1H-MRS Metabolite's Ratios Show Temporal Alternation in Temporal Lobe Seizure: Comparison between Interictal and Postictal Phases

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Highlights

- Investigation of metabolite changes after seizure was done.
- significant decreases in NAA/Cr, NAA/Cho, NAA/Cho+Cr is detected immediately after ictus in ipsilateral hippocampus as compared with control data and controlateral hippocampus.
- No significant differences among all three groups in these metabolite ratios were detected in interictal phase.
- Ictal H-MRS can be considered as a possible adjunct tool in lateralizing and localizing of seizure foci in epileptic patients.

Abstract

Purposes: To determine ^{1}H-MRSI metabolites changes in interictal and postictal phases of patients suffering from mesial temporal lobe epilepsy with hippocampal sclerosis and lateralization of seizure foci.

Materials and Methods: MR spectroscopic imaging was performed in 5 adult patients with refractory temporal lobe epilepsy interictally and immediately after the seizure and in 4 adult control subjects. All patients underwent MR imaging and VideoEEG Monitoring.

Results: The results showed statistically significant decreases in *N*-acetylaspartate/Creatine, *N*-acetylaspartate/Choline and *N*-acetylaspartate/ (creatine + choline) immediately after ictus in ipsilateral hippocampus as compared with control data and contralateral hippocampus of patients while no statistically significant difference was presented in interictal phase.

Conclusion: The present study clearly indicates ^{1}H-MRS abnormalities following an ictus of temporal lobe epilepsy with metabolite recovery in interictal phase. This finding suggests postictal ^{1}H-MRS as a possible useful tool to assist in lateralizing and localizing of seizure foci in epileptic patients with structural lesions.

Keywords: Temporal lobe epilepsy, Proton MR spectroscopy imaging, Seizure, Metabolites ratio.

1. Introduction

Temporal lobe epilepsy (TLE) is the most prevalent cause of both focal and refractory seizures (1). Hippocampal sclerosis (MTS) is the most common pathological finding in drug refractory, chronic temporal lobe epilepsy (TLE) (2). Epilepsy surgery is an important therapy in reducing seizure frequency in this population. Before surgery, identifying the exact localization of seizure foci is necessary. Standard diagnostic procedures included magnetic resonance imaging (MRI) and video electroencephalographic monitoring (V-EEG). The lesion can be verified with high reliability (up to 90% sensitivity and 85% specificity) using magnetic resonance imaging (MRI)(3). However, it has been reported that MRI is non-contributive in 29% of partial epileptic patients. This is the main reason why nowadays use of supplementary neuroimaging methods in epilepsy surgery candidates has been augmented. Multimodal presurgical procedures have provided a significant help in localization and lateralization of seizure foci. Positron emission tomography (PET), single photon emission computed tomography (SPECT), fMRI, Voxel-based Morphometry (VBM), Diffusion Weighted Imaging and proton magnetic Spectroscopic imaging (^{1}H-MRSI) are the popular advance neuroimaging techniques which are applied in epileptic patients previously(4-8).

Proton MR Spectroscopy Imaging (^{1}H-MRSI) is a noninvasive technique that depicts the anatomic distribution of biochemical information. ^{1}H-MRSI includes major contributions from *N*-acetylaspartate (NAA), Creatine and phosphocreatine (Cr), as well as choline-containing compounds (Cho). They can lateralize epileptogenic zone accurately varies from 45% to 100% (9-11).

Among the whole modalities, SPECT is the most appropriate ictal imaging method which brings informative results in identifying epileptogenic foci(12). Ictal imaging with MRS has been primarily limited to a few studies (13-16) each of them indicating specific metabolite

changes during or immediately following a seizure. For instance, Mueller et al (13) showed decrease in NAA concentration during intermittent frontal status epilepticus in one case. In two other studies, mobility of choline has been detected postictally (14, 15), while another study (17) reported generalized reduction of all metabolite ratios. Finally, study conducted by Simister et al (16) introduced ratio Cr144/Cr30 as the most sensitive measure of metabolic disturbance which was highest in the post-ictal period but appeared to normalize within 2 hours of the most recent seizure.

Planned ictal and postictal MRS imaging of patients with frequent or continuous partial seizures may offer a unique opportunity to study the metabolic pattern of the brain during ictal events. This may be especially important in patients with extensive underlying structural brain abnormalities in whom other modalities may not sufficiently localize the epileptogenic zone for surgical planning. However, literature about this application is narrow and limited. We tested the feasibility and clinical value of reading ^{1}H-MR spectroscopic images in patients with TLE immediately after ictal phase. Our aim was to compare metabolite images of post-ictal and interictal phases, and to explore if there are significant differences between these phases that can improve lateralization and localization of seizure foci compared with that of each method alone.

2. Material and Methods

2.1. Subjects

Our study included four healthy subjects (four women; aged 20-30 years; mean age, 28 years) and five patients with temporal lobe epilepsy (two men, three women; aged 26-30 years; mean age, 27 years) refractory to medical treatment. Informed consent was obtained from all the patients and control subjects before the examination. Diagnosis was based on the following criteria: (*1*) documented presence of hippocampal sclerosis confirmed by three

expert neurologists and radiologist, (*2*) focal ictal temporal lobe patterns recorded with Longterm Video EEG Monitoring (LTM), (3) irritative zone which is in accordance with ical onset zone, (*4*) clinical features consistent with seizures of temporal lobe origin. All the patients underwent LTM in which after the occurrence of their habitual seizure and its confirmation by neurologist, they were immediately send to the imaging center when they were in postictal phase. The average time of MRS acquisition after the seizure occurrence was almost 60 minutes. Epileptogenic zone was lateralized and localized in left mesial temporal in one patient and in right mesial temporal in four of them (Table 1).

2.2. MR Imaging

MR imaging was performed on a clinical 1.5-T system (Siemens Magnetom Avanto). The following image data sets were acquired: axial T1- weighted gradient echo (MPRAGE) TR/TE/TI = 1630/2.82/1100 ms, 15o flip angle, slice thickness 1 mm, FOV= 256×192, axial and coronal T2-weighted 2D turbo spin echo TR/TE= 5200/92 ms, slice thickness 3 mm with gap= 3.3 mm, FOV= 180×180, T2-weighted Fluid Attenuated Inversion Recovery (FLAIR) TR/TE/TI= 7800/82/2300.8 ms, slice thickness 3 mm, gap= 3.3 mm, FOV= 163×190.

2.3. Proton MR Spectroscopy

In all cases, the proton MR spectroscopic imaging studies were acquired by a 1.5-T system (Siemens Magnetom Avanto) with these parameters: 3D Point Resolved Spectroscopy (PRESS) and added phase encoding, including both hippocampi TR/TE= 1200/135 ms, flip angel 90˚, vector size= 512, number of phase encoding steps= 12, 5.62×8.125×8.75 mm resolution, and total acquisition time= 7 min. The PRESS box was chosen to temporal lobe coverage (Fig. 1). A single voxel was obtained in white matter or gray matter (only one type of tissue) for correction of eddy current artifact with these parameters: TR/TE= 1000/30 ms,

flip angle= 90˚, vector size= 512, and acquisition time= 5 min. For localization, FLAIR images (TR/TE/TI= 7800/82/2300.8 ms) were used in coronal view.

2.4. MRS Data Analysis

Data analysis includes two stages; pre-processing and quantification. Data were processed by a software developed in MATLAB based on subtract_QUEST (quantitation based on semi-parametric quantum estimation)(18) algorithm. The regions-of-interest (ROIs) were determined on the involvement hippocampus by three neurologists, and the ratios of NAA/Cr, NAA/Cho, and NAA/(Cr+Cho) were calculated on the ROIs.

2.4.1. Pre-processing of the MRS signal

The MRS signals seldom purely exponentially decay due to experimental conditions such as physiological movements, the residual water signal, and shimming imperfections. Therefore, pre-processing step, as part of the quantification strategy is an important stage to minimize analysis errors. Pre-processing steps performed in this study are; (19) eddy current compensation (ECC), residual water suppression using maximum-phase finite impulse response (MP-FIR) filter method, phase correction, and SNR enhancement.

2.4.2. Quantification of the MRS signal

After data pre-processing, as mentioned, the data were quantified by subtract_QUEST algorithm. A time-domain model function, consist of a simulated basis set from whole-metabolite signals by the software package NMR-SCOPE are fitted to low-SNR in vivo data(18). The ratios of NAA/Cr, NAA/Cho, and NAA/(Cr+Cho) are calculated by using this nonlinear least-squares algorithm. In Fig. 2, activation map for NAA/(Cr+Cho) ratio in both hippocampi is depicted.

Fig. 1. (a) Activation map for NAA/(Cr+Cho) ratio in both hippocampi; **(b)** FLAIR image in the coronal plane, placement of the reign of interest (ROI) over the ipsilateral and contralateral hippocampi by a neurologist.

2.5. Statistical Analysis

Statistical analyses of the MR spectroscopic imaging data were performed by using Mann-Whitney test. Differences of statistical significance (P value>0.05) were taken into consideration. This analysis was performed using SPSS (version 21).

3. Results

Metabolites ratios were obtained from five temporal lobe epileptic patients and five normal adults. Demographic and clinical characteristic of subjects are given in Table 1. The ratio of *N*-acetylaspartate/Creatine, *N*-acetylaspartate/ Choline as well as *N*-aspartate/ (creatine+ choline) were evaluated. The mean value of our final data of the NAA/Cho, NAA/Cr and NAA/(Cr+Cho), shown separately for the postictal , interictal in a patient group and for the controls, are given in Table 2 and 3.

3.1. NAA/Cr

As it presented in Table 2 this metabolite ratio is significantly decreased in affected hippocampal area in comparison to non-affected hippocampus and normal group in postictal phase. There was no significant difference between non-affected ROI and normal group in this ratio in postictal phase (Figure 2).

When comparing this value in interictal phase no significant statistical difference was obtained from three groups of study (Table 3).

3.2. NAA/Cho

In postictal phase, The *N*-acetylaspartate/Choline ratio was substantially decreased in the ipsilateral hippocampus in compared with normal group. NAA/Cho ratio of contralateral hippocampus was not statistically different with normal hippocampus postictally (Table 2).

All groups were not different in *N*-acetylaspartate/Choline in interictal phase (see Table and Figure 3).

3.3. NAA/Cho+Cr

The NAA/(Cho+Cr) data from individual patients were also analyzed with respect to the normal data, in particular to determine the contribution of such data to lateralization of the seizure focus. This value was significantly reduced in the affected hippocampus of patients in comparison with both hippocampi of controls. No statistically significant difference was revealed between the non-affected hippocampus of patients and both hippocampi of controls in postictal phase (table 2). Moreover, no significant differences were observed in NAA/(Cr+Cho) of all three groups in interictal phase (Table 3) (Figure 4).

4. Discussion

Novel imaging techniques over the past 20 years have been provided an opportunity to analyze the abnormalities preceding epileptic seizures in non-invasive manner and yield to new insight toward brain mechanisms and etiologies of epilepsy (20). Different modalities like conventional MRI, PET, SPECT and ^{1}H-MRS have been applied in parallel with EEG to lateralize and localize epileptogenic zone(9, 21). Previous literatures have suggested ^{1}H-MRS as a potential tool in presurgical evaluation of patients with interactable epilepsy (7, 22, 23). Previous studies on a role of ^{1}H-MRS in localization of seizure foci was being performed usually interictally. There are few studies which investigate the possible role of this modality in ictal and postictal phase. In this study, we studied ^{1}H-MRS findings of five intractable

mesial temporal epileptic patients interictally and immediately after ictal phase. The results showed statistically significant decreases in *N*-acetylaspartate/Creatine, *N*-acetylaspartate/Choline and *N*-acetylaspartate/ (creatine + choline) immediately after ictus in ipsilateral hippocampus as compared with control data and contralateral hippocampus of patients. There were no significant differences among all three groups in these metabolite ratios in interictal phase. This result was in accordance with previous finding which reported significant decrease in amount of different metabolite ratios in ictal phase or immediately after it (13-17). However in one study, Maton et al (2001) showed no significant differences in metabolite peak area ratios in ictal versus interictal phase(15). One possibility for detecting no change might be related to the time of postictal MRS acquisition which is in average 150 minutes delay. Since Simister et al (2008) showed that metabolic disturbance (Cr144/Cr30 in their study) was highest in the post-ictal period but appears to normalise within 2 h of the most recent seizure(16).

In previous studies, the high correspondence of between abnormal spectra in ^{1}H-MRS and atrophic alterations in MRIVol in epileptogenic foci was considered as an evidence which reflect metabolic alternations as an indicator of neuronal loss or damage in a region of seizure focus. This result has been supported by early pathological studies(24). A lot of current studies strongly suggest that the mentioned topic is more complex and decrease of the metabolite in such cases reflects mainly functional changes of neurons (25-27).

In one study, cendes et al.(26) showed that while N-acetylaspartate resonance intensity relative to creatine (NAA/Cr) was abnormally low preoperatively in at least one temporal lobe in all of their patients, postoperatively, it increased to the normal range on the side of surgery in all patients who became seizure free. This implied that the NAA and Cr abnormalities in patients with TLE, at least in part, are dynamic markers of both local and

remote physiologic dysfunction associated with ongoing seizures. In similar study Serles et al.(28) showed NAA recovery in postoperative seizure free patients in a time course of six months. Moreover, in an interesting study, Kuzniecky et al.(29) investigated the correlation between the degree of metabolic changes in ^{1}H-MRS and hippocampal cell loss in TLE in which they showed no significant correlation between the CA- or fascia dentata neuronal-glial ratios and the corresponding hippocampal Cr/NAA compound ratio. These findings support the concept that the metabolic dysfunction measured by MRS imaging and the hippocampal volume loss detected by MR imaging volumetry do not have the same neuropathologic basis and MRS imaging metabolic measures reflect neuronal and glial dysfunction rather than neuronal cell loss.

The cause of this recovery is not entirely clear but Serles et al.(28) suggest that this increase may resulted from recovery of neuronal metabolism, and possibly increased dendritic sprouting, synaptogenesis, and neurogenesis

Congruent with these result, significant metabolite changes from postictal to interictal phase in our study suggested that metabolite changes in ^{1}H-MRS reflects mainly a functional changes of neurons. In this study ^{1}H-MRS could highly lateralized and localized seizure foci immediately after seizure.

The most notable limitation of this study was our small sample size. Study which enrolls greater number of subjects will result in firmer conclusion. Moreover, all of our control group's subjects and most of our patients are female and also epileptogenic zone was localized in right hippocampus in four of five among our patients which both of these factors can limit the generalization of these results.

In addition, ratios of NAA/Cr NAA/Cho and NAA/ (Cr+Cho) have been applied, and quantitation of metabolites was not provided. Although absolute quantitation avoids potential confounds due to changes in the ratio denominator, it is technically challenging in practice since many necessary correction factors (e.g. % CSF in voxel, coil loading, T1 and T2 relaxation measurements, etc.) must be addressed.

In conclusion, we found significant ^{1}H-MRS abnormalities immediately after ictal in temporal lobe epileptic patients following by metabolite recovery in interictal phase. This finding suggests ictal and postictal ^{1}H-MRS as a possible adjunct tool in contribution with other modalities to lateralize and localize of seizure foci in epileptic patients with structural lesions. This hypothesis needs to be tested in a prospective manner, with larger sample size, in nonlesional epileptic patients as well as extratemporal epileptic groups to determine the utility of this modality as a predictor of epileptogenic foci.

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Figure captions

Fig. 1. (a) Activation map for NAA/(Cr+Cho) ratio in both hippocampi; (b) FLAIR image in the coronal plane, placement of the reign of interest (ROI) over the ipsilateral and contralateral hippocampi by a neurologist.

Fig. 2. NAA/ Cho in normal population and different phases of seizure in ipsilateral hippocampus

Fig. 3. NAA/ Cr+Cho in normal population and different phases of seizure in ipsilateral hippocampus

Fig. 4. NAA/ Cr in normal population and different phases of seizure in ipsilateral hippocampus

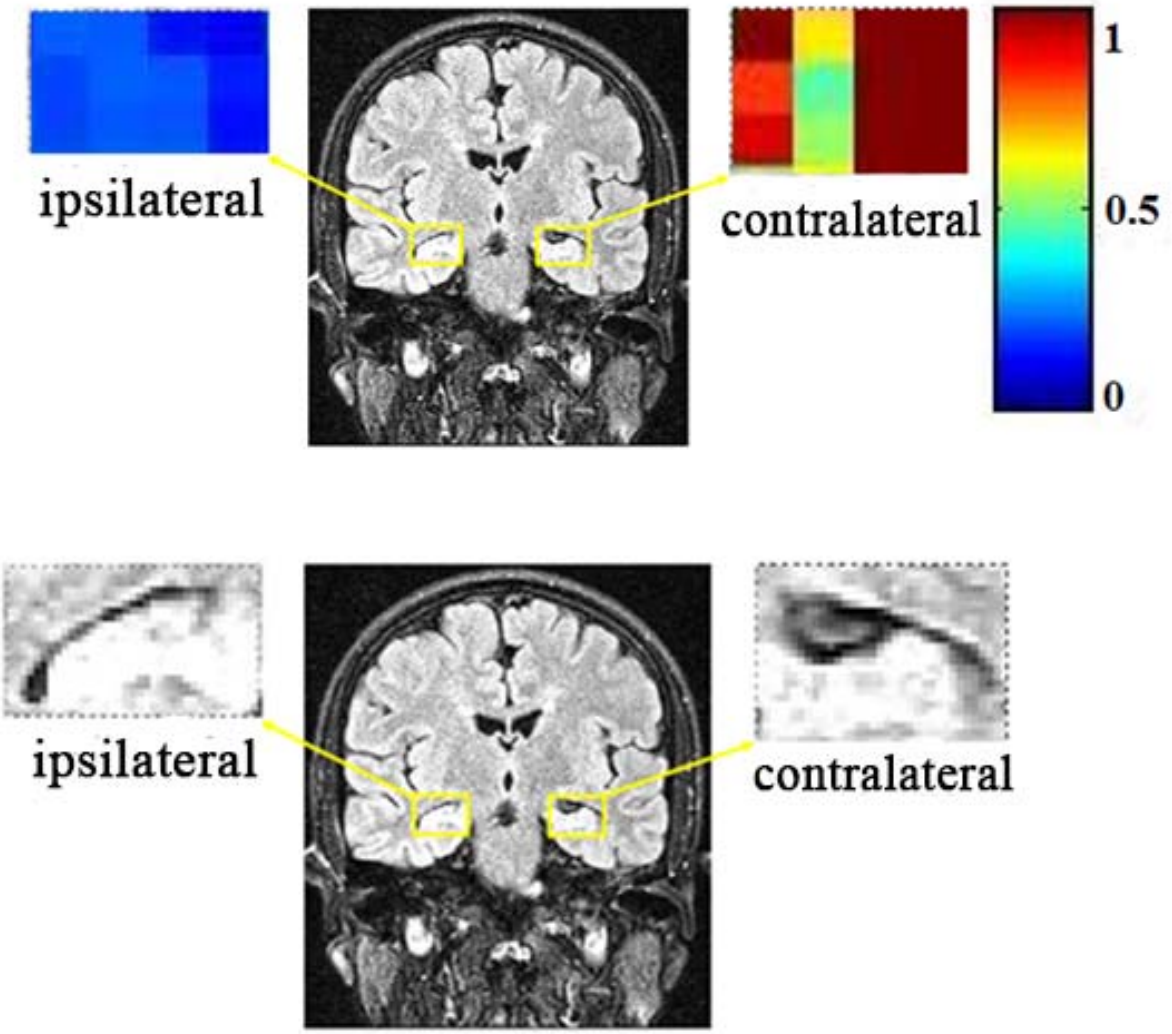

Fig 1

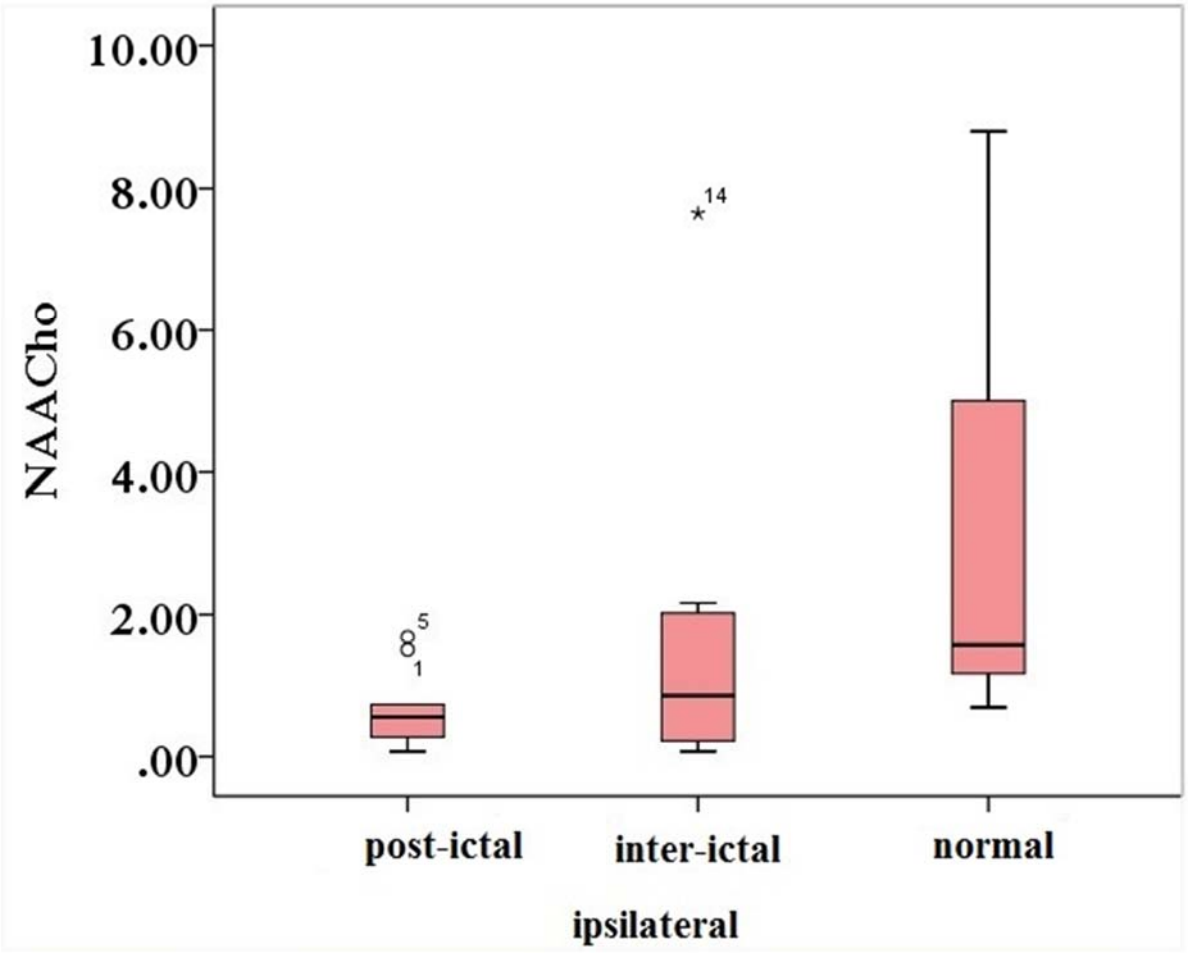

Fig 2

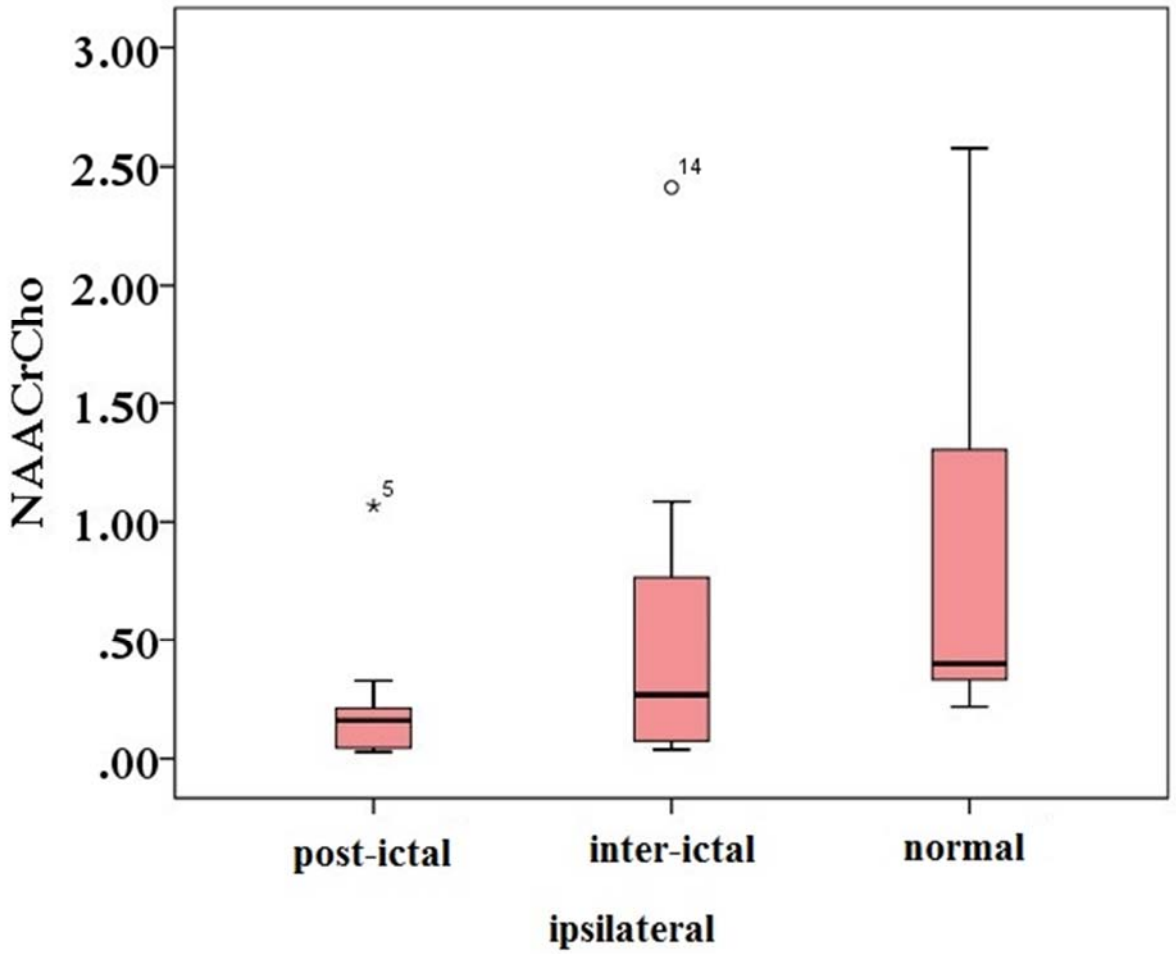

Fig 3

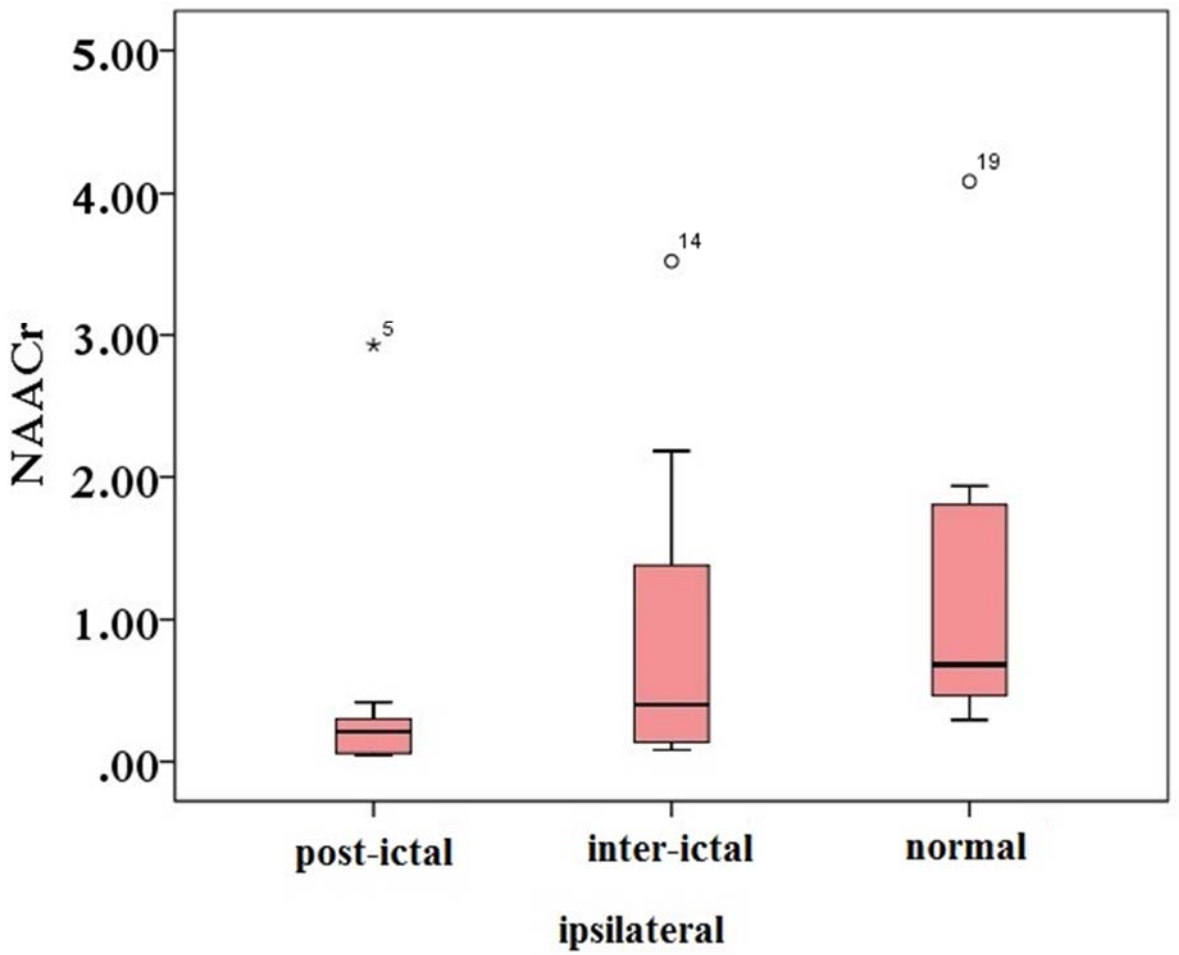

Fig 4

Table 1. Demographic and clinical characteristic of subjects

Patient No	Gender	DOB	Hand preference	Seizure Type	Interictal EEG	Ictal EEG	Seizure duration	MRI
1	male	1988	Right-handed	Automotor seizure	Right temporal	Right side	30 seconds	Right MTS
2	female	1977	Right-handed	Automotor seizure	Right side	Right side	33 seconds	Right MTS

3	male	1988	Right-handed	Automotor secondry generalized seizure	Right side	Right TLE	98 seconds	Right MTS
4	female	1987	Right-handed	Automotor seizure	Right side	Right TLE	226 seconds	Right MTS
5	female	1982	Right-handed	Automotor secondry generalized seizure	Left temporal	Left temporal	108 seconds	Left MTS

Table 2. Comparsion of ipsilateral and contralateral hippocampi with normal group in postictal phase

	Comparison of ipsilateral with normal			Comparison of contralateral with normal		
	ipsilateral	normal	P-value	contralateral	normal	P-value
NAA/Cr	0.46±0.87	1.28±1.28	0.008	0.58±0.55	1.28±1.28	0.178
NAA/Cho	0.66±0.54	3.11±2.92	0.01	2.39±2.99	3.11±2.92	0.374
NAA/(Cr+Cho)	0.23±0.31	0.86±0.83	0.003	0.42±0.39	0.86±0.83	0.211

P-value<0.05

Table 3. Comparsion of ipsilateral and contralateral hippocampi with normal group in interictal phase

	Comparison of ipsilateral with normal			Comparison of contralateral with normal		
	ipsilateral	normal	P-value	contralateral	normal	P-value
NAA/Cr	1.01±0.78	1.28±1.28	0.203	0.93±1.25	1.28±1.28	0.248
NAA/Cho	1.74±2.51	3.11±2.92	0.172	2.09±3.01	3.11±2.92	0.247
NAA/(Cr+Cho)	0.58±0.81	0.86±0.83	0.172	0.55±0.73	0.86±0.83	0.165

P-value >0.05