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Increased interleukin-11 levels in thoracic aorta and plasma from patients with acute thoracic aortic dissection

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ABSTRACT

Background: Interleukin (IL) 11 is closely related to tumor and hematological system diseases. Recent studies have demonstrated that IL-11 also participates in cardiovascular diseases, including ischemia-reperfusion mediated heart injury and acute myocardial infarction. This study aimed to investigate whether IL-11 is involved in acute thoracic aortic dissection (TAD).

Methods: Aortic tissue samples from normal donors and acute TAD patients were collected, and the expression of IL-11 in all aortic tissue was analyzed. In addition, blood samples from patients with chest pain were collected and divided into a non-AD (NAD) group and a TAD group according to the results of computed tomography angiography of the thoracic aorta. The plasma IL-11, IL-17 and interferon (IFN) γ in all blood samples were measured.

Results: Compared with aortic tissue of normal controls, IL-11 was significantly increased in aortic tissue of acute TAD patients, especially in the torn section. The IL-11 was derived from aorta macrophages in TAD. In addition, the plasma IL-11, IL-17 and IFN-γ were significantly higher in acute TAD patients than in NAD patients, and the correlation analysis showed that IL-11 levels were positively correlated with levels of IFN-γ, IL-17, glucose, systolic blood pressure, diastolic blood pressure, white blood cells, C-reactive proteins and D-dimers. Binary logistic regression analyses showed that elevated IL11 in patients who may have diagnostic value of TAD, but less that D-dimer.

Conclusion: IL-11 was increased in thoracic aorta and plasma of TAD patients and may be a promising biomarker for diagnosis in patients with TAD.

1. Introduction

Aortic dissection (AD) is characterized by separation of the aortic wall [1–3]. AD is a complex clinical cardiovascular emergency because it could accumulate in multiple organs and exhibit a variety of clinical symptoms. A small number of patients do not even have any symptoms. Approximately 1–2% of patients may die in each minute following the occurrence of aortic dissection [4]. Therefore, early diagnosis and treatment is important for reducing mortality from AD.

Interleukin (IL) 11 is a pro-inflammatory cytokine and belongs to the IL-6 cytokine family [5]. It can play both pro-inflammatory and anti-inflammatory roles according to different inflammatory micro-environments [6,7]. IL-11 is also a multifunctional cytokine and participates in a variety of diseases, including the injury of mucosal cells [8], immunological activities [9], multiple sclerosis [10], pregnancy [11], hematopoietic activities [12] and spinal cord injury [13]. In addition, a large number of studies have demonstrated that IL-11 is involved in a variety of tumors [14,15], and elevated IL-11 levels were even associated with prognosis and survival in non-cell lung cancer [16].

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Previous studies also demonstrated that IL-11 was involved in cardiovascular diseases. In a hydrogen peroxide-induced cell death model, a protective role of exogenous IL-11 was observed [17]. In addition, using a mouse model of heart ischemia reperfusion and acute myocardial infarction, treatment with IL-11 reduced infarction area and partly improved cardiac function [18,19]. In a recent study, increased serum IL-11 levels were found in patients with coronary artery disease (CAD) when compared with non-CAD patients [20]. Although the expression of IL-11 in thoracic aortic dissection (TAD) is still unknown, this study aimed to investigate the IL-11 expression in thoracic aortas and plasma from patients with TAD.

2. Materials and methods

2.1. Collection of human aortic tissue samples

The aortic tissue ($n = 10$) was donated by patients who suffered from acute TAD and underwent emergency thoracic aorta replacement surgery. The control samples ($n = 8$) were obtained from heart donors who had suffered traffic accidents or stroke and were declared brain-dead by doctors who had > 25 years of clinical experience. Donors had no history of cardiovascular disease, and aortic tissues showed no signs of pathology. All the aortic tissues were collected by surgeons during heart transplantation procedures at the People's Hospital of Guangxi Zhuang Autonomous Region. The patients themselves or their families provided informed consent for donation, and this study protocol was approved by the Medical Ethics Committee of the People's Hospital of Guangxi Zhuang Autonomous Region.

2.2. Western blot

A small piece of thoracic aortic tissue was successively lysed by radioimmunoprecipitation assay (RIPA) lysis buffer and sonication instrument. After centrifugation at 3000*g* for 20 min, the homogenate of each sample was collected, and the protein concentration was quantified with a BCA Protein Assay Kit. Approximately 20 μg of total protein was loaded and run on 10% Laemmli sodium dodecyl sulfate (SDS) polyacrylamide gels and were transferred to Immobilon-FL PVDF membranes (Millipore, Massachusetts). Then, the membranes were blocked with 5% non-fat milk and incubated with anti-IL-11 (GeneTex, UAS) and anti-GAPDH (Cell Signaling Technology UAS) antibodies at 4 °C overnight, followed by incubation with the secondary antibody at room temperature for 1 h. The blots were scanned using a two-color infrared imaging system (Odyssey; LI-COR Biosciences, USA).

2.3. Histological analysis

All aorta samples were fixed with 4% neutral paraformaldehyde, and after being embedded in paraffin, the samples were cut into 4–5-mm slices and mounted onto slides. Immunohistochemistry and immunofluorescence staining were used to detect the IL-11 expression in each sample. In addition, to determine the source of IL-11, the macrophages were stained with anti-CD68 antibody.

2.4. Collection and processing of human blood samples

Consecutive patients ($n = 115$) who suffered from sudden chest pain and were hospitalized in the People's Hospital of Guangxi Zhuang Autonomous Region from March 2016 to August 2017 were enrolled in this study. Of the 115 patients, some of them had a history of CAD ($n = 5$), valvular heart disease (VHD, $n = 3$), or peripheral arterial disease (PAD, including carotid atherosclerosis, $n = 4$ and arteriosclerosis in lower extremity, $n = 1$). In addition, 2 patients also had acute left heart failure (ALHF), and these 15 patients were excluded from the study. The remaining 100 patients returned to the intensive care unit (ICU) after undergoing computed tomography angiography (CTA) of the thoracic aorta. Blood samples were collected in Vacutainer tubes containing sodium heparin by nurses who had > 10 years of clinical experience. After centrifugation at 4000*g* for 20 min, the supernatants were collected and stored at −80 °C until the beginning of the experiments. According to the computed tomography (CT) scan results and clinical features, the diagnosis was decided by a doctor who had > 20 years clinical experience, and these 100 patients were divided into a non-AD group (NAD, $n = 36$) and a TAD group ($n = 64$). The patients in the TAD group were further divided into Stanford A ($n = 30$) and Stanford B groups ($n = 34$) (as shown in Fig. 1). Patients themselves or their families provided informed consent, and this study protocol was approved by the Medical Ethics Committee of the People's Hospital of Guangxi Zhuang Autonomous Region.

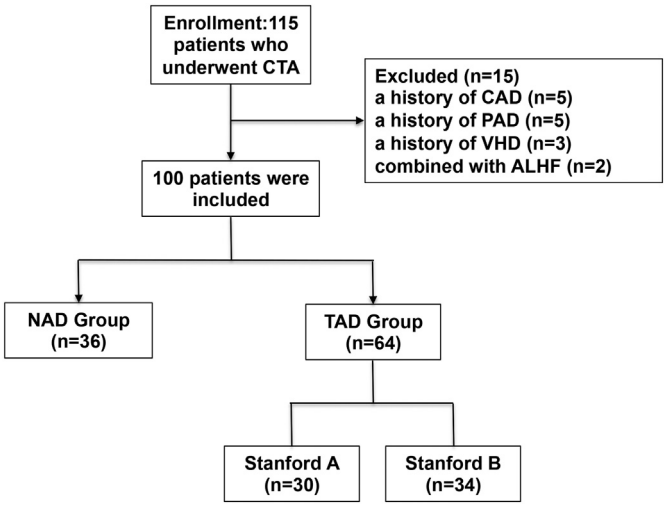

Fig. 1. The inclusion and exclusion criteria for all patients. CTA: computed tomography angiography; CAD: coronary artery diseases; PAD: peripheral artery disease; VHD: valve heart disease; ALHF: acute left heart failure.

2.5. Measurement of IL-11, IFN-γ and IL-17

The 100 blood samples above were taken out from a −80 °C environment and thawed at room temperature, and then the plasma IL-11 (Neoscience, China), IFN-γ and IL-17 (both from ebioscience, UAS) levels were measured using enzyme-linked immunosorbent assay (ELISA) kits following the manufacturer's instructions.

2.6. Statistical analysis

The plasma cytokine concentrations and clinical characteristics were expressed as medians (minimum–maximum) and compared with Mann–Whitney *U* tests. The correlations between IFN-γ, IL-17, clinical characteristics and IL-11 were calculated using Spearman's correlation analysis. Simple linear regression analyses and subsequent binary logistic regression analyses were performed to identify whether IL-11 was an independent predictor of the onset of acute TAD. All the data were analyzed by SPSS 19.0 software, and $p < 0.05$ was considered statistically significant.

3. Results

3.1. Basic clinical characteristics of patients who provided aortic tissue samples

Of the patients who provided acute thoracic aorta tissue for analysis, there were significantly increased D-dimer, WBC and CRP in the TAD group compared to the control group, whereas no differences were found between the two groups in terms of other clinical characteristics,