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Predictors of oedema type in reversible posterior leukoencephalopathy syndrome with preeclampsia or eclampsia

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ABSTRACT

Objective: To explore the predictive factors of oedema types in reversible posterior leukoencephalopathy syndrome (RPLS) with preeclampsia (PE) and eclampsia, which is closely related to reversible lesions and clinical recovery. *Method:* We collected data from 44 consecutive patients diagnosed with RPLS in PE or eclampsia between 2013 and 2017. All patients were classified into vasogenic oedema (n = 31) or cytotoxic oedema (n = 13) groups according to magnetic resonance imaging (MRI) results. General information, clinical data, biochemical indicators and imaging features were collected retrospectively to explore the differences between the groups. Furthermore, we analysed potential predictive factors by logistic regression. *Results:* The occurrence rates of immune disease and stillbirth, hospitalization time and the levels of serum albumin (ALB), lactate dehydrogenase (LDH), aspartate transaminase (AST) and alanine aminotransferase (ALT) were higher, while the values of systolic blood pressure (SBP), mean arterial pressure (MAP) and 24-h urine protein were lower in the cytotoxic oedema patients than those in the vasogenic oedema patients ($p < .05$). The ALB concentration was closely correlated with vasogenic oedema, while AST and ALT were closely correlated with cytotoxic oedema by logistic regression ($p < .05$). *Conclusion:* The levels of ALB, AST and ALT are potential predictors for the development of oedema in RPLS. ALB is related to vasogenic oedema by a possible mechanism of decreased colloid osmotic pressure, while AST and ALT are related to cytotoxic oedema by a possible mechanism of endothelial dysfunction.

1. Introduction

Reversible posterior leukoencephalopathy syndrome (RPLS) is identified by clinical imaging and was first described by Hinchey [1] in 1996 as a combination of symptoms, such as headaches, visual changes, seizures, consciousness impairment, mental disorders, and focal neurological deficits. Typically, RPLS is reversible for most patients by clinical and imaging standards [1]. Nevertheless, RPLS is a critical maternal complication in preeclampsia (PE) or eclampsia during pregnancy that could endanger maternal and foetal safety. Magnetic resonance imaging (MRI) is the gold standard for the diagnosis and evaluation of RPLS [2]. A typical feature is involvement of the posterior cerebral circulation (bilateral and symmetrical cerebral oedema in the subcortical white matter), which indicates vasogenic oedema; however, a small proportion of patients show cytotoxic oedema. To the best of our knowledge, untreated vasogenic oedema progresses to cytotoxic oedema. Additionally, cytotoxic oedema may be related to irreversible lesions or clinical symptoms [3], so early detection of cytotoxic oedema is critical and may prevent vasogenic oedema from progressing to irreversible cytotoxic oedema [4].

The cause of progression from vasogenic oedema in RPLS into cytotoxic oedema and the differences between these oedema types remain unknown. In addition, previous findings regarding the differences between vasogenic oedema and cytotoxic oedema, such as serum albumin (ALB) and lactate dehydrogenase (LDH) levels, are confusing or even conflicting [4–7]. The type of oedema in RPLS can be distinguished by

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diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps. In this retrospective study, we collected general information, clinical data, biochemical indicators and imaging features to explore the differences between patients with vasogenic oedema and cytotoxic oedema in RPLS. Furthermore, we analysed the predictive factors of oedema type by logistic regression.

2. Materials and methods

This retrospective study was approved by the institutional ethics committee of the Third Affiliated Hospital of Guangzhou Medical University. A total of 44 women met the inclusion criteria of a) patients who were diagnosed with PE or eclampsia after 20 weeks of gestation or within 6 weeks postpartum, b) patients who underwent MRI examination including at least DWI and ADC after providing informed consent, and c) patients with complete data who were diagnosed with RPLS at Guangzhou Medical Center for Critical Pregnant Women from January 2013 to January 2017. General information, blood pressure (BP), biochemical indicators, clinical symptoms and imaging features were collected retrospectively.

PE was defined as complications of hypertension, proteinuria, and oedema between the 20th week of gestation and the sixth postpartum week. Eclampsia was defined as PE plus seizures unrelated to other cerebral conditions [8,9]. HELLP was defined as haemolysis (LDH level > 600 IU/l), elevated liver enzymes (aspartate transaminase [AST] and/or alanine aminotransferase [ALT] level > 70 IU/l), and low platelets (platelet count < 100×10^9/l) at a gestational length of less than 30 weeks [10].

All 44 patients were examined via whole-brain MRI (Achieva 3.0T, Philips, Amsterdam, the Netherlands), including T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), T2 fluid-attenuated inversion recovery (FLAIR), DWI and ADC sequencing methods. The imaging features were described by their location including frontal, parietal, occipital, temporal, cerebellum, basal ganglia, brain stem, deep white matter and callosum, and 1 point was recorded for each location involved. The extent and severity of vasogenic oedema in the lesion area were graded on a scale of 0–5 by evaluating the FLAIR images [11] (0, normal; 1, limited cortical or subcortical white matter oedema; 2, white matter oedema > cortical oedema, white matter oedema extending into deep white matter; 3, white matter oedema > cortex oedema, oedema extending to the ventricular surface; 4, the involved regions substantially extend to the ventricular surface and are almost completely confluent; 5, involved regions are fully confluent and continuous, ventricular deformity due to the oedema). Vasogenic oedema was defined as a lesion with hyperintensity on FLAIR and ADC maps and hypointensity on DWI sequencing. Cytotoxic oedema was defined as a lesion with hyperintensity on DWI and hypointensity or isointensity on ADC maps. MRI was performed within 3 days of the onset of clinical symptoms or signs. MRI diagnosis and confirmation were evaluated by two neuroradiologists independently, and the neuroradiologists then tried to reach a consensus.

In this study, the diagnosis of RPLS was determined based on a combination of clinical symptoms (headache, vision changes, seizures, consciousness disorders or hypertension) and standard radiological criteria (hyperintensity on T2WI and FLAIR in the subcortex and gyrus as focal vasogenic oedema). Regular prenatal examination was defined as examination times that were consistent in terms of the time interval (i.e., for gestation less than 28 weeks, 4-week interval; for 28–36 weeks of gestation, 2-week interval; for 36–40 weeks of gestation, 1-week interval; for gestation more than 40 weeks, 3-day interval).

The BP of PE patients was obtained immediately at the onset of symptoms, and the BP of eclampsia patients was obtained immediately at the onset of seizure. The mean arterial pressure (MAP) was defined as 2/3 diastolic blood pressure (DBP) + 1/3 systolic blood pressure (SBP).

Biochemical indicators, including ALB, serum creatinine (Crea), urea (UA), blood urea nitrogen (BUN), LDH, C reactive protein (CRP), white blood cell (WBC) count, 24-h urine protein, AST and ALT, were collected during hospitalization.

All patients underwent primary disease treatment, BP management, magnesium sulfate antispasmodic administration and other measures, which were performed by experienced obstetricians. The delivery mode was decided by the obstetrician. The indicators for pregnancy outcomes included gestational weeks, delivery mode, hospitalization time, neurological sequelae and death. The variables for neonatal outcomes included stillbirth, premature delivery and Apgar scores.

3. Statistical analyses

Descriptive statistics for continuous variables are presented as the mean ± standard deviation, and categorical variables are presented as frequencies and percentages. We used Student's t tests (normally distributed variables) or Z tests (not normally distributed variables) for the continuous variables and chi-square tests or Fisher's exact tests for the categorized variables to examine the two groups of patients. Logistic regression was used for predictive factor analysis. The threshold for statistical significance was set at $p < .05$. We analysed our data using the SPSS 13.0 statistical software package (SPSS Inc., Chicago, IL, USA).

4. Results

A total of 44 patients met the inclusion criteria and were divided into two groups: 31 patients were included in the vasogenic oedema group, and 13 were included in the cytotoxic oedema group based on the analyses of DWI, ADC maps and FLAIR MRI. General information and BP data are presented in Table 1. The vasogenic oedema group included 22 (70.97%) women with preeclampsia and 9 (29.03%) women with eclampsia; the mean age of the group was 30.35 ± 7.37 years, and the mean body mass index (BMI) was 22.46 ± 3.19 kg/m^2. The cytotoxic oedema group included 9 (69.2%) women with preeclampsia; the mean age of the group was 30.92 ± 6.71 years, and the mean BMI was 21.14 ± 2.36 kg/m^2. A total of 16 (51.61%) primiparous patients were in the vasogenic oedema group and 5 (38.46%) were in the cytotoxic oedema group. The vasogenic oedema patients exhibited a higher rate of immune disease than those in the cytotoxic oedema group ($p = .037$). In addition, SBP ($p = .027$) and MAP ($p = .036$) were increased in vasogenic oedema patients compared with SBP and MAP in the cytotoxic oedema patients. However, no statistically significant differences were noted between the oedema groups in terms of DBP, HELLP syndrome rate, regular prenatal examination rate or gestational weeks ($p > .05$). Longer hospitalization times ($p = .036$) and a higher frequency of stillbirth ($p = .037$) were observed in the cytotoxic oedema group compared to the corresponding values in the cytotoxic oedema group (Table 1).

Clinical symptoms and imaging features are presented in Table 2. In both groups, headache was the most common symptom in RPLS patients (77.42% of vasogenic oedema patients vs. 76.92% of cytotoxic oedema patients), followed by visual changes (54.84% of vasogenic oedema patients vs. 61.54% of cytotoxic oedema patients). The occurrence rates of seizures and consciousness impairment were increased in the patients with cytotoxic oedema compared with the occurrence rates in the patients with vasogenic oedema; however, the differences were not significant between the two groups. In addition, dizziness, nausea and vomiting were common symptoms in both groups, with no significant differences between the two groups. Characteristic changes in imaging features were observed: T1WI of MRI exhibited a slightly low signal, while T2WI and FLAIR produced high signals. In the vasogenic oedema group, lesions showed hypointensity or isointensity on DWI but hyperintensity on ADC maps, while in the cytotoxic oedema group, lesions showed hyperintensity on DWI but hypointensity or isointensity on ADC maps (Fig. 1). In both groups, the occipital lobe was the most frequently affected area (90.32% of vasogenic oedema patients vs. 92.31% of cytotoxic oedema patients), followed by the parietal lobe