Clinica Chimica Acta 473 (2017) 60–64

Contents lists available at ScienceDirect

Clinica Chimica Acta

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

Macrophage migration inhibitory factor as a serum prognostic marker in patients with aneurysmal subarachnoid hemorrhage

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ARTICLE INFO

Keywords:
Aneurysm
Subarachnoid hemorrhage
Macrophage migration inhibitory factor
Inflammation
Severity
Outcome

ABSTRACT

Background: Macrophage migration inhibitory factor (MIF) has been implicated in inflammation. We clarified whether serum MIF could be used as a marker of inflammation, brain damage and outcome after aneurysmal subarachnoid hemorrhage (aSAH).

Methods: Serum samples from 102 aSAH adults and 102 healthy controls were determined. The World Federation of Neurological Surgeons (WFNS) scale was used for neurological evaluation and radiological severity was estimated in accordance with the Fisher scale.

Results: Serum MIF, C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α) and S100B concentrations were significantly higher in patients than in controls. Serum MIF concentrations correlated with WFNS scores and Fisher scores and serum concentrations of CRP, IL-6, TNF-α and S100B. Serum MIF was identified as an independent predictor for 6-month unfavorable outcome (defined as Extended Glasgow Outcome Scale score of 1–4). Area under receiver operating characteristic curve of serum MIF concentrations was similar to those of WFNS scores, Fisher scores and serum S100B concentrations and significantly exceeded those of serum CRP, IL-6 and TNF-α concentrations.

Conclusions: Serum MIF provides information about inflammation, brain injury severity and outcome after aSAH, which can be useful as a complement to clinical data.

1. Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating event encountered in emergency and neurosurgery practice [1–3]. The neurological condition after the initial hemorrhage is an important prognostic factor for outcome [4–6]. However, at a neurointensive care unit, the neurological status can sometimes be difficult to evaluate because of sedation or impaired consciousness. Thus, a marker of tissue damage, which is measurable in blood, could be useful for clinical monitoring.

Macrophage migration inhibitory factor (MIF) is identified as a homotrimer protein and is implicated in several biological processes including chemo-attraction, cytokine activity and receptor binding [7–9]. Notably, numerous studies have demonstrated that MIF functions as a proinflammatory cytokine, and plays an important role in pathophysiological mechanisms underlying inflammation-associated diseases such as sepsis, autoimmune liver disease, cancer, and rheumatoid arthritis [10–13]. Intriguingly, MIF can be found in glial cells [14]. Moreover, it is capable of activating inflammatory reaction in central nervous system [15]. Seemingly, MIF might be detrimental to neurons because it can promote cell death and aggravate neurologic deficits after experimental stroke [16] and its deletion attenuates neuronal death and promotes functional recovery after compression-induced spinal cord injury in mice [17]. Recently, it was found that serum MIF concentrations were related to severity and long-term outcomes in patients with acute ischemic stroke [18], traumatic brain injury [19] or spontaneous intracerebral hemorrhage [20]. Thus, it is postulated that serum MIF concentrations might reflect injury severity after acute brain injury. However, there is a paucity of data available on the change of circulating MIF concentrations following aSAH.

2. Methods

2.1. Subjects

All patients with first-ever aSAH admitted to the Jinhua People's Hospital between October 2012 and April 2016 were considered for inclusion in this prospective study. Alternatively, we required that aSAH patients be admitted within 24 h of hemorrhage onset and aneurysms be secured with neurosurgical clipping or endovascular coiling

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http://dx.doi.org/10.1016/j.cca.2017.08.018
Received 6 August 2017; Received in revised form 16 August 2017; Accepted 16 August 2017
Available online 17 August 2017
0009-8981/ © 2017 Published by Elsevier B.V.

within the 48 h after admission due to single intracranial aneurysm identified by computerized tomography (CT) angiography with or without digital subtraction angiography. As controls, we enrolled age- and sex-matched healthy volunteers. Participants were excluded if they had surgery, trauma or infection within recent month, previous neurological diseases such as intracerebral hemorrhage and ischemic stroke, autoimmune diseases with or without immunosuppressive therapy, prior use of antiplatelet or anticoagulant medication or other prior systemic diseases such as uremia, liver cirrhosis, malignancy, chronic heart disease, chronic lung disease, diabetes mellitus and hypertension.

This study was executed according to the Code of Ethics of the World Medical Association (Declaration of Helsinki). The medical ethics committee at our hospital approved the study and the patient or next of kin gave their written informed consent to participate in this study.

2.2. Assessment

The very first status of the patients, before any interventions, was graded according to the World Federation of Neurological Surgeons subarachnoid hemorrhage scale (WFNS) [21]. A neuroradiologist blinded to the laboratory data graded the initial CT findings in accordance with the Fisher radiological scale [22]. 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 CT when the cause was felt to be ischemia attributable to vasospasm after other possible causes of worsening (e.g., hydrocephalus, seizures, metabolic derangement, infection, or oversedation) had been excluded [23,24]. Outcome was assessed after 6 month and categorized according to the 8-grade Extended Glasgow Outcome Scale (GOSE) [25]. GOSE 1 to 4 was regarded as an unfavorable outcome and GOSE 5 to 8 was considered a favorable outcome.

2.3. Laboratory examinations

Venous blood samples of patients, which were obtained as soon as possible after admission, were taken from a tube without anticoagulant, centrifuged and immediately stored at − 80 °C until the final analysis. The same procedures were performed for venous blood samples, which were taken from controls at study entry. Serum MIF, C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α) and S100B concentrations were quantified using sandwich enzyme-linked immunosorbent assay kits (MIF and S100B: R & D Systems, Minneapolis, MN, USA; CRP, IL-6 and TNF-α: Cusabio Biotech). All determinations were completed in duplicate and the results were averaged. The person carrying out the assays completely had no access to the clinical information.

2.4. Statistical analysis

All analyses were done with SPSS ver 19.0 for windows and MedCalc ver 9.6.4.0. Categorical variables were reported as number (percentage). Because continuous variables of the evaluated data do not fit a normal distribution, they were presented as median (interquartile range). Consequently, the Mann-Whitney *U* test was used for two-group comparisons. For comparison of more than two groups, the Kruskal-Wallis analysis of variance followed by Bonferroni-corrected Mann-Whitney *U* test was used. Spearman test was performed for correlations.

Univariate logistic regression analysis was performed to predict the outcome, i.e. 6-month unfavorable outcome. To assess the independent contribution of serum MIF in prediction of outcome, some confounding factors, for instance, age, neurological status graded according to the WFNS and CT findings according to Fisher, were entered into a binary logistic regression analysis. Subsequently, odds ratio and 95% confidence interval values were calculated. A receiver operating characteristic (ROC) curve was performed to evaluate and compare discriminatory ability of serum MIF, S100B, CRP, IL-6 and TNF-α concentrations, WFNS scores and Fisher scores for 6-month unfavorable outcome. Area under curve (AUC) was calculated. All the tests were 2-tailed and were conducted at a $p < 0.05$.

3. Results

3.1. Participants characteristics

A total of 142 aSAH patients were initially assessed. According to the exclusion criteria, 40 patients we excluded because of surgery, trauma or infection within recent month (7 cases), previous neurological diseases (9 cases), autoimmune diseases (3 cases), former use of antiplatelet or anticoagulant medication (5 cases), other prior systemic diseases (10 cases), refusal of participation (1 case), unavailable samples (2 cases), incomplete information (2 cases) and loss of follow-up (1 case). Ultimately, 102 (71.8%) aSAH patients were reserved. In addition, 102 sex- and age-matched controls were enrolled in this study.

Among this group of aSAH patients, aged 53 (38–61) years (range, 21–77 years) and consisting of 37 males and 65 females, in terms of the WFNS, there were WFNS I in 30 patients, WFNS II in 27, WFNS III in 20, WFNS IV in 18 and WFNS V in 7; according to the Fisher scale, Grade 1 were found in 0 patients; Grade 2, in 31; Grade 3, in 45; Grade 4, in 26. Target aneurysm size was ≦5 mm in 35 patients, 6–10 mm in 48 and ≧11 mm in 19. Target aneurysms were located in anterior circulation for 87 patients and in posterior circulation for 15. Cystic aneurysm accounted for 89.2% (91/102) among all patients. A total of 46 patients underwent clipping of aneurysm; 53, endovascular coiling; 3, clipping and endovascular coiling. Alternatively, an external ventricular drain was performed for 38 (37.3%) patients. Also, we observed 34 (33.3%) patients with acute hydrocephalus and 37 (36.3%) patients with symptomatic cerebral vasospasm. At 6 months after aSAH, 16 patients had GOSE 1; 4, GOSE 2; 6, GOSE 3; 5, GOSE 4; 17, GOSE 5; 17, GOSE 6; 14, GOSE 7; and 23, GOSE 8. Totally, 31 (30.4%) patients experienced an unfavorable outcome.

3.2. MIF concentrations and other variables in aSAH patients

In Table 1, serum MIF, S100B, CRP, IL-6 and TNF-α concentrations were found to be significantly higher in patients than in controls. Additionally, in Fig. 1, serum MIF concentrations positively correlated with serum S100B, CRP, IL-6 and TNF-α concentrations among all patients. Moreover, in Fig. 2, serum MIF concentrations were significantly increased with increasing clinical or radiological severity reflected by WFNS scores and Fisher scores.

3.3. Relationship with long-term outcome

In Table 2, serum concentrations of MIF, S100B, CRP, IL-6 and TNF-α were obviously increased in patients suffering from an unfavorable

Table 1
Serum concentrations of biomarkers in controls and patients with aneurysmal subarachnoid hemorrhage.

	Patients	Controls	*P*
MIF (ng/ml)	30.1 (19.1–37.9)	7.9 (6.3–9.4)	< 0.001
CRP (mg/l)	17.7 (13.9–25.0)	1.5 (2.5–3.2)	< 0.001
IL-6 (pg/ml)	12.9 (7.5–18.0)	1.9 (1.3–2.8)	< 0.001
TNF-α (pg/ml)	8.0 (6.0–13.5)	3.6 (2.9–5.1)	< 0.001
S100B (pg/ml)	562.0 (421.3–721.5)	35.0 (25.0–46.5)	< 0.001

Data were reported as median (interquartile range) and 2-group comparisons were conducted using the Mann-Whitney *U* test. MIF indicates macrophage migration inhibitory factor; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha.

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