Temporal pole proton preoperative magnetic resonance spectroscopy in patients undergoing surgery for mesial temporal sclerosis

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Object. The purpose of this prospective study was to compare the results of proton MR spectroscopy (MRS) in temporal poles in patients with unilateral mesial temporal sclerosis (MTS) with the histopathological findings of the resected temporal poles.

Methods. A total of 23 patients (14 male and 9 female) with a mean age of 25.2 years (range 17–45 years) were included in this study, which was conducted over a 4-year period. All patients suffered medically refractory epilepsy due to unilateral, MRI-proven MTS, with no other imaging abnormalities. All participants underwent preoperative single-voxel proton MRS using a 3-T MRI unit. The hippocampi and temporal poles were examined bilaterally. The concentrations of N-acetyl-aspartate (NAA), choline (Cho), and creatine (Cr) were measured, and the NAA/Cho, NAA/Cr, and NAA/Cho+Cr ratios were calculated. All patients underwent anterior temporal lobectomy and ipsilateral amygdalohippocampectomy, and surgical specimens from the temporal poles were sent for histopathological examination. Comparisons of the spectroscopic and histopathological results of the resected temporal poles were performed. The modified Engel classification system was used for evaluating seizure outcome in the cohort.

Results. The preoperative spectroscopic profiles of the sclerotic hippocampi were abnormal in all patients, and the contralateral hippocampus showed altered spectroscopic findings in 12 patients (52.2%). Spectroscopy of the temporal poles demonstrated severely decreased concentrations of NAA, markedly increased concentrations of Cho, and increased concentrations of Cr in the temporal pole ipsilateral to the MTS in 15 patients (65.2%). Similarly, the NAA/Cho, NAA/Cr, and NAA/Cho+Cr ratios were severely decreased in the temporal pole ipsilateral to the MTS in 16 patients (69.6%). Histopathological examination of the resected temporal poles demonstrated ischemic changes in 5 patients (21.7%), gliotic changes in 4 (17.4%), demyelinating changes in 3 (13.0%), and microdysplastic changes in 1 patient (4.3%). Comparisons of the spectroscopic and histopathological findings showed that the sensitivity of proton MRS was 100%, its specificity was 80%, its positive predictive value was 87%, and its negative predictive value was 100%. The mean follow-up time in this study was 3.4 years. At the end of the 2nd postoperative year, 17 patients (73.9%) were in Engel Class I, 5 (21.7%) were in Class II, and 1 (4.3%) was in Class III.

Conclusions. Proton MRS detected altered ipsilateral temporal pole metabolism in patients with unilateral MTS. These metabolic changes were associated with permanent histological abnormalities of the temporal pole. This finding demonstrates that MTS may be a more diffuse histological process, and exact preoperative knowledge of its temporal extent becomes of paramount importance in the selection of the best surgical approach in these patients. Further validation of the observations is necessary for defining the role of temporal pole proton MRS in cases of temporal lobe epilepsy.

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Key Words • epilepsy • gliosis • ischemia • mesial temporal sclerosis • temporal pole

It is widely accepted that MTLE constitutes the most common form of partial epilepsy in adults.18,23 It has been estimated that approximately 20% of patients suffering from MTLE eventually develop medically refractory epilepsy.6 Mesial temporal sclerosis represents one of the most common pathological entities responsible for MTLE.19,24,26 The imaging and histopathological features of MTS regarding the hippocampus and the mesial temporal structures are well documented and have been extensively described in the literature. However, there is a growing body of evidence suggesting that MTS constitutes a more diffuse pathological entity, affecting

Abbreviations used in this paper: Cho = choline; Cr = creatine; EEG = electroencephalography; GABA = γ-aminobutyric acid; MRS = MR spectroscopy; MTLE = mesial temporal lobe epilepsy; MTS = mesial temporal sclerosis; NAA = N-acetyl-aspartate; TLE = temporal lobe epilepsy.
not only the mesial temporal lobe but also the temporal neocortex and even more distant cerebral areas, such as the frontal, parietal, and occipital lobes and the ipsilateral thalamus. Proton MRS is a noninvasive diagnostic tool that may provide valuable information regarding the biochemical profile and the metabolism of the brain. It has been extensively used in the preoperative evaluation of patients with medically intractable epilepsy, especially in cases of TLE, with varying specificity and accuracy rates. The recent improvement of MR spectroscopic applications along with the accumulating experience with brain MRS have increased the use of proton MRS in the preoperative evaluation of patients with TLE. Proton MRS may detect even subtle changes in the concentration of the studied metabolites that may be implicated in seizure generation. 

The absolute concentrations of NAA, Cho, and Cr are usually measured, and their ratios NAA/Cho, NAA/Cr, NAA/Cho+Cr are calculated in the vast majority of temporal epilepsy cases. Furthermore, the concentrations of inhibitory and excitatory neurotransmitters such as GABA and glutamate plus glutamine (GLX) have been used in a limited number of epilepsy cases of temporal origin. There is a general consensus that proton MRS of the hippocampus in patients with MTS demonstrates decreased concentrations of NAA as a result of hippocampal gliosis and neuronal loss. On the contrary, concentrations of Cho and Cr are increased, mainly due to the development of gliosis of the sclerotic hippocampus.

In our current study, we present our findings from proton MRS of temporal poles in patients with MRI-proven unilateral MTS and medically refractory epilepsy. With this opportunity, we review the pertinent literature regarding the role of proton MRS in the extrahippocampal temporal lobe in patients with medically intractable epilepsy due to MTS.

Methods

Our prospective clinical study’s protocol was approved by the institutional review boards of the participating institutions (University Hospital of Larissa and Institute “Euromedica-Encephalos”). All collected data were analyzed according to the Health Insurance Portability and Accountability Act regulations. A detailed written consent form was obtained from all participants or their legal guardians. The study covered a 4-year period (January 2006 to December 2009). Our inclusion criteria included patients older than 16 years with medically intractable epilepsy (duration > 2 years while taking adequate doses of the appropriate anticonvulsant medications), unilateral MTS as noted on MRI, and clinically and electrographically proven seizures of temporal origin. Patients unable to undergo MRI or patients unable to cooperate for obtaining a proton MR spectroscopic study were excluded from the study. A total of 26 patients met our inclusion criteria. However, 3 of these patients decided not to undergo surgery and were excluded from this study, leaving a population of 23 patients (14 male and 9 female). The mean age of our participants was 25.2 years (range 17–45 years), and the mean duration of epilepsy was 10.4 years (range 3–22 years). Detailed demographic data, as well as seizure-related and family histories, are summarized in Table 1.

All participants underwent preoperative evaluation including detailed clinical neurological examination, seizure semiology analysis, ictal and interictal surface video-EEG, brain MRI (special epilepsy protocol using a 3-T MRI unit for obtaining coronal oblique FLAIR and T1-weighted, high resolution T1-weighted, and 3D inversion recovery images), functional MRI study for language lateralization, and neuropsychological examination. Invasive EEG monitoring via depth and strip and/or grid subdural electrodes was necessary in 4 (17.4%) of the 23 patients.

Single-voxel proton MRS using a 3-T MRI unit (Signa HDxt, General Electric) was performed in all participants within 1 month prior to their resection. Bilateral hippocampi and both temporal poles were spectroscopically examined using a 1.5 × 1.5 × 1.5-cm voxel. The voxel size was determined using single-voxel proton MRS at a 1.5-T MRI unit (Signa HDxt, General Electric) with a 3-T MRI unit (Signa HDxt, General Electric) was performed in all participants.

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Temporal pole spectroscopy

Placement was manual, and visual inspection ensured that the voxel contained only the temporal lobe without contamination from the surrounding tissues. Point-resolved spectroscopy (PRESS) was used with the following parameters: TE 35 msec, TR 1500 msec, and number of excitations 8. The average spectroscopic study duration for each temporal pole was approximately 5 minutes. The actual concentrations of NAA, Cho, and Cr, as well as the metabolic ratios NAA/Cr, NAA/Cho, and NAA/Cho+Cr, were calculated (Fig. 1).

All participants underwent anterior temporal lobectomy and ipsilateral amygdalohippocampectomy. A standard subpial aspiration/resection technique was routinely used in all cases. General endotracheal anesthesia was induced in 17 patients (73.9%), and awake craniotomy for language cortical mapping was used in the remaining 6 (26.1%). Postresection intraoperative corticography was used in all patients. Surgical specimens from the resected neocortex, as well as from the amygdala and the hippocampus, were sent for histopathological and immunohistochemical analyses in all cases.

The surgical outcome was evaluated using the modified Engel scale. The mean follow-up time was 3.4 years (range 2–5 years).

Results

There were 15 patients with right-sided and 8 patients with left-sided MTS on the preoperatively obtained MRI studies (Table 2). The existence of hippocampal pathology was histologically confirmed in all cases in our series. Histopathological examination of the resected hippocampus revealed gliosis in 21 patients (91.3%), and ischemic changes were detected in 16 (69.6%).

Findings of proton MRS of the sclerotic hippocampi were abnormal in all cases. There was a significant decrease in the concentration of NAA on the sclerotic side compared with the contralateral hippocampus. It has to be mentioned, however, that in 12 patients (52.2%) even the theoretically normal hippocampus showed lower concentrations of NAA than sex- and age-matched controls from a historical healthy control group. Increased concentrations of Cho were found in the sclerotic hippocampus in 22 patients (95.7%) compared with the contralateral side, and increased Cr concentrations were measured in the affected hippocampus in 21 patients (91.3%). The NAA/Cho ratio of the sclerotic hippocampus was decreased in all patients, as were the NAA/Cr and NAA/Cho+Cr ratios.

Analysis of the proton MRS data obtained from the temporal poles demonstrated that there was a significant decrease in the NAA concentration on the same side as the MTS in 15 patients (65.2%). Similarly, increased concentrations of Cho and Cr were found in the temporal pole on the same side as the MTS in 13 patients (56.5%). The NAA/Cho ratio was decreased in the temporal pole on the same side as the MTS in 15 patients (65.2%), the NAA/Cr was decreased in 15 patients (65.2%), and the NAA/Cho+Cr ratio was decreased in 16 patients (69.6%). On the contrary, the spectroscopic analysis of the temporal pole contralateral to the MTS revealed no abnormalities in any of our study participants.

Comparisons of the sclerotic hippocampal and ipsilateral temporal pole spectroscopic findings showed significantly lowered NAA concentrations and markedly higher concentrations of Cho and Cr in the hippocampus. However, these differences were very subtle on the side contralateral to the MTS in 12 patients (52.2%), with slightly decreased NAA and mildly elevated Cho and Cr concentrations in the nonsclerotic hippocampus compared with the ipsilateral temporal pole, which showed a normal spectroscopic profile. In the remaining 11 patients (47.8%) the spectroscopic profiles of the nonsclerotic hippocampi and the contralateral to the MTS temporal poles were within normal limits.

Histopathological analysis of the resected temporal poles revealed that in 13 patients (56.5%) there was evidence of abnormality in the resected specimen. More
specifically, ischemic changes were found in 5 patients (21.7%), gliosis was evident in 4 (17.4%), demyelination was found in 3 (13.0%), and microdysplastic changes were found in 1 patient (4.3%).

Comparative analysis of the temporal pole proton MRS and the neocortical temporal histopathological data shows that proton MRS detected the presence of metabolic abnormalities in the temporal neocortex ipsilateral to the MTS in 15 patients (65.2%). Interestingly, these metabolic changes were confirmed by the presence of pathological changes in 13 patients (56.5%). It has to be emphasized that none of the patients with normal temporal spectroscopic profiles had any neocortical histopathological abnormalities. In this series, the sensitivity of temporal pole proton MRS was 100%, its specificity was 80%, its positive predictive value was 87%, and its negative predictive value was 100%.

The use of postresection intraoperative corticography revealed no abnormalities on EEG in any of our cases, and therefore it played no role in modifying our initial resection plan. The observed seizure outcome at the 1st postoperative year was Class I in 18 patients (78.3%), Class II in 4 patients (17.4%), and Class III in 1 patient (4.3%). At the completion of the 2nd postoperative year, 17 patients (73.9%) were in Class I, 5 (21.7%) were in Class II, and 1 patient (4.3%) was in Class III. The relationship, if any, of temporal pole spectroscopic abnormalities with the surgical outcome cannot be established, since the population of our current study is very limited and any statistical analysis is essentially meaningless.

**Discussion**

Proton MRS has been extensively used in the evaluation of cerebral metabolism in epileptic patients and particularly in cases of MTS. Several clinical series have documented that in patients with MTS there is a significant decrease in the concentration of NAA and increases in the concentrations of Cho and Cr in the affected hippocampus. Several clinical investigators have demonstrated with the aid of proton MRS that in cases of MTS, the ipsilateral extrahippocampal temporal lobe may have altered metabolism. Meiners et al. reported their experience with a series of 11 patients with hippocampal sclerosis who underwent single-voxel extrahippocampal temporal lobe proton MRS (Table 3). They found that the white matter of the temporal lobe ipsilateral to the hippocampal sclerosis demonstrated decreased concentrations of NAA, marked increase in Cho concentrations, a slight increase in Cr concentrations, and decreased NAA/Cho and NAA/Cr ratios. Their findings are in agreement with our current study results. However,
the histological examination of the temporal lobe white matter in their series showed no abnormalities.\textsuperscript{17} Similarly, Shih et al.\textsuperscript{23} reported their results from a series of 8 patients with MTS who underwent proton MRS of the lateral temporal lobe. These authors found that the NAA concentration was lower in the lateral temporal lobe on the same side as the MTS in 50\% of their cases, while the concentration of Cho was increased in these patients. Moreover, these spectroscopic changes were accompanied by magnetoencephalographic changes originating from the same temporal neocortical areas. Capizzano et al.\textsuperscript{6} reported similar temporal extrahippocampal spectroscopic findings from a series of 15 patients with MTS. These authors found severely decreased NAA concentrations in the temporal lobe ipsilateral to the MTS. Their findings are in agreement with the results of our study.

Likewise, Mueller et al.\textsuperscript{18,19} reported their experience with spectroscopic imaging of patients suffering TLE. They found that MTS is associated with extrahippocampal reduction of NAA concentration, increased Cho and Cr concentrations, and a decreased NAA/Cho+Cr ratio. Their findings are in agreement with our current observations. They also postulated that these MTS-associated NAA, Cho, and Cr changes may not be limited to the ipsilateral temporal lobe but may extend and affect the ipsilateral frontal and parietal lobes. Vermathen et al.\textsuperscript{26} reported their results from using extrahippocampal temporal lobe proton MRS in 11 patients with MTS. They found decreased concentrations of NAA and increased concentrations of Cho and Cr on the ipsilateral to the MTS temporal lobe. Their findings are in agreement with our results. They also claimed that NAA, Cho, and Cr changes were detectable not only in the ipsilateral temporal lobe but also in the entire ipsilateral hemisphere. Simister et al.\textsuperscript{24} used proton MRS in 35 patients with MTS. They found that the temporal lobe affected by MTS showed decreased concentrations of NAA and increased concentrations of Cr, while the concentrations of GABA and glutamate/glutamine were essentially unchanged.\textsuperscript{24}

The pathophysiological mechanism or mechanisms responsible for these extrahippocampal spectroscopic changes remain highly controversial. It has been postulated by Meiners et al.\textsuperscript{17} that neuronal axonal loss may be responsible for the observed extrahippocampal NAA decrease. This loss of neuronal axons may explain the increased concentrations of Cho, since demyelination has been associated with increased Cho production. It is widely accepted that the obtained spectra from neonatal brains demonstrated increased Cho peaks, due to the incomplete myelination process.\textsuperscript{23} However, Meiners et al. found no histological abnormalities in their temporal extrahippocampal specimens to support such demyelination process. Another proposed theory suggests that the spectroscopic extrahippocampal changes may be the result of extrahippocampal neuronal dysfunction caused by deafferentation due to loss of input from the hippocampal focus.\textsuperscript{19} This may explain the observed extrahippocampal spectroscopic changes, which are accompanied by no or very subtle structural changes in these areas.\textsuperscript{18} On the contrary, in our current series the well-documented temporal pole spectroscopic changes were associated with permanent structural changes of the temporal neocortex and white matter on the side affected by MTS. This may be another explanatory mechanism for the observed extrahippocampal metabolic changes in cases of MTS. Other investigators have suggested that MTS may be a more widespread pathological process than a focal structural abnormality.\textsuperscript{23} If these structural and histopathological changes observed in our series are induced by the excitotoxic effect of hippocampal sclerosis and medially originated seizure propagation, or constitute part of a widespread pathological process that involves both the hippocampus and the adjacent ipsilateral temporal lobe, remains to be defined. There is, however, a growing body of evidence that the extrahippocampal spectroscopic changes represent actual metabolic changes, since their presence has been demonstrated not only by proton MRS but also by PET and magnetoencephalography studies.\textsuperscript{1,14,21,23}

Our proposed theory that extrahippocampal temporal spectroscopic measurements represent permanent structural and histological abnormalities is not supported by the observations of some clinical investigators.\textsuperscript{21,22,24} Others have demonstrated that this abnormal extrahippocampal spectroscopic profile returns to normal after resection of the sclerotic hippocampus.\textsuperscript{22,24} It has to be

**TABLE 3: Synoptic presentation of the most important clinical series regarding extrahippocampal temporal lobe proton MRS in patients with MTS**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Type of Study</th>
<th>No. of Patients/No. of Controls</th>
<th>MRI Field Strength (T)</th>
<th>MRS Findings in Extrahippocampal Temporal Lobe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mueller et al., 2004</td>
<td>prospective</td>
<td>14/12</td>
<td>1.5</td>
<td>NAA ↓↓, Cho ↑↑, Cr ↑, NAA/Cho ↓↓, NAA/Cr ↓</td>
</tr>
<tr>
<td>Meiners et al., 2000</td>
<td>prospective</td>
<td>11/12</td>
<td>1.5</td>
<td>NAA ↓↓, Cho ↑↑, NAA/Cr ↓</td>
</tr>
<tr>
<td>Mueller et al., 2011</td>
<td>prospective</td>
<td>25/0</td>
<td>4</td>
<td>NAA/Cho + Cr ↓↓</td>
</tr>
<tr>
<td>Capizzano et al., 2002</td>
<td>case-control horizontal</td>
<td>15/12</td>
<td>1.5</td>
<td>NAA/Cho + Cr ↓↓</td>
</tr>
<tr>
<td>Vermathen et al., 2003</td>
<td>prospective</td>
<td>11/13</td>
<td>1.5</td>
<td>NAA ↓↓, NAA/Cho + Cr ↓</td>
</tr>
<tr>
<td>Mueller et al., 2011</td>
<td>prospective</td>
<td>16/15</td>
<td>1.5</td>
<td>NAA ↓↓, Cr ↑↑, NAA/Cr ↓↓, GABA unchanged</td>
</tr>
<tr>
<td>Shih et al., 2011</td>
<td>prospective</td>
<td>8/0</td>
<td>1.5</td>
<td>NAA/Cho ↓↓</td>
</tr>
<tr>
<td>current study</td>
<td>prospective</td>
<td>23/0</td>
<td>3</td>
<td>NAA ↓↓, Cho ↑↑, Cr ↑↑, NAA/Cho ↓↓, NAA/Cr ↓↓, NAA/Cho + Cr ↓↓</td>
</tr>
</tbody>
</table>

* † = mild increase in concentration; †† = moderate to severe increase in concentration; ‡ = mild decrease in concentration; ‡‡ = moderate to severe decrease in concentration.
emphasized, however, that this postoperative normalization of spectroscopic profile regards, in the vast majority of the reported cases, the contralateral hippocampus and not the ipsilateral extrahippocampal temporal lobe.\textsuperscript{7,12,22,24} It may be postulated that some of the spectroscopically detected metabolic changes may well be a temporary result of tissue dysfunction, while some other changes, particularly of the adjacent ipsilateral temporal lobe, may be indicative of permanent structural changes. Further comparative studies between extrahippocampal temporal lobe spectroscopy and histopathological examination are necessary for clarifying this highly controversial issue.

Complete understanding of the underlying pathophysiological mechanism is of paramount importance not only for clarifying the MTS pathological process but also for selecting the most efficient surgical approach for these patients. If the spectroscopic changes represent permanent structural changes in the temporal neocortical and white matter on the side of the MTS, resection of these areas may increase the possibility of achieving better seizure outcome postoperatively. If the observed histopathological changes of the involved extrahippocampal temporal lobe in our series had not been resected, the postoperative seizure outcome could have been worse, since ischemic and/or gliotic foci would have remained intact to continue their potential epileptogenic activity. It could be postulated that the findings of proton MRS in the temporal pole could influence the decision for a selective amygdalohippocampectomy or a more extensive anterior temporal lobectomy and amygdalohippocampectomy.

It has to be emphasized that proton MRS constitutes a highly susceptible methodology to artifacts and intrinsic errors. Voxel contamination by the surrounding tissues may significantly alter the obtained spectrum and may lead to erroneous interpretations. The importance of signal contamination from a misplaced voxel has been adequately addressed in the literature.\textsuperscript{24} In our current study, the voxel placement was manual and this was done with extreme caution by experienced spectroscopists. In addition, the proximity of bone and muscle tissue to the temporal fossa may influence the accuracy of the obtained spectra in rare instances.\textsuperscript{24} It is well known that temporal lobe is a nonhomogeneous structure, and this may alter the accuracy of the obtained spectrum.\textsuperscript{24} Moreover, it is known that gray and white matter have different spectroscopic profiles, thus making the interpretation of the obtained spectra quite puzzling.\textsuperscript{16,24} In addition to the technical pitfalls of proton MRS, the limited number of cases included in our current study represents another limitation and decreases the strength of our study. The drawing of any conclusions regarding the role of any predisposing factors in developing diffuse temporal neocortex metabolic and histopathological changes is impossible due to the limited number of cases in our study. However, the number of participants in the vast majority of the published series is limited, since cases of unilateral MTS with no other pathology are relatively rare.\textsuperscript{\textsuperscript{5,6,10,23,24,26}} These limitations and technical weaknesses need to be taken into consideration in the clinical interpretation of our findings.

Conclusions

Proton MRS is a noninvasive imaging modality that provides valuable information regarding the metabolism not only of the hippocampi but also of the extrahippocampal temporal lobes in patients with MTS. In our current study, proton MRS of the temporal poles in patients with unilateral, clearly defined MTS revealed severely decreased concentrations of NAA, markedly increased concentrations of Cho, increased concentrations of Cr, and severely decreased ratios of NAA/Cho+Cr in the temporal pole ipsilateral to the MTS. The histopathological examination of the resected temporal poles demonstrated ischemic, gliotic, demyelinating, and dystrophic changes, which may be associated with our spectroscopic findings. The role of proton MRS in the preoperative evaluation of patients with MTS, and especially in selecting the most appropriate surgical strategy (anterior temporal lobectomy plus amygdalohippocampectomy vs selective amygdalohippocampectomy), remains to be defined, since the permanent nature of the observed spectroscopic changes and their association with pathological entities requires further validation. Minimization of the technical pitfalls of proton MRS and larger clinical series may enlighten us on the pathophysiology of these spectroscopic changes and their role in the preoperative evaluation of patients suffering medically intractable epilepsy due to MTS.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Fountas, Kapsalaki. Acquisition of data: Fountas, Tsougos, Gotsis, Kapsalaki. Analysis and interpretation of data: Fountas, Tsougos, Gotsis, Kapsalaki. Drafting the article: Fountas. Critically revising the article: Fountas, Smith, Kapsalaki. Reviewed submitted version of manuscript: Giannakodimos. Approved the final version of the manuscript on behalf of all authors: Fountas. Administrative/technical/material support: Kapsalaki. Study supervision: Kapsalaki.

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