

Clinical Research

MR Spectroscopy Shows Reduced Frontal Lobe Concentrations of *N*-Acetyl Aspartate in Patients with Juvenile Myoclonic Epilepsy

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Summary: *Purpose:* Neuropsychological studies suggest frontal lobe dysfunctions in patients with juvenile myoclonic epilepsy (JME). In this study we investigated whether an underlying mechanism could be a regional neuronal damage not visible with structural magnetic resonance (MR), but detectable with magnetic resonance spectroscopy (MRS).

Methods: The study included 15 patients with JME and 10 matched healthy controls. Quantitative single voxel MRS was conducted at 1.5 Tesla by using a STEAM sequence (TR/TE/TM = 6,000/30/13.7 ms). The voxels were placed over the right cerebellum, right thalamus, and the prefrontal and occipital cortex. The quantitation included fitting of transmitter gain, and correction for partial volume of cerebrovascular fluid. LC-

Model was used for estimation of the absolute concentrations of total *N*-acetyl aspartate (NAA), cholines, total creatine, and myoinositol.

Results: Patients with JME had significantly reduced prefrontal concentrations of NAA in relation to controls (9.1 ± 1.0 vs. 10.2 ± 0.8 mM; $p = 0.031$ after Bonferroni correction). The other regions showed normal NAA values, as did the other metabolites.

Conclusions: The observed reduction in NAA levels suggests a prefrontal neuronal lesion in patients with JME. **Key Words:** Magnetic resonance spectroscopy—Juvenile myoclonic epilepsy—*N*-acetyl aspartate—Frontal lobe—Magnetic resonance imaging.

Patients with primarily generalized epilepsy (PGE) usually show normal findings in routine clinical neuroimaging, and according to the criteria of International League Against Epilepsies, a precondition for the diagnosis of primarily generalized epilepsy is absence of structural brain abnormalities (1,2). This concept is, however, contradicted by neuropathologic studies showing migrational disturbances in PGE (3–5), and positron emission tomography (PET) studies suggesting that the benzodiazepine (BDZ) receptor density is reduced in the thalamus and increased in the deep cerebellar nuclei in generalized tonic-clonic epilepsy (6), and that the frontal lobe binding to BDZ receptors could be elevated in patients with juvenile myoclonic epilepsy (JME) (7). Furthermore, specific cerebral and cerebellar distortions have been detected in PGE when combining conventional magnetic resonance (MR) with computerized ana-

tomic brain atlas (8), and widespread structural changes when using a specific tissue segmentation program (9).

Taken together, these observations raise the question whether the view that anatomic substrate is lacking in PGE merely reflects a lack of appropriate tools to detect pathology. A further question is whether a possible pathology varies with the specific type of generalized epilepsy.

JME is a hereditary epilepsy syndrome that comprises 5–11% of patients with epilepsy (10). It is characterized by myoclonic jerks and generalized tonic-clonic seizures. The electroencephalogram (EEG) in JME typically shows generalized 4- to 6-Hz spike-wave, or polyspike and wave activity with a maximum in frontocentral regions. JME is associated with normal intelligence and lack of pathology on the MR and computed tomography (CT) scans. Recent neuropsychological studies, however, suggested that subjects with JME have a deficient performance in several tests measuring frontal lobe functions (11,12). Furthermore, in a PET study with 18-fluorodeoxyglucose (18-F FDG), Swartz et al. (13) found

Accepted October 8, 1999.

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inability to activate the dorsolateral prefrontal, premotor, and basal frontal cortex during visual match to sample tasks. Unlike the control subjects, patients with JME, instead, activated the medial temporal structures. These observations suggest that JME may be associated with frontal lobe abnormalities, perhaps affecting the epileptogenic potential, as well as the cognitive functioning.

N-acetyl aspartate (NAA) is produced in neuronal mitochondria via *N*-acetyl aspartase, and degraded by membrane-bound aminohydrolase, which is released in the event of cellular disruption (14). A reduced level of NAA can therefore reflect neuronal damage or a mitochondrial dysfunction. NAA can be detected by proton magnetic resonance spectroscopy (MRS) (15), and MRS measurements of NAA have proved useful for identification of neuronal lesions when structural MR fails in detecting morphologic correlates to regional dysfunctions (16–18).

Based on previous electrophysiologic data in PGE and the referred current information about JME, we hypothesized that patients with JME may have tissue abnormalities within the cerebellothalamocortical loop (19), and that these abnormalities could be reflected by abnormal concentrations of NAA, even when the conventional structural MR is normal.

MATERIALS AND METHODS

Patients

Fifteen right-handed patients with JME were examined. Their major clinical data are presented in Table 1. The JME diagnosis was based on seizure history, seizure semiology as described by relatives or recorded during hospitalization, and results from scalp EEG recordings. All patients had late childhood/teenage onset of awakening myoclonic jerks, most often in the upper, but sometimes also in the lower extremities. None of the patients had a progressive cerebral disease, other neurologic symptoms, or a history of somatic or psychiatric disorder. Five patients reported lack of seizures during the last year, four had currently only myoclonic jerks, whereas the remaining six still experienced both myoclonies and sporadic generalized tonic-clonic seizures without signs of focal onset or termination.

All patients had normal CT of the head. Patients with a history of phenytoin (PHT) treatment were excluded because of the toxic effect of this drug on Purkinje cells (20), which could affect the cerebellar concentrations of NAA.

The control group consisted of 10 unmedicated right-handed healthy volunteers (28 ± 7 years; six female subjects) without family history of neuropsychiatric disorders.

The study was approved by the local human subject protection committee, and informed written consent was obtained from each subject.

MRI protocol and choice of volumes of interest

MR examinations were carried out on a 1.5-Tesla clinical MR system (Signa Advantage; General Electric Medical Systems, Milwaukee, WI, U.S.A.) by using the standard quadrature birdcage head coil. To minimize variation in positioning of the head, the subjects were positioned by the same investigator, using the orbitomeatal line as landmark. Incidence of possible seizures during the scan was evaluated from patient reports and by continuous supervision by an assistant.

The MRI protocol consisted of axial T_2 -weighted fast spin echo (FSE) images (effective TE = 56 ms, TR = 2,500 ms, FOV = 24 cm, 23 slices of 3-mm thickness) and axial T_1 -weighted 3-D spoiled GRASS (SPGR; TE = 7 ms, TR = 23 ms, FOV = 24 cm, flip angle, 50°; 60 slice partitions of 2.5-mm thickness, 1 NEX). Four volumes of interest (VOIs) were selected by using the 3-D SPGR images in the following regions: right thalamus, right cerebellum, prefrontal cortex, and occipital cortex. The occipital VOI served as the presumably unaffected reference region.

The thalamus VOI covered all thalamic nuclei. The cerebellar VOI was located lateral to dentate nuclei (Fig. 1). These regions were examined on only one side because of the measuring time constraints. This restriction was justified because all the subjects were right-handed and investigated with an identical protocol. The prefrontal VOI was placed anterior to the corpus callosum by using the plane of anterior and posterior cerebral commissure as the caudal border, and including the cranio-lateral portion of the frontal lobe. The caudomesial portion of the frontal lobe was avoided to reduce distortions of the spectra due to susceptibility artifacts in the vicinity of bone and air (21).

The occipital VOI covered the Brodmann area 17 and 18 (Fig. 1). Each of the studied regions was easy to identify, and the position of VOIs, therefore, were reproducible from one subject to another. VOI size and fraction of cerebrospinal fluid (CSF) is presented in Table 3.

MR spectroscopy

The standard STEAM sequence ("steamcsi") was used for localization of the MR signal. Sixty-four water-suppressed scans were acquired with short echo time (TE = 30 ms) and long repetition time (TR = 6,000 ms) to reduce the influence of relaxation times (22), which may be altered in pathologic tissue. Each single acquisition was stored separately. Shimming on the localized water signal and adjustment of the water suppression was done manually to improve the spectral quality. The residual water signal was not inverted and provided a reference for the correction of arbitrary frequency shift and zero-order phase.

As in (23), the averaged data was analyzed in the time domain by using the LCModel program (24) (distributed

TABLE 1. Patient data

| Patient | Age (yr) | Duration (yr) | Heredity | EEG | Seizure type | Present seizure type | Medication | Last seizure | Frontal lobe NAA (mM) |
|---------|----------|---------------|-----------------|--------------------------|--------------------------|-------------------------------------|----------------------|-----------------------------|-----------------------|
| 1 | 26 | 13 | First pedigree | Bil spike-wave activity | Myoclonies, gm | Myoclonus (2-3/mo), gm (5/yr) | Valproate | Myoclonus, 3 day | 7.8 |
| 2 | 27 | 12 | No | Bil spike-wave activity | Myoclonies, gm | Myoclonus (3/mo), gm (1/yr) | Valproate | Myoclonus, 3 wk | 7.2 |
| 3 | 40 | 27 | First pedigree | Bil spike-wave activity | Myoclonies | No seizures for 8 yr | Valproate | Gm, 8 yr | 9.9 |
| 4 | 35 | 24 | No | Bil spike-wave activity | Absences, myoclonies, gm | No seizures for 5 yr | Valproate, lamictal | Gm, 5 yr | 8.2 |
| 5 | 34 | 21 | First pedigree | Bil spike-wave activity | Myoclonies | Myoclonus (1/mo), gm (1 every 5 yr) | Valproate | Myoclonus, 1 wk | 8.2 |
| 6 | 29 | 17 | No | Bil spike-wave activity | Myoclonies, gm | Myoclonus (1/mo) | Valproate | Myoclonus, 1 yr | 9.1 |
| 7 | 31 | 19 | No | Bil spike-wave activity | Absences, myoclonies | Myoclonus (1/wk), gm 5 yr ago | Valproate | Myoclonus, 1 mo | 8.3 |
| 8 | 32 | 19 | No | Poly spike-wave activity | Myoclonies, gm | Myoclonus (1/mo), gm (1/yr) | Carbamazepine | Myoclonus 1 wk, gm 3 mo | 9.3 |
| 9 | 37 | 22 | No | Bil spike-wave activity | Myoclonies, gm | Myoclonus (1/mo), gm (1/yr) | Valproate | Myoclonus, 1 mo | 9.4 |
| 10 | 27 | 6 | No | Poly spike-wave activity | Myoclonies, gm | No seizures for 1 yr | No medication | Myoclonus 1 yr, gm 5 yr | 9.7 |
| 11 | 42 | 29 | Second pedigree | Bil spike-wave activity | Myoclonies, gm | Gm (0.5/yr), myoclonus (2/mo) | Valproate | Myoclonus, 1 mo | 10.7 |
| 12 | 26 | 13 | No | Bil spike-wave activity | Myoclonies, gm | No seizures for 6 yr | Valproate | Gm, 6 yr | 10.7 |
| 13 | 38 | 23 | No | Bil spike-wave activity | Myoclonies, gm | Myoclonies (1/day) | Lamictal, clonazepam | Gm, 1 mo; myoclonus, 1 day | 11.5 |
| 14 | 35 | 17 | First pedigree | Bil spike-wave activity | Myoclonies, gm | Myoclonus (1/mo) | Clonazepam | Myoclonus, 2 mo | 8.4 |
| 15 | 28 | 14 | No | Bil spike-wave activity | Myoclonies, gm | Myoclonus (1/wk), gm (6/yr) | Valproate | Gm, 14 day; myoclonus, 1 wk | 7.8 |

gm, generalized tonic-clonic seizures.

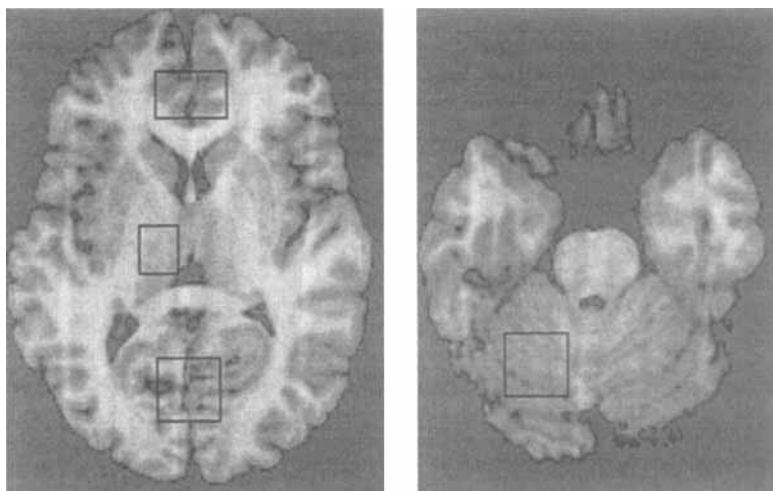
by S. Provencher, Göttingen, Germany), which fits a set of single metabolite spectra under the constraints of a common arbitrary lineshape and a common baseline. Thus the whole spectral information of the metabolites was used in the analyzed spectral interval. Absolute concentrations of metabolites were estimated from a calibration experiment by using a solution of known concentrations, as described elsewhere (25). In addition to total NAA (representing the sum of NAA and NAA-glutamate), total creatine (Cr), cholines (Cho), and myoinositol (mI) also were evaluated.

The variable fraction of CSF in the VOIs was determined from 10 single acquisitions of the water signal, where the TE of the STEAM sequence was increased

from 30 to 2,000 ms. The amplitudes of the echo signal were fitted biexponentially, separating the long T_2 component, which has been identified as the CSF signal, and the short T_2 component, representing the tissue water signal (26). The T_2 -corrected amplitudes β_{CSF} and β_{tissue} were expressed in percentage of the T_2 -corrected water signal obtained from the calibration experiment, which served as a reference for 100% water in the VOI.

Because the macromolecular constituents are minimal in CSF, 100% visibility of the CSF signal was assumed. Because the total volume of the VOI (V_{VOI}) corresponds to 100% signal, the percent CSF signal β_{CSF} is identical to the CSF volume fraction. The volume of the tissue in the VOI (V_{tissue}) is then calculated as

FIG. 1. Placement of the volumes of interest (VOIs).



$$V_{\text{tissue}} = (1 - \beta_{\text{CSF}}/100\%) \times V_{\text{VOI}} \quad (1)$$

The V_{tissue} was then used to calculate average tissue concentrations of metabolites (rather than average VOI concentration of metabolites), and the percentage tissue water content (TWC):

$$\text{TWC} = (1 - \beta_{\text{CSF}}) \times \beta_{\text{tissue}} \quad (2)$$

Spectral acquisition, quantification and analysis were performed by one investigator (I.S.). The evaluation was cross-checked by an spectroscopist (G.H.). The quality of the spectral analysis may be judged from the parameters linewidth (FWHM), signal-to-noise ratio (SNR), and the relative SD of each metabolite provided by the LCModel analysis. When a spectrum appeared affected by motion, visible as poor linewidth due to frequency shifts during the MRS measurement, the single acquisitions were added coherently to improve the spectral quality. This was accomplished by extracting the residual in-phase water signal of each acquisition by low-pass filtering, determining frequency and phase, and correcting the whole scan to zero phase and a consistent frequency shift. Spectra with poor quality (altogether four of 100 spectra) were omitted from the statistical analysis.

Statistics

Absolute concentrations of NAA, Cho, Cr, and ml were tested for regional differences between patients and controls with one-way analysis of variance (ANOVA) and Fisher's post hoc analysis. The separate regions in each population of subjects were used as the parameters of variance. Given that concentrations of measured metabolites vary between different regions (21–23), only the values from same region (VOI) were compared between patients and controls in the post hoc analysis. A value of $p < 0.05$ was chosen as level of significance after Bonferroni correction for the multiple analyses (one for each metabolite).

Possible abnormalities in individual patients were

evaluated with the 95% confidence interval of corresponding normal values for the respective metabolite and VOI. Correlations between the metabolic concentrations, seizure frequency, duration of epilepsy, and time (days) between the MRS measurement and the preceding seizure were tested with Pearson's correlation coefficient (r). Differences between patients and controls in the content of tissue water (TWC) within different VOIs, as well as differences in spectral linewidth, and signal-to-noise ratio were tested with unpaired Student t tests ($p < 0.05$ after Bonferroni correction for the separate analyses).

RESULTS

All the scans were interictal. The MR images showed pineal cyst in one patient, enlargement of the lateral ventricle on the right side in another, and small white matter lesions without particular regional distribution in a third patient. All the other patients had normal MRI findings as diagnosed by an neuroradiologist (D.G.). No signs of cortical dysplasia were observed on the T_1 -weighted 3-D SPGR images, which were inspected in axial, coronal, and sagittal views. The absolute concentration of NAA was significantly lower in the frontal lobe of patients compared with controls (9.1 ± 1.0 vs. 10.2 ± 0.8 mM; $p = 0.0078$ before Bonferroni's correction), whereas the corresponding values in other VOIs were within the normal range (Table 2, Fig. 2). No significant difference in regional concentrations of Cr, Cho, and ml were found between patients and controls (Table 2).

Three patients (patients 1, 2, and 15 in Table 1) showed abnormally low NAA concentrations (below the 95% confidence interval) in the frontal lobe. Patients 2 and 15 also had reduced concentrations of Cho in the thalamus. No correlation was observed between the seizure frequency, duration of seizures, time between the MRS scan and the preceding seizure, and the frontal concentration of NAA.

TABLE 2. Measured metabolites in patients and controls

| | NAA (mM) | Cho (mM) | Cr (mM) | Mi (mM) |
|--------------------------|------------------------|-------------|------------|------------|
| Healthy controls | | | | |
| Frontal cortex | 10.2 ± 0.8 | 1.6 ± 0.3 | 6.9 ± 0.9 | 4.2 ± 0.8 |
| Cerebellum | 9.7 ± 0.8 | 1.9 ± 0.3 | 8.2 ± 0.9 | 5.2 ± 1.3 |
| Thalamus | 10.5 ± 0.7 | 1.7 ± 0.2 | 6.5 ± 0.6 | 3.9 ± 1.6 |
| Occipital cortex | 10.7 ± 0.9 | 0.8 ± 0.1 | 6.4 ± 0.5 | 4.1 ± 0.5 |
| Patients with JME | | | | |
| Frontal cortex | 9.1 ± 1.0 ^a | 1.4 ± 0.2 | 6.1 ± 1.1 | 4.2 ± 1.0 |
| Cerebellum | 10.1 ± 0.7 | 1.7 ± 0.4 | 7.7 ± 0.9 | 4.5 ± 1.1 |
| Thalamus | 9.7 ± 0.7 | 1.4 ± 0.3 | 6.5 ± 0.6 | 3.9 ± 1.6 |
| Occipital cortex | 10.7 ± 0.6 | 0.8 ± 0.1 | 6.4 ± 0.8 | 4.1 ± 0.6 |

Values are given as mean ± SD.

^a p = 0.031 after Bonferroni correction.

This study included subjects with frequent (more than one per month, n = 6), as well as rare seizures (one per month or less, n = 9). The frontal lobe values in NAA tended to be lower in patients with frequent seizures (8.9 ± 1.7 vs. 9.3 ± 0.8, respectively, NS).

The TWC did not differ between patients and controls

in any of the VOIs, nor did the linewidth, fraction of CSF, tissue volume, or the signal-to-noise ratio (Table 3). Consequently, as shown in Table 3, the spectral quality was similar in the two investigated populations.

Post hoc comparisons were conducted for the NAA/Cr, NAA/Cho, and NAA/ml ratios from the frontal lobe spectra. None of the ratios showed significant differences between patients and controls: NAA/Cr, 1.5 ± 0.2 vs. 1.5 ± 0.2; NAA/Cho, 6.2 ± 0.9 vs. 6.4 ± 0.9; NAA/ml, 2.4 ± 0.8 vs. 2.7 ± 0.3 [NAA/ml was, however, significant (p = 0.04) if one outlying value was excluded].

DISCUSSION

This study was carried out with the hypothesis that the frontal lobe dysfunctions in patients with JME (12,13) may be associated with localized neurochemical changes. The finding of reduced prefrontal concentrations of NAA supports this hypothesis. This finding may reflect general neuronal dysfunction (associated with an

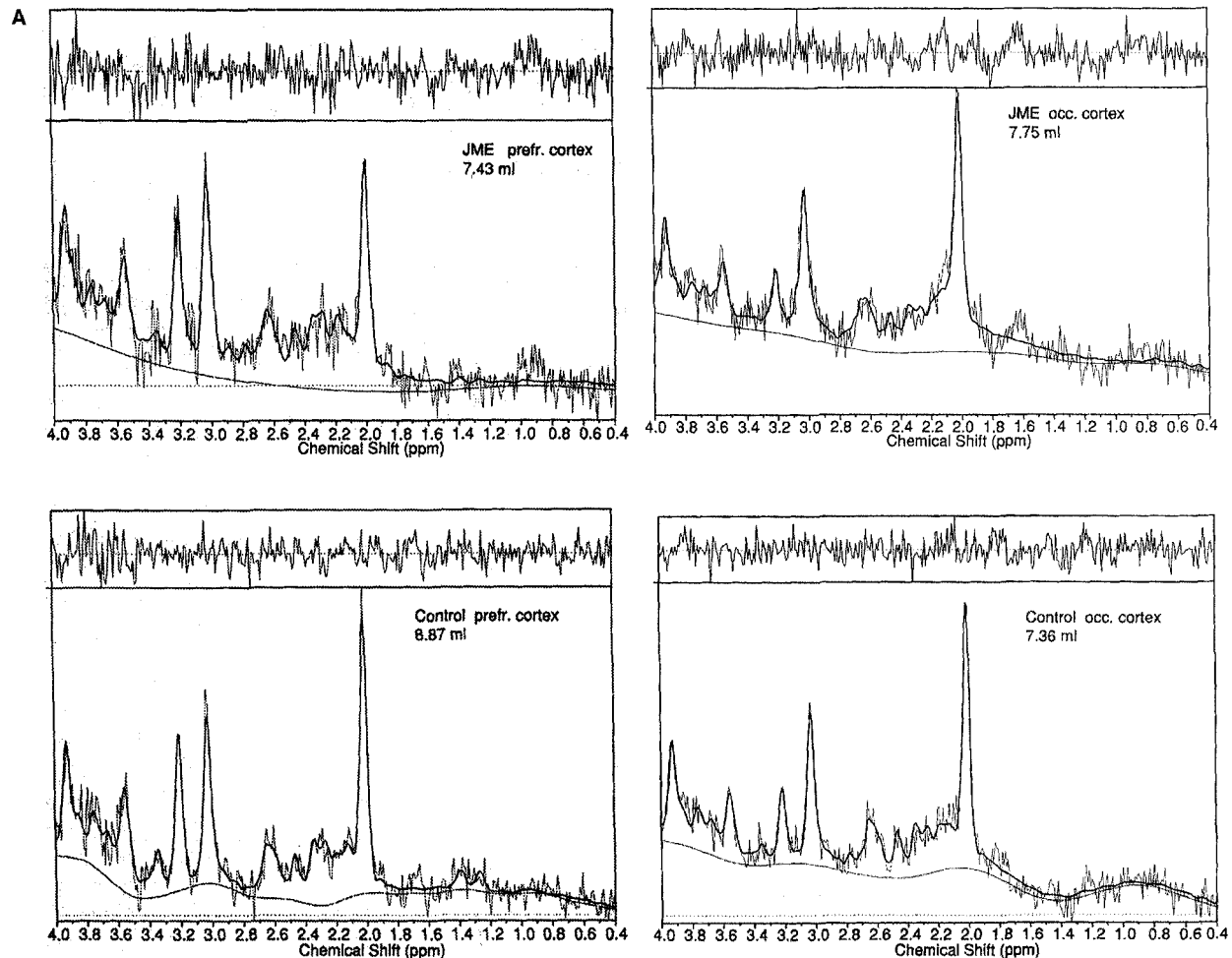


FIG. 2. Example of regional spectra; the upper curve indicates noise. **A:** The prefrontal spectrum in patient 11 (**top**) and a normal control (**bottom**). **B:** The occipital lobe spectrum in patient 11 (**top**) and a normal control (**bottom**). The main peaks of measured metabolites are indicated (NAA at 2.0 ppm, Cr at 3.0 ppm, Cho at 3.2 ppm, and ml at 3.5 ppm).

TABLE 3. Various spectral parameters in patients and controls

| | Total water (%) | FWHM (mm) | Signal-to-noise ratio | VOI size (cc) | V tissue (cc) | CSF (%) |
|-------------------|-----------------|-----------|-----------------------|---------------|---------------|-----------|
| Healthy controls | | | | | | |
| Frontal cortex | 74.0 ± 2.0 | 5.9 ± 1.0 | 7.0 ± 1.4 | 8.7 ± 1.2 | 8.6 ± 2.3 | 6.6 ± 1.8 |
| Cerebellum | 69.0 ± 3.7 | 5.4 ± 0.5 | 6.9 ± 1.1 | 8.2 ± 0.8 | 8.0 ± 0.6 | 1.4 ± 0.4 |
| Thalamus | 67.5 ± 3.2 | 5.1 ± 0.9 | 3.3 ± 1.1 | 3.6 ± 1.0 | 3.5 ± 0.7 | 2.1 ± 1.0 |
| Occipital cortex | 68.0 ± 2.3 | 4.4 ± 0.4 | 9.3 ± 1.6 | 8.1 ± 1.0 | 7.2 ± 0.4 | 8.4 ± 1.7 |
| Patients with JME | | | | | | |
| Frontal cortex | 74.5 ± 2.1 | 6.0 ± 1.0 | 6.7 ± 2.5 | 9.3 ± 2.4 | 8.7 ± 1.4 | 6.4 ± 1.3 |
| Cerebellum | 68.0 ± 3.0 | 6.1 ± 1.1 | 6.7 ± 2.3 | 8.0 ± 0.9 | 7.7 ± 0.5 | 2.7 ± 1.8 |
| Thalamus | 64.8 ± 2.2 | 6.2 ± 1.1 | 3.3 ± 1.1 | 3.5 ± 1.4 | 3.5 ± 1.3 | 1.3 ± 0.4 |
| Occipital cortex | 69.0 ± 2.1 | 4.8 ± 0.4 | 8.7 ± 1.3 | 7.8 ± 0.8 | 7.2 ± 0.8 | 7.2 ± 1.5 |

Values are given as mean ± SD.

FWHM, full width at half maximum of the spectral linewidth.

impaired NAA-precursor pool), specific mitochondrial dysfunction, neuronal lesion leading to release of *N*-acetyl-L-aspartate aminohydrolase and degradation of NAA, or a neuronal loss.

Another possibility, although incongruent with the lack of difference in frontal lobe TWC, is tissue atrophy. A condition that could be associated with each of these four alternatives is cortical dysplasia: although sometimes elevated, the neuronal density can also be reduced in cortical dysplasia (27–29). Further, a reduced concentration of NAA has been found even when the cell density is normal or elevated (27–29). Finally, the metabolic processes in dysplastic tissue may be dysfunctional, which would be compatible with our finding of reduced absolute concentration of NAA along with a normal NAA/Cr ratio. Cortical dysplasia is a condition compatible with our findings, as well as with the reported elevation of frontal lobe uptake of ¹¹C flumazenil, the frontal lobe hypometabolism, and an impaired activation of frontal lobes (7,12,13,30). However, the 3-D T₁-weighted images showed no visible signs of dysplasia, and the possibility of such changes in JME ought, therefore, to be further investigated.

The method applied has been used in several other studies, yielding reproducible results, in accordance with in vitro data (22–24). Although the obtained NAA difference between patients and controls was at the borderline of current proton MRS sensitivity, it was clearly significant. Seven of 15 patients showed NAA concentrations below the 95% confidence interval of the control group, indicating a shift in distribution. These concentrations of measured metabolites correspond well to the previously published data (22,26,31,32), which supports the reliability of findings in the JME patients.

For signal-to-noise reasons, the thalamus VOIs had to be sufficiently large. A partial inclusion of areas outside the lateral thalamic border (globus pallidus and the internal capsule) could, therefore not be avoided (Fig. 1). Thus although these data suggest a lack of pronounced thalamic abnormalities, minor alterations may have been missed.

Because a single voxel MRS was used, no information is given about the spatial extension or homogeneity of the observed NAA reductions. Changes in NAA can be even more pronounced in other parts of the frontal lobe. Therefore follow-up studies with MRS imaging would be necessary to visualize the exact distribution of NAA abnormalities. Another consequence of the single-voxel acquisition is the variation in the proportion of white and gray matter in the individual VOIs. However, because the TWC [which is higher by about 25% in gray matter (26)], did not differ between patients and controls in any of the VOIs analyzed, the probability is low for a systematic difference in the proportion of gray and white matter. Furthermore, at short TE, the difference in concentration of NAA differs between white and gray matter by ~5% (22).

In conclusion, this study offers support for the view that prefrontal cerebral changes exist in JME. These changes are of neuronal origin. Their etiology is uncertain, but one working hypothesis is that they may be associated with regional cortical dysplasia.

Acknowledgment: This study was supported by the Swedish Medical Research Council, Karolinska Institute, the Lundberg Foundation, The Captain Ericsson's, and the Åke Wiberg foundations. We thank Dr. Martin Lindberger, Dr. Ulla Lindbom, and Dr. Christina Anell for the referral of some patients.

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