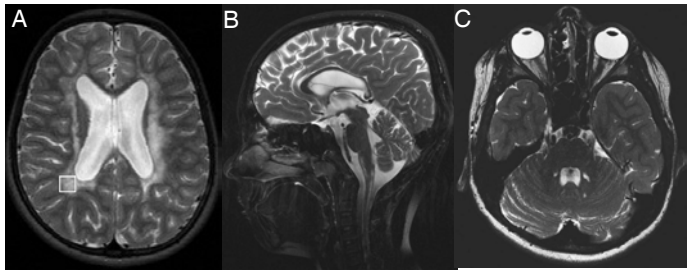
Introduction:

Leukoencephalopathy with brainstem and spinal cord involvement and elevated lactate (LBSL) is defined by its distinct neuroradiologic features. Cerebral white matter (WM) reveals widespread signal abnormalities. Most striking is the selective involvement of the pyramidal and sensory tracts to the level of the spinal cord. Proton MRS of affected WM has shown elevated lactate (Lac), decreased N-acetylaspartate, increased myo-inositol, and a slight increase of choline-containing compounds [1]. The pathologic basis of the disease remains unsolved. An autosomal recessive trait of inheritance seems likely [2]. Here, we report the results of a serial MRS and DTI study extending over 6.5 years of a child with LBSL to further elucidate the underlying pathophysiologic processes.

Clinical findings:

The now 11.5 years old boy developed normally until the age of three years as a sudden unsteadiness of gait was noted followed by increasing fatigue and shortening of walking distance over the next months. One year after onset, a slight hand ataxia was observed. Over the last five years no progression could be noted except for a mild spasticity of the legs during the last year. His mental development has been normal. Extensive laboratory investigations remained inconclusive. MRI showed widespread signal hyperintensities on T2-weighted images in the cerebral WM (**Fig. A**). An involvement of the pyramidal tracts to the level of the spinal cord and of the dorsal columns was seen (**Fig. B**). Signal abnormalities could be detected at the intraparenchymal tract of the left trigeminal nerve, the inferior cerebral peduncles (**Fig. C**), and the cerebellar WM. Except for a ventricular enlargement no significant changes could be observed over time.



Methods:

Localized proton MRS of cerebral WM (STEAM, TR/TE/TM = 6000/20/10 ms, 64 averages, volume-of-interest [VOI] = 4.85/4.1/2.7 ml) was performed 2, 2.5, 3, 3.5, 7.5 and 8.5 yrs after onset of symptoms. Four examinations were performed at 2 T (Siemens Vision) and two at 3 T (Siemens Trio). The VOI was placed within the right parieto-occipital (RPO) affected WM (**Fig. A**). Absolute concentrations of N-acetylaspartate and N-acetylaspartylglutamate (tNAA), creatine and phosphocreatine (tCr), choline-containing compounds (Cho), inositol (Ins) and Lac were determined by LCModel [3]. DTI, available for the last four examinations, was performed using single-shot STEAM MRI at 2×2 mm^2 in-plane resolution (b = 1000 s/mm^2, 6 or 24 gradient directions, 6 or 2.2 mm slices at 2 and 3 T, respectively). Maps of fractional anisotropy (FA) and mean diffusivity (MD) were calculated.

Results and Discussion:

The **Table** shows metabolite concentrations as well as FA and MD values of the RPO affected WM. Initially, MRS revealed elevated Lac, low tNAA (−46% of normal controls), and slightly decreased tCr as well as normal Cho and Ins (**Fig. D**). During the course of the following 18 months Lac decreased gradually to normal values, tNAA recovered up to 74%, and Ins showed a temporary increase (up to +59%) (**Fig. E**). The last two measurements revealed a stable normal metabolite pattern (**Fig. F**). DTI showed reduced FA (down to −62%) and increased MD (up to +99%) without considerable recovery over time.

The initial metabolite alterations indicated severe and preferential impairment of neuroaxonal structures rather than involvement of myelin. The observed recovery of tNAA points to an early acute event with apparently subsiding metabolic disturbance rather than to a permanent neurodegeneration. Interestingly, the decrease of Lac paralleled the tNAA recovery. A mitochondrial deficiency as well as a failure of neurons to utilize (or properly transfer) the Lac produced by astrocytes have been discussed as possible explanations for its accumulation [4]. The transient elevation of Ins points to the involvement of gliotic processes.

In contrast to MRS and clinical findings, the persistence of low FA values suggests that the main myelin and/or axonal structures remain severely and chronically impaired. Thus, there seems to be a better correlation between the clinical course and MRS changes than DTI results, although it cannot be fully excluded that current DTI methods fail to depict minor recovery processes. As DTI was not available for first two studies, we cannot speculate about possible recovery processes during that phase. Follow-up studies are required to discern whether Lac elevation depended on the acuteness of the disease, or if it was a long term consequence of the acute stage and if minor relapses occur during the disease course.

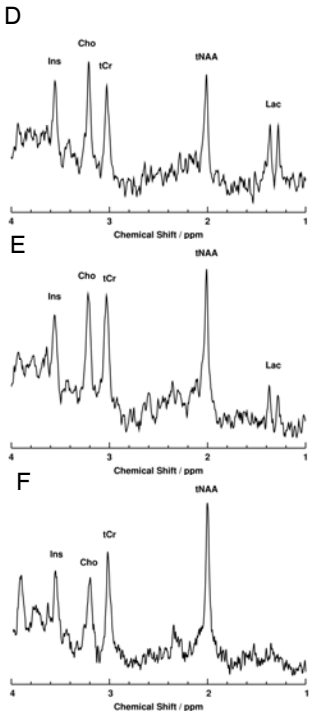


Figure: Patient with LBSL. **A** Axial T2W MRI with VOI, **B** sagittal T2W, **C** axial T2W at the level of the pons. **D** MRS at 2 yrs, **E** at 3.5 yrs, and **F** at 8.5 yrs after onset of symptoms.

Table: FA, MD, and absolute concentrations of brain metabolites (mean ± SD, mmol/l) of the LBSL patient as a function of time after onset of symptoms in comparison to age-matched controls [5]. *: > ± 2SD; n.p.: not performed.

	2 yrs	2.5 yrs	3 yrs	3.5 yrs	7.5 yrs	8.5 yrs	control (n=7)	control (n=6)
tNAA	3.7*	3.2*	4.7*	5.1*	6.5	6.1	6.9 ± 0.6	
tCr	3.9*	4.2	4.3	5.4	4.7	4.4	4.9 ± 0.4	
Cho	1.6	1.6	1.6	1.9	1.3	1.5	1.6 ± 0.3	
Ins	4.8	4.8	5.9*	5.6*	4.6	5.1*	3.7 ± 0.6	
Lac	4*	3.2*	3*	2.4*	<1	<1	<1	
FA	n.p.	n.p.	0.12	0.14	0.14	0.14		0.32 ± 0.06
MD	n.p.	n.p.	1.28	1.3	1.61	1.32		0.81 ± 0.07

References: 1. van der Knaap, et al., *Ann Neurol* 53:252, 2003; 2. Serkov, et al., *Neuropediatrics*, 35:510, 2004; 3. Provencher, *MRM* 30:672, 1993; 4. Linnaniviki, et al., *Neurology* 63:688, 2004; 5. Pouwels, et al., *Pediatric Research* 46:474, 1999.