# Cerebral Metabolic Alterations in McLeod Syndrome

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## Introduction

The McLeod neuroacanthocytosis syndrome is an X-linked multi-system disorder with hematological, neuromuscular, and central nervous system (CNS) involvement caused by mutations of the *XK* gene [1-3]. Onset age of neurological symptoms ranges between 30 and 40 years. Neuromuscular manifestations include a skeletal muscle myopathy of variable degree and a sensory-motor axonal neuropathy. CNS manifestations resemble Huntington's disease, and comprise choreatic movement disorder, psychiatric symptoms, subcortical cognitive decline, and generalized epileptic seizures. Cerebral MRI demonstrates caudate nucleus and putamen atrophy of variable degree, and quantitative FDG-PET shows a reduced striatal glucose uptake correlating with the disease duration [3]. The aim of the present MRS study was to investigate cerebral metabolic alterations in male McLeod patients and asymptomatic heterozygous females. The main metabolites of interest were N-Acetylaspartate (NAA), creatine (Cr) and choline containing compounds (Cho).

## Materials & Methods

5 male patients (mean age 46.2+/-6.4 years) suffering of McLeod's syndrome and 5 heterozygous females (mean age 45.0+/-9.8 years) as well as 11 healthy controls (mean age 42.3 ± 10.2, male /female: 5/6) participated in this study. All subjects gave written informed consent prior to participating. Measurements were carried out on a 3T Philips Intera whole body system (Philips Medical Systems, Best, The Netherlands), using a dedicated transmit/receive head coil. Multiple spin-echo spectroscopic imaging (TSI) [4] data was acquired from a slice oriented along the ac-pc line on the level of the caudate. Acquisition parameters comprised: 32x32 voxels, TR/TE = 1700/288 ms, echo spacing = 144 ms, BW = 2250 Hz, 256 samples. Total acquisition time per TSI measurement was around 7 min. In addition T1-weighted inversion recovery (IR) images with high tissue contrast were acquired for tissue segmentation purposes.

Raw data was k-space filtered with a cosine function before Fourier transformation. Postprocessing of the data further included exponential spectral filtering, a digital shift algorithm for improved water suppression, B0-correction, as well as a linear phase correction. Voxels showing spectra of good quality (no baseline distortions, all peaks resolved) were selected from the following regions of interest (ROI): left and right frontal lobe, insula, temporal lobe, occipital lobe, putamen/globus pallidus, thalamus and caudate. Spectra were then analyzed with jMRUI2.1. After removal of residual water and baseline correction, the peak areas of NAA, Cr and Cho were fitted using AMARES. Tissue composition for each voxel was computed by segmenting the IR images, aligning the MRI data with the CSI slice and convolving each tissue map with the spatial response function of the MRSI acquisition. For all voxels the ratio of NAA/(Cr+Cho) was calculated to correct for inter-slice variations of metabolite intensities due to B0 inhomogeneities.

In patients, the mean NAA/(Cr+Cho) and mean % white matter (WM) of all voxels in each ROI was calculated. In order to identify ROI with abnormally low NAA/(Cr+Cho) in patients, an individual threshold value for each ROI in a patient was defined. For this purpose, voxels were selected in the corresponding ROI of controls matching the mean %WM found in the ROI of each individual patient. After calculation of mean and standard deviation (SD), the threshold for an individual ROI in a patient was defined as: Threshold = mean (NAA/(Cr+Cho)) of controls – 2 SD (NAA/(Cr+Cho)) of controls. ROI at or below this threshold value were defined as "abnormal".

## Results

In three male McLeod patients, significantly lower NAA/(Cr+Cho) ratios were found in the insula (ML02, ML18), in frontal and temporal regions (ML16, ML18), and in thalamus (ML16, ML18). One patient had alterations in the occipital areas (ML21). Three patients with more widespread metabolic abnormalities had also prominent psychiatric or cognitive symptoms (ML02, ML16, ML18), whereas the other 2 patients with predominant movement disorder had no alterations (ML12) or possibly unspecific occipital alterations (ML21). Asymptomatic female heterozygotes showed no metabolic alterations, with the exception of one case with alterations in the left insular cortex (ML20). Since there were a high number of low-quality spectra in the ROI's covering the caudate nucleus, no conclusion about this region was possible. ROI's covering the putamen demonstrated no significant differences between individual patients and the mean of the control group.

| Patient | Gender | Age | Brain regions found to be abnormal |
|---|---|---|---|
| ML02 | m | 51 | R,L insula |
| ML04 | f | 45 | - |
| ML10 | f | 45 | - |
| ML12 | m | 42 | - |
| ML16 | m | 51 | L temporal, L thalamus |
| ML18 | m | 51 | L,R frontal, L,R temporal, L,R insula, L thalamus |
| ML20 | f | 53 | L insula |
| ML21 | m | 37 | L occipital |
| ML22 | f | 53 | - |
| ML23 | f | 29 | - |

***Table 1**: Summary of brain regions in the patient group showing abnormal NAA/(Cr+Cho) ratios.*

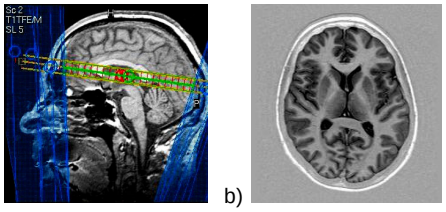


***Figure 1:** Setup of the MRSI slice placed along the ac-pc line on the level of the caudate. b) Axial IR image of the MRSI slice, as was used for tissue segmentation purpose.*

## Discussion

Using fast, high-resolution spectroscopic imaging (TSI) we were able to demonstrate metabolic alterations in frontal, temporal and insular areas as well as thalamus of McLeod patients. Noteworthy, the most extended alterations were only found in McLeod patients with prominent psychiatric symptoms, and were absent in McLeod patients who had a predominant movement disorder. Our methodology might therefore be useful in the examination of metabolic alterations in other neuropsychiatric disorders.

Due to the movement disorder of several patients a fast MRSI needed to be used. As a compromise somewhat lower spectral quality was accepted. Our methodology did not allow obtaining conclusive spectroscopic results from striatal areas, mainly due to prominent susceptibility artifacts arising from the neighboring sinus. Alternatively, a higher iron content in the basal ganglia might have contributed to the poor quality of the spectra in these regions.

*References:*

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