



## Oxidative stress in patients with refractory temporal lobe epilepsy and mesial temporal sclerosis: Possible association with major depressive disorder? ☆

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### ABSTRACT

**Objective:** The objective was to evaluate the genetic and biochemical profiles associated with oxidative stress (OS) in patients with temporal lobe epilepsy with mesial temporal sclerosis (TLE-MTS) and a healthy control group, and also to verify the possible existence of association between OS markers and psychiatric disorders (PD) in group with TLE-MTS.

**Methods:** Forty-six patients with refractory TLE-MTS and 112 healthy controls were included. Psychiatric evaluation occurred through Diagnostical and Statistical Manual of Mental Disorders (DSM-5) criteria. A peripheral blood sample was collected for analysis of glutathione S-transferase (GST) T1/M1 polymorphisms and serum levels of malondialdehyde (MDA) and antioxidant capacity equivalent to the trolox (TEAC), serum markers of OS. Student's *t*-test, Fisher's exact test, Chi-square test, and Analysis of Variance (ANOVA) were used, with a significance level of  $P < 0.05$ .

**Results:** The PD were observed in 27 patients of the group with TLE-MTS (58.6%); major depressive disorder (MDD) was the most frequent. Serum levels of MDA ( $P < 0.0001$ ) and TEAC ( $P < 0.0001$ ) were higher in group with TLE-MTS. When patients with MDD were compared with patients without PD, significant differences were observed between MDA ( $P = 0.002$ ) and TEAC ( $P = 0.003$ ) serum levels. Patients with TLE-MTS and MDD presented higher levels when compared with patients with TLE-MTS without PD and with another PD except MDD.

**Conclusions:** The present study observed significantly higher serum levels of MDA and of TEAC in patients with refractory TLE-MTS in comparison with the control group. The MDD was observed as an important issue associated with higher OS levels in refractory TLE-MTS. Further studies are needed to investigate the association of OS, TLE-MTS, and PD.

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### 1. Introduction

Temporal lobe epilepsy (TLE) is the most frequent epilepsy syndrome, which may be associated with head trauma, cerebral malformations, infections, and febrile seizures [1]. Mesial temporal sclerosis (MTS) is the etiology most frequently associated with TLE (TLE-MTS), and is also the most frequent etiology observed in patients with epilepsy with seizures that are refractory to pharmacological

therapy [1–4]. Psychiatric disorders (PD), in turn, are among the most frequent and important aspects associated with TLE-MTS, causing several behavioral changes and making difficult the clinical and surgical management of these patients [5]. Due to the high frequency of PD in patients with TLE-MTS, there is a need for careful psychiatric evaluation especially for surgery candidates [5,6].

Oxidative stress (OS), defined as the instability of free radical (FR) production, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) [7], is involved in many neurological diseases, including epilepsy [1,8]. The cells of the brain are sensitive to ROS, which can cause irreversible damage to biological molecules such as proteins, lipids, carbohydrates, and deoxyribonucleic acid (DNA), and can lead to cell death [9]. Glutathione S-transferases (GSTs) are a family of

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Phase II dimer proteins (conjugation reactions) that have a polymorphic character, with role in the detoxification of several ROS and RNS [10]. The OS processes activate GSTs, and their glutathione S-transferase M1 (GSTM1) and glutathione S-transferase T1 (GSTT1) variants act as catalysts in the detoxification of numerous ROS and RNS products [11].

The products of lipid peroxidation, such as the dosage of malondialdehyde (MDA) and the antioxidant capacity equivalent to the trolox (TEAC) in biological systems have been considered important parameters for evaluating cellular OS. The MDA has a cytotoxic and genotoxic actions, being found at high levels in some diseases associated with OS, while TEAC evaluates the antioxidant ability in eliminating ROS and RNS [12,13]. To date, there are few studies which have evaluated the levels of serum markers of OS in patients with TLE-MTS, as well as their association to GST polymorphisms, including GSTT1 and GSTM1. The objective of this controlled study was to verify the genetic and biochemical profiles in a series of patients with refractory TLE-MTS, considering the serum levels of MDA and TEAC, biomarkers of OS, and the genetic polymorphisms of GSTs.

## 2. Methods

### 2.1. Subjects

All patients were followed-up in the outpatient's clinic of a tertiary center (Epilepsy Section of the Faculdade de Medicina de São Jose do Rio Preto, São Paulo, Brazil), from February 2015 to July 2016. After local ethics committee approval and the informed consent has been assigned, 46 patients with refractory TLE-MTS were included in the study. Inclusion criteria were patients with age above 18 years old, presence of electroclinical diagnosis of TLE based on International League Against Epilepsy (ILAE) classification [14] and followed-up for at least 6 months in our unit. All patients also had clear magnetic resonance imaging (MRI) findings consistent with unilateral MTS and concordant interictal and ictal electroencephalogram (EEG) data. Exclusion criteria were clinical or other neurological illnesses besides epilepsy, cognitive impairments precluding psychiatric and clinical evaluations, and anti-histamine administration or alcohol consumption within 72 h prior to the psychiatric evaluation. The control group consisted of 112 healthy individuals from the community. All participants answered a questionnaire to register clinical and sociodemographic data and collected a peripheral blood sample for genetic GSTT1/GSTM1 polymorphism analysis and measurements of MDA/TEAC serum levels.

### 2.2. Procedures

All patients with TLE-MTS underwent 2–6 days of continuous video-electroencephalographic (VEEG) monitoring with 32-channel EEG recording, with electrodes placed according to 10–10 system on the temporal lobe, including sphenoidal electrodes. The MTS was defined if atrophy, an increased T2-weighted signal, a decreased T1-weighted signal, and disrupted internal structure of the hippocampus were present accompanied by atrophy of the amygdala and/or temporal pole signal alteration on visual inspection of MRI pictures. The epileptogenic zone was determined by predominantly ipsilateral interictal epileptiform discharges (80% cutoff) and seizure onset recorded during prolonged VEEG monitoring. The association between MTS side and the frequency of interictal epileptiform discharges on VEEG was also analyzed, and a cutoff of >80% was considered for a predominant ipsilateral activity. Epilepsy was considered resistant to medical treatment when seizures persisted after the utilization of at least two first-line medications for partial seizures at highest tolerated doses. Initial precipitant injury (IPI) was defined as the occurrence of severe cerebral events in the first year of life before the appearance of epilepsy that required medical intervention and/or hospitalization. Febrile seizures, meningo-encephalitis, head trauma, or severe perinatal hypoxia were considered as IPI.

### 2.3. Psychiatric evaluation

A single psychiatrist (GMAF) conducted the clinical interviews through the Diagnostical and Statistical Manual of Mental Disorders (DSM-5) criteria [15]. Since each patient could have had more than one axis I psychiatric diagnosis, the number of patients diagnosed and all comorbid PD diagnosed were both considered. The presence of other specific psychiatric diagnoses of epilepsy not covered by DSM-5 and well-described in literature, such as the interictal dysphoric disorder (IDD) and the psychoses of epilepsy were evaluated using the ILAE criteria, and such criteria were also utilized to differentiate postictal psychosis (PIP) from interictal psychosis (IIP) [16]. Data about lifetime history of psychiatric treatment, defined as any treatment with psychiatric drugs occurred in the past, were collected with patients in the first clinical interview. In addition, information about family history of epilepsy and PD were also obtained from patients through broad questions asking if any first-degree relative was in treatment for epilepsy and/or any PD at the moment of clinical interview.

### 2.4. Biochemical evaluation

To establish the genetic profile of the GSTM1 and GSTT1 variants, the genomic DNA was extracted from whole blood (5 mL), collected with ethylenediamine tetraacetic acid (EDTA), by the salting-out method carried out in three stages, comprising the following: 1) lysis of blood cells; 2) deproteinization; and 3) DNA precipitation and resuspension, followed by polymerase chain reaction (PCR) amplification [17,18]. These polymorphisms do not require enzymatic restriction after PCR, being identified by the presence or absence of alleles. Individuals were classified as having one or two copies of the gene (nonnull genotype), or lacking any copies of the gene (null genotype). The post-PCR product was separated by 1.5% agarose gel electrophoresis under a constant current of 150 V for 45 min, separating fragments with 423 base pairs (bp) (GSTT1), 310 bp (control Cytochrome (CYP)), and 230 bp (GSTM1).

A method based on the reaction of MDA with thiobarbituric acid (TBA), which was detected by means of high performance liquid chromatography coupled to UV-vis/detector (HPLC-UV/VIS) at 535 nm [19,20]. The TEAC was determined according to its equivalence to a known potent antioxidant, TROLOX (6-hydroxy-2,5,7,8-tetramethrotonone-2-carboxylic acid; Aldrich Chemical Co., 23881-3), synthetic analogue of water-soluble vitamin E, according to the method proposed by Miller et al. and modified by Re et al. The absorbance was measured at 734 nm using a Spectrophotometer (T60 Visible) [21,22].

### 2.5. Statistical analyses

Student's *t*-test was applied for quantitative variables with mean and median values and Fisher's exact test or Chi-square test for qualitative variables. The Analysis of Variance (ANOVA) was applied for multiple comparisons, and Bonferroni adjustment for multiple tests was applied as a post hoc test for statistically significant differences. The GSTM1 and GSTT1 polymorphisms were analyzed according to the presence or absence of the independent and associated M1/T1 variants (M1/\_, T1/\_, M1/T1, and \_/\_). A multivariate analysis through a logistic regression model was performed to identify possible clinical and sociodemographic predictors of higher levels of MDA and TEAC. Variables included in the initial model were gender, age, presence and type of IPI, lifetime history of psychiatric treatment, family history of epilepsy and PD, presence and type of PD, epilepsy duration, age at epilepsy onset, number and types of antiepileptic drug (AED), and laterality of MTS. The Kolmogorov-Smirnov test was applied in order to verify the possibility of normal distribution of residuals, and the Breusch-Pagan test was applied to verify the possibility of homoscedasticity on the model. In addition, analyses of colinearity and multicollinearity matrices between variables were performed. The odds ratio (OR) and  $\beta$  coefficient were calculated for risk factors. The

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