Clinica Chimica Acta 486 (2018) 214–218

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Increased serum interleukin-33 concentrations predict worse prognosis of aneurysmal subarachnoid hemorrhage

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ARTICLE INFO

Keywords:
Aneurysm
Subarachnoid hemorrhage
Interleukin-33
Inflammation
Prognosis

ABSTRACT

Background: Interleukin-33 (IL-33) is an inflammatory biomarker. We elucidated the relationship between serum IL-33 concentrations, severity and prognosis in aneurysmal subarachnoid hemorrhage (aSAH).

Methods: We prospectively recruited 175 controls and 175 aSAH patients. Serum IL-33 concentrations were gauged using an enzyme-linked immunosorbent assay. Clinical and radiological severity was assessed by World Federation of Neurological Surgeons (WFNS) scale and modified Fisher grading scale respectively. Poor outcome was defined as Glasgow Outcome Scale score of 1–3.

Results: Serum IL-33 concentrations were significantly higher in patients than in controls. IL-33 concentrations were significantly increased with increasing WFNS scores, modified Fisher scores and serum C-reactive protein concentrations. Serum IL-33 emerged as an independent predictor for 6-month mortality and poor outcome. Under receiver operating characteristic curve, the prognostic predictive ability of serum IL-33 was equivalent to those of WFNS scores and modified Fisher scores. Moreover, serum IL-33 significantly improved the prognostic predictive performance of WFNS scores and modified Fisher scores.

Conclusions: High serum IL-33 concentrations have close relation to the inflammation, severity and poor outcome in aSAH, indicating IL-33 might have the potential to be an inflammatory biomarker for assessing severity and reflecting prognosis of aSAH.

1. Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is the most common form of non-traumatic subarachnoid hemorrhage [1–3]. The World Federation of Neurological Surgeons (WFNS) scale and modified Fisher grading scale are often used to assess severity and predict prognosis in aSAH [4–6]. Although pathophysiological mechanisms underlying early brain injury after aSAH are very complex, inflammation has been verified to develop at a sufficiently early stage to participate in early brain injury after aSAH [7–9]. During several decades, inflammatory biomarkers have drawn the clinician's attention for assessing severity and reflecting prognosis of aSAH [10–12].

Interleukin-33 (IL-33) is a newly identified member of the interleukin-1 superfamily [13]. IL-33 has dual functions, acting both as a traditional cytokine through the activation of its receptor complex and as an intracellular nuclear factor with transcriptional regulatory properties [14–16]. A growing body of evidence has shown that IL-33 is involved in the inflammatory process of several human diseases, such as asthma, inflammatory bowel disease and acute myocardial infarction [17–20]. Its expression is up-regulated in rat brain tissue after subarachnoid hemorrhage [21]. Moreover, IL-33 has been fully demonstrated to be implicated in inflammation of central nervous system [22]. Accumulating evidence has indicated that IL-33 exerts a neuroprotective effect on brain injury in animal experiments [23–27]. Notably, it has been found that serum IL-33 concentrations were increased in humans with acute cerebral infarction, and high IL-33 concentrations were positively associated with the infarction volume [28]. Hence, it is postulated that IL-33 might be a prognostic biomarker for acute brain injury. There is a paucity of data available regarding the change of IL-33 concentrations in the peripheral blood from aSAH patients.

2. Methods

2.1. Design and subjects

From April 2013 to September 2016, we performed a prospective, observational study at the Department of Neurosurgery, First Affiliated Hospital, College of Medicine, Zhejiang University. We recruited first-

Abbreviations: `aSAH, aneurysmal subarachnoid hemorrhage; WFNS, World Federation of Neurological Surgeons; IL-33, interleukin-33

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https://doi.org/10.1016/j.cca.2018.08.011
Received 2 August 2018; Received in revised form 8 August 2018; Accepted 9 August 2018
Available online 10 August 2018

ever aSAH patients with single intracranial aneurysm confirmed by computerized tomography angiography with or without digital subtraction angiography. We required that all patients should be admitted within 24 h after hemorrhage onset and undergo clipping or coiling within 48 h after admission. We excluded patients with surgery, trauma or infection within recent a month, previous neurological diseases like intracerebral hemorrhage and ischemic stroke, autoimmune diseases, usage of immunosuppressive drug, prior use of antiplatelet or anticoagulant medication, rebleeding after presentation, suspected pseudoaneurysm, or other prior systemic diseases such as uremia, liver cirrhosis, malignancy, chronic heart disease, chronic lung disease, diabetes mellitus and hypertension. During the period of September 2015 and September 2016, a group of healthy volunteers constituted a control group. This study was approved by the ethical committee at our hospital. And, written informed consent was obtained from each participant or their representative.

2.2. Assessment

WFNS score was recorded to assess clinical severity and modified Fisher score was estimated to evaluate radiological severity of aSAH. Symptomatic cerebral vasospasm was defined as the development of new focal neurological signs, deterioration in concentration of consciousness, or the appearance of new infarction on brain computerized tomography examination when the cause was felt to be ischemia attributable to vasospasm after exclusion of other possible causes of worsening (e.g. hydrocephalus, seizures, metabolic derangement, infection, or over-sedation) [29, 30]. Alternatively, aneurysmal position, aneurysmal shape, aneurysmal size, hydrocephalus and intraventricular hemorrhage were investigated via radiological examination.

Patients were followed up until death or completion of 6 months after hemorrhagic stroke. The Glasgow outcome scale (GOS) is a 5-category scale used for assessing the neurological outcome after brain injury. For statistical analyses, the outcome was further dichotomized in death (GOS 1) versus survival (GOS 2–5) and unfavorable (GOS 1–3) versus favorable (GOS 4–5).

2.3. Assays

Venous blood samples were collected from patients at admission and from controls at study entry. The blood samples were then centrifuged and supernatants of serum were immediately preserved −80 °C until assay. IL-33 concentrations were in duplicates detected using the DuoSet ELISA kit (R&D Systems, USA) following the manufacturer's protocol. Samples were all processed by the same laboratory technician blinded to all clinical data using the same equipment. Serum IL-33 concentration was determined in batches every 3 months.

2.4. Statistical analysis

All data were analyzed with SPSS 19.0 for and MedCalc 9.6.4.0. The normality of data distribution was tested using the Kolmogorovor-Smirnov test or Shapiro-Wilk test. Because of non-normalized distribution of all continuous data, they are reported in the form of medians (interquartile ranges). In addition, categorical variables were reported as number (percentage). Intergroup differences were determined using Mann-Whitney *U* test for continuous variables and chi-square test for categorical variables. Bivariate correlations were assessed using Spearman's correlation coefficient.

The relationship between serum IL-33 concentrations and poor clinical outcome was assessed with a binary logistic regression analysis. The variables, which were revealed to be significant in univariate analysis, were incorporated into the multivariate model. Odds ratio (OR) and 95% CI were calculated. A receiver operating characteristic (ROC) curve was conFig.d to assess the discriminatory ability for patients at risk of poor clinical outcome. Area under curve (AUC) and the corresponding 95% CI values was estimated. We conFig.d a combined logistic-regression model, which was used to investigate the additive benefit of serum IL-33 concentrations to WFNS scores and modified fisher scores. All tests were bilateral. $P < .05$ were considered significant.

3. Results

3.1. Participants characteristics

Initially, a total of 246 aSAH patients were initially evaluated. According to the exclusion criteria, 71 patients were excluded because of the following reasons: surgery, trauma or infection within recent a month (12 cases), previous neurological diseases (10 cases), autoimmune diseases (4 cases), use of immunosuppressive drug, antiplatelet or anticoagulant medication (8 cases), rebleeding after presentation (12 cases), suspected pseudoaneurysm (7 cases), other prior systemic diseases (14 cases), refusal to participation (2 cases) and loss of follow-up (2 cases). Eventually, a total of 175 aSAH patients were assessed. A total of 175 healthy controls, of which, 80 were males and 95 were females, had a median age of 52 y (interquartile range, 44–59 y; range, 29–78 years). A total of 175 patients, 78 being males and 97 being females, had a median age of 48 y (interquartile range, 42–60 y; range, 26–75 y). There were not significant differences between controls and patients in terms of gender percentage and age.

This group of patients had a median WFNS score of 3 (interquartile range, 2–3; range, 1–5) and a median modified Fisher score of 2 (interquartile range, 1–3; range, 1–4) respectively. A total of 45 (25.7%) aneurysms were located at posterior communication artery; 23 (13.1%), at internal carotid artery; 38 (21.7%), at anterior communication artery; 31 (17.7%), at middle cerebral artery; 24 (13.8%), at anterior cerebral artery; 10 (5.7%), at posterior cerebral artery; 4 (2.3%), at vertebral artery. Cystic aneurysms were found in 81.7% (143/175) patients. Aneurysm had a median diameter of 8.2 mm (interquartile range, 5.8–13.2 mm; range, 4.0–28.2 mm). A total of 34 (19.4%) patients experienced acute hydrocephalus, intraventricular hemorrhage occurred in 27 (15.4%) patients and 52 (29.7%) patients suffered from symptomatic cerebral vasospasm. Aneurysm was clipped in 99 (56.6%) patients and others underwent endovascular coiling. An external ventricular drain was done in 41 (23.4%) patients. Patients were admitted from 0.5 h to 24.0 h after hemorrhagic stroke (median, 9.5 h; interquartile range, 7.4–12.0 h). Blood samples were collected from 1.0 h to 26.3 h after hemorrhagic stroke (median, 12.7 h; interquartile range, 10.1–18.6 h). During 6-month follow-up, 28 (16.0%) patients were deceased and 62 (35.4%) patients had an unfavorable outcome.

3.2. Change of serum IL-33 concentrations after aSAH

Fig. 1 showed that (1) serum IL-33 concentrations in patients were significantly higher than those in controls; (2) serum IL-33 concentrations were markedly higher in non-survivors than in survivors within 6 months; (3) as compared to patients with 6-month favorable outcome, serum IL-33 concentrations were significantly increaseed in patients experiencing 6-month unfavorable outcome. Additionally, Fig. 2 showed that serum IL-33 concentrations were significantly enhanced with increasing serum C-reactive protein concentrations, WFNS scores and modified Fisher scores.

3.3. Serum IL-33 concentrations and 6-month mortality

In this study, serum IL-33 concentrations were dichotomized according to its median value (600 pg/ml). In Table 1, univariate logistic regression analysis showed that parameters associated with 6-month mortality were serum IL-33 concentrations > 600 pg/ml, WFNS scores, modified Fisher scores and other variables listed in the Table 1. When