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Research report

Oxidative stress in status epilepticus: A clinical-radiological correlation

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HIGHLIGHTS

- The patients with status epilepticus had reduced antioxidants and increased reactive oxygen and nitrogen species.
- Oxidative stress was higher in the patients with comorbidity.
- Glutathione negatively and malondialdehyde and nitric oxide positively correlated with age.
- Oxidative stress however did not determine in-hospital death and disability at discharge.

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ABSTRACT

Purpose: To report oxidative stress in the patients with status epilepticus (SE), and correlate these with severity, MRI and outcome.

Methods: Thirty-five patients with SE and 34 controls were included. Blood sample was collected at admission for measuring superoxide dismutase (SOD), catalase, protein carbonyl, glutathione, total antioxidant capacity (TAC), malondialdehyde (MDA) and nitric oxide (NO). The type of SE, duration and Status Epilepticus Severity Score (STESS) at admission and refractoriness to treatment were noted. Cranial magnetic resonance imaging (MRI) findings, in-hospital deaths and disability at discharge were noted.

Results: The median age of the patients was 35 and 14 were females. The median STESS was 3 (0–5), and the score was unfavorable in 21(60%) patients. MRI was abnormal in 27(77%) patients. The patients with SE had significantly lower concentrations of SOD, catalase, protein carbonyl, GSH and TAC and higher concentrations of MDA and NO compared to the controls. These levels did not differ between refractory and non-refractory SE. Glutathione level inversely correlated with age. Malondialdehyde and NO levels positively correlated with age and inversely with GSH level. Five (14.3%) patients died in hospital. At discharge, 14 patients had good and 16 had poor outcome. The oxidative stress markers did not correlate with death or disability.

Conclusion: Oxidative stress is increased in the patients with SE. Further study is needed in larger sample size to explore probable adjunctive treatment option.

1. Introduction

Status epilepticus (SE) is a life threatening condition with an overall mortality ranging from 15% to 22% in adults and 3% to 5% in children (Amare et al., 2008). The annual incidence of SE is 10–61/100,000 which is likely to be higher in developing countries because of prevalent infections, infestations, stroke and head injury (Kalita et al., 2010). The underlying etiology, duration of SE before treatment and refractoriness are the important predictors of outcome (Amare et al., 2008). Excessive neuronal excitation and firing may result in oxidative stress which may not be cleared by endogenous antioxidant defense mechanisms. Reactive oxygen species (ROS) and reactive nitrogen species (NOS) have both beneficial and harmful effects. The beneficial effects of ROS are supplemented by various enzymatic and non-enzymatic antioxidants. Antioxidants are capable of delaying or preventing oxidation of substrate (Martinc et al., 2012; Cardenas-Rodriguez et al., 2013). Antioxidants may be of high or low molecular weight; high molecular weight antioxidants are superoxide dismutase (SOD), catalase, glutathione peroxidase, glutathione reductase and thioredoxin reductase; whereas low molecular weight antioxidants may be lipophilic (vitamin A, vitamin E, bilirubin) or hydrophilic (glutathione, vitamin C and uric acid) (Cardenas-Rodriguez et al., 2013). Glutathione (GSH) is a robust water soluble antioxidant found in most of the cells, and total antioxidant capacity (TAC) measures the antioxidant status (Shin et al., 2011). Malondialdehyde (MDA) is the end product of lipid peroxidation and indicates the status of reactive oxygen species (ROS)

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(Shin et al., 2011). A number of experimental and human studies have shown increased oxidative stress in epilepsy (Dalton et al., 1995; Ziegler et al., 2003; Aguiar et al., 2012). Similarly studies have also shown increased oxidative stress following antiepileptic drugs such as phenytoin, carbamazepine, oxcarbazepine, phenobarbitone, sodium valproate, lamotrigine, levetiracetam and zonisamide (Martinic et al., 2012). In animal experiment of SE, reduction of various enzymatic and non-enzymatic antioxidants has been reported (Martinic et al., 2012; Mahle and Dasgupta, 1997). There is paucity of studies evaluating role of oxidative stress in the patients with SE. In the patients with epilepsy, oxidative stress has been associated with teratogenicity of fetus (Meador et al., 2007). In SE, oxidative stress may be associated with underlying etiology, refractoriness of SE and may determine death and disability. In this communication, we report the status of antioxidants (catalase, SOD, protein carbonyl, GSH, TAC) and markers of reactive oxygen (MDA) and nitrogen species (nitric oxide) in SE patients, and evaluate their role in determining severity and outcome.

2. Results

Thirty-five patients with SE were included whose median age was 35 years and 14 were females. Sixteen patients had comorbidities; 10 were hypertensive, 4 diabetic and 5 had coronary artery disease. Fourteen patients received amlodipine and telmisartan, five atenolol, five aspirin, seven atorvastatin, one glimipride and three received insulin.

Twenty patients (57.2%) had generalized convulsive SE and 15 (42.8%) had focal with bilateral convulsive SE. Majority [31 (88.5%)] of patients had new onset SE and four (11.4%) was due to antiepileptic drug (AED) default. The antiepileptic drugs in these four patients with drug default SE included carbamazepine and clobazam in two, phenytoin in one, and levetiracetam and clobazam in one. The underlying etiology was central nervous system infections in seven (20%) and stroke in 14(40%) patients. Median Status Epilepticus Severity Score (STESS) was three (0–5), which was unfavorable (STESS 3–5) in 21(60%) patients. Focal motor deficit was present in 12 (34.2%); hemiplegia in eight (22.8%) and quadriplegia in four (11.4%) patients. Tendon reflexes were brisk in 18 (51.4%), normal in 13 (37.1%) and reduced in four (11.4%) patients. Cranial MRI was done in 34 patients and was abnormal in 27 (77%). The MRI abnormalities were located in the frontotemporal cortex in 11 (31.4%), parietal in five (14.3%), occipital in two (5.7%), subcortical white matter in four (11.4%) and in basal ganglia and thalamus in seven (20%) patients. Electroencephalography was done after cessation of convulsive SE and revealed theta to delta slowing in 20, focal slowing in five, periodic lateralizing epileptiform discharges in three and occasional discrete epileptiform discharges in 10 patients.

2.1. Treatment response

24 patients responded either to lorazepam (LOR) or one more second line AED, and 14 had refractory SE.

2.2. Oxidative stress markers

The patients with SE had lower level of catalase ($P = 0.002$), SOD ($P < 0.001$), protein carbonyl ($P < 0.001$), TAC ($P < 0.001$) and GSH ($P < 0.001$) compared to the controls. The MDA ($P = 0.003$) and NO ($P < 0.001$) levels in the SE patients were higher compared to the controls (Table 1). These levels however were not different between refractory and non-refractory SE (Fig. 1). The details of clinical parameters between refractory and non-refractory SE are presented in table 2. The patients with comorbidities had lower level of catalase ($P = 0.047$), GSH ($P = 0.02$) and TAC ($P = 0.004$), and higher level of MDA ($P = 0.01$) and NO ($P = 0.02$) compared to those without comorbidities (Fig. 2). Glutathione level correlated with age ($r = -0.52$), pretreatment SE duration ($r = -0.66$) and total duration of SE ($r = -0.48$). After removal an outlier data, GSH did not correlate with both pretreatment and total duration of SE. TAC did not correlate with any of the demographic and clinical parameters. Nitric oxide correlated with age ($r = 0.33$) but SOD and catalase did not correlate with age, duration of SE and STESS, Malondialdehyde level correlated with age ($r = 0.90$), catalase ($R = -0.43$), SOD ($r = -0.47$) and GSH ($r = -0.72$). The age of the patients however did not correlate with pretreatment duration of SE ($r = 0.12$) and total duration of SE ($r = -0.003$). The concentration of antioxidants and oxidative stress markers in the patients with abnormal MRI was not significantly different from those with normal MRI. The details of the correlation of biomarkers with clinical variables are presented in Table 3 and the significant variables are shown in Fig. 3.

Table 1
Comparison of demographic and oxidative stress markers in patients with status epilepticus and controls.

Parameters	Patients	Controls	P-value
Age (years)	35 (1–80)	34.50 (10–75)	0.91
Gender (Male/Female)	21/14	20/14	1.00
SOD U/ml	1.68 (0.69–2.90)	3.54 (2.48–4.70)	< 0.001
Catalase U/ml	28.03 (13.90–64.69)	41.91 (34.92–53.93)	0.002
Protein carbonyl nmol/ml	17.39 (10.04–20.00)	10.78 (6.92–16.92)	< 0.001
TAC nmol Trolox eq/l	0.24 (0.12–0.75)	0.94 (0.77–1.22)	< 0.001
GSH mg/dl	0.70 (0.14–0.82)	0.94 (0.82–1.16)	< 0.001
NO µmol/L	57.38 (9.65–207.29)	14.76 (2.80–63.41).	< 0.001
MDA nmol/L	2.05 (0.84–3.36)	1.47 (0.58–2.26)	0.003

Values are expressed in median (range); GSH = glutathione, MDA = malondialdehyde, NO = nitric oxide, SOD = superoxide dismutase, TAC = total antioxidant capacity.

2.3. Outcome

Five patients died in the hospital and 30 were discharged. At discharge, 14 patients had good (mRS 0–3) and 16 had poor (mRS 4–5) recovery. The SOD, catalase, protein carbonyl, GSH, TAC. NO and MDA levels, however, did not have correlation with death or disability at discharge (Figs. 4 and 5).

3. Subjects and methods

Consecutive patients with SE admitted during 2015–2016 were included. The diagnosis of convulsive SE was made if the seizure continued for more than 5 min or having recurrent seizures without regaining consciousness in between (Trinka et al., 2015). Nonconvulsive SE was diagnosed in patients with altered sensorium with or without subtle movement for 30mins and EEG showing epileptiform discharges (Trinka et al., 2015). Epilepsia partialis continua were defined as a condition of continuously repeated epileptic seizures lasting for one hour with preserved consciousness (Mameniskiene et al., 2001).

Status Epilepticus Severity Score was used to assess the severity of SE, which was computed on the basis of level of consciousness (stupor or coma = 1, alert = 0), seizure type (generalized = 1, non-convulsive = 2, others = 0), age (< 65 y = 0, ≥ 65 y = 1), and history of previous seizure (present = 0, absent or unknown = 1). The total score ranged between 0 and 6; the best score was 0 and the worst score was 6. STESS was considered favorable if the total score was ≤ 2 or unfavorable if more than > 2 (Rossetti et al., 2008).

3.1. Exclusion criteria

Pregnant women and patients with kidney or hepatic failure, malignancy, immunosuppressive therapy, corticosteroid, anti-inflammatory and autoimmune disease were excluded.