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PTX3 predicts severe disease in febrile patients at the emergency department

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Summary *Objectives:* The long pentraxin PTX3 is a promising marker of disease severity in severely ill patients. In order to identify patients warranting critical care as quickly as possible, we investigated the value of PTX3 as a biomarker for disease severity in patients presenting with fever at the emergency department.
Methods: Levels of PTX3 were measured in 211 febrile patients at the emergency and the levels were linked to markers of disease severity including admittance to a special care unit, bloodstream infection and congestive heart failure.
Results: In comparison to median baseline levels of 2.30 ng/ml (interquartile range 1.66–3.67 ng/ml), levels of PTX3 were significantly elevated in patients admitted to the intensive-/medium care unit (median value 44.4 ng/ml, interquartile range 13.6–105.9 ng/ml) and in patients referred to the ward (median value 14.2 ng/ml, interquartile range 7.01–25.1 ng/ml). In addition, PTX3 was associated with duration of hospital stay and acute congestive heart failure. The levels were predictive for bloodstream infection (AUC = 0.71; 95% CI 0.62–0.81).

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Conclusions: PTX3 may be a useful marker for differentiation of patients with severe disease in patients presenting with fever to the emergency department.

Introduction

Fever is characteristic for many inflammatory conditions, yet it is particularly associated with bacterial infections. At the emergency department, a quick diagnosis is essential in patients with fever to define patients at risk for severe sepsis as soon as possible, as it has implications for treatment and prognosis; this has been referred to as 'the golden hour of sepsis'.[1,2] However, current diagnostic tools lack either speed, e.g. when taking bacterial cultures, or diagnostic value in terms of sensitivity and specificity.[3,4] Plasma derived biomarkers may be helpful to solve this issue. A promising biomarker for differentiation of patients with fever is the acute phase protein pentraxin 3 (PTX3).[5]

The long pentraxin PTX3 belongs to an evolutionary conserved superfamily of pentraxins, which has been categorized into short and long pentraxins based on the structure of their subunits.[6–8] Other key members of this family include the short pentraxins C-reactive protein (CRP) and serum amyloid P component (SAP). Although the short and long pentraxins share common sequences, they are encoded by different genes and are differentially regulated.[5] PTX3 plays a role as a humoral pattern recognition receptor released by macrophages, dendritic cells and neutrophils, and stimulates complement activation and opsonization. Yet, the precise clinical implications of these biological functions of PTX3 are still insufficiently understood.

Increased levels of PTX3 have been reported in multiple inflammatory conditions.[9–12] In critically ill patients with sepsis, highly increased levels were detected, which correlated with disease severity, ranging from the systemic inflammatory response syndrome (SIRS) to sepsis and septic shock.[13] Moreover, PTX3 was found to correlate significantly with mortality.[11,13] Furthermore, PTX3 has also been linked to severity of disease in patients with cardiovascular disease including acute myocardial infarction, unstable angina pectoris and heart failure.[14–19]

Considering the potential of PTX3 as a biomarker in inflammatory disease, the marker is of interest to the relatively large group of patients presenting with fever to the emergency department. Therefore, we here aimed to determine levels of PTX3 in a cohort of 211 patients who presented to the emergency department with fever. In addition, the relationship was investigated between PTX3 and clinical markers linked to severity of disease, including admission to a special care unit, presence of bloodstream infection and congestive heart failure.

Patients and methods

Study design and definitions

The study was conducted at the emergency department of the Slotervaart hospital, Amsterdam, The Netherlands, between April 2004 and October 2006; the study protocol has been described in detail elsewhere.[20] The study was approved by the institutional scientific and ethics committee of the Slotervaart hospital, Amsterdam, The Netherlands. Written informed consent was obtained from all subjects. Adult patients, 18–85 years old, presenting with fever to the emergency department were included. Fever was defined as an ear temperature of 38.0 °C or higher. For diagnosis of bacteraemia, a total of 3 blood cultures were taken. Other, local bacterial and viral cultures were taken from the suspected focus of infection as judged by the treating physician. Mortality and admission to the intensive care unit or medium care (ICU/MC) were determined for a period of 30 days after admission. The medium care unit in the study hospital is a unit offering special, intensive nursing care to hemodynamic instable patients, characterized by 24-h/day close monitoring and administration of inotropic drugs if needed, but lacks facilities for mechanic ventilation. Bacteraemia was defined as a positive blood culture with a likely pathogen, considering the underlying disease, within 7 days of admission. According to the results, pathogens were classified into Gram-negative or Gram-positive organisms. Congestive heart failure was diagnosed by the treating physician, and was only scored positive as heart failure in case of presence of dyspnea, positive imaging findings and response to diuretic therapy. A medical history of heart failure in patient records was considered positive only in combination with current use of heart failure medication. At a one-month follow-up visit samples were collected from patients who had returned after full recovery from their illness. An additional control cohort was provided by baseline samples from 8 healthy young male volunteers who had participated in a previous study investigating the effects of prednisolone during endotoxin administration.[21]

Laboratory methods

Blood samples were obtained by venapuncture at inclusion and follow-up. The samples were centrifuged within 15 min (2× 3000 rpm at 5 °C for 10 min), aliquoted and stored at −80 °C. Plasma levels of PTX3 were measured using a sandwich enzyme-linked immunosorbent assay as previously described.[22] Plasma PTX3 levels are expressed as ng/ml. Other laboratory investigations were routinely performed by the clinical laboratory and the Department of Microbiology of the Slotervaart Hospital, Amsterdam, The Netherlands.

Statistical analysis

Data analyses were performed using SPSS version 15.0. Group differences were calculated using Mann–Whitney *U* test. To determine correlations between plasma levels of PTX3 and relevant clinical parameters, logistic regression analysis was performed for binominal variables and Spearman's ranked correlation test for continuous variables. Data are presented as medians with corresponding interquartile ranges or as numbers with percentages; odds ratios