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Research paper

Malondialdehyde: A novel predictive biomarker for post-stroke depression

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ABSTRACT

Background: There is evidence that stroke is accompanied by oxidative stress. However, the links between oxidative stress and depression in stroke patients are poorly understood. This study examines whether post-stroke depression (PSD) is associated with oxidative stress.

Methods: Overall, 216 acute stroke patients were consecutively recruited and followed up for 1 month. Blood specimens were collected within 24 h after admission and measured for the following oxidative stress biomarkers: malondialdehyde (MDA), superoxide dismutase (SOD) and glutathione peroxidase (GSH-PX). All enrolled patients were divided into the PSD group or the non-PSD group according to an assessment of clinical depression. One hundred normal control subjects were also recruited.

Results: There was a positive correlation between serum MDA levels and HAMD scores in stroke patients ($r = 0.536$, $p < 0.001$). Based on the Receiver-operating characteristic (ROC) curve, the optimal cutoff value of serum MDA levels as an indicator for an auxiliary diagnosis of PSD was projected to be 2.898 nmol/ml, which yielded a sensitivity of 77.9% and a specificity of 81.1%, with an area under the curve of 0.883 (95% CI, 0.836–0.929). Elevated MDA (≥ 2.898 nmol/ml) was an independent predictive marker of PSD (odds ratio OR = 24.295; 95% CI, 9.461–62.388; $p < 0.001$, adjusted for relevant confounders).

Limitations: We excluded patients with severe aphasia or with serious conditions. In addition, the information for dietary intake was not recorded, which may influence oxidative stress levels.

Conclusion: Our study demonstrated that an elevated serum MDA level at admission was positively associated with an increased risk of developing depression after acute stroke, especially minor stroke.

1. Introduction

Post-stroke depression (PSD) is the most common neuropsychiatric complication after stroke (Hackett et al., 2014) and may lead to poor functional outcome (Maaijwee et al., 2016) and higher mortality (Ellis et al., 2010). Depression occurs frequently in patients after stroke, with its prevalence ranging from 29% to 35% (Ayerbe et al., 2013; Hackett and Pickles, 2014).

Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) categorizes post-stroke depression as depressive disorder due to stroke. PSD occurs subsequent to stroke, and PSD is related to various kinds of factors associated with stroke, such as biological, psychosocial and social factors. Thus, patients with a previous history of depression must be excluded before making a diagnosis of PSD. Moreover, a patient with a diagnosis of PSD must have core symptoms of depression lasting 2 weeks or longer. PSD had been widely documented to be related to several biological factors of stroke, such as lesion location (Rajashekaran et al., 2013), stroke severity (Robinson and Spalletta, 2010) and stroke type (De Ryck et al., 2014). The pathophysiology of PSD is complex and in need of clarification; however, research into the biochemical changes in PSD is still not systematized and is lacking in both quality and quantity.

Stroke is accompanied by increased formation of free radicals (Galecki et al., 2007), leading to lipid peroxidation, protein oxidation, DNA damage and harmful autoimmune responses in neural tissue (Leonard and Maes, 2012). Oxidative stress is implicated in the pathogenesis of stroke by up-regulating the p53 signaling pathway (Niizuma et al., 2009), which may lead to neuronal death. The oxidative stress pathway can produce excitatory and oxidative neurotoxicity, but neurons are also protected from oxidative damage, and excitatory neurotoxicity is attenuated via antioxidants, such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-PX) (Lushchak, 2014).

Abbreviations: PSD, post-stroke depression; MDA, malondialdehyde; SOD, superoxide dismutase; GSH-PX, glutathione peroxidase; MDD, major depressive disorder; BMI, body mass index; CAD, coronary artery disease; NIHSS, National Institutes of Health Stroke Scale; BI, modified Barthel Index; MMSE, mini mental state examination; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation; IQR, interquartile range; ROC, Receiver-operating characteristic

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These endogenous enzymes can be assisted by exogenous compounds, such as carotenoids and vitamin E and C from dietary sources (Sies and Stahl, 1995). SOD and GSH-PX can tightly regulate free radicals by scavenging or binding free radicals or forming less reactive complexes. SOD can neutralize superoxide (O2-), one of the most important initiating radicals in the process of oxidative stress generation (Halliwell, 1996). The disruption of balance etween oxidant and antioxidant factors can inflict extensive damage. The brain is extremely sensitive to oxidative damage compared to other body tissues due to the relatively rich concentration of iron and large generation of hydrogen peroxide (Shichiri, 2014). Previous studies have demonstrated that elevated oxidative damage and decreased antioxidant status in stroke patients was indicative of a poor prognosis (Hsieh et al., 2014; Milanlioglu et al., 2016) and an increased risk of mortality (Lorente et al., 2016).

Several lines of evidence indicate that free radicals may be involved in the pathophysiology of depression (Leonard and Maes, 2012; Moylan et al., 2013). Abnormalities in the levels of SOD and GSH-PX were confirmed in depressed patients, which provides indirect evidence for a role of free radicals in depression. Recently, malondialdehyde (MDA), which is a major endogenous product of lipid peroxidation, was found to be elevated in patients diagnosed with major depression (Rybka et al., 2013). Stefanescu et al. observed that the MDA concentrations were even greater in patients suffering from a recurrent episode of depression (Stefanescu and Ciobica, 2012). Elevated levels of MDA were also identified in depressed patients with physical ailments, such as chronic heart failure (Michalakeas et al., 2011) and newly diagnosed gastric adenocarcinoma (Wei et al., 2009).

Although oxidative parameters have been extensively investigated in major depressive disorder to make an inference for neurobiology, few studies have explored the role of oxidative stress in PSD. A recent study has reported that the oxidative damage of proteins is correlated with the degree of PSD (Cichon et al., 2015). However, to date, there is no study detecting the serum levels of SOD, GSH-PX and MDA in PSD. Therefore, the purposes of the study were to investigate (1) whether serum MDA, SOD and GSH-PX were altered in PSD patients and (2) whether there was a relationship between altered MDA, SOD and GSH-PX and the development of PSD.

2. Methods

2.1. Study population

First-ever or recurrent acute stroke patients who were hospitalized in the First Affiliated Hospital of Wenzhou Medical University's Stroke Unit during the period from October 2013 to September 2014 were consecutively screened for study entry. Almost none of the enrolled patients took antidepressants or other medications to treat depression during hospitalization or after hospital discharge because of the short duration of symptoms, the possible interference of somatic symptoms related to hospitalization and the mild degrees of depressive symptoms. Additionally, few patients took vitamins for treatment during the acute phase of stroke during hospitalization.

Written informed consent was obtained from all patients or their relatives, and this study conformed to the principles of the Declaration of Helsinki and was approved by the Medical Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University.

Inclusion criteria included the following: (1) age 18–80 years; (2) admitted to the hospital within 7 days of stroke onset; (3) stroke verified by computed tomography (CT) or magnetic resonance imaging (MRI) reports performed within 24 h of admission; and (4) the ability and willingness to provide informed consent. Exclusion criteria included the following: 1) a previous history of depression (clinical diagnosis or previous treatment) or a family history of depression (via standardized questionnaires) or other psychiatric disorders; 2) severe aphasia or dysarthria; 3) significant acute medical illness (e.g., infection, autoimmune disease, tumor, heart failure) and significant acute neurological illness other than stroke; 4) traumatic procedure, such as DSA, CTP, stenting, kinds of tubes; 5) the use of psychotropic drugs prior to stroke onset; and 6) patients who failed to have serum GSH-PX, SOD and MDA measured at admission.

One hundred normal controls with a similar age and gender distribution to the acute stroke patients were enrolled at the First Affiliated Hospital of Wenzhou Medical University during physical check-ups, and they were free of severe physical diseases, such as acute stroke, any personal or familial history of psychiatric illness and the conditions mentioned in the exclusion criteria.

2.2. Assessment

At baseline, demographic data (age and sex), lifestyle characteristics (e.g., smoking status, alcohol intake), level of education, a family history of psychiatric disorders, and drug treatment, body mass index (BMI) and a history of conventional vascular risk factors were obtained from standardized questionnaires, which were given in face-to-face interviews by trained physicians.

Stroke subtype was classified according to TOAST criteria (Adams et al., 1993). Stroke severity was evaluated by using the National Institutes of Health and Stroke Scale (NIHSS) at admission (Brott et al., 1989). Cognitive impairment was assessed by the Mini-Mental State Examination (MMSE) (Folstein et al., 1983) 1 month after admission. Functional outcome was evaluated by the Barthel Activities of Daily Living Index (BI) (Mahoney and Barthel, 1965) at discharge. Sleep quality of the patients was evaluated using the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) at discharge and PSQI score ≥ 6 points were diagnosed as insomnia. All of the scales were measured by trained physicians who were blind to the patients' laboratory results.

2.3. Diagnosis of PSD

The assessments of clinical depression were performed by trained psychiatrists who were blind to the laboratory results of stroke patients at the 1-month follow-up. The 17-item HAMD (HAD-17) (Muller and Dragicevic, 2003) was used to screen for depressive symptoms in all stroke survivors in this study. Patients with a HAMD-17 score (≥ 7), which was indicative of possible depressive symptoms, were further interviewed by using the Structured Clinical Interview for DSM-IV (SCID-I) (Lobbestael et al., 2011). Patients who met the DSM-IV diagnostic criteria for depressive disorder due to stroke were considered PSD in our study. Depressive symptom severity was classified by the following severity range for the HAMD: mild depression (7–17), moderate depression (18–24) and severe depression (> 24) (Zimmerman et al., 2013).

2.4. Laboratory test

Peripheral blood samples were obtained and were collected within 24 h of admission. A laboratory technician blinded to all clinical data processed all the samples. Serum MDA levels were measured spectrophotometrically at 532 nm. The assay detection limit was 0.5 nmol/ml. The inter- and intra-assay coefficient of variation (CV) was 4.11% and 3.5%, respectively. The serum MDA levels were expressed in nmol/ml.

Serum SOD was examined by an enzyme-linked immunosorbent assay (ELISA) kit. The assay detection limit of SOD was 3 U/ml. The intra- and inter-assay CV were 9% and 15%, respectively. The results of serum SOD were expressed as U/ml.

Serum GSH-PX was also examined by using an ELISA kit. The assay detection limit of GSH-PX was 6 pg/ml. The intra-assay and inter-assay CV were 9% and 11%, respectively. The results of serum GSH-PX were expressed as pg/ml.

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