Seizure (2007) **16**, 287–295

SEIZURE

www.elsevier.com/locate/yseiz

REVIEW

Proton magnetic resonance spectroscopy study of bilateral thalamus in juvenile myoclonic epilepsy

Cemile Haki [a], **Oğuzhan G. Gümüştaş** [b,*], **İbrahim Bora** [a], **Ayşem U. Gümüştaş** [b], **Müfit Parlak** [b]

[a] *Department of Neurology, Uludag University Medical Faculty, Gorukle Campus, Bursa, Turkey*
[b] *Department of Radiology, Uludag University Medical Faculty, Gorukle Campus, Bursa, Turkey*

Received 10 June 2006; received in revised form 29 October 2006; accepted 20 February 2007

KEYWORDS
Proton magnetic resonance spectroscopy;
Generalized seizures;
Abnormal thalamocortical circuity;
Thalamic neuronal dysfunction

Summary

Purpose: To investigate neuronal dysfunction in the thalami of juvenile myoclonic epilepsy (JME) by using proton magnetic resonance spectroscopy (MRS).
Methods: We performed single-voxel proton MRS over the right and the left thalami of 15 consecutive patients (10 women, 5 men) with JME (mean age 20.3 years) and 16 healthy volunteers (10 women, 6 men) (mean age 24.5 years). All patients had seizure onset in late childhood–teenage, normal neurologic examination, typical electroencephalogram (EEG) of JME and normal magnetic resonance imaging (MRI). We determined *N*-acetylaspartate (NAA) values and NAA over creatine–phosphocreatine (Cr) values. Mann–Whitney *U*-test was used to evaluate group differences.
Results: Group analysis showed that echo time (TE) 270 integral value of NAA over left thalamus were significantly decreased in JME patients as compared with controls (34.6033 ± 15.8386; 48.0362 ± 22.2407, respectively, $P = 0.019$). Also group analysis showed that thalami NAA/Cr ratios were significantly decreased in JME patients (right side, 2.21 ± 1.07; left side 2.00 ± 0.72) as compared with controls (right side, 3.45 ± 1.50; left side, 3.08 ± 1.60; $P = 0.011$ and $P = 0.030$, respectively).
Conclusion: In the previous studies, NAA values in patients with JME found that they were not statistically lower in thalami than control group. But, in our study, NAA value was found low as well. It has been known that NAA is a neuronal marker and hence it is a valuable metabolite in the neuron physiopathology. As a result, in the patients with JME we tried to support the theory that the underlying mechanism of the generalized seizures was the abnormal thalamocortical circuity, determining the thalamic neuronal dysfunction in MRS statistically.

* Corresponding author. Tel.: +90 2244510824.
E-mail address: oggugu@mynet.com (O.G. Gümüştaş).

1059-1311/$ – see front matter
doi:10.1016/j.seizure.2007.02.017

Contents

Introduction

Juvenile myoclonic epilepsy (JME) is a hereditary epilepsy syndrome that comprises 5—11% of patients with epilepsy.[1] It is characterized by myoclonic jerks and generalized tonic-clonic seizures. The electroencephalogram (EEG) in JME typically shows generalized 4—6 Hz spike and wave or poly-spike and wave activity maximum in frontocentral regions. JME is associated with normal intelligence and lack of pathology on the MRI and computed tomography (CT) scans.[2,3]

Recent neuropsychological studies, however suggested that subjects with JME have a deficient performance in several tests measuring frontal lobe functions. Furthermore, in a PET study with 18-fluorodeoxyglucose (18-F FDG), Swartz et al. found inability to activate the dorsolateral prefrontal, premotor and basal frontal cortex during visual match to sample tasks.[4] 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. Positron emission tomography (PET) studies suggest that the benzodiazepine (BDZ) receptor density is reduced in the thalamus and increased in the deep cerebellar nuclei in generalized tonic-clonic epilepsy[5] and that frontal lobe binding to BDZ receptors could be elevated in patients with JME.[6] Proton magnetic resonance spectroscopy (MRS) of the human brain in vivo allows non-invasive quantification of important biologic chemical compounds. Proton magnetic spectra of the human brain in vivo contains a large signal from *N*-acetyl groups that originates largely from *N*-acetylaspartate (NAA), a compound localized exclusively in neurons and neuronal processes. The neuronal marker NAA is reduced in certain diseases with neuronal loss or dysfunction, including epilepsy.[7,8]

The exact mechanisms of generalized seizures are still unclear. Nevertheless, evidence exists that thalami participate in the generation of generalized spike and wave discharges and absence seizures.[9,10] Functional brain imaging has shown increased thalamic blood flow during absence seizures.[11]

The objective of the present study was to investigate whether evidence exist of neuronal dysfunction in the thalami in patients with JME by using proton magnetic resonance spectroscopy (MRS).

Patients and methods

Fifteen patients observed with JME diagnosis were included in this study. Their mean age was 20.3 (range, 16—30 years). The mean onset age of seizures was 13.6 (range, 8—20 years). Five of those 15 patients were males and 10 were females. The diagnosis of the patients was in accordance with their EEG results, seizure semiology and medical background. None of the patients had the other kind of neurological and psychiatric diseases.

In all the patients seizures had started in late childhood—teenage and their neurological examinations were normal. There were typical 4—6 Hz spike and poly-spike slow wave paroxysms in the EEG recordings of all patients. Six of whom had generalized tonic-clonic, myoclonic and absence seizures, seven of whom had generalized tonic-clonic and myoclonic jerks, one of whom had myoclonic and absence seizures and one of whom also had myoclonic seizures.

Thirteen patients have had valproic acid monotheraphy and two patients have had valproic acid and lamotrigine treatment. Five patients had photosensitivity. In all of them seizures had their onset in late childhood or teenages. All patients had been controlled for generalized tonic-clonic seizures for 1 year or longer before the MRS examinations. All had been seizure-free for at least 24 h prior to the MRS experiments. Also MRI results of whole patients were normal.

This study was performed using circular polarized head bandage at 1.5 Tesla supertransmitter magnet (Magnetom Vision Plus, Siemens, Erlangen, Germany). Our MRI protocol consisted of T1 weighted axial, T1 weighted sagittal, T2 weighted axial, T1 weighted inversion recovery 3 mm thick images, perpendicular to long axis of hippocampus and T2 weighted coronal fluid attenuated inversion recovery (FLAIR) images were used.

In both cerebral hemispheres white and gray nuclei were normal. Both hippocampi, parahippocampal gyrus and amigdalas were observed normal. There was not a view that could be in accordance with mesial temporal sclerosis. Furthermore, both thalami and frontal lobes have been observed to be normal. In both thalamic areas volume of interest (VOI) has been defined as 8 ml in the examination of single voxel proton MR spectroscopy. VOI has been performed to both thalami separately as a single voxel proton MR spectroscopy (Fig. 1).

In the study point resolved surface coil spectroscopy (PRESS) was used. For the spectra, spin echo (SE) sequence containing 135 and 270 ms echo time was used. Time of repetition (TR) was obtained as 1500 ms and the mean signal to noise ratio 16 and number of excitations (NEX) = 256 respectively. VOI having been placed in a suitable area before sequence, automatic shimming was performed using 3—7 Hz line width for the optimum signal of the voxel. Localized shimming was repeated three or four times, if necessary, to ensure good field homogeneity.

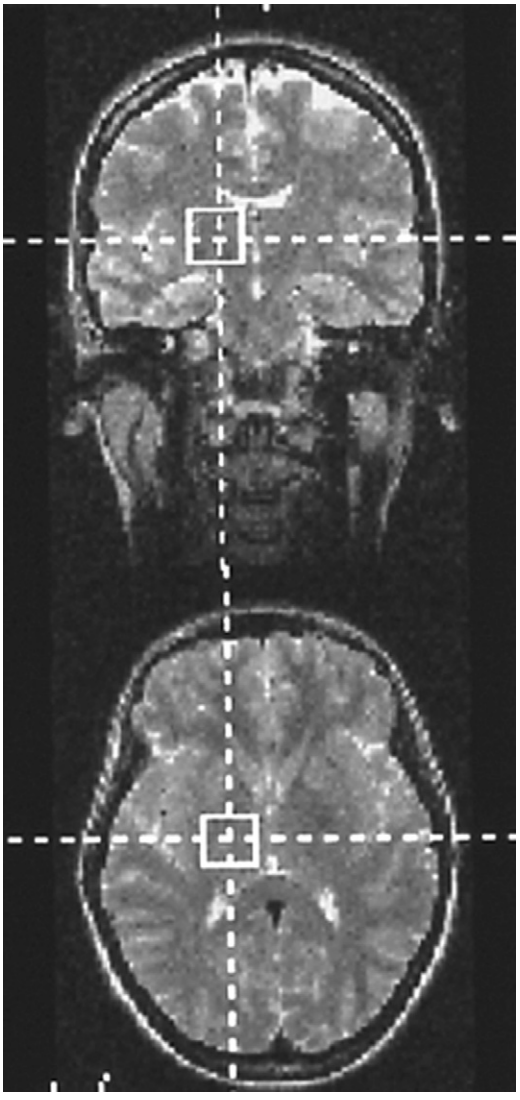

Figure 1 In the right thalamus, it can be seen where the sample with 8 ml dimension is.

To suppress water, 90° gaussian pulse was performed after the spoiler gradient. Before the Fourier inversion, 2048 time sequence data spots and 128 ms weak gaussian filters were selected to make the eddy current correct. After the Fourier reversing, linear basal line correction was made. After the application of SE sequence which contains TE 270 and 135 ms echo time, using longer TE, T2 weighted spectrum had been obtained from both thalami and the evaluation of creatine (Cr), *N*-acetylene aspartate (NAA) was primarily made. These are the crucial metabolites supporting information neurochemically. After the spectrum was obtained, post-processing procedure was performed. All data acquired with long echo times were processed with software provided by Siemens. Peak areas of metabolites were quantified and then the position (the place as parts per million (ppm)), integral (quantity as millimol), width (the width of metabolites as ppm at half pike length: 1/T2 time) and amplitude (as maximum intensity) of the metabolites were held. The ratio of NAA shows us the appearance of methyl groups. Also, 2.0 ppm reaches to resonance. NAA is accepted as neuronal marker and its concentration becomes less in many diseases with brain damage. It is not found outside the central nerve system and it has the widest and highest pike in normal spectrum.[12—16]

Creatine (Cr) reaches to resonance at 3.03 ppm. The second added pike is seen at 3.94 ppm. Therefore, Cr pike is sometimes defined as the total Cr pike. Creatine in ATP and ADP serves as reserve for high-energy phosphate and also as a plug. It also takes an important role in brain cells as an energy dependent system.

While creatine increases in conditions where the metabolism rate reduces, it reduces in instances where metabolism increases. Much of the creatine pike might be stable in diseases and it could be used as the control value. Getting the integral and amplitude values of NAA and NAA/Cr ratio in left and right thalami which contains both 135 and 270 ms echo time in SE sequence, it was comparatively evaluated with a volunteered control group consisting of total 16 healthy people (6 males and 10 females). The mean age of them was 24.5 (range, 16—35 years). It was seen that 10% and 20% of MR spectroscopy voxel had non-thalamic tissue inside. The measurement of the 10—20% of non-thalamic tissue was done as this way; VOI that has been defined as 8 ml in the examination of single voxel proton MR spectroscopy

was divided into eight equal components. The result was VOI of 1 ml volume. The non-thalamic tissue in the 8 ml VOI varied between 1/8 and 1.5/8. That was correspondence to 10–20% of non-thalamic tissue in our VOI. Together with this, it was perceived that this partial volume did not cause a remarkable change in the evaluation of NAA signals. Because, the non-thalamic tissue is formed from axons, which have close relation with thalamic nuclei.[17]

The measuring was evaluated by two different radiologists (O.G.G. and A.U.G.). Spectral acquisition, quantification and analysis were performed by one investigator (O.G.G.). Spectra with broad peaks and poor separation of individual peaks were excluded from study. The cause of this was basically the movement of the patients. The normal and patient groups whose spectras were that kind, recalled again after few days later for new spectroscopy examination. Only spectra with restricted peaks and good separation of individual peaks were included in our study. Informed written consent was obtained from each subject. Our study was approved by the Ethic Committee of the Medical Faculty.

Results

There are many studies in which they explain that it is a valid method to use the integral[18,19] or the amplitude[20,21] values between patients and controls. In our study, we use both integral and amplitude values between patients and controls.

In our study, Mann–Whitney *U*-test was used statistically ($P < 0.05$ was accepted remarkable). Age, gender, NAA and NAA/Cr ratios (as TE 135 and 270) between the patient group with JME and the control group were compared. Age and gender were unremarkable when the control group was compared with the patient group ($P > 0.05$). The values of NAA and NAA/Cr were presented in Tables 1–4. When NAA in left thalamus was compared with the control group, which was in the value of TE 270 integral, it was determined as lower in the patient group ($P = 0.019$, shown in Table 5). In addition, in the left thalamus, TE 135 integral, amplitude and TE 270 amplitude values were seen as lower in the patient group when compared with the control group. But, no statistically difference was found ($P > 0.05$, presented in Table 5). Again, in the right thalamus, though TE 270 amplitude values were observed as lower in the patient group in contrast to the control group they were not found statistically significant ($P > 0.05$, shown in Table 5).

NAA/Cr was found lower in the patient group when TE 270 integral values in the right and left thalami were compared with the control group (right, $P = 0.0011$; left, $P = 0.030$; presented in Table 6). In the right thalamus, TE 135 integral, TE 270 amplitude values of NAA/Cr were found as lower in the patient group in contrast to the control group. But it was statistically unremarkable ($P > 0.05$ shown in Table 6).

The spectroscopic images of a patient from both the patient and control groups were comparatively presented in Fig. 2.

Table 1 The distribution of MRS measuring of thalamic NAA values of patients with JME diagnosis

Patient	Integral value of NAA				Amplitude value of NAA				*A*
	R thalamus		L thalamus		R thalamus		L thalamus		
	TE 135	TE 270	TE 135	TE 270	TE 135	TE 270	TE 135	TE 270	
1	56.96	29.81	34.32	33.42	22.12	18.06	31.38	18.09	22
2	58.07	33.05	48.43	32.39	28.09	15.24	17.22	19.51	22
3	60.36	41.51	65.65	38.82	27.83	18.85	21.33	16.61	17
4	54.58	36.06	61.62	31.48	22.07	12.38	22.45	12.90	26
5	59.41	34.40	59.39	11.09	30.23	10.15	25.40	5.11	19
6	60.68	36.51	71.03	38.55	25.95	13.64	27.23	14.97	27
7	53.16	30.05	53.11	32.09	23.07	15.56	25.28	15.41	25
8	57.26	34.23	57.16	29.76	23.47	11.48	19.85	9.55	23
9	54.34	31.75	58.37	35.83	23.94	14.87	25.33	14.90	26
10	52.74	83.51	53.39	35.54	25.52	17.98	22.19	13.99	21
11	50.36	90.44	43.95	25.12	22.52	11.82	17.07	11.51	22
12	55.75	81.28	56.93	86.87	25.71	13.00	24.35	17.84	25
13	43.96	27.17	41.46	26.91	22.93	11.46	13.90	9.93	20
14	48.20	32.45	51.72	32.16	22.94	14.08	25.44	13.96	16
15	49.83	27.27	50.62	30.06	23.34	11.50	28.73	15.57	30

JME, juvenile myoclonic epilepsy; NAA, *N*-acetylaspartate; R, right; L, left; *A*, age (year); TE, time of echo.

Table 2 The distribution of MRS measuring of thalamic NAA values of the control group

Normal	Integral value of NAA				Amplitude value of NAA				*A*
	R thalamus		L thalamus		R thalamus		L thalamus		
	TE 135	TE 270	TE 135	TE 270	TE 135	TE 270	TE 135	TE 270	
1	53.19	30.96	49.73	30.69	27.54	18.65	25.31	16.47	22
2	43.42	25.65	42.02	23.46	19.33	9.35	19.75	7.61	29
3	53.16	30.42	57.38	31.15	22.10	10.32	21.99	9.19	28
4	68.74	34.55	64.95	36.26	28.89	15.93	22.03	15.97	27
5	60.98	38.87	60.38	42.97	26.08	14.90	24.75	17.86	27
6	56.11	36.31	58.28	35.23	27.60	15.31	24.93	14.05	35
7	59.01	41.34	64.14	34.23	23.23	15.64	21.51	14.64	34
8	55.80	39.61	57.38	41.06	39.84	17.71	21.99	17.31	25
9	51.08	83.28	56.13	85.37	25.55	15.84	27.16	12.70	24
10	65.99	46.05	63.60	42.66	31.41	21.24	27.60	17.25	18
11	63.87	88.40	67.76	40.52	29.00	13.33	33.90	19.61	18
12	27.88	58.69	53.61	83.97	8.40	24.39	22.93	13.92	18
13	54.94	84.22	52.10	35.11	22.52	17.32	22.50	12.95	29
14	51.54	84.53	50.57	80.60	22.05	14.99	21.02	11.88	16
15	53.08	86.20	54.46	37.78	27.98	16.44	25.92	16.16	16
16	64.56	84.63	61.03	87.52	25.97	14.60	29.53	16.28	26

NAA, *N*-acetylaspartate; R, right; L, left; A, age (year); TE, time of echo.

Discussion

The basic underlying mechanism of absence seizures appears to involve thalamocortical circuity and the generation of abnormal oscillatory rhythms from particular neuronal networks.[17,22–25] Both human and animal data suggest that 3–4 Hz generalized spike and wave discharges arise from abnormal thalamocortical rhythms. EEG monitoring with depth electrodes in the thalamic nuclei demonstrated that thalamic epileptiform discharges correlated with widespread surface cortical activities and clinical symptoms of absence seizures and generalized tonic-clonic seizures.[26]

Experimental evidence that implicates thalamic and thalamocortical mechanisms as important in the pathophysiology of absence may offer an explanation for the generalized nature of the ictus.[27,28] However, the generalized nature of absence seizures appears to be more a convention of interpretation rather than a description of the EEG evidence. Examination of EEG patterns in spike

Table 3 The distribution of MRS measuring of thalamic NAA/Cr values of patients with JME diagnosis

Patient	Integral value of NAA/Cr				Amplitude value of NAA/Cr				*A*
	R thalamus		L thalamus		R thalamus		L thalamus		
	TE 135	TE 270	TE 135	TE 270	TE 135	TE 270	TE 135	TE 270	
1	1.931	1.951	1.811	1.758	1.911	1.806	5.591	1.809	22
2	2.007	1.631	2.031	1.931	1.811	2.381	2.031	2.531	22
3	2.007	1.931	2.541	1.791	2.031	2.611	1.961	2.141	17
4	1.481	1.981	2.911	1.281	1.831	2.141	2.191	1.781	26
5	1.731	1.641	2.231	2.251	1.731	1.641	1.651	2.081	19
6	1.761	1.701	2.841	2.651	1.651	2.551	1.651	2.151	27
7	2.031	1.671	1.541	2.041	1.711	2.021	1.541	2.222	25
8	1.751	1.591	2.341	1.641	1.911	1.771	2.121	1.791	23
9	1.897	1.607	2.056	1.730	1.841	2.398	1.904	2.292	26
10	1.996	4.624	2.132	1.734	1.865	2.528	1.891	2.312	21
11	2.400	4.747	1.820	1.371	2.073	1.912	1.700	2.048	22
12	1.806	3.082	1.959	4.352	1.806	1.670	1.617	2.241	25
13	1.379	1.301	2.270	1.819	1.522	1.860	1.933	2.068	20
14	1.550	1.855	1.796	1.871	1.599	1.963	1.706	2.065	16
15	2.157	2.228	1.780	1.840	1.780	2.228	2.081	2.616	30

JME, juvenile myoclonic epilepsy; NAA, *N*-acetylaspartate; Cr, creatine; R, right; L, left; *A*, age (year); TE, time of echo.

Table 4 The distribution of MRS measuring of thalamic NAA/Cr values of the control group

Normal	Integral value of NAA/Cr				Amplitude value of NAA/Cr				*A*
	R thalamus		L thalamus		R thalamus		L thalamus		
	TE 135	TE 270	TE 135	TE 270	TE 135	TE 270	TE 135	TE 270	
1	2.022	1.854	1.742	1.712	1.811	2.612	1.742	2.211	22
2	1.592	5.632	1.772	1.845	1.921	2.175	1.833	2.021	29
3	2.171	3.475	2.401	5.701	1.921	1.865	2.024	2.011	28
4	2.741	3.512	8.402	3.115	2.111	2.201	2.774	2.574	27
5	2.042	1.756	1.562	2.333	1.961	2.142	2.082	2.396	27
6	1.751	1.695	2.524	2.011	1.531	1.895	1.783	2.236	35
7	3.134	3.902	2.875	1.475	2.462	3.705	2.092	2.135	34
8	2.077	1.802	1.975	1.895	1.793	2.456	1.842	2.545	25
9	1.903	5.175	1.932	6.190	1.806	2.534	1.552	2.653	24
10	1.879	1.846	1.845	2.040	2.000	2.365	1.763	2.208	18
11	1.894	5.000	2.685	2.610	2.039	2.454	2.276	2.523	18
12	1.497	2.282	1.825	5.110	1.527	1.832	1.958	2.237	18
13	2.451	3.280	1.765	1.633	1.838	2.258	1.576	2.042	29
14	1.910	3.942	1.565	4.298	1.717	2.368	1.895	2.148	16
15	1.738	6.237	2.038	2.407	1.955	2.660	1.972	2.830	16
16	2.047	3.936	2.000	4.984	2.010	2.302	2.000	2.292	26

NAA, *N*-acetylaspartate; Cr, creatine; R, right; L, left; *A*, age (year); TE, time of echo.

and wave discharges shows that, although they develop rapidly and may be difficult to lateralize, the spike and wave patterns are not diffuse but are predominant over the frontal cortex.[29,30] This frontal distribution of both spikes and waves is clear in textbook examples of conventional EEG in absence seizures, even those that are described as having generalized onset.[30] Other investigators pointed out that epileptiform discharges in some patients with childhood absence may appear fragmentary, especially during sleep, and produce focal spikes over centrotemporal and occipital regions.[31] This evidence of spike and wave seizures associated with activity in mesial frontal cortex during sleep onset may be congruent with the importance of corticothalamic circuity in both spike and wave discharges and in sleep spindles in animal models.[32]

With the advances in physical models of the neural sources of EEG activity in recent decades, it has become possible to relate the frontal distribution of spike and wave patterns to electrical sources in specific regions of frontal cortex. Applying equivalent dipole analysis to generalized spike and wave complexes with the spatiotemporal model has suggested that the most common model includes a source in the midline region of the basal frontal lobe.[33] In further research, current source density analysis was applied to spike and wave patterns in conventional EEG recordings in five children with absence seizures.[34] These analyses again emphasized the importance of inferior frontal generators, with spikes often showing a focal current distribution over frontopolar and orbital frontal cortex.[34] This evidence of a specific frontal cortical focus for

Table 5 The distribution of MRS measure of thalamic NAA values of the patients with the JME diagnosis and their controls

NAA	Patients: 15 (mean ± standard deviation)	Controls: 16 (mean ± standard deviation)	*P*-Value
R 135 amplitude	24.7340 ± 2.5509	24.2181 ± 5.4630	>0.05
L 135 amplitude	23.0580 ± 4.632	25.4899 ± 4.9634	>0.05
R 135 integral	55.0673 ± 62649	53.3344 ± 11.7065	>0.05
L 135 integral	53.1200 ± 8.4002	57.0950 ± 6.6547	>0.05
R 270 amplitude	14.0933 ± 2.7209	15.9850 ± 3.6303	>0.05
L 270 amplitude	13.9013 ± 3.7484	14.9281 ± 3.2417	>0.05
R 270 integral	60.8353 ± 67.1985	55.8569 ± 24.5888	>0.05
L 270 integral	34.6033 ± 15.8386	48.0362 ± 22.2407	0.019[a]

JME, juvenile myoclonic epilepsy; NAA, *N*-acetylaspartate; R, right; L, left; TE, time of echo.

[a] It is statistically significant according to Mann–Whitney *U*-test. In the left thalamus when TE 270 was obtained, it has been observed that in integral value, there was statistically difference in patient group according to normal control group ($P = 0.019$).

Table 6 The distribution of MRS measure of thalamic NAA/Cr values of the patients with the JME diagnosis and their controls

NAA/Cr	Patients: 15 (mean ± standard deviation)	Controls: 16 (mean ± standard deviation)	*P*-Value
R 135 amplitude	1.8049 ± 0.1493	1.9001 ± 0.2236	>0.05
L 135 amplitude	2.1046 ± 0.9854	1.9477 ± 0.2902	>0.05
R 135 integral	1.8590 ± 0.2658	2.0530 ± 0.4184	>0.05
L 135 integral	2.1575 ± 0.3827	2.4317 ± 1.6388	>0.05
R 270 amplitude	2.0988 ± 0.3318	2.3640 ± 0.4375	>0.05
L 270 amplitude	2.1432 ± 0.2437	2.3163 ± 0.2446	>0.05
R 270 integral	2.2175 ± 1.0756	3.4579 ± 1.5005	0.011[a]
L 270 integral	2.0041 ± 0.7264	3.0849 ± 1.6062	0.030[a]

JME, juvenile myoclonic epilepsy; NAA, *N*-acetylaspartate; Cr, creatine; R, right; L, left; TE, time of echo.
[a] It is statistically significant according to Mann–Whitney *U*-test. In the left and right thalami when TE 270 was obtained, it has been observed that in integral value, there was statistically difference in patient group according to normal control group (R, $P = 0.011$; L, $P = 0.030$).

generalized seizures may seem at variance with the evidence that thalamocortical mechanisms are responsible for widespread seizure discharges. However, neurophysiological analyses of thalamocortical augmenting and recruiting responses in animal experiments in the 1940s showed that cortical networks, specifically including orbital frontal cortex, were important in regulating the thalamocortical circuity.[35,36] With the modern recognition that this circuity is mediated by the nucleus reticularis thalami (RE), the cortical modulation of thalamocortical controls by orbital frontal regions has been an important explanatory principle.[37,38] The necessity of cortical involvement is clear in the corticothalamic circuity of sleep spindles, also mediated by RE mechanisms and taken as abnormal model for the circuity that becomes pathological in spike and wave complexes.[39,40] Furthermore, in an animal model of absence using intracranial EEG recordings, a cortical focus has been shown to drive spike and wave thalamocortical discharges, implying that the fundamental pathophysiology may, in fact, originate cortically.[41] A previous work showed no change in the NAA/Cr values in temporal lobes of five adult patients with JME.[8] One patient had a MRS examination <4 h after absence status and four others also had MRS examinations during the interictal state (seizure free for >24 h).[8]

Another study using short TE stimulated echo acquisition (STEAM) proton MRS found that absolute NAA values were significantly lower in the frontal lobes of patients with JME as compared with controls, but found no significant differences in NAA values from right thalamus on group analysis. Three

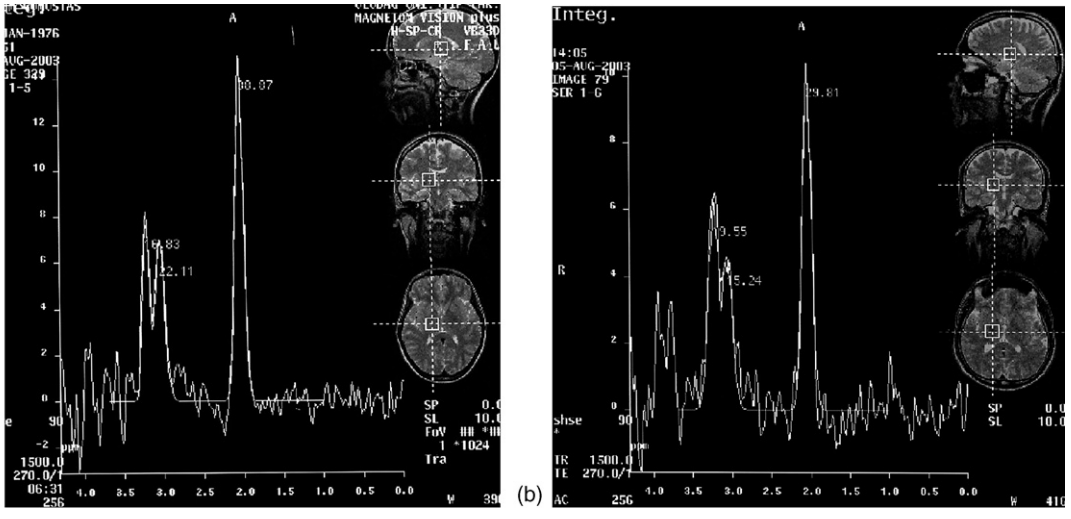

Figure 2 At 2.0 ppm NAA integral values in a sample of the right thalamus taken from a female of the normal control group and a male of the patient group with JME could be seen. Please pay attention to NAA integral value, which was much lower in the patient with JME. Furthermore, pike of lipid-lactate in the patient with JME (0.7–1.33 ppm) could be followed. (a) Control group and (b) patient group.

of their patients had abnormally low absolute NAA values in the frontal lobes. However, NAA/Cr ratios and NAA/Cho ratios did not differ between patients and controls in thalami, frontal lobes and occipital lobes.[18] Discrepancies between those findings[18] and our study could be explained by differences in acquisition and postprocessing techniques. The VOI selection with STEAM yields a volume larger than the one selected with PRESS under the same experimental conditions.[42,43] Sequence design considerations, especially with regard to placement of the spoiler and refocusing gradients, make STEAM more sensitive to diffusion than PRESS.[42,43] Furthermore, when only variations in the major metabolite peaks (NAA, Cho, Cr, lactate) are considered[7] long TE PRESS sequences, as in our study, offer the benefit of more simplified spectra with reduced contribution from lipid signals and more rectilinear baseline, which facilitate interpretation and quantitation of peak areas.

Moreover, as well as STEAM sequence is known to be more sensitive to movement; PRESS sequence is known to be less sensitive to movement and the signal to noise (SNR) ratio is much more. It is declared that with the application of MR spectroscopy in the same time with cardiac movements metabolite pikes become much clearer in brain and it reduces artefacts.[44–46] In a previous study Li et al. studied patients with localization-related epilepsy. Patients were divided into three groups according to the EEG investigation: temporal lobe epilepsy, extratemporal lobe epilepsy and multilobar epilepsy. They found NAA/Cr reduction was more often widespread in the multilobar group than in temporal or extratemporal groups.[47] In another study (Bernasconi et al.[48]) they showed that there was an abnormally low concentration of thalamic NAA/Cr in idiopathic generalized epilepsy (IGE) patients compared with healthy controls, but there was no difference in the concentration of NAA/Cr in the insular cortex, posterior temporal lobe, white matter and splenium of the corpus callosum. Also there was no difference in NAA/Cr between patients whose seizures were well controlled and those in whom seizures were not controlled. They found a significant negative correlation between thalamic NAA/Cr and duration of epilepsy.[48] In the study of Savic and co-workers, JME patients showed significantly lower concentrations of frontal lobe NAA than controls, as well as patients with generalized tonic clonic epilepsy (GTCS). In contrast the frontal lobe values in patients with GTCS were not different from normal. Patients with GTCS, on the other hand had significantly reduced concentration of NAA in thalamus compared with controls. Also they found the corresponding value in patients with JME was also lower, but the difference did not reach the level of significance.[19]

In the study of Mory et al.[17] in both thalami related with PRESS sequence (TE 135) on 10 patients with JME; they found NAA/Cr ratio lower in contrast to the control group.[17] Also, our study was performed with the PRESS sequence and TE 135 and 270 were taken from both thalami. Although there is statistically a significant difference for TE 270 integral NAA/Cr value in both right and left thalami (right, $P = 0.011$; left, $P = 0.030$) there is statistically observed a crucial difference for TE 270 integral NAA value in the left thalamus ($P = 0.019$).

In the studies before, it was seen that in thalamus NAA values for the patients with JME were not statistically lower than the control group. But, NAA value was found lower in our study. It is evident that NAA is a neuronal marker and so it is a very crucial metabolite for neuron physiopathology.

In conclusion, these preliminary findings of abnormal NAA/Cr ratios and left thalamic NAA value in patient with JME support the hypothesis of a thalamic dysfunction as part of the underlying mechanisms of epileptogenesis (abnormal thalamocortical circuity) in this form of generalized epilepsy.

References

1. Janz D. The idiopathic generalized epilepsies of adolescance with childhood and juvenile age of onset. *Epilepsia* 1997;**38**:4–11.
2. Devinsky O, Gerhergon J, Brown E. Frontal functions in juvenile myoclonic epilepsy. *J Neurol Neurosurg Psychiat* 1997;**10**:243–6.
3. Swartz BE, Simpkins F, Syndulkp K. Primary memory in patients with frontal and primary generalized epilepsy. *J Epilepsy* 1994;**7**:232–41.
4. Swartz BE, Simpkins F, Halgren E. Visual working memory in primary generalized epilepsy: an 18 FDG-PET study. *Neurology* 1996;**5**:1203–12.
5. Savich I, Pauli S, Thorell JO, Blomqvist G. In vivo demonstration of altered benzodiazepine receptor density in patients with generalized epilepsy. *J Neurol Neurosurg Psychiat* 1994;**57**:797–804.
6. Koepp MJ, Richardson MP, Brooks D. Central benzodiazepine/γ-amino butyric acid receptors in idiopathic generalized epilepsy: an (11C) flumazenil positron emmision tomography study. *Epilepsia* 1997;**38**:1089–97.
7. Cendes F, Knowlton RC, Novotny E. Magnetic resonance spectroscopy in epilepsy: clinical issues. *Epilepsia* 2002;**43**(Suppl. 1):32–9.
8. Cendes F, Stanley JA, Dubeau F. Proton magnetic resonance imaging for discrimination of absence and complex partial seizures. *Ann Neurol* 1997;**41**:74–80.
9. Gloor P. Generalized epilepsy with spike-and-wave discharge: a reinterpretation of its nelectrographic and clinical manifestations. *Epilepsia* 1979;**20**:571–88.
10. Vuileumier P, Assal F, Blanke O. Distinct behavioral and EEG topographic correlates of loss of consciousness in absences. *Epilepsia* 2000;**41**:687–93.

11. Prevent MC, Duncan JS, Jones T. Demonstrations of thalamic activation during typical absence seizures using H2(15)O PET. *Neurology* 1995;**45**:1396—402.
12. Orrison WW, Lewine JD, Sanders JA, Hartshorne MF. *Functional brain imaging*. 1st ed. St. Louis: Mosby; 1995. p. 419—67.
13. Young IR, Charles HC. *MR spectroscopy*. 1st ed. Cambridge: Martin Dunitz Ltd.; 1996.
14. Castillo M, Kwock L, Mukherji SK. Clinical applications of proton MR spectroscopy. *AJR* 1996;**17**:1—15.
15. Cousins JP. Clnical MR spectroscopy: fundomentals, current applicatons, and future potential. *AJR* 1995;**164**:1337—47.
16. Şener RN. *MRI of the pediatric brain*. 1st ed. St. Louis: Mosby; 1995. p. 419—67.
17. Mory SB, Li LM, Guerreiro CAM, Cendes F. Thalamic dysfunction in juvenile myoclonic epilepsy: a proton MRS study. *Epilepsia* 2003;**44**(11):1402—5.
18. Savic I, Lekvall A, Greitz D. Spectroscopy shows reduced frontal lobe concentrations of *N*-acetylaspartate in patients with juvenile myoclonic epilepsy. *Epilepsia* 2000;**41**:290—6.
19. Savic I, Österman Y, Helms G. MRS shows syndrome differentiated metabolite changes in human-generalized epilepsies. *NeuroImage* 2004;**21**(1):163—72.
20. Meena V, Cecil C, Larry T. Focal and lateralized subcortical abnormalities in unipolar major depressive disorder. An automated multivoxel proton magnetic resonance spectroscopy study. *Biol Psychiat* 2003;**54**(7):744—50.
21. Jin Z, Zang F, Zeng YW. Striatal neuronal loss or dysfunction and choline rise in children with attention deficit hyperactivity disorder: a H-magnetic resonance spectroscopy study. *Neurosci Lett* 2001;**315**:45—8.
22. Huguenard JR. Neuronal circuitry of thalamocortical epilepsy and mechanism of antiabsance drug action. In: Engel J, Pedley A, editors. *Alper's basic mechanism of the epilepsies Advances in neurology*, 3rd ed., vol. 79. Philadelphia: Lippincott Williams &Wilkins; 1999. p. 991—9.
23. Snead III OC. Basic mechanisms of generalized absence seizures. *Ann Neurol* 1995;**37**:146—57.
24. Stephan H, Snead III OC. Absence seizures. In: Engel J, Pedley A, editors. *Epilepsy: a comprehensive textbook*. Philadelphia: Lippincott-Raven; 1997. p. 579—90.
25. Kostopulus GK. İnvolvement of the thalamocortical system in epileptic loss of consciousness. *Epilepsia* 2001;**42**(Suppl. 3):13—9.
26. Velasco M, Velasco F, Velasco AL. Epileptiform EEG activities of the centromedian thalamic nuclei in patients with intractable partial motor, complex partial and generalized seizures. *Epilepsia* 1989;**30**:295—306.
27. McCormick D. Cortical and subcortical generators of normal and abnormal rhythmicity. *Int Rev Neurobiol* 2002;**49**:99—114.
28. Slaght S, Leresche N, Denian J. Activity of thalamic reticular neurons during spontaneous genetically determined spike and wave discharges. *J Neurosci* 2002;**22**:2323—34.
29. Goldensohn E, Legatt A, Koszer S, Wolf S. *Goldensohn's EEG interpretation: problems of overreading and underreading*. Armonk, NY: Futura; 1999.
30. Niedermeyer E. Epileptic seizure disorders. In: Niedermeyer E, da Silva FL, editors. *Electroencephalography: basic principles, clinical applications, and related fields*. Baltimore: Urban & Schwarzenberg; 2000. p. 476—585.
31. Panayiotopoulus C. The clinical spectrum of typical absence seizures and absence epilepsies. In: Malafosse A, Genton P, Hirsch E, et al. editors. *Idiopathic generalized epilepsies*. London: John Libbey; 1994. p. 75—85.
32. Steriade M, Amzica F. Sleep oscillations developing into seizures on corticothalamic systems. *Epilepsia* 2003;**44**(Suppl. 12):9—20.
33. Rodin E, Rodin M, Thompson J. Source analysis of generalized spike—wave complexes. *Brain Topogr* 1994;**7**:113—9.
34. Rodin E. Decomposition and mapping of generalized spike—wave complexes. *Clin Neurophysiol* 1999;**110**:1868—75.
35. Morrison R, Dempesy E. A study of thalamocortical relations. *Am J Physiol* 1942;**135**:281—92.
36. Morrison R, Dempsey E. Mechanism of thalamocortical augmentation and repetition. *Am J Physiol* 1943;**138**:297—308.
37. Yingling C, Skinner J. Selective regulation of thalamic sensory relay nuclei by nucleus reticularis thalami. *Electroencephologr Clin Neurophysiol* 1976;**41**:476—82.
38. Yingling C, Skinner J, Gating of thalamic input to cerebral cortex by nucleus reticularis thalami.Desmedt JE, editor. *Attention voluntary contraction and event-related cerebral potentials: progress in clinical neurophysiology*, vol. I. Basel: Karger; 1977. p. 70—96.
39. Steriade M. *Neuronal substrates of sleep and epilepsy*. New York: Cambridge University Press; 2003.
40. Steriade M, Amzica F. Sleep oscillations developing into seizures in corticothalamic systems. *Epilepsia* 2003;**44**(Suppl. 12):9—20.
41. Meeren H, Pijn J, Van Luijtelaar E. Cortical focus drives widespread corticothalamic networks during spontaneous absence seizures in rats. *J Neurosci* 2002;**22**:1480—95.
42. Yongbi NM, Payne GS, Collins DJ. Quantification of signal selection efficiency, extra volume suppression and contamination for ISIS, STEAM and PRESS localized 1H NMR spectroscopy using an EEC localization test object. *Phys Med Biol* 1995;**40**:1293—303.
43. Moonen CTW, Von Kienlin M, Van Zjil PCM. Comparison of single-shot localization methods (STEAM and PRESS) for in vivo proton NMR spectroscopy. *NMR Biomed* 1989;**2**:201—8.
44. Wiederman D, Schuff N, Matson GB, Soher BJ, Du AT, Maudsley A, et al. Short echo time multislice proton magnetic resonance spectroscopic imaging in human brain: metabolit distributions and reliability. *Magn Reson Imag* 2001;**19**:1073—80.
45. Tzika AA, Vigneron DB, Dunn GB, Nelson SJ, Ball WS. İntracranial tumors in children: small single-voxel proton MR spectroscopy using short-and long-echo sequences. *Neuroradiology* 1996;**38**(3):254—63.
46. Pattany PM, Khamis IM, Bowen BC, Goodkin K, Weaver RG, Murdoch JB, et al. Effect of physiologic human brain motion on proton spectroscopy: quantitative analysis and correction with cardiac gating. *AJNR Am J Neuroradiol* 2002;**23**:225—30.
47. Li LM, Cendes F, Andermann F, Dubeau F, Arnold DL. Spatial extent of neuronal metabolic dysfunction measured by proton MR spectroscopic imaging in patients with localization-related epilepsy. *Epilepsia* 2000;**41**(6):666—74.
48. Bernasconi A, Bernasconi N, Natsume J, Antel SB, Andermann F, Arnold DL. Magnetic resonance spectroscopy and imaging of the thalamus in idiopathic generalized epilepsy. *Brain* 2003;**126**:2447—54.