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Correlation between memory, proton magnetic resonance spectroscopy, and interictal epileptiform discharges in temporal lobe epilepsy related to mesial temporal sclerosis

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ABSTRACT

Objective: The aim of the study described here was to examine the relationship between memory function, proton magnetic resonance spectroscopy (^{1}H-MRS) abnormalities, and interictal epileptiform discharge (IED) lateralization in patients with temporal lobe epilepsy (TLE) related to unilateral mesial temporal sclerosis.
Methods: We assessed performance on tests of memory function and intelligence quotient (IQ) in 29 right-handed outpatients and 24 controls. IEDs were assessed on 30-minute-awake and 30-minute-sleep EEG samples. Patients had ^{1}H-MRS at 1.5 T.
Results: There was a negative correlation between IQ ($P = 0.031$) and Rey Auditory Verbal Learning Test results ($P = 0.022$) and epilepsy duration; between ^{1}H-MRS findings and epilepsy duration ($P = 0.027$); and between *N*-acetylaspartate (NAA) levels and IEDs ($P = 0.006$) in contralateral mesial temporal structures in the left MTS group. ^{1}H-MRS findings, IEDs, and verbal function were correlated.
Conclusions: These findings suggest that IEDs and NAA/(Cho + Cr) ratios reflecting neural metabolism are closely related to verbal memory function in mesial temporal sclerosis. Higher interictal activity on the EEG was associated with a decline in total NAA in contralateral mesial temporal structures.

1. Introduction

Temporal lobe epilepsy (TLE) related to mesial temporal sclerosis (MTS) is the most frequent partial epilepsy in adults and the most common type of medically refractory epilepsy amenable to surgical treatment in this age group. The selection of these patients for surgery depends on the concordance of clinical, electroencephalographic, and MRI findings [1].

Cognitive decline has long been recognized as a consequence of TLE, and memory dysfunction is a well-known phenomenon [2]. It has been attributed to underlying pathology, seizure frequency, duration of epilepsy, antiepileptic drugs (AEDs), and interictal epileptiform discharges (IEDs) [3–6].

In patients with epilepsy, IEDs characterize the irritative zone and are considered to be an important predictor of surgical outcome [7]. However, up to 61% of patients with TLE have IEDs over both temporal regions [8].

Proton magnetic resonance spectroscopy (^{1}H-MRS) is a reliable method to detect and lateralize mesial temporal lobe neuronal loss and glial abnormalities found in intractable MTS. ^{1}H-MRS measures *N*-acetylaspartate (NAA), creatine + phosphocreatine (Cr), and choline-containing compounds (Cho). NAA is located exclusively in neurons, and its reduction may reflect neuronal dysfunction [9].

The relationship between presurgical NAA/(Cho + Cr) and NAA/Cr ratios has been used as a way of linking cerebral metabolic abnormalities with cognitive functions. Studies in TLE have reported a coupling between metabolism and function [10–12]. Taken together, they suggest that ^{1}H-MRS may be more dependent on the function rather than structure of a neuroanatomical substrate. As such, this technique appears to be particularly useful in

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studies of brain–behavior relationships. However, characterization of the neuropsychological correlates associated with ^{1}H-MRS has been examined only sparsely [10–15].

Previous investigations between IEDs and neuronal dysfunction suggest that interictal electrical activity may cause or reflect altered cerebral metabolism [16–18]. The pathophysiological meaning of NAA reduction in TLE in unclear, and its relationship to other physiological markers has not been elucidated.

There is a lack of studies analyzing the relationship between epileptiform discharges, metabolic dysfunction as disclosed by ^{1}H-MRS, and memory impairment. The aim of this study was to examine the relationship between IEDs, metabolic dysfunction diagnosed by ^{1}H-MRS, and memory impairment in a homogeneous cohort of patients with TLE with unilateral MTS.

2. Methods

2.1. Subjects

This prospective study, conducted during 2007 and 2008, involved 29 consecutive outpatients from the Epilepsy Section of Hospital São Paulo, Universidade Federal de São Paulo, Brazil, and 24 healthy control subjects. Originally, data from 48 patients were available. However, after initial enrollment in the study, 19 patients were excluded, either because they had a seizure on the first day of monitoring, which might have biased the counting of epileptiform discharges, or because there were artifacts in the MRS sequences, which rendered these exams not suitable for proper analysis. All patients had TLE related to unilateral MTS, defined after extensive presurgical evaluation including detailed clinical history, neurological examination, high-resolution cerebral MRI, neuropsychological and psychiatric evaluations, and psychosocial assessment. Patients younger than 16, with other neurological or psychiatric disorders, or with evidence of MRI abnormalities other than MTS were excluded.

Control subjects, recruited from the community, were matched to patients with respect to age, gender, and educational level. Exclusion criteria for controls included substance abuse, medical or psychiatric conditions that could affect cognitive functioning, history of loss of consciousness, and developmental learning disorders.

The study was approved by the ethics committee of our institution.

2.2. MRI and MRS procedures

2.2.1. MRI procedures

The exams were performed with 1.5-T equipment (Magnetom Sonata [Maestro Class], Siemens AG, Erlangen, Germany) using a standard quadrature head coil and were blindly analyzed by a single neuroradiologist with expertise in epilepsy (H.C.). A standardized MRI protocol for imaging the temporal lobes was applied: sagittal spin-echo T1 and axial spin-echo T2, 6-mm slices; coronal FLAIR and inversion–recovery, both perpendicular to the longer axis of the hippocampus, 3-mm slices; and coronal FFE-T1 volumetric acquisition of the whole hemispheres, 1.5-mm slices.

2.2.2. MRS procedures

A series of orthogonal T2-weighted images for localization were obtained using a fast imaging technique with a steady-state precession sequence (TR/TE, 5420/131 ms; matrix, 320×212; field of view, 265 mm; slice thickness, 5 mm; interslice gap, 5 mm; number of acquisitions, 1; scan time, 56 seconds). For single-voxel spectroscopic studies, the volume of interest ($20 \times 15 \times 15$ mm) was placed over the left anterior hippocampal region (including part of the head and body). The position of the volume of interest was meticulously adjusted in orthogonal images to ensure standard placement. The same procedure was repeated for the right hippocampus. The method of point-resolved spectroscopy was applied for spectrum acquisition. After the transmitter and receiver were automatically adjusted, water signal was automatically shimmed to within a linewidth of 3–5 Hz. After preirradiation of water resonance by application of three chemical shift selective pulses, water-suppressed single-voxel spectroscopy was performed (TR/TE, 1500/135 ms; field of view, 240 mm; number of acquisitions, 192; data points, 1024; scan time, 4 minutes 48 seconds).

Automated processing of the raw data was accomplished using a commercially available spectral analysis software package (Leonardo, Syngo MR 2004 A). After zero filling and baseline correction, metabolic resonance intensities were determined automatically. Metabolite signals were expressed as ratios of integral values of NAA at 2.0 ppm to creatine and phosphocreatine-containing compounds (Cr) at 3.0 ppm, which are relatively homogeneously distributed throughout the brain and are not significantly influenced by the epileptic state.

With respect to values of NAA, Cho, and Cr, outliers, defined as values outside 2 SD of the mean of normal controls, were excluded from statistical analyses. Data were presented in terms of the intensity ratio NAA/(Cho + Cr).

2.3. Video/EEG and IEDs

Patients underwent prolonged video/EEG monitoring using 32-channel EEG recording equipment (Ceegraph software, Biologic Systems Corp.), with electrodes placed according to the 10–20 International System plus intermediary temporal and sphenoidal electrodes. To record ictal events, AEDs were tapered off or completely withdrawn at the physician's discretion (no standardized protocol for AED manipulation was applied).

Video/EEG recording was continuously monitored by technical staff. To avoid the effect of tapering off or completely withdrawing AEDs, the frequency and location of IEDs were visually assessed in two epochs of 30-minute-awake and 30-minute-sleep EEG samples on the first day of monitoring by a single observer (L.M.F.F.G.) who was blinded to memory tests and to the ^{1}H-MRS. IEDs were manually counted on the basis of morphological criteria (i.e., transients clearly distinguishable from background activity on a bipolar montage, with a characteristic morphology and duration of 70–200 ms).

IEDs were considered unilateral if >80% were recorded over one temporal lobe or bilateral if >20% of discharges were recorded over the contralateral temporal lobe.

2.4. Neuropsychological measures

Tests assessing memory and Intelligence Quotient (IQ) were selected from an extensive neuropsychological examination comprising hand preference, attention, executive function, language, visuospatial perception, and memory. A standard clinical measure of intelligence was administered (estimated IQ from Wechsler Adult Intelligence Scale—Revised [WAIS-R]) [19]. Logical Memory I and II (immediate and delayed recall) were used to assess verbal memory, and Visual Reproduction I and II (immediate and delayed recall) were used for visual memory. Both tests are part of the Wechsler Memory Scale—Revised [20]. Additionally, the Rey–Osterrieth complex figure test [21], immediate and delayed recall, was employed to assess spatial memory; and the Rey Auditory Verbal Learning Test (RAVLT) [21], including Total Learning, Postinterference, Delayed Recall, and Recognition, was used for assessment of verbal learning.

2.5. Statistical analysis

Statistical analyses were performed using SPSS 10.0 software. Results (means ± SD) of all memory tests of control subjects and of patients with right and left MTS were compared. For this comparison, the Mann–Whitney *U* or Kruskal–Wallis *H* test was used.

Spearman's correlation was used to assess the following correlations: MRS values and material-specific memory function; duration of epilepsy (measured in years) and NAA/(Cho + Cr) values; duration of epilepsy and results of memory tests; IEDs and NAA/(Cho + Cr); and IEDs and material-specific memory function. *P* values <0.05 were considered statistically significant.

3. Results

3.1. Characteristics of the sample

The mean age of the 29 patients (19 women, 10 men) was 37.7 years (range: 20–61). The mean duration of epilepsy was 24.1 years (range: 3–48), and age at seizure onset, 13.5 (range: 2–30). Patients had, on average, 10 years of education (range: 5–16 years). The mean age of the control subjects (15 women, 9 men) was 37.3 years(range: 20–61) and their mean education level was 12.08 years (range: 5–16). These data showed no statistical difference.

As expected, there was a significant difference in IQ results: mean IQ was 83.2 in the patient group and 92.4 in the control group ($P < 0.001$).

Demographic characteristics showed no differences between the left and right MTS groups with respect to IQ, age, education, gender distribution, age at epilepsy onset, and duration of epilepsy (Table 1).

3.2. Analysis of memory tests

Patients with left and right MTS did not differ across measures of IQ, Logical Memory Immediate and Delayed Recall, and Rey–Osterrieth Complex Figure Immediate and Delayed Recall; both groups showed impairment when compared with controls.

On RAVLT Postinterference, both the left and right MTS groups performed worse than controls (left, $P < 0.001$; right, $P < 0.045$). The left MTS group also showed impairment when compared with the right MTS group ($P = 0.050$).

The left MTS group performed worse than controls ($P < 0.001$) and the right MTS group ($P = 0.006$) on RAVLT Delayed Recall. The right MTS group showed no impairment when compared with controls.

Left and right MTS groups did not perform worse than controls on the remaining tests (Table 2).

There was a negative correlation between IQ and duration of epilepsy in the left MTS group ($r = 0.551$, $P = 0.031$) and between

Table 1
Demographic characteristics of patients with mesial temporal sclerosis.

	Left MTS group ($n = 15$)	Right MTS group ($n = 14$)	*P* value
Mean age (years)	38.9 ± 9.84	36.4 ± 10.10	0.354
Years of education	9.7 ± 2.34	10.3 ± 2.87	0.533
Gender			
Male	5 (33.34%)	5 (35.71%)	
Female	10 (66.66%)	9 (64.29%)	
IQ	82.5 ± 6.93	83.9 ± 7.18	0.847
Duration of epilepsy (years)	24.5 ± 14.09	23.7 ± 11.04	0.780
Age at onset (years)	14.3 ± 8.39	12.6 ± 7.39	0.621

Table 2
Results (means ± SD) in specific domains of memory tests for the control and left and right MTS groups.[a]

	Control group	Left MTS group	Right MTS group	*P* value (Kruskal–Wallis test)
Logical Memory I	27.8 ± 7.20^{L,R}	16.10 ± 6.62	17.6 ± 5.97	CS × L <0.001[b] CS × R <0.001[b] L × R 0.551
Logical Memory II	23.1 ± 7.75^{L,R}	9.7 ± 5.75	13.2 ± 6.72	CS × L <0.001[b] CG × R <0.001[b] L × R 0.185
RAVLT Total Learning	49.0 ± 8.78	41.9 ± 7.79	44.9 ± 10.05	0.060
RAVLT Postinterference	10.8 ± 3.12^{L,R}	6.3 ± 3.01^{R}	8.6 ± 3.32^{L}	CS × L <0.001[b] CS × D 0.045[b] L × R 0.050[b]
RAVLT Delayed Recall	10.8 ± 2.91^{L}	5.8 ± 2.98^{R}	9.0 ± 3.21^{L}	CS × L <0.001[b] CS × R 0.090 L × R 0.006[b]
RAVLT Recognition	14.0 ± 1.55	12.3 ± 2.85	13.4 ± 1.60	0.064
Visual Reproduction I	33.6 ± 5.28	29.6 ± 5.85	30.4 ± 5.63	0.090
Visual Reproduction II	28.8 ± 7.07	21.8 ± 10.69	24.3 ± 10.56	0.117
Rey-Osterrieth Complex Figure Immediate	24.0 ± 4.99^{L,R}	13.3 ± 6.08	13.3 ± 6.24	CS × L <0.001[b] CR × R <0.001[b] L × R 0.982
Rey-Osterrieth Complex Figure Delayed Recall	23.4 ± 5.08^{L,R}	14.1 ± 6.45	12.1 ± 5.92	CS × L <0.001[b] CS × R <0.001[b] L × R 0.352

[a] L, significant statistical difference in relation to left mesial temporal sclerosis group; R, significant statistical difference in relation to right mesial temporal sclerosis group.

[b] Statistically significant.

RAVLT Total Learning and duration of epilepsy in the same patients ($r = 0.585$, $p = 0.022$) (Fig. 1).

3.3. ^{1}H-MRS results

NAA/(Cho + Cr) ratios of patients and controls are listed in Table 3. Ratios were lower in the ipsilateral mesial temporal lobe than in the contralateral region ($P = 0.025$).

Eighteen patients (62.07%) had a reduction in the NAA/(Cho + Cr) ratio in mesial temporal structures, and five (17.24%) had bilateral abnormalities.

In the left MTS group, there was a negative correlation between NAA/(Cho + Cr) ratio and duration of epilepsy ($r = 0.569$, $P = 0.027$) (Fig. 2). This was not observed in the right MTS group.

3.4. Interictal epileptiform discharges

Sixteen patients (55.2%) had unilateral and 13 (44.8%) bilateral temporal IEDs. Six patients (40%) in the left MTS group had unilateral and nine (60%) bilateral temporal IEDs, whereas in the right MTS group, 10 (71.4%) had unilateral and four (28.6%) bilateral temporal IEDs.

3.5. Correlation between memory, interictal epileptiform discharges, and NAA/(Cho + Cr) ratio

In the left MTS group, ipsilateral NAA/(Cho + Cr) ratio was correlated with RAVLT Postinterference ($r = 0.535$, $P = 0.040$) and Delayed Recall ($r = 0.522$, $P = 0.046$) (Fig. 3), and IEDs were negatively correlated with Logical Memory Immediate Recall ($r = 0.531$, $P = 0.042$) and Delayed Recall ($r = 0.515$, $P = 0.049$) (Fig. 4).

In the right MTS group, contralateral NAA/(Cho + Cr) ratio was correlated with IQ ($r = 0.669$, $P = 0.012$) and Logical Memory Delayed Recall ($r = 0.551$, $P = 0.050$) (Fig. 5). Patients with right MTS and bilateral IEDs showed impairment on RAVLT Postinterference when compared with controls ($P = 0.022$), whereas no impairment was observed in patients with unilateral IEDs ($P = 0.225$).

A significant negative correlation was found between contralateral total NAA and contralateral IEDs ($r = 0.689$, $P = 0.006$) in

Table 3
NAA/(Cho + Cr) ratios of control and MTS groups.

	Control group	MTS group	
		Ipsilateral[a]	Contralateral
Mean ± SD (Range)	0.561 ± 0.1111 0.502–0.621	0.487 ± 0.0986[b] 0.449–0.524	0.571 ± 0.1281 0.519–0.623

[a] Contralateral, contralateral to side of the seizure onset; Ipsilateral, side of seizure onset.

[b] Kruskal–Wallis test, $P < 0.05$.

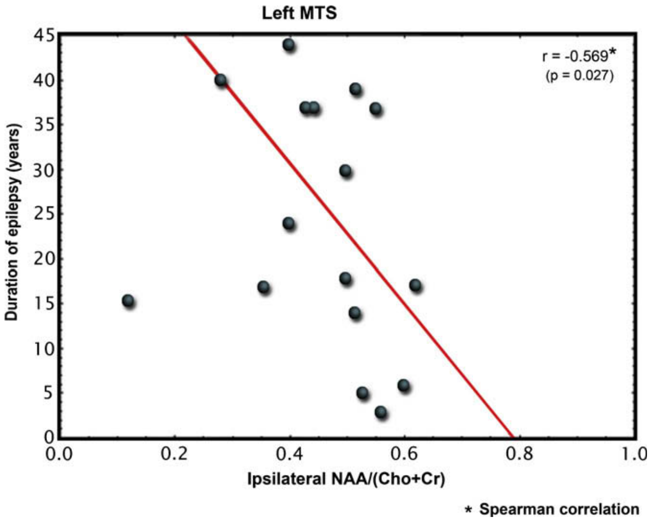

Fig. 2. Correlation between duration of epilepsy and NAA/(Cho + Cr) ratio in patients with left mesial temporal sclerosis.

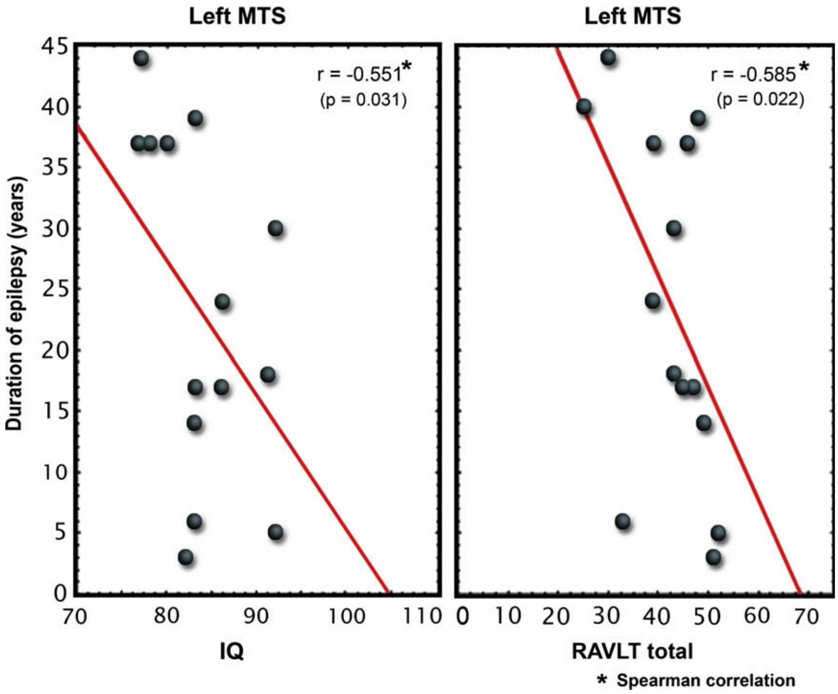

Fig. 1. Correlation of duration of epilepsy with IQ and Rey Auditory Verbal Learning Test (RAVLT) Total Learning scores in patients with left mesial temporal epilepsy (MTS).

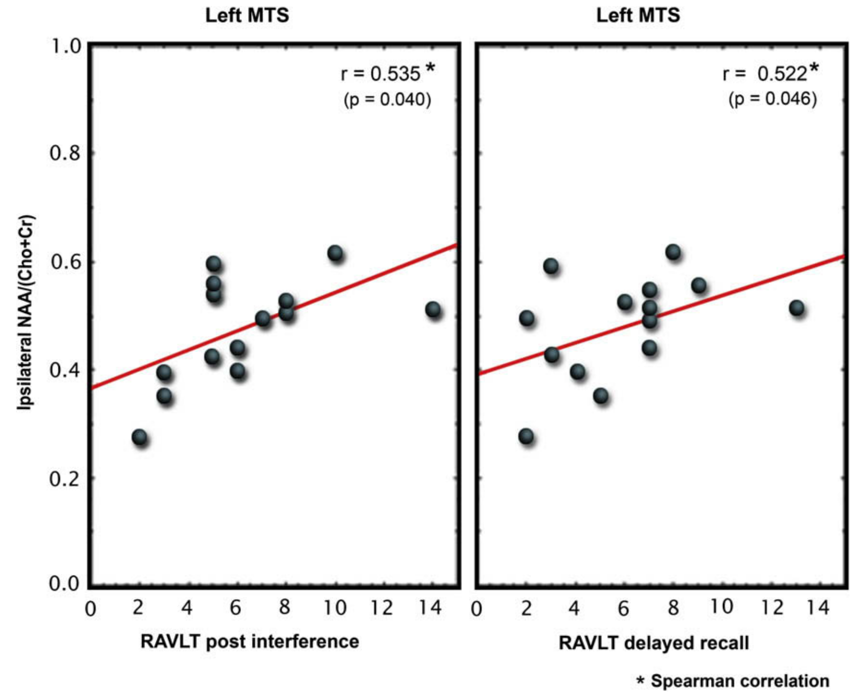

Fig. 3. Correlation between NAA/(Cho + Cr) ratio and Rey Auditory Verbal Learning Test (RAVLT) Postinterference and Delayed Recall in patients with left mesial temporal sclerosis.

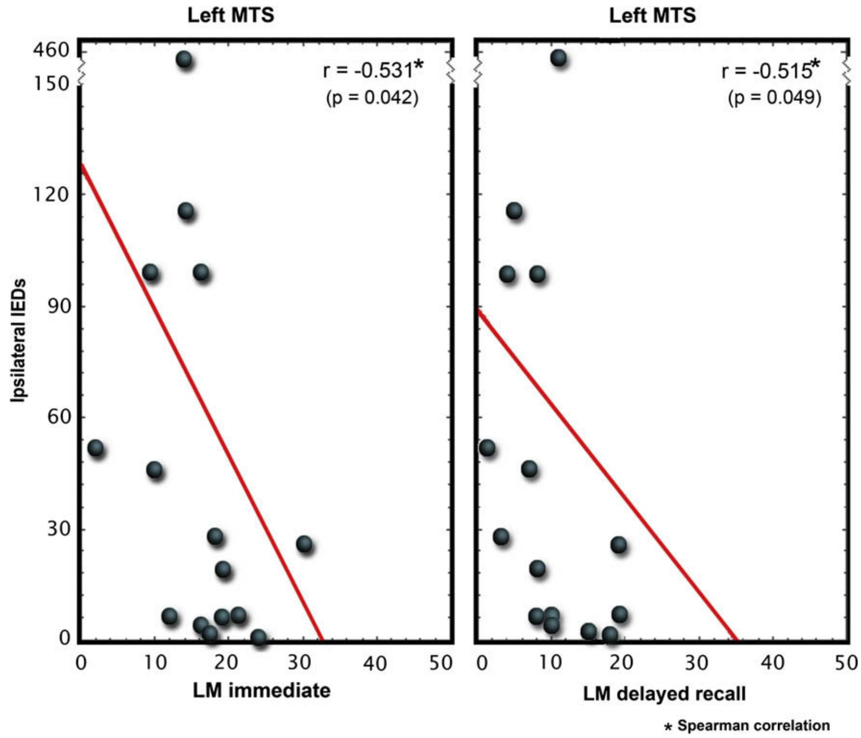

Fig. 4. Correlation between ipsilateral interictal epileptiform discharges (IEDs) and Logical Memory (LM) Immediate Recall and Delayed Recall in patients with left mesial temporal sclerosis.

patients with left MTS. Fig. 6 illustrates that more frequent interictal activity on the EEG was associated with a decline in total NAA. There was no correlation between ipsilateral IEDs and MRS values.

4. Discussion

Over the past decade various studies have been carried out to characterize cognitive dysfunction in patients with TLE and MTS.

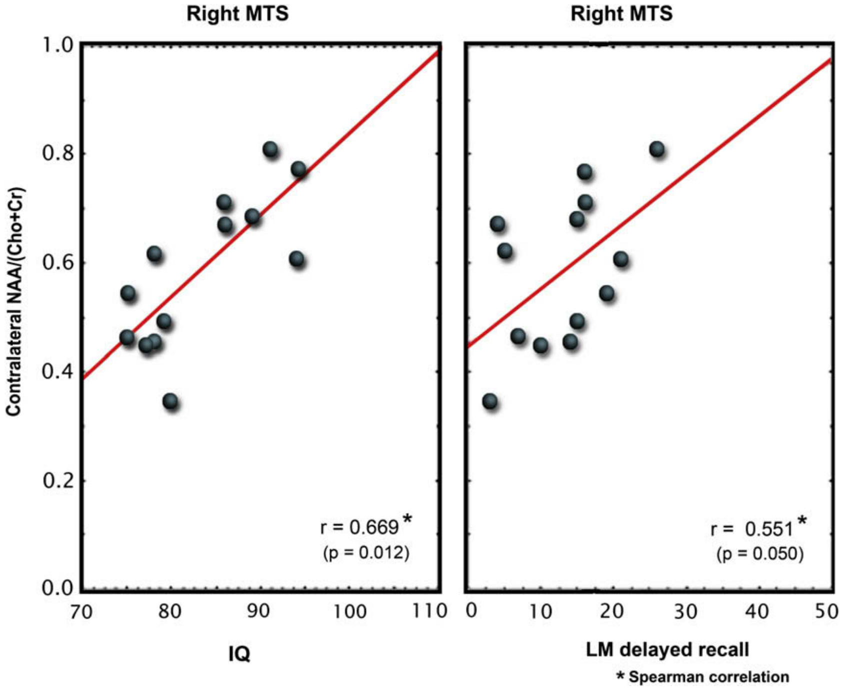

Fig. 5. Correlation of contralateral NAA/(Cho + Cr) ratios with IQ scores and Logical Memory (LM) Delayed Recall in patients with right mesial temporal epilepsy.

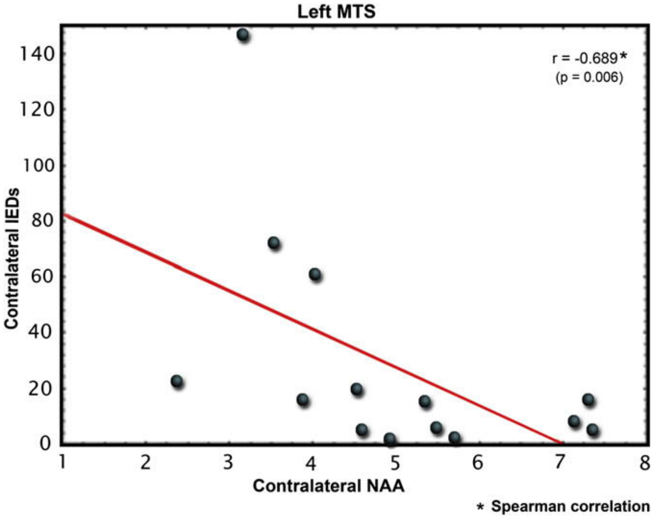

Fig. 6. Correlation between contralateral interictal epileptiform discharges (IEDs) and contralateral NAA in patients with left mesial temporal epilepsy.

In these patients, cognitive dysfunction extends beyond memory impairment [22]. A number of factors seem to correlate with cognitive decline in refractory TLE, including underlying pathology, seizures, medication, and IEDs [2,5,23].

The aim of this study was to correlate, in a series of patients with MTS, memory to functional findings of presurgical evaluation, such as IEDs and ^{1}H-MRS.

Memory impairment is characteristic of mesial TLE. The function of the hippocampus and the adjacent structures in memory has been established in patients undergoing temporal lobectomy [24]. The type and anatomic location of brain pathology have a crucial impact on the specific cognitive deficit: verbal memory deficit is more commonly associated with a left-sided mesial epileptogenic zone, whereas nonverbal memory impairment is associated with the nondominant temporal lobe [25].

Longer duration of epilepsy has been associated with greater cognitive impairment [26–29]. In our series, a negative correlation between IQ, verbal learning, and duration of epilepsy was found only in patients with left MTS. The negative impact of duration may be due in part to the cumulative impact of seizures, but also to AED treatment and pathological interictal brain activity [2]. In our series this impact may due to bilateral IEDs, higher in the left MTS.

IEDs have also been associated with cognitive decline [30]. In our series, 44.8% of patients manifested bilateral IEDs. Patients with right MTS and bilateral IEDs showed impairment in verbal learning, whereas no impairment was observed in patients with unilateral IEDs.

The high incidence of bilateral IEDs supports the view that epilepsy related to MTS functionally impairs both temporal lobes, even though an ipsilateral predominance of IEDs is a common finding [31–34]. A possible mechanism for the bilateral dysfunction in TLE could be a phenomenon of secondary epileptogenesis due to massive repetitive electrical discharges from the ipsilateral side [35] and, in our series, may be responsible for the verbal memory impairment found in patients with right MTS. However, autospy series have shown that even in those cases considered as manifesting unilateral MTS, there is a variable level of sclerosis on the contralateral hippocampus [36,37].

Bilateral abnormalities have also been revealed by MRS, and abnormally decreased NAA has been reported in the contralateral temporal lobe in 40–50% of patients with proven unilateral MTS [38,39]. The pathophysiological meaning of NAA reduction in both temporal lobes is unclear. Some studies have raised the possibility that the increased interictal electrical activity on the contralateral side might cause or reflect altered cerebral metabolism in the same region [16–18]. In our series, patients with left MTS who showed contralateral interictal activity also had a decrease in contralateral NAA. Park et al., in a study involving 34 patients with MTS, also demonstrated a correlation between neuronal dysfunction or damage detected by MRS and epileptic activity in contralateral medial temporal structures [17]. The association of both dysfunctional findings may suggest that the reduction in NAA/(Cho + Cr) or

NAA/Cr ratios on the contralateral side, frequently noted in patients with MTS, might represent a possible marker of epileptogenicity of the contralateral medial temporal lobe.

Levels of hippocampal NAA/(Cho + Cr) or NAA/Cr have been found to correlate with episodic and [12,13] semantic [40] memory functions and intelligence [16] in patients with TLE related to MTS. In our series, left-sided levels of NAA/(Cho + Cr) were correlated with IQ and verbal functions, whereas no association was detected between right-sided levels of NAA/(Cho + Cr) and any neuropsychological tests. These findings are in accordance with some studies that have analyzed this association [10,13]. One relatively unexpected finding in our patients was the fact that those with right MTS showed impairment of verbal memory and abnormal NAA/(Cho + Cr) ratios in the left mesial temporal structures. These patients also had bilateral IEDs, suggesting coupling of both metabolic and electric functional measures in the left mesial temporal lobe. Interestingly, incisa della Rocchetta et al. [41] found impairment in verbal memory after right temporal lobectomy in patients with contralateral metabolic abnormalities detected by ^{1}H-MRS before surgery.

In conclusion, IEDs and NAA/(Cho + Cr) ratios, which reflect neural metabolism, are closely related to verbal memory function in mesial temporal lobes. Higher interictal activity on the EEG is associated with a decline in total NAA in contralateral structures. This association suggests that the reduction in NAA on the contralateral side may be a marker of epileptogenicity of contralateral mesial temporal structures.

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