Serial Proton MRS of Neurometabolic Alterations in Hereditary Spastic Paraplegia with Thin Corpus Callosum (HSP-TCC)

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Introduction:

Hereditary spastic paraplegia with thin corpus callosum (HSP-TCC) is a complicated form within the heterogeneous group of hereditary spastic paraplegias. Characteristic clinical features comprise progressive spastic gait, cognitive impairment, and ataxia. Diagnostic MRI findings include thinning of corpus callosum (CC) and non-progressive white matter (WM) alterations [1]. Additional pathological signal changes have been described to various degrees in basal ganglia and thalamus. Onset of symptoms occurs in the second decade in most patients. HSP-TCC follows an autosomal recessive trait and has been linked to chromosome 15q13-15, and the locus designated SPG11 [2].

Here, we report a serial MRS evaluation and DWI over five years in a patient diagnosed with HSP-TCC. The aim was to understand the underlying neurochemical alterations giving rise to the characteristic MRI features and clinical symptoms in this rare disorder.

Clinical findings:

The now 25-year-old woman showed normal early motor and mental development. She was walking at 12 months of age and attended regular kindergarten and school. At 10 yrs. of age her school performance started to deteriorate. At the age of 14 yrs. a slowly progressive gait disturbance was noted and she was wheelchair-bound at 18 yrs. of age. Physical examination at the age of 25 yrs. revealed marked spasticity and hyperreflexia, ataxia most prominent in the legs, mild dementia, and a dysarthria. She was unable to walk, but could stand up with support [3].

Methods:

Localized proton MRS (STEAM, TR/TE/TM = 6000/20/10 ms, 64 accumulations) was performed at 20 and 25 yrs. of age. The first examination was carried out at 2T (Siemens Vision), the second at 3T (Siemens Trio). Volumes of interest (VOI = 4.85 and 4.1 ml) were placed within the frontal and parieto-occipital WM, and paramedian parietal gray matter (GM). Absolute concentrations of N-acetylaspartate and N-acetylaspartylglutamate (tNAA), creatine and phosphocreatine (tCr), choline-containing compounds (Cho), inositol (Ins), and lactate (Lac) were determined by LCModel [4]. Imaging protocols included T1-weighted 3D FLASH MRI (2T: TR/TE 15/4 ms, flip angle 20°, 0.8 x 0.8 x 4 mm^3; 3T: TR/TE 11/4 ms, flip angle 15°, 1 mm^3 isotropic resolution) (**Fig. MRI**) and T2-weighted fast spin-echo MRI (2T: TR/TE 3500/16 and 98 ms, respectively, flip angle 120°, 0.8 x 0.8 x 4 mm^3 resolution; 3T: TR/TE 8000/16 and 97 ms, respectively, flip angle 120°, 1 x 1 x 4 mm^3 resolution). Concomitant DWI at age 25 yrs. was performed with use of single-shot STEAM MRI at 2x2x4 mm^3 resolution (24 gradient directions, b=0 and 1000 s/mm^2) yielding maps of the fractional anisotropy (FA) and apparent diffusion coefficient (ADC).

Results and Discussion:

The **Table** shows metabolite concentrations in WM. The most striking finding was the reduction of tNAA showing a marked progression frontally and mild deterioration parieto-occipital. Similar results were obtained for Cho. This was accompanied by an elevation of Ins which remained unchanged in parieto-occipital WM and regressed in fontal WM (**Figure MRS**). The spectrum of GM showed normal metabolite concentrations at age 20 yrs. The follow-up data were affected by patient motion. An increased Lac of 2.2 mmol/l was found only in the first study in parieto-occipital WM. DWI resulted in reduced FA of 0.1 (age/region matched control: 0.68) and increased ADC of 1.44 $mm^2/s*10^{-3}$ (age/region matched control: 0.3) in periventricular WM. The MRI abnormalities remained largely unchanged over the follow-up period (**Figure MRI**).

Our MRS findings are consistent with progressive neuroaxonal loss in WM accompanied by astrogliosis. The decreased FA in periventricular WM points to altered structural integrity of the myelinated axons. The pattern is in good agreement with described histopathological changes, where CC was found hypoplastic, but well myelinated. Neuronal loss and gliosis were detected in upper and lower motor neuron system. Fibrillary gliosis has been observed in deep WM. Atrophy of cerebral WM was found to be most prominent in frontal regions [5]. Pattern and course of the metabolic changes indicate that the pathologic process in HSP-TCC is primarily affecting the axons and do not support a myelin disorder. In fact, recent studies provide evidence for an impaired axonal transport of NAA [6]. In summary, the MRI abnormalities remained essentially unchanged over the course of five years, whereas the metabolic alterations depicted by MRS correlate well with the ongoing clinical deterioration. MRS must be considered a valuable tool to monitor disease progression in HSP-TCC.

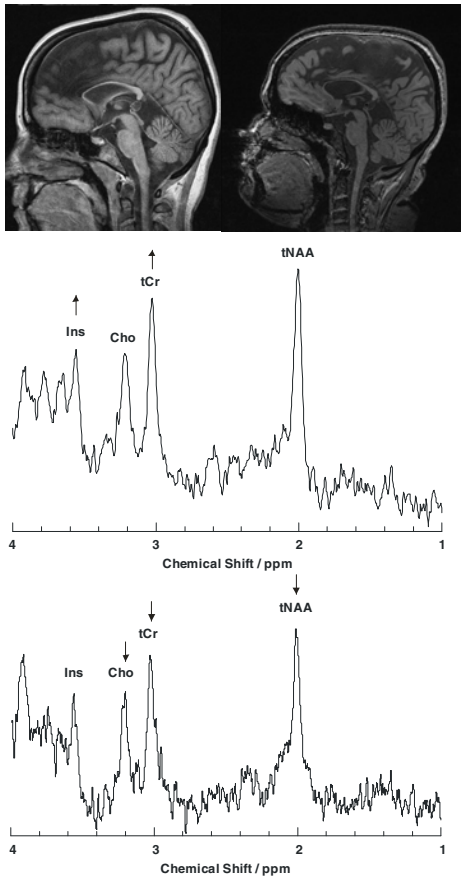

Figure: Sagittal T1-weighted images at (left) 20 yrs. and (right) 25 yrs. of age as well as proton MRS of right frontal WM at (middle) 20 yrs. and (bottom) 25 yrs. of age.

Table: Absolute concentrations of brain metabolites given as % difference to the mean concentrations of age and scanner matched controls [7, 8]. *: significant difference ≥ 2 SD.

	WM parieto-occipital		WM frontal	
	20 yrs.	25 yrs.	20 yrs.	25 yrs.
tNAA	-17*	-23*	-11	-47*
tCr	+14	+9	+30*	-26*
Cho	0	-32*	+12	-50*
Ins	+42*	+42*	+40*	+3

References:

1. Oshini J et al., *Acta Neurol Scand* 104: 191, 2001; 2. Shibasaki Y et al., *Ann Neurol* 48: 108, 2000; 3. Brockmann K et al., *Neuropediatrics* 36: 274, 2005; 4. Provencher SW, *MRM* 30: 672, 1993; 5. Wakabayashi K et al., *Acta Neuropathol* 101: 69, 2001; 6. Crosby AH et al., *Am J Hum Genet* 71: 1009, 2002; 7. Pouwels P et al., *Pediatr Res* 46: 474, 1999; 8. Natt O et al., *Magn Reson Med* 23: 3, 2005.