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High levels of serum mannose-binding lectins are associated with the severity and clinical outcomes of severe traumatic brain injury

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ABSTRACT

Background: Mannose-binding lectin (MBL) is a key component of innate immunity. The expression of cortical MBL is up-regulated after clinical and experimental head trauma. This study aimed to assess the association of serum MBL levels with injury severity and long-term clinical outcomes after severe traumatic brain injury (STBI).
Methods: Serum MBL levels were measured in 122 patients and 100 healthy controls. Multivariate analyses were used to analyze the relationship between serum MBL levels and trauma severity reflected by Glasgow Coma Scale scores as well as between serum MBL levels and 6-month mortality and unfavorable outcome (Glasgow Outcome Scale score: 1–3). A receiver operating characteristic (ROC) curve was structured to evaluate the prognostic predictive performance of serum MBL levels.
Results: Compared with healthy controls, serum MBL levels of patients were markedly elevated. Using multivariate analyses, serum MBL levels were found to be associated closely with Glasgow Coma Scale (GCS) scores and MBL emerged as an independent predictor for 6-month mortality and unfavorable outcome. Under ROC curve, serum MBL levels and GCS scores possessed similar prognostic predictive values.
Conclusion: Increased serum level of MBL was independently associated with head trauma severity and long-term clinical outcomes of STBI.

1. Introduction

Severe traumatic brain injury (STBI) is known to be one of the major causes of mortality worldwide and the leading cause of long-term disability as well [1]. The complement system is a major component of the innate immune system [2]. After complement system activation, the sequential production of complement products increases cell injury and death through opsonophagocytosis, cytolysis and inflammatory cell responses [3,4]. Various studies have revealed the wide ranging involvement of complement system in the secondary injury after STB, highlighting the potential for complement-targeted therapeutics to alleviate the devastating consequences of STBI [5,6].

Complement mannose-binding lectin (MBL), a member of the collectin subfamily of C-type lectins, is a key component of innate immunity and activates the complement and promotes opsonophagocytosis [7]. The deficiency of MBL due to several common gene polymorphisms significantly enhances the risk of severe infections, particularly in the neonatal age and in childhood [8]. On the contrary, some studies conclude on the protective role of low levels of MBL toward some diseases [9–11]. To our best knowledge, in the central nervous system, except an experimental study showing that MBL gene deficiency increases susceptibility to TBI in mice [12], other studies have demonstrated that low levels of MBL expressions exert the neuroprotective effects in experiment TBI and ischemic stroke [13–16]. Recently, it is verified that the expression of cortical MBL is up-regulated after clinical and experimental traumatic brain injury [13]. Some data have shown that high circulating MBL levels are associated with the risk, disease severity and poor clinical outcomes of ischemic stroke [17,18]. However, at present there is a paucity of data available on the change of circulating MBL levels after STBI.

2. Methods

2.1. Participants

This prospective, observatory study continuously enrolled the patients with isolated head trauma and postresuscitation Glasgow Coma Scale (GCS) score of 8 or less, who were hospitalized within 6 h since trauma at the People's Hospital of Beilun District during the period from May 2011 to June 2014. Isolated head trauma was defined as head computed tomography scan-confirmed brain injury without other major extracranial injuries, such as pelvis or femur fractures, or severe abdominal or thoracic invasive injuries, as indicated by an

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extracranial abbreviated injury scale score of <3. The current study had excluded the patients with infectious diseases, immunological diseases, use of immunosuppressant, fever within recent 1 month before head trauma, an elevated white blood cell count, positive chest X-ray, <18 y, previous severe head trauma, neurological disease including ischemic or hemorrhagic stroke, use of anti-platelet or anticoagulant medication and presence of other prior systemic diseases including diabetes mellitus, hypertension, uremia, liver cirrhosis, malignancy and chronic heart or lung disease. The control group consisted of healthy volunteers who came to our hospital for healthy examination during the period from June 2013 to June 2014. The study followed the tenets of the Declaration of Helsinki and was approved by the institutional review board of the People's Hospital of Beilun District. The participants or relatives provided written informed consent in advance and potential risks were fully explained.

2.2. Clinical and radiological assessments

The recorded information included age, sex, blood pressure, time from trauma to admission, and papillary reactivity. Trauma severity was assessed using postresuscitation GCS scores. Brain lesions were classified according to the Marshall computed tomography criteria [19]. Abnormal cisterns, midline shift at >5 mm and subarachnoid hemorrhage were also recorded after computerized tomography scans. Radiological procedures were completed according to the neuroradiology department protocol. The investigative group comprised a neurosurgeon and a radiologist and they were blinded to clinical information.

2.3. Clinical outcome evaluation

The clinical endpoints for this analysis were mortality and unfavorable outcome within 6 months after admission. The functional outcome was defined by Glasgow Outcome Scale score. Glasgow Outcome Scale was defined as follows: 1 = death; 2 = persistent vegetative state; 3 = severe disability; 4 = moderate disability; and 5 = good recovery [20]. Unfavorable outcome was defined as Glasgow Outcome Scale scores of 1–3. For follow-up, structure telephone interviews were performed by a doctor who was blinded to clinical information.

2.4. Assay

Venous blood was drawn with minimal stasis through an antecubital vein from patients on admission and from healthy controls at study entry. Clotted blood was centrifuged within 30 min and serum stored at −70 °C until assayed. Microwells coated with europium-labeled anti-MBL antibody were incubated with dilutions of patient serum and europium was quantified with time-resolved immune-fluorometric assay (Baoman Biological Technology Co., Ltd) as described previously [21]. Samples were all processed in duplicate by the same laboratory technician using the same equipment and blinded to all clinical data.

2.5. Statistical analysis

The results were reported as counts (percentage) for the categorical variables, mean ± SD if normally distributed and median (interquartile range) if not normally distributed for the continuous variables. Univariate data were compared by Student's *t* test or Mann–Whitney U-test for the continuous variables and by χ^2 test or Fisher exact test for the categorical variables as appropriate. Correlations were assessed by Spearman correlation coefficient or Pearson correlation coefficient as appropriate. A multivariate linear regression was used further to verify their associations. A multiple binomial logistic regression analysis was performed to identify the association between serum MBL levels and clinical endpoints and the results were reported as odds ratios (ORs) and 95% confidence intervals (CIs). A receiver operating characteristic (ROC) curve analysis was carried out to test the predictive performance of MBL and area under the curve (AUC) and 95% CI were calculated. Intergroup comparisons of AUCs were performed using the Z test. All statistical analyses were performed with SPSS for Windows, ver 20.0. Statistical significance was defined as $P < 0.05$.

3. Results

3.1. The subject characteristics

During the study period, 158 patients were initially evaluated and 36 patients were excluded because of the reasons listed in Fig. 1. 122 patients were finally included in this study. In addition, 100 healthy controls were recruited in this study. The patients, consisting of 69 men and 53 women, had a mean age of 42.7 ± 17.8 y. The healthy controls, composed of 60 men and 40 women, had a mean age of 40.8 ± 16.1 y. There were not statistically significant differences in gender and age.

Among the patients with median initial postresuscitation GCS score of 5 (3), 58 patients (47.5%) had unreactive pupils on admission; 60 patients (49.2%), CT classification 5 or 6; 56 patients (45.9%), abnormal cisterns on initial CT scan; 64 patients (52.5%), midline shift >5 mm on initial CT scan; 68 patients (55.7%), presence of traumatic subarachnoid hemorrhage on initial CT scan; 66 patients (54.1%), and intracranial surgery in 1st 24 h. In terms of mechanism of injury, 69 patients (56.6%) suffered from automobile/motorcycle; 30 patients (24.5%), fall/jump; 23 patients (18.9%), and others. Within 6 months after trauma, 36 patients (29.5%) died from head trauma and 62 patients (50.8%) suffered from unfavorable outcome.

3.2. The change of serum MBL levels

The admission serum MBL levels were significantly elevated in all patients (1.7 ± 0.7 mg/l), compared with healthy controls (0.7 ± 0.3 mg/l, $P < 0.001$). Moreover, the serum MBL levels were obviously higher in non-survivors (2.2 ± 0.7 mg/l) than in survivors (1.4 ± 0.5 mg/l, $P < 0.001$) and in patients with unfavorable outcome (2.0 ± 0.6 mg/l) than in those with favorable outcome (1.3 ± 0.4 mg/l, $P < 0.001$).

3.3. The correlative analysis

Table 1 showed that the serum MBL levels were highly associated with GCS scores, shock on admission, hyperglycemia on admission, blood oxygen saturation on admission, unreactive pupils, computerized

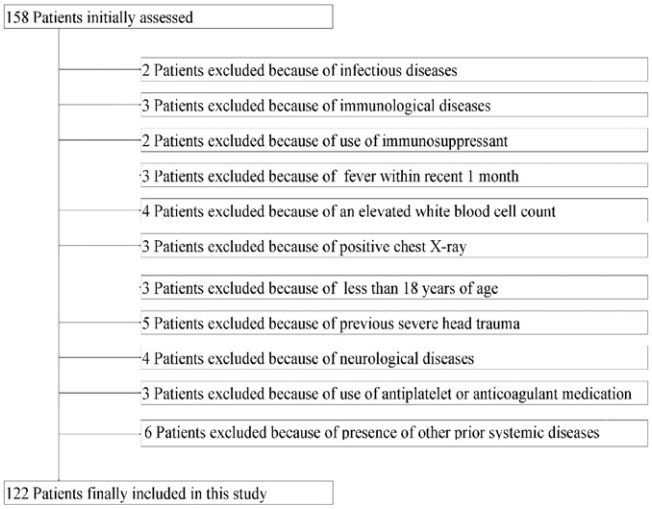

Fig. 1. Excluded and included patients with severe traumatic brain injury.