Relationship between plasma copeptin levels and complications of community-acquired pneumonia in preschool children

Jian-Min Du [a],[1], Gao Sang [b],[1], Chun-Ming Jiang [a],[*], Xiao-Jun He [a], Yong Han [a]

[a] Department of Paediatrics, The First People's Hospital of Hangzhou, Nanjing Medical University, 261 Huansha Road, Hangzhou 310006, China
[b] Department of Paediatrics, Tongde Hospital of Zhejiang Province, 234 Gucui Road, Hangzhou 310012, China

ABSTRACT

High plasma copeptin level has been associated with clinical outcomes after acute illness. The present study was undertaken to investigate the plasma copeptin concentrations in preschool children with community-acquired pneumonia (CAP) and to analyze the correlations of copeptin with CAP-related complications and pleural effusion. Plasma copeptin concentrations of 100 healthy children and 165 preschool children with CAP were measured. 35 children (21.2%) presented with complicated CAP and 28 children (17.0%) presented with pleural effusion. The admission copeptin levels were significantly increased in all patients (49.7 ± 21.4 pmol/L), children with complicated CAP (73.0 ± 16.9 pmol/L), those with uncomplicated CAP (43.4 ± 17.8 pmol/L), those with pleural effusion (70.9 ± 17.4 pmol/L) and those without pleural effusion (45.3 ± 19.5 pmol/L) compared with healthy control individuals (9.0 ± 2.7 pmol/L, all $P < 0.001$). Multivariate logistic regression analysis showed that plasma copeptin levels were independently related to CAP-related complications (odds ratio 1.214, 95% confidence interval 1.104–1.872, $P < 0.001$) and pleural effusion (odds ratio 1.226, 95% confidence interval 1.109–1.917, $P < 0.001$). A receiver operating characteristic curve analysis showed plasma copeptin level better predicted CAP-related complications (area under curve 0.876, 95% confidence interval 0.815–0.922) and pleural effusion (area under curve 0.831, 95% confidence interval 0.765–0.885). Thus, plasma copeptin level may represent a novel biomarker for predicting CAP-related complications in preschool children.

© 2013 Elsevier Inc. All rights reserved.

1. Introduction

Community-acquired pneumonia (CAP) is the most severe form of acute respiratory infection, accounting for 80% of all deaths from acute respiratory infection in children [23]. The impact of CAP on childhood mortality is a cause for concern, especially in developing countries [16]. Pleural effusion, pneumothorax, pneumatocele, and lung abscess are considered as complications of CAP [5]. Pleural effusion is the most common one [13]. These complications are the main determinants of clinical worsening and risk of death in children under 5 years of age [20].

Copeptin, a glycoprotein containing 39 amino acid sequences with a molecular mass of about 5 kD, is the terminal part of carboxyl group of vasopressin, has a stable biological effect and serves as marker of vasopressin activity [8]. Secretion of copeptin from the hypothalamus increases in response to individual stress response and higher copeptin levels in peripheral blood are highly associated with prognosis of acute illness [9,19]. Previous clinical study has

shown that elevated plasma copeptin levels predict clinical deterioration, persistent instability and mortality in adult CAP [2,12]. However, at present there is a paucity of data available on circulating plasma copeptin concentrations in pediatric CAP patients. The present study was undertaken to investigate the plasma copeptin concentrations in preschool children with CAP and to analyze the correlations of copeptin with CAP-related complications and pleural effusion.

2. Materials and methods

2.1. Study population

This study was conducted in the Department of Paediatrics, The First People's Hospital of Hangzhou, Nanjing Medical University. During the period from January 2010 to January 2012, all preschool children with CAP were initially assessed. Children with cystic fibrosis, heart disease with hemodynamic repercussions, pulmonary malformations, neurological disorders, or genetic diseases were excluded from the study. Children were eligible as controls if they presented to our hospital and had blood collected as part of well-child care between February 2012 and July 2012. Written informed consent to participate in the study was obtained from

* Corresponding author. Tel.: +86 0571 87065701; fax: +86 0571 87065701.
E-mail address: hanrdxcb@163.com (C.-M. Jiang).
[1] These authors contributed equally to this work.

the subjects or their relatives. This protocol was approved by the Ethics Committee of The First People's Hospital of Hangzhou before implementation.

2.2. Clinical assessment

The diagnosis of pneumonia was based on clinical findings (fever, cough, and difficulty breathing), physical examination findings (chest retraction and decreased breath sounds or rales), and radiological findings (unilateral or bilateral homogeneous consolidation on chest X-ray) [18]. Pleural effusion, pneumothorax, pneumatocele, and lung abscess were considered as complications of CAP. The patients who were included in the complicated CAP group presented with such complications at admission.

2.3. Immunoassay method

The informed consents were obtained from their parents in all cases before the blood was collected. Venous blood was drawn at study entry in the control group and on admission in the patients. The blood samples were immediately placed into sterile EDTA test tubes and centrifuged at $3000 \times g$ for 30 min at $4\,^\circ$C to collect plasma. Plasma was stored at $-70\,^\circ$C until assayed. Copeptin was detected with a novel commercial chemiluminescence assay (B.R.A.H.M.S. Aktiengesellschaft, Hennigsdorf/Berlin, Germany) as described previously [15]. The analytical detection limit of the assay was 1.7 pmol/L. The person carrying out the assays was completely blinded to the clinical information.

2.4. Statistical analysis

Statistical analysis was completed using the SPSS 10.0 statistical package (SPSS Inc., Chicago, IL, USA) and MedCalc 9.6.4.0. (MedCalc Software, Mariakerke, Belgium). The categorical variables are presented as percentages, and the continuous variables are presented as mean ± standard deviation if normally distributed or median (interquartile range) if not normally distributed. Statistical significance for intergroup differences was assessed by chi-square or Fisher exact test for categorical variables, and by Student t or Mann–Whitney U test for continuous variables. Receiver operating characteristic (ROC) curves were configured to establish cutoff points of plasma copeptin level that optimally predicted the CAP complications. Multivariable logistic regression analyses were performed to determine factors that could be considered as independent predictors of the CAP complications, adjusted by confounding variables according to the results of the univariate analysis. Variables showing $P < 0.1$ in univariate analysis were included in the multivariate model. The logistic regression results are presented as odds ratio (OR) and 95% confidence interval (CI). A P value of <0.05 was considered significant for all tests.

3. Results

3.1. Patient characteristics

During the study period, 165 patients were finally included in the analysis. The main baseline demographic and clinical characteristics of the series are summarized in Table 1. 100 healthy children were eligible as controls. The intergroup differences of patients and healthy children in the age and sex were not statistically significant (both $P > 0.05$). 35 children (21.2%) presented with complicated CAP and 28 children (17.0%) presented with pleural effusion.

Table 1
Characteristics of children with community-acquired pneumonia.

Characteristics	Overall ($n = 165$)
Age (months)	25 (29)
Gender (male/female)	92/73
Level of maternal education (years)	5.1 ± 2.1
Work	
Formal	99 (60.0%)
Informal	52 (31.5%)
No work	14 (8.5%)
Breastfeeding	141 (85.5%)
Smokers in the household	65 (39.4%)
Previous finding	
Pneumonia	39 (23.6%)
Wheezing	32 (19.4%)
Antibiotic therapy	46 (27.9%)
Admission time (days)	4 (8)
Duration of fever prior to admission (days)	3 (3)
C-reactive protein (mg/dL)	6.6 ± 2.6
Copeptin (pmol/L)	49.7 ± 21.4

Numerical variables were presented as mean ± standard deviation or median (interquartile range). Categorical variables were expressed as counts (percentage).

3.2. The change of plasma copeptin level in CAP patients

The admission copeptin levels were significantly increased in all patients (49.7 ± 21.4 pmol/L), children with complicated CAP (73.0 ± 16.9 pmol/L), those with uncomplicated CAP (43.4 ± 17.8 pmol/L), those with pleural effusion (70.9 ± 17.4 pmol/L) and those without pleural effusion (45.3 ± 19.5 pmol/L) compared with healthy control individuals (9.0 ± 2.7 pmol/L, all $P < 0.001$) (Fig. 1).

3.3. Association of plasma copeptin level with CAP complications

Potential predictors of CAP complications are shown in Table 2. Patients with CAP complications had higher C-reactive protein and copeptin level, lower age and level of maternal education, longer admission time and duration of fever prior to admission, and more frequently showed previous pneumonia, wheezing and antibiotic therapy. Multivariate logistic regression analysis showed that variables independently related to CAP complications were plasma copeptin level (OR 1.214, 95% CI 1.104–1.872, $P < 0.001$) and age (OR 0.706, 95% CI 0.541–0.908, $P < 0.001$). ROC curves identified cutoff points for plasma copeptin level on admission as the value that better predicted CAP complications (Fig. 2).

3.4. Association of plasma copeptin level with CAP pleural effusion

Potential predictors of CAP pleural effusion are shown in Table 3. Patients with CAP pleural effusion had higher C-reactive protein and copeptin level, lower age and level of maternal education, longer admission time and duration of fever prior to admission, and more frequently showed previous pneumonia, wheezing and antibiotic therapy. Multivariate logistic regression analysis showed that variables independently related to CAP pleural effusion were plasma copeptin level (OR 1.226, 95% CI 1.109–1.917, $P < 0.001$) and age (OR 0.714, 95% CI 0.549–0.923, $P < 0.001$). ROC curves identified cutoff points for plasma copeptin level on admission as the value that better predicted CAP pleural effusion (Fig. 3).

4. Discussion

This study was conducted to determine if copeptin is increased in the circulation of children with CAP and whether this increment correlates with CAP-related complications and pleural effusion in these preschool children. The admission plasma copeptin levels