# Abnormal Metabolic and Structural Changes in Juvenile Myoclonic Epilepsy using MRI Volumetry and 1H MR Spectroscopy

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## Purpose

Juvenile myoclonic epilepsy (JME) is a syndrome of idiopathic generalized epilepsy (IGE) with an age-related onset of seizures, and is characterized by absences, tonic-clonic seizures, and myoclonic jerks. A precondition for the diagnosis of JME proposed by International League Against Epilepsy (ILAE) [1] is normal findings in routine clinical neuroimaging. However, in some of the recent studies proton magnetic resonance spectroscopy ($^1$H-MRS) has shown that JME patients had a significant decrease in thalamic N-acetyl aspartate (NAA) concentration [2] and NAA/creatine (Cr) ratio [3]. In addition, MRI volumetry of the thalamus indicated a structural abnormality in JME [4]. More studies are still needed to confirm these observations. In the present study the thalamus, the cingulated gyrus, and dorsal prefrontal cortex in JME patients were studied to investigate whether metabolic abnormalities are associated with thalamo-cortical loop dysfunction. Moreover, thalamic and cingulate volumes of JME patients were examined with MRI volumetry and compared with findings obtained from a healthy control group.

## Methods

This study included 28 subjects, 14 JME patients (6 men and 8 women; mean age 33.7 years) and 14 age-matched healthy controls (7 men and 7 women; mean age 32.3 years). The examinations were performed on a Philips Eclipse 1.5 T MR system with the standard quadrature birdcage head coil. After the MR study was completed, single-voxel MR spectroscopy was performed using a STEAM sequence. The spectroscopic voxels were placed over the right dorsal prefrontal cortex, right thalamus, and the anterior cingulate. The parameters were TR/TE 1600/20 ms, 192 averages, 2500 Hz spectral width, and 2048 data points. An unsuppressed spectrum was also measured for phase correction (16 averages). After automatic phase and baseline corrections, the peak area was obtained from the spectrum by employing the Levenberg-Marquardt algorithm to fit Gaussian to Lorenzian type. The metabolite ratios of NAA/creatine (Cr), choline (Cho)/Cr, $(NAA/H_2O)\times10^3$, $(Cr/H_2O)\times10^3$, and $(Cho/H_2O)\times10^3$ were calculated for analysis. Ratios are given as the mean ± SD. Statistical significance was determined using Student's *t*-test (independent) with $p < 0.05$ as significant.

For MRI volumetric analysis, regions of interest were drawn using an in-house Matlab based program (ROITOOL). The images from three orthogonal views were displayed together, and the outlined structures referenced to internal landmarks on 3 planes could be clearly seen (Fig. 1). After tracing, the volume was automatically calculated. The thalamus and cingulate volumes were analyzed and the ratios to the whole brain volumes were compared to those of control group, respectively.

## Results

No patients showed morphological abnormalities on the anatomical MRI. The metabolite ratios (mean ± SD) measured from the thalamus, anterior cingulate, and dorsal prefrontal cortex in JME patients and controls are summarized in Table 1. JME patients showed significantly lower NAA/Cr in the thalamus compared to controls (1.13±0.25 vs. 1.42±0.35, $p$= 0.03). This result indicates the presence of a thalamic functional abnormality in JME patients. In the cingulate, NAA/Cr and $(NAA/H_2O)\times10^3$ were also significantly decreased in JME patients compared to controls (1.15±0.18 vs. 1.51±0.52, $p$= 0.035; 0.60±0.17, vs. 0.78±0.16, $p$= 0.01). In 14 JME patients, the mean total cerebral volume was 1419 ± 122 ml, and that of controls was 1442 ± 118 ml. There was no difference in mean total cerebral volume between JME patients and controls ($p$ = 0.66, in Table 2). When compared with controls, however, JME patients had an increased total thalamic volume ($p < 0.001$), which is consistent with the previously reported finding by Betting et al. [4]. The cingulate volumes of patients with JME were not statistically different from those of controls ($p$ = 0.66).

Table 1. Metabolite ratio from thalamus, cingulate, and dorsal prefrontal cortex

| | NAA/Cr | Cho/Cr | $(NAA/H_2O)$ | $(Cr/H_2O)$ | $(Cho/H_2O)$ |
|---|---|---|---|---|---|
| Pt_RT | 1.13 ± 0.25* | 0.75 ± 0.20 | 0.65 ± 0.10 | 0.59 ± 0.14 | 0.44 ± 0.14 |
| Cl_RT | 1.42 ± 0.35 | 0.75 ± 0.18 | 0.71 ± 0.08 | 0.55 ± 0.14 | 0.42 ± 0.13 |
| Pt_CG | 1.15 ± 0.18* | 0.94 ± 0.24 | 0.60 ± 0.17* | 0.50 ± 0.17 | 0.42 ± 0.18 |
| Cl_CG | 1.51 ± 0.52 | 0.83 ± 0.35 | 0.78 ± 0.16 | 0.53 ± 0.20 | 0.41 ± 0.13 |
| Pt_PC | 1.47 ± 0.32 | 0.83 ± 0.38 | 0.71 ± 0.09 | 0.47 ± 0.09 | 0.44 ± 0.11 |
| Cl_PC | 1.42 ± 0.33 | 1.00 ± 0.51 | 0.65 ± 0.08 | 0.49 ± 0.06 | 0.39 ± 0.10 |

Note.-Pt = patient, Cl = control, RT = right thalamus, CG = cingulate, PC = dorsal prefrontal cortex. Ratio = mean ± SD. *$p < 0.05$, significant difference between JME and controls

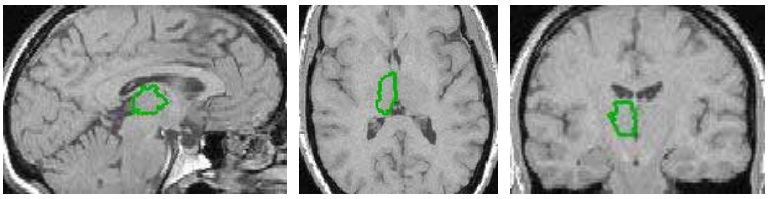

**Figure.1 Example of thalamic segmentation in sagittal, axial, and coronal T1-weighted images in one JME patient using an in-house Matlab-based program (ROITOOL).**

Table 2. MRI volumetry results measured by manual drawing

| Subjects | Thalamus (ml) | Cingulate (ml) | total brain (ml) | thalamus/total brain |
|---|---|---|---|---|
| Controls | 7.51 ± 0.55 | 33.26 ± 5.65 | 1442 ± 118 | $52.3 \times 10^{-4}$ |
| Patients | 9.01 ± 1.08*** | 31.85 ± 4.46 | 1419 ± 122 | $63.6 \times 10^{-4}$*** |

Note.- Patients compared to controls, significant with ***$p < 0.001$.

## Discussion

The main observation in this work was the significant NAA/Cr reduction in thalamus and anterior cingulate of patients with JME compared to control subjects. These results are consistent with the previously reported findings by Mory et al. [3] and Savic et al. [5], respectively. The results suggested that $^1$H-MRS can be used to detect the neuronal loss or dysfunction in JME patients, which may be associated with mechanisms of seizure generation in this form of generalized epilepsy. Moreover, MRI volumetric analysis showed that thalamic volumes were structurally different in patients with JME compared to controls although cingulate volumes were not different. This finding may support the presence of a thalamic neuronal dysfunction (i.e., NAA/Cr reduction measured by $^1$H-MRS) in JME patients. However, it remains unclear what could be the cause of the increased volumes in patients with JME. It is known that inflammation may cause signal intensity reduction on T1-weighted images, which may be mistakenly determined as the increased gray matter. Further investigation with better images collected with a higher spatial resolution at a higher field may be helpful to explain the finding.

**References** [1]. Commission on Classification and Terminology of ILAE. Epilepsia 30:389-399 (1989). [2]. Helms et al. J Neurol Neurosurg Psychiatry 77:489-494 (2006). [3]. Mory et al. Epilepsia 44:1402-1405 (2003). [4]. Betting et al., Epilepsy & Behavior 8: 575-580 (2006). [5]. Savic et al. Neuroimage 21:163-172 (2004).

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