

Extratemporal abnormalities in phosphorus magnetic resonance spectroscopy of patients with mesial temporal sclerosis

Anormalidades extratemporais na espectroscopia de fósforo por ressonância magnética em pacientes com esclerose mesial temporal

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ABSTRACT

Objective: We evaluated extratemporal metabolic changes with phosphorus magnetic resonance spectroscopy (³¹P-MRS) in patients with unilateral mesial temporal sclerosis (MTS). **Method:** ³¹P-MRS of 33 patients with unilateral MTS was compared with 31 controls. The voxels were selected in the anterior, posterior insula-basal ganglia (AIBG, PIBG) and frontal lobes (FL). Relative values of phosphodiesteres- PDE, phosphomonoesters-PME, inorganic phosphate - Pi, phosphocreatine- PCr, total adenosine triphosphate [ATP_γ + α + β-ATP] and the ratios PCr/ATP_γ, PCr/γ-ATP, PCr/Pi and PME/PDE were obtained. **Results:** We found energetic abnormalities in the MTS patients compared to the controls with Pi reduction bilaterally in the AIBG and ipsilaterally in the PIBG and the contralateral FL; there was also decreased PCr/γ-ATP in the ipsilateral AIBG and PIBG. Increased ATP_γ in the contralateral AIBG and increased γ-ATP in the ipsilateral PIBG were detected. **Conclusion:** Widespread energy dysfunction was detected in patients with unilateral MTS.

Keywords: phosphorus spectroscopy, magnetic resonance imaging, neurometabolism, mesial temporal sclerosis, epilepsy.

RESUMO

Objetivo: Nós avaliamos as alterações metabólicas através da espectroscopia de fósforo por ressonância magnética (³¹P-MRS) em pacientes com esclerose mesial temporal (EMT) unilateral. **Método:** ³¹P-MRS de 33 pacientes com EMT unilateral foram comparadas aos de 31 controles. Foram selecionados os voxels nas regiões insulonuclear anterior e posterior (RINA e RINP) e frontal (RF). Os valores relativos de fosfodiésteres - PDE, fosfomonoésteres- PME, fosfato inorgânico- Pi, fosfocreatina -PCr, adenosina trifosfato total [ATP_γ + α + β-ATP] e as razões PCr/ATP_γ, PCr/γ-ATP, PCr/Pi e PME/PDE foram obtidas. **Resultados:** Nós encontramos anormalidades em pacientes com EMT em comparação aos controles. Redução de Pi nas RINA bilateralmente, RINP ipsilateral e RF contralateral, redução de PCr/γ-ATP nas RINA e RINP ipsilaterais foram detectadas. Aumentos de ATP_γ na RINA contralateral e aumento de γ-ATP na RINP ipsilateral também foram encontradas. **Conclusão:** Disfunção energética difusa foi encontrada em pacientes com EMT unilateral.

Palavras-chave: espectroscopia de fósforo, ressonância magnética, neurometabolismo, esclerose mesial temporal, epilepsia.

Temporal lobe epilepsy (TLE) is the most common form of epilepsy in adult patients and the mesial temporal sclerosis (MTS) is the most frequent entity associated with medically refractory TLE. MTS is characterized by selective neuronal loss in CA1, CA3 and the dentate gyrus of the hippocampus. MTS may also involve the amygdala, parahippocampal gyrus, and entorhinal cortex. More widespread temporal lobe involvement may also occur¹.

Previous studies have discovered metabolic dysfunction in the temporal and extratemporal regions in mesial temporal

sclerosis. Interictal ¹⁸-FDG-PET studies in MTS² have shown ipsi- and contralateral decreased glucose metabolism not only in the temporal lobe but also in the basal ganglia³ and frontal lobes⁴. These findings are in agreement with proton magnetic resonance spectroscopy (¹H-MRS), phosphorous magnetic resonance spectroscopic imaging (³¹P- MRS)⁵ and single-photon emission computed tomography (SPECT)⁶ studies in which extensive temporal and extratemporal structural and metabolic involvement in epilepsy has been associated with MTS.

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¹H-MRS studies have reported decreased *N*-acetylaspartate/creatine (NAA/Cr) in ipsilateral mesial temporal structures compared to the contralateral side and to controls^{7,8} with 87% sensitivity, 92% specificity and lateralization in 86% of patients^{9,10}. Significant decreases in the NAA/Cr ratio were also found in the contralateral hippocampus and thalamus¹¹, as well as in the frontal, parietal and occipital lobes bilaterally compared to control group⁷. These findings were more pronounced in the ipsilateral hemispheres of MTS patients compared to controls⁷. Patients who presented with bitemporal or extratemporal abnormalities on ¹⁸F-FDG-PET and ¹H-MRS have poorer surgical outcomes¹² and more severe cognitive impairment⁴ than patients who presented with unilateral temporal changes.

Phosphorous magnetic resonance spectroscopic imaging (³¹P-MRS) allows a non-invasive measurement of the phosphorus metabolites related to the energy state and membrane composition as well as an evaluation of mitochondrial function, considering that ATP is mainly generated by mitochondria¹³.

Previous studies have investigated the lateralizing ability of ³¹P-MRS in patients with TLE. These studies found reduced PCr/Pi and PCr/ATP ratios in the temporal lobes, which was more pronounced ipsilaterally, allowing for correct seizure focus lateralization in 70 to 73% of cases¹⁴. In extratemporal locations, decrease of PCr/ γ -ATP ratio in the patient's ipsilateral parietal gray matter compared to the same region in controls¹⁴ and reduced PCr/ATP ratios were found bilaterally in the hippocampi and ipsilaterally in the thalamus and striatum¹⁵.

The temporal lobe metabolic abnormalities were well characterized by the methods mentioned above however, further characterization of the extratemporal abnormalities in MTS, specially considering the information that ³¹P-MRS can provide, can facilitate our understanding of the extent of metabolic dysfunction and their role in refractoriness to clinical treatment, as well as of the cognitive and psychiatric impairment associated with refractory epilepsy. This characterization may also contribute for predicting the postoperative outcome.

There are few reports in the literature regarding ³¹P-MRS in patients with MTS, most of which with small sample sizes, some performed in low magnetic field. The aim of this study was to use ³¹P-MRS to evaluate extratemporal metabolic changes in a strict, large selection of patients with refractory epilepsy related to unilateral MTS.

METHOD

Subjects

We analyzed a consecutive series of patients with TLE secondary to unilateral MTS. Diagnosis of TLE was established by MRI and EEG findings. Brain MRI findings of unilateral hippocampal volume loss on T1-weighted images

and increased signal intensity on T2-weighted and/or FLAIR images, without other MRI lesions except minor white matter changes on T2 or FLAIR sequences, also supported the diagnosis of MTS. All patients presented with medically refractory epilepsy and were in the process of surgical evaluation. All patients underwent prolonged video-EEG monitoring with recording of at least one epileptic seizure and had electrographic onset in the temporal lobe. Patients with other neurological or active psychiatric disease, previous or current ethanol abuse and comorbidity with nonepileptic psychogenic seizures were excluded. Healthy controls, fulfilling the other inclusion and exclusion criteria served as a control group.

We studied 33 patients (20 women, age range 23 to 55 years, mean age 35.9 \pm 9.7 years) and 31 controls (19 women, age range 18 to 53 years, mean age 32.5 \pm 9.9 years). All patients reported being seizure-free for at least 48 hours prior to MRS examination.

The institution ethics committee approved this study. All patients and controls signed the approved informed consent form prior to study enrollment.

³¹P-MRS

Three-dimensional (3D) ³¹P-MRS was performed on an Inera Achieva 3.0 T system (Philips, Best, The Netherlands) using a double-tuned ³¹P/¹H head coil (AIRI, Cleveland, USA). A T1-fast field echo axial sequence was acquired (TR = 7.6 ms; TE = 3.7 ms; flip angle = 8°; isotropic 1-mm³ resolution) with sagittal and coronal plane reconstructions.

³¹P-MRS acquisition was based on a pulse-acquire type sequence (TE/TR = 0.31 ms/5093 ms), using an adiabatic pulse, broadband decoupling (power factor = 0.4; offset = 100 Hz) and an automatic shimming procedure. Saturation bands were placed around the grid to avoid muscle contamination. The total field of view was 180 x 210 x 120 mm (right to left x anterior to posterior x superior to inferior), divided into six slices with six columns and seven lines each, resulting in 30 x 30 x 20 mm individual voxels. Following ³¹P-MRS acquisition, low resolution T1 images (TR = 9.4 ms; TE = 4.6 ms; flip angle = 8°; section thickness = 3 mm) were obtained to ensure the same head location throughout the examination. The total exam time was 43 minutes.

Spectral processing and quantification were performed with jMRUI software using the AMARES algorithm¹⁶. The postprocessing included truncation of the first two data points to reduce the baseline broadline component distortion effects. Starting values for line-width constraints, chemical shifts and J coupling were used as prior knowledge in the fitting algorithm. Zero- and first-order phase corrections were applied for convergence during spectral fitting.

These steps were repeated for all analyzed voxels and were always performed by the same investigator.

The relative values of each metabolite divided by the sum of all metabolites (phosphodiester- PDE, phosphomonoesters-PME,

Table 1. Comparison of the metabolite profile in the ipsilateral regions.

Location	Metabolites and ratios	Patients		Controls		p-value
		mean	SD	mean	SD	
AIBG	Pi	0.081	0.013	0.089	0.007	0.009
	PCr	0.194	0.017	0.198	0.014	0.289
	γ -ATP	0.100	0.014	0.094	0.011	0.071
	ATP _T	0.293	0.022	0.286	0.018	0.165
	PCr/ATP _T	0.668	0.100	0.699	0.081	0.183
	PCr/ γ -ATP	1.966	0.310	2.146	0.327	0.027
	PCr/Pi	2.465	0.599	2.264	0.235	0.081
	PME	0.173	0.017	0.174	0.014	0.706
	PDE	0.196	0.018	0.194	0.015	0.616
	PME/PDE	0.889	0.133	0.903	0.086	0.604
PIBG	Pi	0.077	0.011	0.083	0.008	0.009
	PCr	0.197	0.017	0.200	0.012	0.520
	γ -ATP	0.098	0.009	0.093	0.009	0.024
	ATP _T	0.294	0.019	0.286	0.019	0.080
	PCr/ATP _T	0.674	0.085	0.704	0.075	0.132
	PCr/ γ -ATP	2.023	0.249	2.194	0.306	0.017
	PCr/Pi	2.629	0.533	2.437	0.303	0.081
	PME	0.167	0.013	0.168	0.011	0.739
	PDE	0.206	0.015	0.207	0.016	0.736
	PME/PDE	0.817	0.088	0.819	0.082	0.929
FL	Pi	0.088	0.012	0.093	0.010	0.106
	PCr	0.195	0.021	0.195	0.015	0.941
	γ -ATP	0.102	0.014	0.101	0.011	0.977
	ATP _T	0.296	0.019	0.303	0.016	0.121
	PCr/ATP _T	0.663	0.107	0.645	0.069	0.420
	PCr/ γ -ATP	1.969	0.418	1.957	0.303	0.892
	PCr/Pi	2.252	0.443	2.139	0.279	0.233
	PME	0.175	0.017	0.173	0.012	0.689
	PDE	0.185	0.018	0.180	0.016	0.261
	PME/PDE	0.954	0.131	0.971	0.099	0.560

AIBG: anterior insula-basal ganglia regions; PIBG: posterior insula-basal ganglia regions; FL: frontal lobes. γ -ATP: gamma adenosine triphosphate; Pi: inorganic phosphate; PCr: phosphocreatine; PDE: phosphodiesterases; PME: phosphomonoesters; ATP: total adenosine triphosphate; SD: standard deviation; p-value obtained with student's t-test.

inorganic phosphate - Pi, phosphocreatine- PCr, total adenosine triphosphate [ATP_T = γ - + α - + β -ATP]), as well as the metabolite ratios PCr/ATP_T, PCr/ γ -ATP, PCr/ γ -ATP, PCr/Pi and PME/PDE, were obtained for patients and controls. A typical ³¹P- MRS is presented in Figure 1.

Although a large number of voxels was obtained, to avoid multiple comparisons errors, muscle contamination and to provide reproducibility, the most homologous voxels in the basal ganglia and frontal lobes were analyzed. Therefore, we selected the anterior insula-basal ganglia (AIBG) regions, posterior insula-basal ganglia (PIBG) regions and frontal lobes (FL) voxels (Figure 2), located ipsi- or contralaterally to the MTS.

Statistical analysis

All metabolite measurements and studied ratios of each selected voxel for the patients were compared to the average values of controls.

The t test was used to compare groups; p < 0.05 was considered statistically significant. Statistical analyses were performed with the SPSS version 17.0.1 software package (SPSS Inc., Chicago, IL, U.S.A.).

RESULTS

Twenty patients with left MTS and 13 patients with right MTS were studied.

In the ipsilateral AIBG, we found reduced Pi (patients = 0.081 vs. controls = 0.089, p = 0.009) and PCr/ γ -ATP (patients = 1.966 vs. controls = 2.146, p = 0.027) in the patients compared to controls (Table 1).

In the contralateral AIBG, we detected reduced Pi (patients = 0.082 in patients vs. controls = 0.089, p = 0.013) and increased total ATP (patients = 0.298 vs. controls = 0.286, p = 0.026) in the patients compared to controls (Table 2).

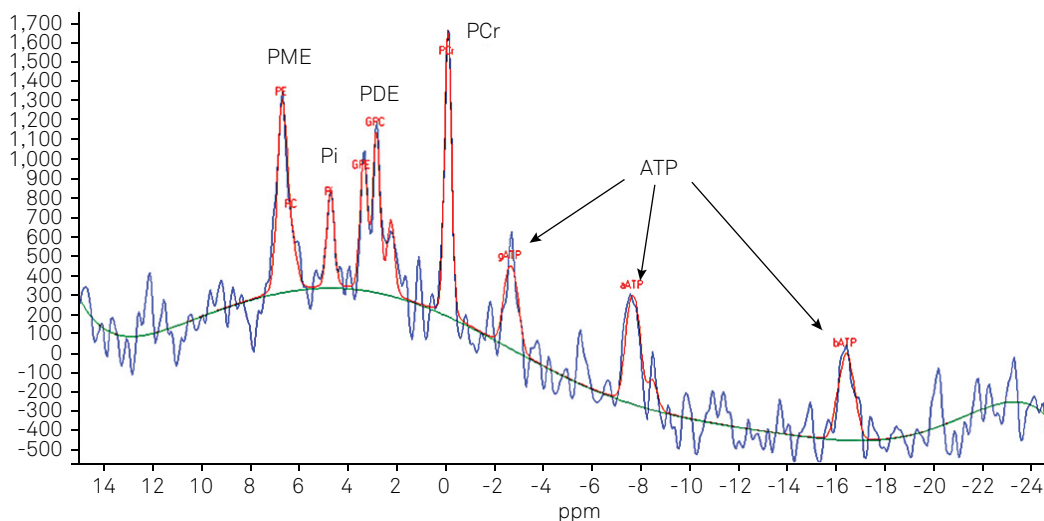


Figure 1. Normal ³¹P- MRS: PCr (phosphocreatine), Pi (inorganic phosphate), γ -, α -, β -ATP (adenosine triphosphate) representing energetic pool. PME (phosphomonoesters), PDE (phosphodiesters) representing membrane turnover.

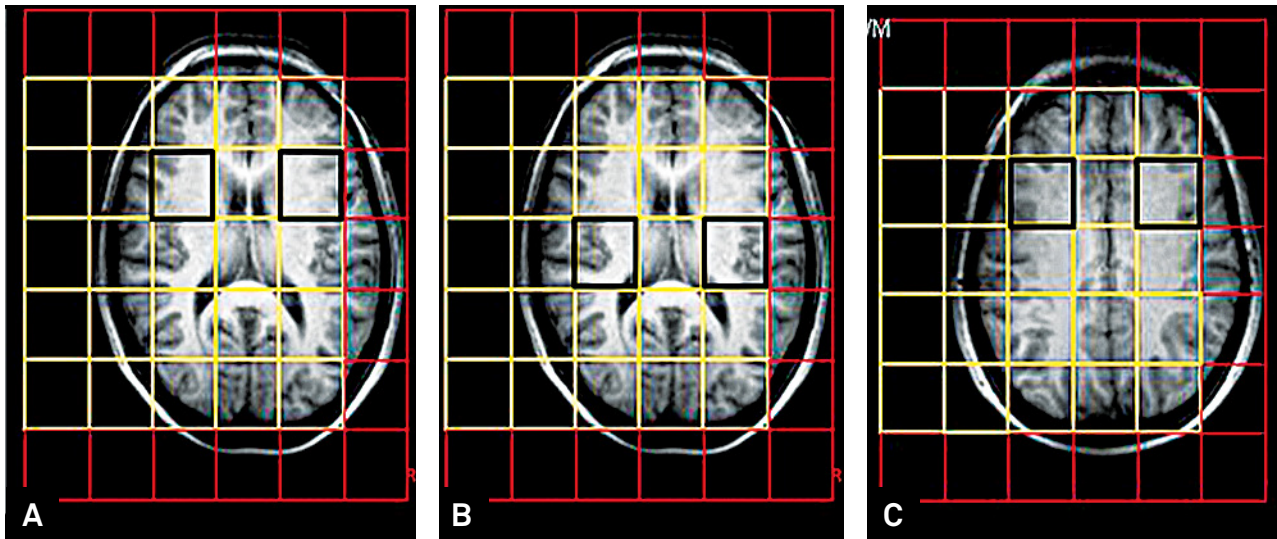


Figure 2. Location of the selected voxels. (A) Anterior insula-basal ganglia (AIBG) regions. (B) Posterior insula-basal ganglia (PIBG) regions (C). Frontal lobes (FL).

Table 2. Comparison of the metabolite profile in the contralateral regions.

Location	Metabolites and ratios	Patients		Controls		p-value
		mean	SD	mean	SD	
AIBG	Pi	0.082	0.011	0.089	0.007	0.013
	PCr	0.194	0.017	0.198	0.014	0.369
	γ -ATP	0.099	0.013	0.094	0.011	0.101
	ATP _T	0.298	0.025	0.286	0.018	0.026
	PCr/ATP _T	0.659	0.105	0.699	0.081	0.096
	PCr/ γ -ATP	1.996	0.376	2.146	0.327	0.095
	PCr/Pi	2.409	0.447	2.264	0.235	0.108
	PME	0.172	0.016	0.174	0.016	0.434
	PDE	0.197	0.021	0.194	0.019	0.506
	PME/PDE	0.886	0.163	0.903	0.104	0.184
PIBG	Pi	0.082	0.010	0.083	0.008	0.488
	PCr	0.195	0.015	0.200	0.012	0.219
	γ -ATP	0.096	0.013	0.093	0.009	0.300
	ATP _T	0.296	0.024	0.286	0.019	0.074
	PCr/ATP _T	0.668	0.100	0.704	0.075	0.103
	PCr/ γ -ATP	2.087	0.403	2.194	0.306	0.240
	PCr/Pi	2.424	0.372	2.437	0.303	0.879
	PME	0.167	0.014	0.168	0.011	0.601
	PDE	0.206	0.019	0.207	0.016	0.877
	PME/PDE	0.816	0.126	0.819	0.082	0.910
FL	Pi	0.087	0.010	0.093	0.01	0.014
	PCr	0.187	0.015	0.195	0.015	0.051
	γ -ATP	0.103	0.014	0.101	0.011	0.741
	ATP _T	0.307	0.020	0.303	0.016	0.430
	PCr/ATP _T	0.613	0.077	0.645	0.069	0.087
	PCr/ γ -ATP	1.869	0.354	1.957	0.303	0.291
	PCr/Pi	2.199	0.363	2.139	0.279	0.468
	PME	0.174	0.017	0.173	0.012	0.789
	PDE	0.185	0.019	0.180	0.016	0.294
	PME/PDE	0.958	0.171	0.971	0.099	0.709

AIBG: anterior insula-basal ganglia regions; PIBG: posterior insula-basal ganglia regions; FL: frontal lobes. γ -ATP: gamma adenosine triphosphate; Pi: inorganic phosphate; PCr: phosphocreatine; PDE: phosphodiesterases; PME: phosphomonoesters-; ATP_T: total adenosine triphosphate; SD: standard deviation; p-value obtained with student's t-test.

In the ipsilateral PIBG, we found reduced Pi (patients = 0.077 vs. controls = 0.083, $p = 0.009$) and PCr/ γ -ATP (patients = 0.249 vs. controls = 0.286, $p = 0.017$) as well as increased γ -ATP (patients = 0.098 vs. controls = 0.093, $p = 0.024$) in the patients compared to controls (Table 1).

In the contralateral FL, we found reduced Pi in the patients compared to controls (patients = 0.087 vs. controls = 0.090, $p = 0.014$) (Table 2).

The PCr, PCr/ATP_T, PCr/Pi, PME, PDE and PME/PDE values in the patients were not significantly different from controls.

No significant differences were found between the patients and controls in the contralateral PIBG (Table 2) and in the ipsilateral FL (Table 1) for any of the metabolites or ratios.

DISCUSSION

We found extratemporal energy metabolism abnormality in patients with unilateral MTS.

More extensive metabolic changes involving Pi and PCr/ γ -ATP in the AIBG and PIBG were identified. In the FL, the findings were less prominent; the Pi decrease was the only metabolic abnormality noted in the contralateral FL, while none of the metabolites or ratios were abnormal in the ipsilateral FL.

³¹P -MRS reflects five primary resonance groups related to the energy metabolism and membrane turnover. PCr, Pi and ATP (encompassing γ -, a- and b-ATP) are related to the energetic pool. PCr acts as an energy reservoir. Upon energy demand, PCr donates a phosphate group to adenosine diphosphate (ADP), which allows for ATP synthesis. Inversely, in resting states and ATP excess, PCr is produced. ATP is the main energy source for the majority of cellular functions and it is predominately generated by oxidative phosphorylation

in the mitochondria¹⁷. The PCr/ATP ratio serves as a robust bioenergetics measure, reflecting the cellular energetic demand and production⁵. Pi represents a mixture of the phosphoric acid ions; the concentration of Pi increases upon high energy demand or cellular damage¹³.

While PME represents membrane anabolism, PDE reflects membrane catabolism. Two metabolites from each are detectable in higher resolution spectra: PME is composed of phosphocholine and phosphoethanolamine, while PDE is composed of glycerophosphocholine and glycerophosphoethanolamine. The PME/PDE ratio indicates the membrane turnover¹³.

Previous ³¹P-MRS studies discovered energetic changes in the mesial portion of the temporal lobe in MTS patients, with reduced PCr/Pi, PCr/ATP and γ -ATP/Pi ratios in the epileptogenic mesial temporal region compared to controls and to the contralateral temporal lobe¹⁵. Regarding other metabolites, an increased Pi concentration and reduced PME levels were found ipsilateral to the epileptogenic focus^{18,19}.

In extratemporal locations, Chu et al. using ³¹P-MRS found a decreased PCr/ γ -ATP ratio in the patient's ipsilateral parietal gray matter compared to the same region in controls¹⁴. Pan et al found reduced PCr/ATP ratios in the hippocampi bilaterally and in the thalamus and striatum ipsilaterally in patients with unilateral medically refractory mesial TLE¹⁵.

The decreased PCr/ATP ratio observed in this study reflects high energy demand, in line with previous ³¹P-MRS studies which investigated MTS^{14,15}.

Interictal Pi decrease and ATP increase detected in extratemporal sites could be a consequence of frequent seizures and represent a compensatory mechanism to high energetic consumption during the ictal period. The ictal period is characterized by reduced PCr and ATP and increased Pi in animal models and in studies with humans^{20,21}.

It is possible that mitochondrial injury represents the underlying basis of the ¹H-MRS and ³¹P-MRS metabolic changes seen in MTS patients considering that NAA is synthesized only in neuronal mitochondria²² and it is strongly correlated with oxidative metabolism²³ and disturbances in energy metabolism were the main finding in previous ³¹P-MRS studies.

Mitochondrial oxidative stress and dysfunction appear to represent not only a consequence of seizures but may indeed

be related to epileptogenesis²⁴. Epilepsy frequently occurs in association with inherited mitochondrial disorders, such as myoclonic epilepsy and mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes²⁵, which is additional evidence that mitochondrial dysfunction has a role in epilepsy. Furthermore, mice that are partially deficient in a critical mitochondrial antioxidant have a decreased seizure threshold²⁶. Other evidence for the role of mitochondrial dysfunction in seizure generation in humans is the increased prevalence of epilepsy with aging. Mitochondrial oxidative stress is a well established mechanism of aging and age-related degenerative disease²⁷.

Our study is limited by the size of the MRS voxels with contamination from the surrounding structures, especially considering that the number of phase encoding steps was limited by the time of scanning. Only patients with MTS were studied, thus it is unclear if this abnormality is typical of MTS or can happen in other epilepsies. All the patients in our sample were receiving multiple epilepsy drugs and were scheduled for surgery due to refractoriness; therefore no attempt was made to stratify them according to medical therapy. Another limitation is that the absence of seizure was questionnaire based instead of EEG proven in the 48 hours prior to exam. Therefore internal and external validities were limited by the aforementioned shortcomings.

It is currently unknown whether the control of refractory epilepsy with medication or after epilepsy surgery will result in normalization of energy metabolism parameters. It is also unclear whether the correction of metabolic abnormalities may contribute to seizure control and improvement of the cognitive and psychiatric symptoms of refractory epilepsy.

Future studies should investigate the correlation between energetic changes and other factors associated with refractory epilepsy, such as seizure severity, epilepsy features and etiologies, cognitive and psychiatric complications and the postoperative outcome.

A better understanding of the energy dysfunction profile may elucidate the features associated with refractoriness and brain dysfunction associated with chronic epilepsy.

In conclusion, our results indicate extratemporal energetic dysfunction in patients with epilepsy associated with unilateral MTS.

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