Neuronal Dysfunction in Children With Newly Diagnosed Temporal Lobe Epilepsy

Steven P. Miller, MDCM* †, Li M. Li, MD*, Fernando Cendes, MD, PhD*, Zografos Caramanos, MA*, Bernard Rosenblatt, MDCM†, Michael I. Shevell, MDCM†, Frederick Andermann, MD* †, and Douglas L. Arnold, MD* 

We sought to determine whether neuronal dysfunction throughout the temporal lobes of children with temporal lobe epilepsy (TLE) is already as severe at the time of diagnosis as it is in patients with long-standing intractable TLE (INT-TLE). Proton magnetic resonance spectroscopic imaging was used to measure N-acetylaspartate/creatine (NAA/Cr) ratios in the temporal lobes of five consecutive children with newly diagnosed TLE (ND-TLE), five with INT-TLE, and 30 normal control subjects. The median age of those with ND-TLE and those with INT-TLE did not significantly differ (P = 0.92). All five patients with ND-TLE had bilateral reductions in the NAA/Cr ratio. Two of the five patients with INT-TLE had bilateral reductions in the NAA/Cr ratio; three had unilateral reductions in the NAA/Cr ratio. In the three patients with lesions the NAA/Cr ratio decrease extended outside these lesions. No significant differences were detected in any temporal lobe region between the ND-TLE and INT-TLE groups. The severity of the neuronal dysfunction in the children with ND-TLE was at least as severe as in those with INT-TLE and was not restricted to one temporal lobe, implying that the neuronal abnormalities observed in patients with TLE occur before the clinical manifestations. © 2000 by Elsevier Science Inc. All rights reserved.

Introduction

Whether progressive temporal lobe neuronal damage in humans with temporal lobe epilepsy (TLE) is acquired as a consequence of repeated seizures remains controversial. One form of progressive neuronal damage is secondary epileptogenesis. Secondary epileptogenesis refers to the induction by an actively discharging epileptogenic region of similar paroxysmal behavior in the cellular elements of otherwise normal and often contralateral neuronal networks [1]. Secondary epileptogenesis is readily demonstrated in animals in the kindling experimental model [2-4]. However, secondary epileptogenesis and other forms of progressive neuronal damage have not conclusively been demonstrated in humans [1-3,5,6]. Knowledge of the extent of neuronal damage present at the clinical onset of TLE would help to clarify the extent to which neuronal damage in TLE relates primarily to recurrent seizures or to the underlying epileptogenic process itself.

Proton magnetic resonance spectroscopic imaging (1H-MRSI) allows the measurement of the neuronal marker N-acetylaspartate (NAA) [7,8], the main contributor to the N-acetyl group signal apparent at 2.02 ppm of the brain spectrum [9]. The side of maximal NAA signal reduction has been proved to coincide with the side of seizure origin in patients with TLE [10-16]. The decreased temporal lobe NAA signal indicates neuronal damage that may be secondary to neuronal metabolic dysfunction or acquired microscopic abnormalities not visualized on magnetic resonance imaging (MRI).

In patients with intractable TLE (INT-TLE), ipsilateral and contralateral NAA/creatine (Cr) ratios were negatively correlated with the duration of epilepsy [17]. Extrapolation of this data backward in time suggests that NAA values are abnormally low at the onset of epilepsy and that the ipsilateral NAA/Cr ratio is lower than the contralateral values even at an early age [17]. However, to our knowledge, no direct observation has been made of the degree of neuronal damage at the time of diagnosis of TLE. The objective of this study was to define the extent of any
NAA/Cr decreases in the temporal lobes of children presenting with TLE and to determine whether these abnormalities differed from those in children with more long-standing INT-TLE undergoing preoperative evaluation.

Methods

Using 1H-MRSI, a consecutive series of 10 patients with electroclinical manifestations of TLE were prospectively studied [18]. Five presented with newly diagnosed TLE (ND-TLE), and five were undergoing evaluation for INT-TLE. In the INT-TLE group, all patients had recurrent complex partial seizures with automatisms and underwent intensive prolonged video-electroencephalographic telemetry, with unilateral temporal lobe ictal onset documented in all patients. The diagnosis of ND-TLE was made after recurrent complex partial seizures with automatisms and unilateral temporal lobe spikes or sharp waves (or both) on interictal electroencephalogram (EEG) recordings. The temporal lobe origin of the seizures was clear in all patients but was less firm in the ND-TLE group, which was based on routine EEG and not video EEG. All the patients with ND-TLE underwent imaging within 4 weeks of the initial diagnosis. Written informed consent was obtained before the 1H-MRSI studies, using a form approved by the Montreal Children’s Hospital Institutional Review Board. Because values for the NAA/Cr ratio approach adult values by 3-6 years of age [19-21], the pediatric groups were compared with 30 normal control adults (mean age = 30.4 years; range = 17.7-51.5 years).

All clinical data were obtained from direct interviews with the patient and family. The epilepsy duration was defined as the period between the first seizure in retrospect and the date of the 1H-MRSI scan. The seizure and family. The epilepsy duration was defined as the period between the

Figure 1. 1H-MRSI ROI. Conventional (water-based) axial T2-weighted MRI (TR = 550 ms, TE = 19 ms) through the temporal lobes, with the original phase encoding grid for 1H-MRSI superimposed. The ROI for acquisition of 1H-MRSI is outlined by the thick white line. Each temporal lobe inside the ROI is subdivided into two anatomic subregions. One anterior, defined as middle temporal (thick gray), comprises the region of the head and body of the hippocampus (lower arrow) and surrounding structures. The second, defined as posterior temporal (thin gray), includes the tail of the hippocampus and the medial aspect of the posterior temporal lobe. The pole of the temporal lobe and the amygdala (upper arrow) are not included in the ROI to avoid artifactual interference from the bone and fat of the clivus and air in the sphenoid bone.

All 10 patients underwent diagnostic MRI using a Philips 1.5-T combined imaging and spectroscopy system (Philips Medical Systems, Best, The Netherlands). MRI included sagittal and coronal T2-weighted (TR = 550 ms, TE = 19 ms) images, followed by axial proton density and T2-weighted (TR = 2,100 ms, TE = 20, 78 ms) images, inversion recovery, and gadolinium-diethylenetriamine pentaacetic acid–enhanced images (when indicated). 1H-MRSI of the temporal lobes was performed during the same examination using the same scanner. After scout images in the axial and sagittal planes a multislice transverse T2-weighted MRI (TR = 500 ms, TE = 20 ms) was obtained. The volume of interest (VOI) included part of the head, body, and tail of the hippocampus and portions of the gray and white matter from the mid-temporal and posterotemporal lobes (Fig 1). The size of the VOI was 80-100 mm in the left-right axis, 65-95 mm in the anteroposterior axis, and 20 mm in thickness. A water-suppressed 1H-MRSI was acquired from the VOI (TR = 2,000 ms, TE = 272 ms, 250 × 250-mm field of view, and 32 × 32 phase-encoding steps), followed by an 1H-MRSI without water suppression (TR = 850 ms, TE = 272 ms, 250 × 250-mm field of view, and 16 × 16 phase-encoding steps). Postprocessing included zero-filling the non–water-suppressed 1H-MRSI to obtain 32 × 32 profiles, followed by application of a mild gaussian k-space filter and an inverse two-dimensional Fourier transformation to both the water-suppressed and non–water-suppressed 1H-MRSIs. The resulting time-domain signal was left shifted and subtracted from itself to improve the water suppression [22]. The same process was performed to obtain the normal control data (30 subjects). The resonance intensities in the individual spectra were determined by integration of the peak areas using locally developed software.

The number of spectra averaged for each subregion (mid-temporal and posterotemporal regions) within the VOI was 10 ± 2. The size of the individual voxel after postprocessing was approximately 2 mL. Voxels on the edge of the VOI that were affected by chemical shift artifact and voxels that were artifactually broadened were excluded from the analysis. In epilepsy, Cr is stable or undergoes minor changes that do not significantly influence the NAA/Cr ratio [11,12,14,23,24]. Changes in the NAA/Cr ratio thus reflect neuronal loss or dysfunction. A normalized measure of asymmetry of the NAA/Cr values between the two temporal lobes was defined as (left – right)/[(left + right)/2]. For individual patients, NAA/Cr ratios and an asymmetry index greater than 2 S.D.
The clinical data are summarized in Table 1. The median age of the patients with ND-TLE (8.4 years) and those with INT-TLE (9.1 years) did not significantly differ (Mann-Whitney U test = 12; P = 0.92).

The median duration of seizures was 8 weeks in the ND-TLE group and 5.7 years in the INT-TLE group (Mann-Whitney U test = 2.0, P = 0.028). The total number of seizures in the ND-TLE group was small. Three patients in the ND-TLE group had experienced only two seizures (partial complex in Patient 2 and partial complex secondary generalized in Patients 4 and 5). The other two patients in the ND-TLE group had experienced less than 10 partial complex seizures (Patients 1 and 3). The patients in the INT-TLE group had experienced hundreds (Patients 8 and 9) to thousands of seizures (Patients 6, 7, and 10). The seizure frequency in the INT-TLE group ranged from one to three monthly (Patients 8 and 9) to one to five daily (Patients 6, 7, and 10).

Two patients with ND-TLE had lesions identified in the temporal lobes on MRI: a left temporal dysembryoplastic neuroepithelial tumor (Patient 1) and a temporal horn periventricular nodular heterotopia (Patient 3). One patient with INT-TLE had a right periventricular nodular heterotopia involving the temporal and frontal horns of both hemispheres (Patient 9). One patient with INT-TLE had left mesial temporal sclerosis (Patient 8).

Two children had a remote family history of epilepsy (Patient 8’s maternal grandfather and Patient 10’s paternal great uncle). Only one child had a history of a single antecedent simple febrile seizure (Patient 7). All patients with INT-TLE were receiving multiple antiepileptic medications. Two in the ND-TLE group (Patients 1 and 5) had received antiepileptic medication for less than 2 weeks before the 1H-MRSI study.

All patients in both groups had at least one temporal lobe region with an abnormal NAA/Cr ratio (less than 2 S.D. below the normal mean) compared with the control values. The abnormalities were bilateral in all five of the ND-TLE group and in two of the INT-TLE group (Patients 6 and 7) (Fig 2). The differences in the ND-TLE group compared with the control group had a more widespread distribution than did the differences in the INT-TLE group. The ND-TLE group appeared to have a lower temporal lobe NAA/Cr ratio than the INT-TLE group. However, the ND-TLE and INT-TLE groups did not differ
significantly from each other in any temporal lobe region, either by right/left or ipsilateral/contralateral analysis (Table 2). A Mann-Whitney U test pairwise comparison of patients with and without lesions for each ipsilateral and contralateral region did not result in significant differences (all P values greater than 0.28). Given the number of pairwise comparisons performed, a conservative alpha of 0.0025 was used a priori. Using a less conservative alpha of 0.01 did not alter the results with respect to statistical significance.

Discussion

Using 1H-MRSI, we demonstrated a diminished temporal lobe NAA/Cr ratio in all subjects of a small consecutive series of children with ND-TLE and INT-TLE. The NAA/Cr values of the ND-TLE and INT-TLE groups both differed significantly from the normal control values but not from each other.

Low temporal lobe NAA ratios are a useful marker of neuronal dysfunction in children and adults with TLE [9,11,12,14,23-27]. The recovery of NAA in the ipsilateral and contralateral temporal lobes after successful surgical treatment of the epilepsy [28,29] indicates that widespread decreases in NAA in patients with TLE primarily reflect neuronal dysfunction rather than irreversible neuronal loss.

The diminished temporal lobe NAA/Cr ratio in patients with ND-TLE shortly after the diagnosis supports the hypothesis that neuronal dysfunction in TLE is related primarily to the underlying epileptogenic process rather than to the effects of the seizures themselves. This finding is in keeping with the previous observations of impaired declarative memory [30,31] and right-left hippocampal asymmetries on MRI volumetric studies [32] in patients with ND-TLE.

A significantly lower NAA/Cr ratio was not observed in the INT-TLE group, with a median duration of TLE of 5.7 years, compared with the ND-TLE group, with a median duration of 5.7 years.
duration of TLE of 8 weeks. Although previous studies have demonstrated small decreases in the NAA/CR ratio with increasing disease duration [15,17], these studies made the observations for much longer periods. The association of increasing duration of epilepsy with NAA/CR ratio decreases [17], hippocampal volume loss as demonstrated by MRI volumetry, and hippocampal neuronal loss at postmortem examination was based on observations for periods extending up to 20 years [33-35]. The relatively short duration of the reported observations in children with TLE may have resulted in an inability to demonstrate a difference between the INT-TLE and ND-TLE groups.

In the present series, all children with ND-TLE and one with INT-TLE had bilateral NAA/CR reductions. 1H-MRSI may detect metabolic abnormalities in a brain that appears structurally normal on MRI in patients with TLE [11,36-38]. Bilateral reductions of NAA are evident in up to 50% of patients with unilateral chronic TLE [11-13,23,36], which is consistent with the frequency of bilateral structural changes in neuropathologic series [39,40]. The presence of bilateral abnormalities in five consecutive children with ND-TLE may have occurred by chance in this small sample. Alternatively, the early phase of TLE may be a distinct period in which bilateral neuronal dysfunction occurs that subsequently becomes more lateraled with time. Bilateral epileptiform EEG abnormalities have been observed to become unilateral during long periods of follow-up in occasional patients with intractable partial epilepsy [41]. Other factors, such as medication use, could cause neuronal metabolic dysfunction to localize more precisely to the side of seizure origin with time.

The high incidence of temporal lobe lesions in this series is characteristic of pediatric TLE [42]. Most pediatric candidates for temporal resection have been observed to have developmental abnormalities or low-grade tumors [43,44]. The low temporal lobe NAA/CR ratio in the patients with malformations of cortical development (Patients 1, 3, and 9) was present outside the lesions, consistent with previous 1H-MRSI data [45,46] and with electrophysiologic data illustrating that the epileptogenic abnormality is more extensive than the lesion visible on MRI [47]. The presence of neuronal dysfunction in all of the children with ND-TLE suggests that the NAA/CR ratio decrease is common to diverse epileptogenic processes.

In conclusion the severity of the neuronal dysfunction in children with ND-TLE was at least as severe as in the patients with INT-TLE and was not restricted to one temporal lobe. This finding implies that the neuronal abnormalities observed in patients with TLE occur before the clinical manifestations of the TLE. This finding is also consistent with the interpretation that NAA is a marker of the underlying epileptogenic process and that alterations of NAA are not limited to the effects of chronic recurrent seizures.

This study was supported by the Medical Research Council of Canada. Dr. Li is a recipient of the Jeanne Timmins Costello Fellowship.

**References**


