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Magnetic resonance spectroscopy of the thalamus in patients with typical absence epilepsy

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Summary

Purpose: To investigate possible neuronal dysfunction of the thalamus in patients suffering from typical absence epilepsy, using magnetic resonance spectroscopy (MRS). Special attention was paid to levels of *N*-acetylaspartate (NAA) and creatine (Cr), and to the NAA/Cr ratio.
Methods: MRS was performed over the right and left thalamus in nine patients suffering from typical absence epilepsy, and in nine sex- and age-matched healthy controls. All patients and controls were examined using a standard MRS-CSI (chemical shift imaging) technique.
Results: Statistical analysis of the obtained data demonstrated a significantly lower thalamic NAA/Cr ratio in patients with typical absence epilepsy when compared to the healthy controls. Our MRS data showed symmetrical distribution of NAA/Cr ratio in the right and left thalamus within both the patient group and the group of healthy controls. No significant correlation between the patients' thalamic NAA/Cr values and the duration of the epilepsy or seizure frequency was revealed.
Conclusions: The present MRS data clearly indicate neuronal dysfunction in the thalami of patients with typical absence epilepsy. In agreement with other recent MRS findings in different idiopathic generalized epilepsy syndromes, our results confirm the role of the thalamus as an important structure in the pathogenesis of typical absence epilepsy.

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Introduction

Absences are generalized non-convulsive seizures. They differ in many respects from other forms of epileptic seizures.[1–3] The International Classification of Epilepsies (1989) recognized the heterogeneity of epilepsies with absence seizures, and proposed the categorization of three syndromes of idiopathic generalized epilepsy (IGE) with absence seizures: childhood absence epilepsy, juvenile absence epilepsy, and juvenile myoclonic epilepsy.[4]

Generalized absence seizures may be defined as a paroxysmal loss of consciousness of sudden onset and sudden end that is associated with recorded bursts of bilaterally synchronous spike-and-wave discharges in the electroencephalogram (EEG).[5] Absence seizures may be typical or atypical. The differentiation of these two types is principally based on EEG findings.[6] Clinically, there is normal neurological status and normal psychomotor development in patients with typical absence epilepsy.

The pathophysiological mechanisms of absence seizures have been studied in various animal models.[7,8] From an ethical point of view, systematic invasive EEG recording simply is not indicated in patients with typical absence epilepsy, and therefore the pathophysiological mechanisms of absences in humans remain poorly understood. Nevertheless, some studies have proven that the major structures that participate in the pathogenesis of typical absence seizures are the thalamus and the cortex, in particular the parietal and frontal areas.[8–10] It has been suggested that the generalized spike-and-wave discharges are generated and sustained by abnormal oscillatory rhythms in a thalamo-cortical circuit that mainly involves the reticular thalamic nucleus, thalamic relay neurons, and neocortical pyramidal cells. Neither the cortex nor the thalamus alone can probably sustain these discharges, which may indicate that both structures together are involved in their genesis.[6,8]

Magnetic resonance spectroscopy (MRS) is a non-invasive imaging technique providing metabolic information from different body tissues, including the human brain.[12–16] MRS is able to detect metabolic abnormalities that are invisible to conventional MRI, because these abnormalities may precede structural changes.[15] Conventional MRI and MRS rely on the same physical principles to collect the MR signal, but differ in the way the data is processed, displayed, and interpreted. Instead of images, as with MRI, data presented as a plot with peak amplitudes compared with a respective frequency is obtained with MRS.[12,13,15] Various metabolites are detected in the spectrum. Three major peaks characterize long-echo time ^{1}H MRS spectra: *N*-acetylaspartate (NAA) — marker of neuronal and axonal viability and density; creatine (Cr) — used as internal reference, since it is the most stable cerebral metabolite; choline — reflecting cellular proliferation. There are two types of MRS techniques — single voxel and multivoxel. The multivoxel technique allows a number of voxels to be positioned in the brain, enabling the simultaneous investigation of the metabolic abnormalities in many small volume units within the structure, and shows the extension of metabolic abnormalities. It is also referred to as "chemical shift imaging".[16]

The present research study was conducted to investigate the potential involvement of thalamic structures in the genesis of typical absence seizures. We hypothesized that the concentration of thalamic NAA might be lower in patients with typical absence epilepsy than in healthy control subjects.

Subjects and methods

Subjects

Nine epileptic patients (six females, three males; all right handed) suffering from typical absence epilepsy were admitted to the study. The patients were selected from the database of patients referred to the regional epilepsy centre. The control group consisted of nine sex (six females, three males) and age matched healthy volunteers. The mean age of the subjects in the patient group was 32.3 ± 6.63 years (ages ranged from 25 to 43 years; median age of 33 years); the mean age in the control group was 27.6 ± 3.70 years (ages ranged from 24 to 35 years; median age of 27 years). Patients did not differ significantly in age distribution from the healthy controls. We reviewed all video EEG records from 1997 to 2002, and selected nine subjects who fulfilled the diagnostic criteria for typical absence epilepsy. Clinical data were prospectively obtained from these subjects through careful interviews with the patients and their family members, and by reviewing hospital charts. In all of the investigated patients, the typical absence epilepsy diagnosis was based on a consonance of history data, ictal (bilateral spike-and-wave activity in all patients) and interictal EEG findings, ictal semiology, and negative neuroimaging. Most of the patients had either childhood or teenage seizure onset (two cited seizure onset at 20 years of age). The mean age of the patients at the time of seizure onset was 13.11 ± 4.09 years; with a median age of 14 years.

All of the patients had been routinely investigated, including long-term video-EEG monitoring, high resolution MRI, and neuropsychological testing. Neither initial insult nor neuropsychological deficits were revealed in our patients. According to history data (seizure diary), the seizure frequency ranged from 1 to 90 seizures per month, with a mean of 16.8 $\pm$ 27.73 seizures per month. The interval between the most recent seizure and the MRS investigation varied from 1 to 365 days, median 10.0. Following adjustments to their pharmacotherapy, two patients had been seizure free for 1 year at the time of MRS investigation. The patients at the time of MRS investigation were on various pharmacotherapy programs: monotherapy of sodium valproate (four patients); a combination of sodium valproate and lamotrigine (two patients); a combination of lamotrigine and ethosuximide (one patient); a combination of sodium valproate, lamotrigine and carbamazepine (one patient); primidone, lamotrigine, sodium valproate with clonazepam (one patient).

The majority of the healthy subjects in the control group were volunteers from the professional sector with no history of neurological or psychiatric diseases. Informed consent was obtained from each participant after all of the procedures were fully explained, and the study received the approval of the local ethics committee.

MRS measurement

MR examinations were carried out on a 1.5 T Siemens Symphony scanner (Erlangen, Germany) equipped with a Numaris 4 System. After the establishment of the localizer, high-resolution anatomical T1-weighted images in the sagittal planes, and T2-weighted images in the coronal and transversal planes, were obtained. Transversal MRI images were acquired by using a turbo spin echo sequence with the basic parameters TE = 90 ms and TR = 3170 ms. These conventional MRI images served as a matrix for the spectroscopic measurement, and served to position a spectroscopic volume of interest (VOI). Positioning of VOI was adjusted to the individual anatomy on MRI images covering the right and the left thalamus (Fig. 1). The proton spectroscopic data were subsequently acquired by using a chemical shift imaging method with the basic parameters: TR = 1360 ms; TE = 80 ms; number of scans = 12; flip angle 90°; FOV (field of view) 80 mm $\times$ 80 mm; VOI = 40 mm $\times$ 40 mm; slice thickness = 10 mm; 8 $\times$ 8 phase-encodes (interpolated on 16 $\times$ 16); vector size = 1024 points; SW (bandwidth) = 1000 Hz. Reduced sampling was used for elliptically scanning the data. The water signal was suppressed to acquire an adequate visualisation of the peaks of the metabolites. The nominal voxel size in-plane

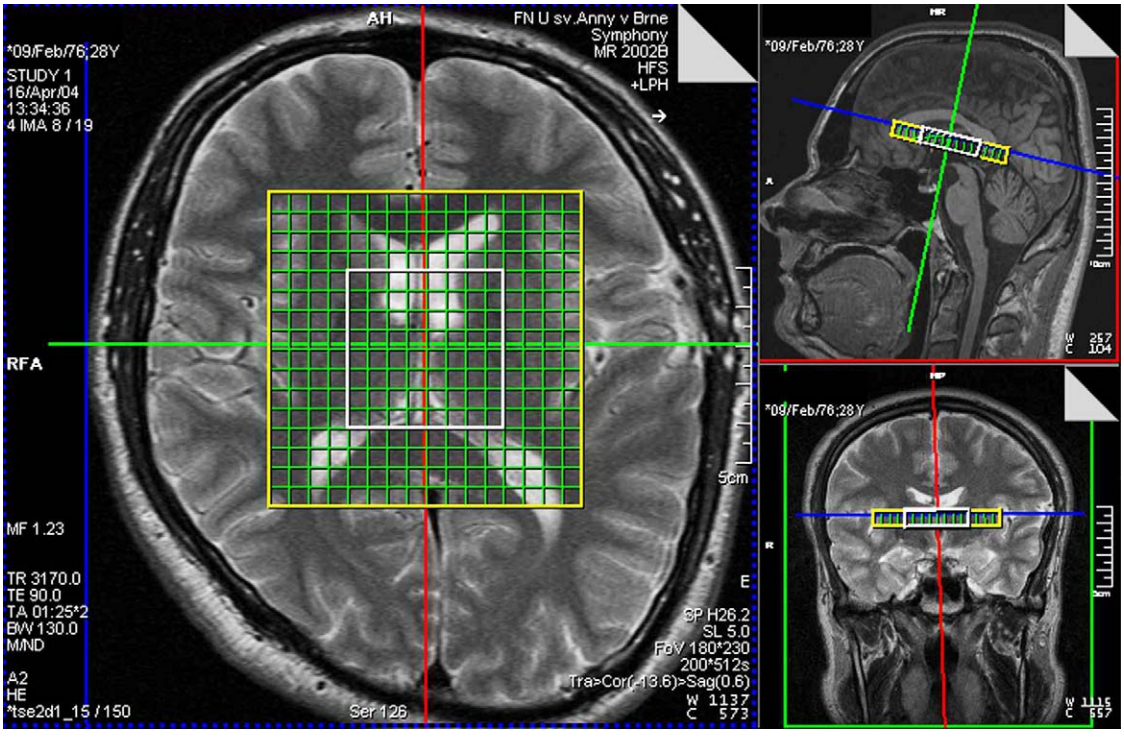

Figure 1 Proton magnetic resonance spectroscopy (MRS) of the thalamus. T2-weighted image in the transversal plane. Placement of the volume of interest over the right and left thalami; multi-voxel spectroscopy technique; positioning of the voxels.

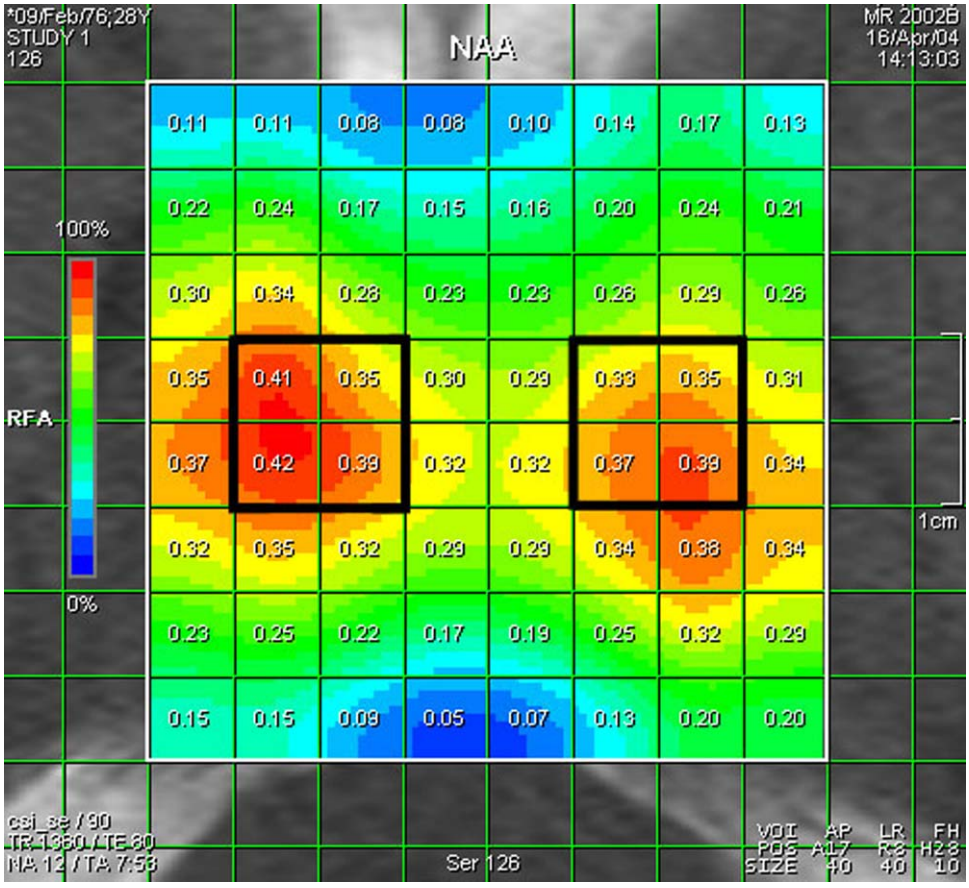

Figure 2 The multivoxel spectroscopy metabolite map for *N*-acetylaspartate (NAA). Graphic demonstration of selecting voxels with NAA concentration. Data are obtained from four adjacent voxels.

was 10 mm × 10 mm × 10 mm; the final voxel size in-plane was 5 mm × 5 mm × 10 mm.

The spectra were post-processed using software supplied by the scanner producer. After post-processing water suppression, zero-filling, baseline correction and phase correction, we determined peak areas by integrating the corresponding signals from *N*-acetylaspartate (NAA) at 2.0 ppm (parts per million), and creatine (Cr) at 3.0 ppm.

Using chemical shift imaging, we obtained two-dimensional data sets. The spectral mapping that enabled a spatial distribution of NAA and Cr concentration was used to analyze the spectroscopic data (Fig. 2).

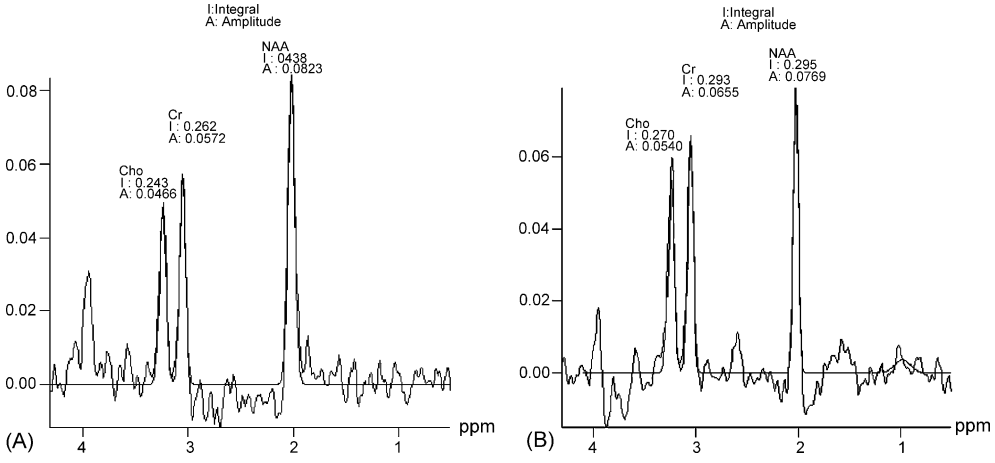

Figure 3 Sample of spectra from the healthy control (A) and the patient (B) depicting the values of analysed metabolites.

The values of NAA and Cr concentration were obtained from a spectral curve present in each small voxel located in the thalamus (Fig. 3). The data of NAA and Cr concentration were distributed in a spectral map. Each analysed voxel was located entirely within the thalamus, to minimize any metabolic contamination from adjacent cerebrospinal fluid or grey and white matter outside the thalamus.

Data for statistical analysis were obtained from four adjacent voxels situated in the centre of the right and left thalamus. AUC (area under the curve, e.g. integral) values of NAA and Cr concentration from these selected voxels were analysed as a ratio of NAA to Cr.

Ratios of NAA/Cr of the determined voxels were compared between both groups. At first, a comparison of data from right and left thalami (right versus right and left versus left) between the patients and the healthy controls was performed. Subsequently, the data from the voxels of both thalami (72 voxels) of the patients and healthy controls were compared.

Statistical analysis

Group differences for age were tested by *t*-test.

To evaluate the differences of the NAA/Cr ratio in the determined voxels, a two-way ANOVA test was performed to compare the patients and the healthy controls and to contrast the right and left thalamus in patients and healthy controls. Statistical significance was considered to be present if $p < 0.05$ in tested parameters.

The Pearson correlation was computed between spectroscopic data and the duration of epilepsy in the patient group. The same approach was used to study the hypothetical relationship between seizure frequency and the values of NAA/Cr ratio.

The Statistica program from StatSoft was used.

Results

Patients and healthy controls did not differ with respect to age (patient group with a mean age of 32.3 years, S.D. = 6.63 years; healthy controls with a mean age of 27.6 years, S.D. = 3.70; $p = 0.084$).

We performed a statistical comparison of the metabolic NAA/Cr ratio between patients and healthy controls and between the right and left thalamus with an ANOVA test. A statistically significant difference was found between the patients and the control group, with lower values of the NAA/Cr ratio in the typical absence epilepsy patients ($p = 0.000066$, $F(1;140) = 16.92$).

When comparing the symmetry of the analysed parameter distribution between the right and left thalami, the ANOVA test showed no significant differences in the mean thalamic NAA/Cr ratio in our normal controls; nor were lateralised abnormalities found in our typical absence epilepsy patients ($p = 0.127$, $F(1;140) = 2.36$).

No significant interactions between our parameters were observed ($p = 0.591$, $F(1;140) = 0.29$).

In our data, no significant correlation between the thalamic NAA/Cr ratio and the epilepsy duration was observed ($r = -0.15$, $p = 0.20$). There was also no correlation found between the level of NAA/Cr ratio and seizure frequency ($r = -0.20$, $p = 0.09$).

Discussion

Since typical absence epilepsies have moderate or normal neurological status and behaviour, it is likely that these disorders will have discrete brain alterations that are not easy to detect by neuroimaging techniques. Proton magnetic resonance spectroscopy might be extremely useful in the assessment of this type of epilepsy, because of its ability to accurately demonstrate focal functional impairment in subjects when conventional MRI results are negative.

Our analysis of spectroscopic images acquired with the multivoxel proton MRS technique revealed a significant reduction in the thalamic NAA/Cr ratio in our group of patients with typical absence epilepsy.

The spectral abnormalities found in our experiment in patients with typical absence epilepsy clearly extend beyond negative neuroimaging findings. Negative MRI findings were also revealed in our patients. In general, no structural lesion of any kind has ever been identified as the substrate of typical absence epilepsies.[3,17]

N-Acetylaspartate is present in the vertebrate brain, where its concentration is one of the highest of all free amino acids. Its prominence in MRS studies has led to its wide use as a neuronal marker in diagnostic human medicine, as an indicator both of brain pathology and of disease progression in the central nervous system. The NAA, when present in the brain, appears to reflect a high degree of cellular integration, and therefore may be a unique metabolic construct of the intact vertebrate brain. It is believed that a reduction in NAA and/or NAA/Cr ratio indicates neuronal and/or axonal loss, loss of neuron viability, and dysfunction.[18–21] It should be recognized that the macroscopic concentration of NAA depends on the fluxes of synthetic and degradation pathways, cellular density and brain water content and distribution. Whether the reduction represents an irreversible loss of cells or a potentially reversible

metabolic process cannot readily be determined. Nevertheless, our results, by showing metabolite signal changes, detect some pathological processes surpassing the structural changes.

Due to technical obstacles, we were unable to statistically analyse the absolute values of respective metabolites (e.g. NAA). Instead, the relative values (ratios) were used. The quantification of NAA in relation to Cr (NAA/Cr ratio) is widely and reasonably used in various clinical and experimental settings.[21,22] Observations and studies using this approach suppose that Cr is a stable internal reference. It is believed that relative signal intensities provide an adequate basis for interpretation of the results and that these intensities are sensitive to neurochemical changes in cell population without regard to absolute metabolite values. As the loss of NAA may be in some cases accompanied by an increase of Cr signal, the NAA/Cr ratios may show the higher relative value, rather than an absolute value in any individual signal.[23] However it is assumed that Cr is relatively homogenously distributed throughout the brain and is not significantly influenced by the epileptic state.[24] It is for this reason that we justified the use of relative values as the markers of changes in cell population in our study.

In the pathophysiological mechanism of absence seizures, thalamocortical and corticothalamic projections play important roles. The pathophysiology of idiopathic generalized epilepsy syndromes is not fully understood, but it is generally accepted that typical absence seizures are the result of abnormal oscillations between the thalamus and cerebral cortex.[7,8] The neurochemical changes underlying typical absence epilepsy have not yet been fully elucidated, but they are a sphere for active research in both affected humans and in animal models.[21] Both inhibitory and excitatory neurotransmissions participate in the genesis and control of absence seizures. Whether the generation of spike-and-wave discharges (SWDs) is the result of an excessive cortical hyperexcitability, as was proposed in feline generalized epilepsy,[10,25] or an excessive thalamic synchronization, possibly under the control of inhibitory GABAergic mechanisms,[26–28] remains controversial. It appears that neurons, mainly involved in the thalamic reticular nucleus (nRt),[29] thalamic relay neurons (RNs), and neocortical pyramidal cells comprise a circuit that sustains the thalamocortical oscillatory burst firing of absence seizures.[7]

Two main hypotheses have been proposed to explain the pathogenesis of absence seizures in animal models: either (1) excessive thalamic oscillations due to hypersynchronization and/or (2) cortical hyperexcitability, which may amplify physiological rhythmic oscillations originating in the thalamus.

Such dysfunctions may result from alterations affecting: (1) synaptic communications within the thalamo-cortical network; (2) intrinsic properties in cortical and/or thalamic neurons; or (3) morphological abnormalities within the thalamo-cortical circuit.[8]

According to some investigators, the cortex seems to play a leading role. The corticothalamic interrelationships were investigated by means of nonlinear association signal analyses of multiple spike-wave discharges. This showed a consistent focus within the perioral region of the somatosensory cortex. From this focus, seizure activity generalizes rapidly over the cortex. During the first cycles of the seizure, the cortex drives the thalamus; thereafter the cortex and thalamus drive each other, thus amplifying and maintaining the rhythmic discharge. In this way the ''cortical focus'' theory for generalized absence epilepsy bridges cortical and thalamic theories.[30]

The idea that the neuronal elements of the thalamocortical loop are crucial to the full expression of SWDs is supported by single-photon emission tomography study in children with childhood absence epilepsy, which reveal hypermetabolism in cortical and thalamic areas during absence seizures.[31]

To examine cortico-thalamic relationships during the generation of SWDs, various cortical and thalamic areas were lesioned in GAERS (Genetic Absence Epilepsy Rats from Strasbourg). The results of these studies demonstrated that SWDs cannot occur in a thalamus that is disconnected from the cortex, and clearly showed that SWDs cannot occur in a cortex deprived of its thalamic input.[10,25,32]

In our study, we presented a significantly lower thalamic NAA/Cr ratio in the patient group than in the healthy control group. The focus of this research did not involve the investigation of adjacent areas or other regions of the brain; nevertheless, an analogous study in patients with juvenile myoclonic epilepsy and generalized tonic clonic seizures on awakening did not report any abnormal concentration of NAA/Cr in the insular cortex, posterior temporal lobe white matter, or splenium of the corpus callosum).[21]

A single voxel MRS study showed abnormally low NAA/Cr levels in at least one thalamus in nine out of ten patients with juvenile myoclonic epilepsy (JME), indicating a neuronal dysfunction of the thalamus in this IGE syndrome.[22] In another single voxel study, significant thalamic reduction of NAA was observed in patients with pure primarily generalized tonic clonic epilepsy in comparison with controls.[33] A recently published study, where authors used proton magnetic resonance spectroscopic imaging, proved a reduction of mean thalamic NAA/Cr in patients

with IGE in comparison to normal controls.[21] These results are in agreement with our investigation; and our MRS findings are in congruence with previous and recent theories that the thalamus plays an important role in the pathophysiology of typical absence epilepsy as has been proven in several subtypes of IGE. To the best of our knowledge, the role of the thalamus in other types of epilepsies (i.e. focal epilepsies) has not yet been clarified.[21,22,33]

Bernasconi et al.,[21] who studied NAA/Cr ratio in idiopathic generalized epilepsy patients, found a negative correlation between thalamic NAA/Cr and the duration of epilepsy. There was no difference in NAA/Cr between the patients whose seizures were well controlled and patients in whom seizures were not controlled. In our present study, there was neither a statistically significant correlation between thalamic NAA/Cr ratio and the duration of epilepsy, nor a correlation with the seizure frequency observed. Due to the small set of values, the absence of correlation may be falsely negative. Our results indicate a downward trend toward the statistical significance in both tested parameters. We can speculate that a statistical significance could be reached with a wider range of values.

The generation of bilateraly generalized spike-wave discharges is only possible in an anatomically and functionally intact corticothalamic network that is in a suitable state to propagate seizures. The presence of abnormalities in the corticothalamic network has been suggested to be the functional basis of absence seizure generation. Neuronal dysfunction in the thalamus has been indicated by MR spectroscopy in several subtypes of IGE. However, there is recent evidence of existing subcortical grey and white matter volume reduction in childhood absence epilepsy patients.[34] Besides the metabolic neuronal dysfunction, we can also assume a reduction of functional thalamic neurons (reflected by the decrease of NAA), and the possibility of derangement of thalamocortical glutamatergic and intrathalamic GABAergic transmission that might be caused by the mentioned reduction. In general, the metabolite or structural changes may be either a result of damage from seizures or a reflection of primary underlying pathology as the cause of absence seizures. MRS studies in IGE suggest a key role for the thalamus in the generation of prolonged runs of generalized SWD, and support the concept of thalamocortical circuit abnormalities as the underlying pathophysiological substrate of IGE.[35] However the significant role of subcortical structures and the pathophysiology of decreased NAA and other metabolite or neurotransmitter disturbances in seizure generation and propagation in idiopathic generalized epilepsy has not yet been elucidated.

As far as we are aware, this is the first study investigating neurochemical changes of the thalamus in typical absence epilepsy patients. Our results, as well as the results of many other studies, support the notion of a common pathophysiological abnormality among different idiopathic generalized epilepsy syndromes.

In conclusion, our presented findings are consistent with the increasing evidence of an important involvement of the thalamus, as a part of underlying substrate, in the pathogenesis of absence seizures. The possible alteration of neuronal pathways in the thalamo-cortical circuit seems to play a critical role in epileptogenesis of idiopathic generalized epilepsies, but has not, thus far, been confirmed, and remains a topic for further studies in several worldwide laboratories.

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