Clinica Chimica Acta 484 (2018) 237–245

Contents lists available at ScienceDirect

Clinica Chimica Acta

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

Predictive value of serum cyclophilin A concentrations after acute pancreatitis

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ARTICLE INFO

Keywords:
Cyclophilin A
Acute pancreatitis
Prognosis
Biomarker
Severity
Inflammation

ABSTRACT

Background: Cyclophilin A is identified as a biomarker for inflammation. We elucidated prognostic significance of serum cyclophilin A (CypA) concentrations in acute pancreatitis (AP).
Methods: In this prospective and observational study, serum CypA concentrations were quantified in 210 AP patients and 100 healthy controls. We recorded local complication, in-hospital mortality and organ failure. Disease severity was assessed using the traditional predictors, namely Acute Physiology and Chronic Health Care Evaluation II score, Ranson score, multiple organ dysfunction score and sequential organ failure assessment score.
Results: Serum CypA concentrations were significantly lower in controls than in AP group. CypA concentrations after AP were highly correlated with the traditional predictors and other inflammatory mediators, including blood erythrocyte sedimentation rate, procalcitonin levels, white blood cell count and C-reactive protein levels. Serum CypA emerged as an independent predictor for in-hospital local complication, organ failure and mortality. Under receiver operating characteristic curve, serum CypA possessed similar prognostic ability, as compared to the traditional predictors. Its predictive ability was almost similar to that of procalcitonin levels and significantly exceeded those of the other inflammatory mediators. Also, it significantly improved prognostic performance of the traditional predictors.
Conclusions: Increased serum CypA concentrations have close relation to the severity, inflammation and prognosis, substantializing CypA as a potential prognostic biomarker of AP.

1. Introduction

Acute pancreatitis (AP), a multifactorial disease, is related to the release of digestive enzymes to the pancreatic interstitium and to the systemic circulation, subsequently leading to deleterious local and systemic reaction [1–3]. Inflammation is implicated in its pathophysiological mechanisms [4–6]. AP might involve peripancreatic tissues or remote organ systems, subsequent inducing various serious complications and even a high risk of death [7–9]. Clinically, its poor prognosis is characterized by a high incidence of local complication, organ failure and in-hospital mortality [7–9]. Some traditional predictors, including the Acute Physiology and Chronic Health Care Evaluation II (APCHCE II) score, multiple organ dysfunction score (MODS), Ranson score and sequential organ failure assessment (SOFA) score, have been widely utilized to evaluate disease severity and predict prognosis of AP [10–13]. However, recently, some circulating biomarkers have drawn an extensive attention for clinician to enable early prediction of disease severity and prognosis of AP [14–17].

Cyclophilin A is known as a ubiquitously distributed intracellular protein of the cyclophilin family and also is identified as the high-affinity receptor for the immunosuppressive drug cyclosporine [18–20]. As an intracellular chaperone protein with peptidyl cis-trans prolyl-isomerase activity, it exerts multiple biological functions, such as intracellular signaling, protein trafficking, and regulating activity of other proteins [21, 22]. Alternatively, cyclophilin A is a potent chemoattractant for human monocytes and neutrophils, as well as can be induced in response to oxidative or inflammatory stress and released into the peripheral blood by inflammatory and by dying/necrotic cells and subsequently functions as a mediator of tissue damage [23, 24]. Of note, cyclophilin A levels in the peripheral blood have been found to be significantly enhanced in inflammation or oxidative stress - related diseases, e.g., rheumatoid arthritis, chronic obstructive pulmonary,

Abbreviations: AP, acute pancreatitis; APCHCE II, Acute Physiology and Chronic Health Care EvaluationII; MODS, multiple organ dysfunction score; SOFA, sequential organ failure assessment; IQR, interquartile range

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https://doi.org/10.1016/j.cca.2018.06.011
Received 16 February 2018; Received in revised form 1 June 2018; Accepted 4 June 2018
Available online 05 June 2018
0009-8981/

ulcerative colitis and coronary artery disease [25–28]. Also, circulating cyclophilin A concentrations are closely related to prognosis of patients with coronary artery disease [28]. Interestingly, obvious up-regulation and expression of cyclophilin A has been verified in disrupted acinar cells, infiltrated inflammatory cells and tubular complexes in experimental AP [29]. Therefore, it is postulated that circulating cyclophilin A levels might be increased after AP.

2. Materials and methods

2.1. Study population

We performed a prospective, observational study and recruited a group of consecutive AP patients suffering from their first episode and referred to our hospital from January 2013 through January 2017. AP was diagnosed based on the criteria proposed by the International Atlanta Symposium on Acute Pancreatitis in 2012 [30]. Exclusion criteria included pregnant women, < 18 y, malignant diseases, immunosuppressive disorders and inflammatory diseases within recent 1 month. During the period of January 2016 and January 2017, a group of healthy volunteers were enrolled as controls. None of the control individuals had systemic diseases, cancer or acute or chronic infection, and they were receiving no medications at the time of the study. This study was done in accordance with the Human Investigations Committee at our Hospital. The study subjects or their legal guardians supplied written informed consent.

2.2. Clinical assessment

The following information was obtained for patients: age, sex, body mass index, time from pain onset to hospital admission, time from pain onset to sample collection, etiology and type of treatment. All patients were treated by conservative therapy, percutaneous drainage or laparotomy. The etiologies of AP included biliary, alcoholic, hypertriglyceremic or others. The etiology was considered biliary when gallstones were diagnosed with abdominal ultrasound either in the gallbladder or in the bile ducts without evidence for another cause; as alcohol induced when the patient reported heavy alcohol consumption (288 g of ethanol/week in males and 192 g of ethanol/week in females) without other predisposing findings; as hypertriglyceremic when suggested by laboratory findings with triglyceridemia > 1000 mg/dl without evidence for another cause [31]. Disease severity was assessed using the traditional predictors, namely 48-h Ranson score, APACHE II score, MODS, and SOFA score [10–13]. We recorded local complication, organ failure and in-hospital mortality. Organ failure is considered when there is a modified Marshall score of ≥2 or more for ≥1 of the 3 organ systems: respiratory, cardiovascular, and renal [30]. Local complications included acute peripancreatic fluid collections, pancreatic pseudocycts, acute necrotic collections and walled-off necrosis [30].

2.3. Laboratory examinations

Blood samples were obtained from the antecubital vein at admission from the patients and at study entry from the controls. Routine laboratory parameters including blood erythrocyte sedimentation rate, procalcitonin level, white blood cell count and C-reactive protein level, were determined. For measurement of serum cyclophilin A, serum samples were stored −80 °C for later batch analysis and every 3 months, serum cyclophilin A concentrations were in duplicates detected using enzyme-linked immunosorbent assay (USCN Life Science, Wuhan, China) in accordance with the manufactures' instructions. Samples were all processed by the same laboratory technician using the same equipment and blinded to all clinical data.

2.4. Statistical analysis

Statistical testing was performed using SPSS 19.0 statistical software and MedCalc 9.6.4.0. Continuous variables were tested for normality by the Kolmogorovor-Smirnov test or Shapiro-Wilk test. All continuous variables were not normally distributed and therefore reported as median [interquartile range (IQR)]. The χ^2 test or Fisher exact test was conducted to compare proportions in categorical data. A Kruskal-Wallis H test was conducted to compare serum cyclophilin A levels among multiple groups, namely, mild AP, moderately severe AP and severe AP. The Mann-Whitney *U* test was undertaken to compare the differences in medians between two groups. Spearman's correlation analysis was done between serum cyclophilin A concentrations, the traditional disease severity predictors and other inflammatory mediators, including blood erythrocyte sedimentation rate, procalcitonin levels, white blood cell count and C-reactive protein levels. A logistic regression model was generated to identify independent predictors with respect to local complication, organ failure and in-hospital mortality. The variables, which were significant in univariate analyses, were incorporated into multivariate model. The logistic regression results are presented as odds ratio (OR) and 95% confidence interval (CI). Cutoff values of serum cyclophilin A levels were obtained automatically from receiver operating characteristic (ROC) curves with optimal prognostic predictive sensitivities and specificities. Area under curve (AUC) and 95% CI were estimated. Comparisons of AUCs were carried out between serum cyclophilin A concentrations and the traditional disease severity predictors using Z test. *P* values < 0.05 was considered statistically significant.

3. Results

3.1. Study population characteristics

Initially, 265 AP patients were assessed. We excluded 55 patients because of the following reasons: pregnant women (12 cases), < 18 y (10 cases), malignant diseases (14 cases), immunosuppressive disorders (8 cases) and inflammatory diseases within recent 1 month (11 cases). Ultimately, 210 AP patients were enrolled in this study. Controls were composed of 100 healthy individuals. They had similar age and percentage of sex.

Among AP patients, there were 151 males and 59 females and their median age was 54 (IQR, 22) y. The median body mass index was 26.6 (IQR, 3.2) kg/m^2. Patients were admitted at a median time of 18.0 (IQR, 10.0) hours after pain onset. Peripheral blood was collected at a median time of 20.4 (IQR, 11.4) hours after pain onset. In terms of etiology, there were biliary (55 patients), alcoholic (101 patients), hypertriglyceremic AP (37 patients) and others (17 patients). As regards type of treatment, conservative therapy was performed in 150 patients, percutaneous drainage was done in 30 patients and laparotomy was carried out in 30 patients. The median APACHE II score, Ranson score, MODS and SOFA score were 12 (IQR, 11), 4 (IQR, 2), 6 (IQR, 6) and 6 (IQR, 6) respectively. There were 2.4 (IQR, 3.6) ng/ml at median procalcitonin levels, 30.7 (IQR, 17.5) mg/l at median C-reactive protein levels, 29.9 (IQR, 14.5) mm/l at median erythrocyte sedimentation rate and 12.6 (IQR, 6.5) × 10^9/l at white blood cell count. A total of 66 patients (31.4%) experienced organ failure, 106 patients (50.5%) suffered from local complications and 18 patients (8.5%) were deceased during hospital stay.

In Table 1, AP patients consisted of 92 mild AP, 71 moderately severe AP and 47 severe AP patients. By comparison, there were no statistically significant differences in age, sex percentage, body mass index, admission time, sample-collecting time and etiologies. Significant variables were blood erythrocyte sedimentation rate, procalcitonin levels, white blood cell count, C-reactive protein levels, APACHE II score, Ranson score, MODS and SOFA score. Moreover, in order of AP severity, those data were gradually promoted. Additionally,