1H MR Spectroscopy and Relaxometry for the Determination of Iron and Metabolite Concentrations in Hallerworden-Spatz Syndrome Patients

M. Hajek[1], M. Adamovicova[2], V. Herynek[1], M. Dezortova[1], A. Skoch[1], F. Jiru[1]

[1]MR-Unit, ZRIR, Institute for Clinical and Experimental Medicine, Prague, Czech Republic, [2]Dept. Children Neurology, Faculty Thomayer Hospital, Prague, Czech Republic

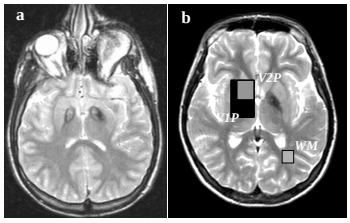
Introduction:

Accumulation of iron in the brain can be studied by using MR imaging. Hypo-intensive lesions in T2 images described as "eye-of-the-tiger sign" are typical MR findings for Hallerworden-Spatz syndrome (HSS) and correspond to the increased iron concentration in the globus pallidus (GP) and substantia nigra. Recently, the gene responsible for HSS was found (2). In humans one of four genes encoding panthothenate kinase (PANK2) is probably expressed in the brain. This gene is responsible for the change of the biochemical pathway of vitamin B5 (panthothenate acid) in the brain. A deficit of coenzyme A is responsible for major metabolic difficulties and also cysteine (not used in biosynthesis of CoA) known as strong chelating agent concentrates iron ions in cells. High concentration of (Fe^{2+}/Fe^{3+}) plays a role in a strong oxidative reaction which induces oxidative damage of cells (3). Both direct metabolic changes due to genetic mutations as well as iron intoxication are responsible for neurodegenerative disorders that are generally discussed as PKAN (panthotenate kinase associated neurodegeneration). The aim of the study was to apply T2 relaxometry and 1H MR spectroscopy to measure the concentration of iron and several metabolites in typical HSS lesions to describe metabolic changes in these patients.

Experimental:

Subjects: Three patients (a boy, 16 years old, and two girls, 14 years old) with typical clinical HSS were examined in the study. A group of 18 volunteers was examined to obtain control spectra from the basal ganglia. Written consent was obtained from all controls according to the Ethical Committee. **MR imaging and relaxometry:** The protocol of MR imaging included T2w sagittal, frontal, and transversal images obtained by a turbo spin echo imaging sequence (TR/TE=5400/99 ms, 1 acquisition, slice thickness 5 mm). T2 relaxation times were obtained using a CPMG sequence with 16 echoes, echo-spacing 22.5 ms, recovery time TR = 2000 ms. Three parallel axial slices through the anterior and posterior commissures were used. T2 values were obtained from T2 maps (T2 maps were calculated on a pixel-by-pixel basis by 3-parameter fitting from a whole slices). **MR spectroscopy:** The MR single-voxel spectra were measured using a STEAM (TR/TE/TM=5000/10/15 ms, 64 acquisitions) pulse sequence. 1H spectra were measured from three VOI (see Fig.1), two of them were positioned in the basal ganglia region (*V1P*~10ml, *V2P*~4.2ml, centered to GP) and one in the region of white matter by the left posterior horn of the lateral ventricles (WM=3.4ml). **Spectrum processing:** Visual inspection of spectra was performed by standard Siemens Numaris software. The spectra were then processed automatically by LCModel version 6.0-0 which takes into consideration lipids and macromolecules; a basis set with 13 metabolites was applied. The output values of concentrations [mM] were corrected by using the quality control coefficient f^{QC}, the contribution of CSF as well as correction coefficients for T1 and T2 saturation were found to be negligible.

Figure 1. *a) T2w image of the lesion in GP of patient 1; b) VOI's used for 1H MR spectroscopy (patient 3).*



Results:

Relaxometry: T2 MR images of two patients correspond to the findings "eye-of-the-tiger sign" which is a typical aspect of HSS due to increased concentration of iron in the lesion. In one patient we found only a decrease in signal intensity in the region of the GP. From T2 maps the mean values of relaxation times were obtained and data are summarized in Table 1. Relaxation times T2 in the area of periventricular white matter are decreased by about 15 ms compared to T2 found in the controls (4). Relaxation times of all patients in the GP show a significant decrease in T2 in the outer part of lesion which, in the case of "tiger eye" lesions, corresponds to the relaxation times in the lesion of patient 3. Relaxometry was used for the estimation of iron concentration in the tissue (see Table 2) according to data previously published by Hallgren (5) and Schenker (6). We constructed a calibration curve to calculate iron concentration. It is possible to estimate that the concentration of iron in the BG lesion is approximately 3x higher than in white matter and in the center of the "eye-of-the-tiger sign" lesions see Table 1.

Spectroscopy: The broadening due to the presence of paramagnetic iron decreased spectral resolution in the basal ganglia region. Spectra measured with 10 ms echo time were evaluated by using the LCModel technique to obtain the concentration of metabolites. We applied the calculation of metabolite concentration with the consideration of possible lipids (Lip) and macromolecules (mm) contributions and Table 2 summarizes results obtained from two volumes of interest in the basal ganglia region. Data were compared with the control concentration obtained from 37 basal ganglia areas. As expected, significant differences between the control and patient data were observed in the concentration of NAA, Cr and Cho compounds. Inter-individual differences among patients explain the high standard deviation of calculated values and correspond to the development of the disease. In the white matter of patients we only observed a decrease in Cho signal concentration compared to control data.

Discussion and conclusion:

The calculation of iron concentration in the BG is based on the assumption that iron is present in the basal ganglia in the form of ferritin. The accuracy of iron content estimation is approximately 15%. For other forms of iron the estimation may be affected by a systematic error. The inner area of the lesion seems not to be influenced by the increased concentration of iron and it is probably the intermediate form of lesion which subsequently transforms into the lesion type observed in the third patient (7). The presence of iron in the BG influences the calculation of concentrations through the LCModel technique. Surprisingly, the concentrations measured from the smaller volume *V2P* were higher than those from observed from the bigger volume *V1P*. Detailed inspection of the spectra calculated from the small and big volumes shows that the explanation can be found in the automatic base-line corrections which, in the case of broad signals, do not follow the shape of lipids and macromolecules and the resulting intensities are overestimated.

Table 1. *Relaxation times* T2(std), ***estimation of iron content [mg/100g]*** *in white matter (WM), outer (LO) and inner (LI) parts of lesions compared to control data*

	WM [ms]	**LO** [ms]	**LI** [ms]
patients	82.4 (2.4) ***10***	44.3 (1.5) ***48***	88.0 (3.3) ***6***
controls	95 ± 6 ***~5***	70.4 ± 2.4 ***17***	

Table 2. Concentration of basic metabolites (mM) in basal ganglia regions - see Figure 1. (*V1C concentrations of controls ± interval of confidence for p=95%, std in brackets)*

	Cho	**Cr**	**Ins**	**NAA+NAAG**	**Lip09**	**mm09**	**Lip20**	**mm20**
mean V1C	*1.6*±0.2	*8.9±0.5*	*3.0±1.8*	*8.8*±0.4	*1.3*±1.1	*10.6*±2.4	*2.4*±2.3	*20.8*±2.6
mean V1P	*1.4(0.3)*	*6.7(1.5)*	*3.0(1.6)*	*6.1(1.6)*	*0.2(0.3)*	*10.9(2.8)*	*0.1(0.2)*	*20.8(5.3)*
mean V2P	*1.8(1.4)*	*10.7(4.3)*	*5.8(1.9)*	*8.2(1.2)*	*1.5(2.2)*	*8.2(5.7)*	*1.0(1.5)*	*13.6(10.3)*

References:

1) Pedespan JM et al: Arch Fr Pediatr 1993, 50(1):35-37; 2) Zhou B et al: Nat Genet 2001, 28:345-9; 3) Rouault TA: Nat Genet 2001, 28:299-300; 4) Dezortová M et al: Acta Radiol 2001, 42: 459-466; 5) Hallgren B, Sourander P: J Neurochem 1958, 3: 41-51; 6) Schenker C et al: Neuroradiology 1993; 35(2):119-24; 7) Seren NR: Am J Neuroradiol 2003, 24:1690-1693.

Acknowledgements:

The study was supported by grants: GAČR 304/03/1189 and CEZ:L17/98:00023001, Czech Republic.