BRAIN 1H-MR SPECTROSCOPY OF PATIENTS WITH LEBER'S HEREDITARY OPTIC NEUROPATHY AND NON-AFFECTED CARRIERS OF mtDNA MUTATIONS

J. Ostojic[1], D. Kozic[2], J. Jancic[3], K. Koprivsek[4], and R. Semnic[5]

[1]Institute of Oncology Sremska Kamenica, Sremska Kamenica, Serbia, Yugoslavia, [2]Diagnostic Imaging, Institute of Oncology, Sremska Kamenica, [3]Clinic of Neurology and Psychiatry for Children and Youth, School of Medicine, University of Belgra, Serbia, Yugoslavia, [4]Institute of Oncology, Sremska Kamenica, [5]Diagnostic Imaging, Institute of Oncology, Serbia, Yugoslavia

Leber's hereditary optic neuropathy (LHON) is a maternally inherited mitochondrial disorder, characterized by bilateral subacute loss of central vision. Since only about 50% of males and 10% of females with mtDNA mutations develop LHON, the purpose of the study was to evaluate the possible metabolic abnormalities in normal appearing brain parenchyma in both affected patients and asymptomatic carriers.

METHODS

MR imaging and 1H MR spectroscopy were performed in 6 LHON patients diagnosed on the basis of mtDNA analysis, and 12 maternally related family members. For each patient, we examined mother and sibling, who also underwent mtDNA analysis. Combined MRI/MRS studies were performed at 1.5T MR imager, using the quadrature transmit/receive head coil. For each patient, the spectroscopic VOI measuring 15×15×15 mm , was positioned in two selected areas: the centum semiovale of the supratentorial white matter and gray matter in the area striata. Localization of the signal was performed using a single-voxel point resolved spectroscopy PRES technique with TR/TE=1500/135. The spectral peaks from NAA (N-acetyl aspartate), Cr (creatine) and Cho (choline) were integrated and expressed as ratios to the total creatine resonance and as absolute values. Absolute quantification of the signal intensities of NAA, Cho and Cr was obtained using an external referencing. The control group consisted of 50 healthy volunteers, examined with the same system and protocol. Alterations of metabolite ratios from those of control group were considered significant if they exceeded two standard deviations.

RESULTS

We found pathologic spectrum in all patients with LHON and in 80% of neurologically asymptomatic carriers of the mtDNA mutation. The statistically significant difference was found between the patients with LHOH and control group ($p<0.001$) and between the asymptomatic carriers of the mtDNA mutation and control group ($p<0.001$). No statistically significant difference was evident between the patients with LHON and asymptomatic carriers of the mtDNA mutation ($p=0.505$). False normal Cho/Cr ratio in the gray matter was noted in an asymptomatic carrier of the mtDNA mutation since the concentration of both choline and creatine was reduced. No statistically significant difference was found in NAA/Cr ratio between the affected/non-affected carriers of mtDNA mutation and the control group. No presence of lactate peak was noted.

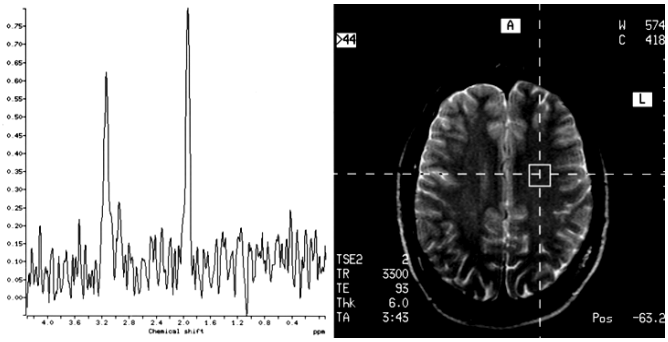

Figure 1. Increased Cho/Cr ratio in a normal appearing white matter, due to increased choline and decreased creatine concentration, in a 21 year-old patient with LHON and 3460 mutation.

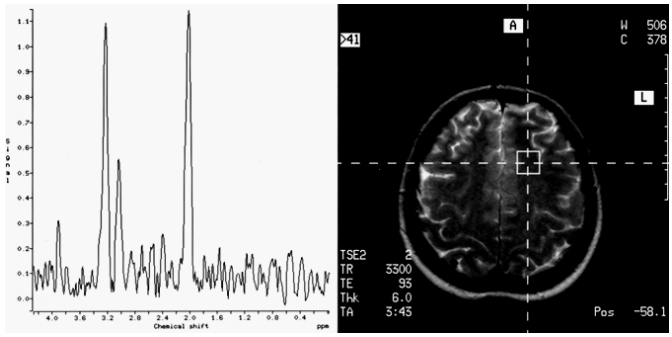

Figure 2. Increased Cho/Cr ratio in a normal appearing white matter, due to increased choline and normal creatine concentration, in a 41 year old asymptomatic family member with 11778 mutation.

DISCUSSION

In the past studies, ^{1}H-MRS has been applied in only four patients with LHON and showed no brain metabolite disorder (Jansen, Salvan).In the study of Bianchi et al. significant reduction of choline and NAA were identified in the normal appearing areas of brain parenchyma in 15 patients with non-LHON mitochondrial disorders (Bianchi).In both affected and non-affected patients with mtDNA mutation we found the decrease of choline concentration in the visual cortex, while both reduced and elevated peak of choline was noted in the normal appearing white matter. The decreased choline peak seems to be most consistent with the impairment of membrane maintenance due to reduced energy production since the choline peak is associated with choline-water-soluble pool, a precursor of the myelin phospholipid synthesis, and from the hydrophilic heads of the membrane phospholipid layers (Bianchi). Increased Cho/Cr ratio in the normal appearing white matter in affected and non-affected carriers of 11778 mtDNA mutation was noted, predominantly due to elevated choline peak. Such spectrum resembles the metabolic profile in active demyelinating diseases, that are associated mainly with this type of genetic disorder.

REFERENCES

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