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Title: Adrenal function in patients with community-acquired pneumonia

Short title: Adrenal function in pneumonia

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Abstract

Background: Adrenal insufficiency has been said to occur frequently in severe sepsis and septic shock.

The question of the study: Is the adrenal function related to the severity of community-acquired pneumonia?

Methods: Sixty-four Japanese patients with community-acquired pneumonia were consecutively enrolled in this study from 2005 to 2006. Serum adrenocorticotropic hormone (ACTH) and cortisol were measured in each subject, as was the response of cortisol secretion to the administration of 250 μg of cosyntropin. Analyses comparing these values with the score calculated by the Pneumonia Patient Outcomes Research Team (PORT) cohort study, the number of in-hospital deaths, and the length of hospital stay were performed.

Results: As the PORT score increased, serum ACTH and cortisol increased (Spearman's rank correlation coefficient: $\rho=0.371$, $p<0.05$ and $\rho=0.396$, $p<0.05$, respectively), while the response of cortisol secretion to the administration of cosyntropin decreased ($\rho=-0.273$, $p<0.05$). In the analysis by receiver operating characteristic (ROC) curves, adrenal dysfunction was related significantly to both the number of in-hospital deaths and the length of hospital stay.

The answer to the question: Adrenal dysfunction was shown to correlate with the PORT score and the clinical outcomes, while adrenal insufficiency defined by the cosyntropin stimulation test was rare in our study.

Keywords: adrenal insufficiency, adrenocorticotropic hormone, cortisol, community-acquired pneumonia,

Introduction

Several studies have revealed that a physiological dose of steroids is effective therapy for patients with septic shock [1,2,3] and that patients with septic shock are lacking cortisol secretion to maintain the normal adrenal function [4,5,6,7]. This status has been called relative adrenal insufficiency [4,8], which is a concept that describes the necessity of steroids for critically ill patients. However, the recently published results of the CORTICUS study have shown that hydrocortisone therapy did not improve the survival of patients with septic shock in either groups of patients who had or didn't have a response to a corticotropin stimulation test. In addition, hydrocortisone therapy was reported to increase the relative risk ratio of complications such as new sepsis and septic shock [9].

Although researchers have been interested in the adrenal function in critically ill patients with severe sepsis and septic shock, there have been only a few small studies that investigated the relation between adrenal function and the severity of community-acquired pneumonia, although the disease has a good scoring system for determining severity. In some papers, "relative adrenal insufficiency" were reported to occur in a high proportion of patients with severe community-acquired pneumonia [10, 11]. Confalonieri M. et al. showed that a physiological dose of steroids may be beneficial for severe community-acquired pneumonia in a randomized control study of steroid administration for patients with severe community-acquired pneumonia, although

they did not show the adrenal function of the patients [12]. In addition, Oppert M et al. reported there are two separate effects of the treatment with low-dose hydrocortisone in patients with early hyperdynamic septic shock; hemodynamic effect which is related to endogenous cortisol levels and immunomodulatory effect which is independent of adrenal function [13]. We hypothesized that there might be some relation between adrenal function and the severity of community-acquired pneumonia. Therefore we examined the standard measures of adrenal function; serum cortisol, serum ACTH, and the response of cortisol secretion to the administration of 250 μg of cosyntropin and compared with the severity of community-acquired pneumonia. We investigated the relation of these measures with the outcome of the number of in-hospital deaths and the length of hospital stay. Recently, Christ-Crain et al [14] have reported that cortisol levels could be used as predictors of severity and death. In our study, we added the analysis of the relation between serum ACTH level and the severity of pneumonia and evaluated the results of cosyntropin stimulation test. We would like to make comments on the issue of the dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis in patients with community-acquired pneumonia in our discussion.

Material and Methods

Study Population

Sixty-nine hospitalized patients with clinical and radiographic evidence of community-acquired pneumonia were consecutively enrolled from October 2005 to October 2006. Seven patients died in the hospital and seven patients were transferred to other hospitals. We could not follow the clinical course of these transferred patients; therefore, we excluded patients who died or were transferred to other hospitals when we calculated the average length of hospital stay. Exclusion criteria included any of the following condition: (1) nosocomial pneumonia; (2) severe immunosuppression; (3) acute burn injury; (4) pregnancy; (5) a condition for which steroids had been administered; (6) age less than 18 years old; (7) a major gastrointestinal bleed within 3 months of the current hospitalization; or (8) recovery from Candida species at multiple sites. They or their legally authorized representatives signed the consent form approved by the Research Ethics Committee at St.Luke's International Hospital. Five patients were excluded; two patients had tuberculosis, one had idiopathic interstitial pneumonia, and two were taking corticosteroids regularly. No patients were prescribed etomidate, or other medications that affects HPA axis.

Data collection

All registered patients were assigned to 5 risk classes based on 20 clinical variables as indicated in the Pneumonia Patient Outcomes Research Team (PORT) cohort study [15]. A cosyntropin stimulation test was performed with 0.25mg of tetracosactrin on the morning after admission from 7:00 a.m. to 10:00 a.m. Blood samples were obtained immediately before the test (T0), and 30 (T30) and 60 (T60) minutes after injection, and were stored at 4˚C. After centrifugation, the concentrations of adrenocorticotropic hormone (ACTH) (normal range 7-56 μg/dL) and cortisol (normal range 6.2-19.4 μg/dL) were measured by immunoradiometric assay (ACTH immunoradiometric assay kit, Mitsubishi Chemical, Tokyo, Japan) or an automated enzyme-linked immunosorbent assay (Roche Diagnostics Corporation, Tokyo, Japan). The cortisol response was defined as the difference between T0 and the higher value of the T30 and T60 concentrations. Antibiotics were administered intravenously for empirical therapy as recommended by the guideline of the Japanese Respiratory Society [16]. We recorded the number of in-hospital deaths and the length of hospital stay.

Statistical analysis

Statistical analyses were conducted using SPSS (version 14.0J). We investigated the relation between the score calculated from 20 clinical variables based on the PORT cohort study and the values of serum cortisol, ACTH, and the increase of serum cortisol after cosyntropin-stimulation

with Spearman's rank correlation coefficient, respectively. We evaluated the relation between patients with positive blood culture and adrenal function with Mann-Whitney U test and the relation between the types of pathogen and adrenal function with ANOVA. We then investigated their correlation with the number of in-hospital deaths and the length of hospital stay, respectively, by using receiver operating characteristic (ROC) curves.

Results

Patients' characteristics

Sixty-four patients with community-acquired pneumonia were consecutively enrolled in this study from October 2005 to October 2006. Forty patients were male, with a median age of 77 years old, and a median PORT score of 110. Fourteen patients were administered steroids to treat community-acquired pneumonia (Table 1), but the decision for steroid administration was independent of the result of the adrenal function test, except for the 5 patients with septic shock. These patients were administered steroids after their clinical condition worsened. The dose of the corticosteroids were referred to the previous studies [12, 17, 18]. Three patients lacked the ACTH value before the administration of cosyntropin because of a failure to measure it. Almost all patients were initially treated empirically with intravenous β-lactum antibiotic agents in our hospital, according to the guideline of the Japanese Respiratory Society [16]. When atypical

pneumonia was suspected, minocycline, macrolide, or fluoloquinolone was added. The causative pathogen was identified in 29 cases; for example, *Streptococcus pneumonia* was identified in sputum or blood culture, or urinary antigen assay from 9 patients, but for 35 cases, we could not identify the causative pathogen because, in some cases, the culture specimen was taken after antibiotics were administered and in other cases sufficient sputum was not submitted (Table 2). In this study, seven patients died in hospital. The average length of the hospital stay excluding patients who died or were transferred to other hospitals was 17.7 days.

Relation between adrenal function and the PORT score, positive blood culture, and types of pathogens

We examined the secretion of serum cortisol, serum ACTH, and the response of cortisol secretion to the administration of 250 μg of ACTH on admission. The median values of serum cortisol, serum ACTH, and the increase of serum cortisol after stimulation were 21.3 μg/dL, 20 pg/ml, and 14.3 μg/dL, respectively (Table 3). We evaluated the correlation of these values with the PORT scores. Serum cortisol and ACTH were significantly correlated with the PORT score (Spearman's correlation coefficient: r=0.396, p=0.001 and r=371, p=0.003, respectively) and the increase of serum cortisol after stimulation was negatively correlated with the PORT score (r=-0.273, p=0.029) (Figure 1). In addition, we confirmed that serum cortisol and ACTH were

significantly correlated with the PORT score in the subgroups of subjects that did not include the patients who were administered corticosteroids. There were four patients with positive blood culture. There were four patients with positive blood culture. Both serum cortisol and ACTH in these patients were significantly greater than those in the patients with negative blood culture. (Mann-Whitney U test, p=0.004, 0.039, respectively). There was no significant relation between the types of pathogens and PORT score (data not shown).

Relation between adrenal function and outcomes (the number of in-hospital deaths and the length of hospital stay).

We studied the correlations of serum ACTH, serum cortisol, and the increase of serum cortisol after cosyntropin-stimulation with the outcomes of the treatment for community-acquired pneumonia. We regarded the number of in-hospital deaths and the length of hospital stay as the most important outcomes in this study. These outcomes were analyzed by receiver operating characteristic (ROC) curves for serum ACTH, serum cortisol, the increase of serum cortisol after stimulation, and the PORT score. Serum ACTH and the PORT score are good indicators of in-hospital deaths (p=0.007, 0.016, respectively) (Figure 2 A). The area under the ROC curves was 0.818 (95%CI: 0.694-0.942) for serum ACTH, 0.650 (95%CI: 0.398-0.902) for serum cortisol, and 0.782 (95%CI: 0.603-0.960) for the PORT score. Specificity of more than 90% was achieved

for more than 56 μg/dl of serum ACTH (with sensitivity of 28.6%) (Figure 2B). On the other hand, serum cortisol and the PORT score can serve as indicators of the length of hospital stay (Figure 3 A). The area under the ROC curves was 0.716 (95%CI: 0.540-0.892) for serum ACTH, 0.818 (95%CI: 0.626-1.010) for serum cortisol, and 0.795 (95%CI: 0.559-1.030) for the PORT score. Specificity of more than 92.5% was achieved for more than 29.7 μg/dl of serum cortisol (with sensitivity of 57.1%) (Figure 3 B). We confirmed significant relation between each of serum ACTH, cortisol, and PORT score and the length of hospital stay in patients without administration of corticosteroids (data not shown). We retrospectively evaluated the effect of corticosteroids on the outcomes of in-hospital death and length of hospital stay, but no significant data were obtained (data not shown).

Discussion

There has been only a few reports that investigated the adrenal function in patients with community-acquired pneumonia, including from moderate to severe cases with septic shock and there has been no previously published data about serum ACTH in patients with community-acquired pneumonia. We have shown that adrenal function was correlated with the PORT score. In particular, the level of serum ACTH before stimulation by cosyntropin was significantly correlated with the number of in-hospital deaths, whereas the level of serum cortisol was significantly correlated with the length of hospital stay. The PORT score correlated not only with the number of in-hospital deaths, but also with the length of hospital stay. We found that the level of serum ACTH or cortisol on admission or the morning after admission becomes positively correlated with the severity of community-acquired pneumonia. This result in our study of hospitalized patients with community-acquired pneumonia is consistent with the previous study of 189 patients with septic shock [1] and with the recent report of Christ-Crain et al. [14]. However, our study provides additional information about serum ACTH level of patients with community-acquired pneumonia.

In the previous report of Annane D et al. [1], the survival curves for baseline serum cortisol and the increase of serum cortisol after cosyntropin-stimulation were analyzed. The group with baseline serum cortisol ≤34 μg/dL showed significantly larger probability of survival than that of

baseline serum cortisol >34 μg/dL ($p < 0.001$), whereas the group with the increase of serum cortisol >9 μg/dL than that of the increase of serum cortisol ≤9 μg/dL ($p < 0.001$).

Christ-Crain et al. [14] have investigated the predictive values of serum total cortisol, free cortisol, procalcitonin, C-reactive protein, leukocytes, and Pneumonia Severity Index (PSI) for the outcome of death. And they reported serum total cortisol and free cortisol increased as PSI increased and that both total and free cortisol levels in patients who died during follow-up were significantly higher than those in survivors. In our study we could not examine the serum free cortisol, because it could not be measured in our hospital. Serum free cortisol is reported to be more precise marker of adrenal function in patients with hypoproteinemia, especially patients whose serum albumin is ≤2.5 g/dL [7]. Instead, we measured serum ACTH and performed cosyntropin stimulation test. This is classically used method to check adrenal function especially in critically ill patients [1, 4, 6]. Interestingly, our data suggested that serum ACTH could be the predictor of death in patients with community-acquired pneumonia and that cosyntropin stimulation test did not serve well to predict outcomes even if we considered the result that the number of patients who had serum albumin of ≤2.5 g/dL was only two. Serum ACTH was shown to increase in critically ill patients in the previous report [7], while no data are documented in a population of community-acquired pneumonia. This is thought to be due to the activation of HPA axis. In stressful condition, cytokines such as IL-1, IL-6, and TNF-α released from the site of

injury or after exposure to endotoxin activate the HPA axis by stimulating the classical pathway of Corticotropin-Releasing Hormone (CRH) and ACTH secretion [19, 20].

The diagnosis of adrenal insufficiency in critically ill patients, that is also termed Critical Illness-Related Corticosteroid Insufficiency (CIRCI) [21], has long been difficult to define, but some data have been reported by Annane D, et al [6]. They suggested that CIRCI is likely when baseline serum cortisol level is ≤10 μg/dL, or when the increase of serum cortisol after cosyntropin-stimulation is ≤9 μg/dL, whereas it is unlikely when the cortisol level after stimulation is >44 μg/dL or when the cortisol increase is >16.8 μg/dL. They suggested methyrapone test might be useful tool for diagnosis of CIRCI. In our study, 9 patients met the criteria, three of which were in septic shock. For the other 6 patients who were not in septic shock, we are not sure whether they had CIRCI, because we did not perform methyrapone test and the diagnostic criteria are constructed from the study of patients with septic shock and because they lack specific features of adrenal insufficiency, such as hypoglycemia, hypotension, and increased eosinophil count.

Moreover, our results gave new aspects to the concept of CIRCI. We have disclosed the fact that the severity of community-acquired pneumonia increased as the levels of serum cortisol and ACTH increased, while no patients in our study showed baseline cortisol level of ≤10 μg/dL. This may suggest that such CIRCI in community-acquired pneumonia might be rare, although the

dysfunction of HPA axis is correlated with the severity of community-acquired pneumonia. This observation is contrary to the previous reports that evaluated patients with severe sepsis and septic shock [4, 5, 6] and with severe community-acquired pneumonia [10], but was consistent with the report of Christ-Crain M. et al [14]. What caused this discrepancy? One interpretation is that the subject population of the former studies were different from those of Christ-Crain's report and of ours in the point that more severely ill patients who needed intensive care were included in the former studies.

According to the previous studies, most critically ill patients including severe sepsis but not in septic shock were considered to have the dysfunction of HPA axis, which is often called adrenal "stress" endocrinologically [22]. We suggest that there might be some critical turning point from just the dysfunction of HPA axis to CIRCI. We also suggest that CIRCI might be rare in patients with community-acquired pneumonia and that the severity of community-acquired pneumonia might be predicted significantly by the dysfunction of HPA axis rather than CIRCI.

The limitation of our study is that it was a small sample size in a single institution; therefore, there was only a small number of in-hospital deaths. This might be the reason why we could not see a significant correlation in survival with the level of baseline serum cortisol or the increase of serum cortisol after cosyntropin-stimulation. The efficacy of steroid replacement therapy for community-acquired pneumonia with severe sepsis or septic shock has been supported in

previous studies [12, 17, 18] and even recommended in the Infectious Diseases Society of America / American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults published in 2007 [23], but criteria for steroid replacement therapy is controversial and it is still unknown whether CIRCI is preceded by severe pneumonia or vice versa. We think that the adrenal function of patients with community-acquired pneumonia should be investigated in a larger population, and criteria for steroid replacement therapy should be established from the viewpoint of the risk and benefit of steroid administration, because the CORTICUS study reported that hydrocortisone therapy increased the relative risk ratio of complications such as new sepsis and septic shock [9].

In conclusion, our study showed that serum cortisol, serum ACTH were correlated with the PORT score. In particular, both of these were correlated with clinical outcomes such as the number of in-hospital deaths and the length of hospital stay. Adrenal function may play a significant role in predicting the severity of community-acquired pneumonia.

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TABLE 1. General characteristics of 64 hospitalized patients with community-acquired pneumonia [*]

Sex, male	**40**	**(63)**
Median age (range)	**77**	**(27-96)**
PORT score, median (range)	**110**	**(0-207)**
Pneumonia Severity Index		
□	**6**	**(9)**
□	**3**	**(5)**
□	**11**	**(17)**
□	**23**	**(36)**
□	**21**	**(33)**
Comorbidity		
Heart failure	**11**	**(17)**
Liver disease	**8**	**(13)**
Septic shock	**7**	**(11)**
Malignancy	**7**	**(11)**
Cerebrovascular disease	**6**	**(9)**
Kidney disease	**6**	**(9)**
Steroid administration after stimulation test	**14**	**(22)**
Number of patients whose tests were started		
□**between 7:00 – 10:00 a.m.**	**54**	**(84)**

[*] **Data are presented as a number (percentage) unless otherwise indicated.**

TABLE 2. Type of pathogen and type of anti-microbial agents used in 64 patients with community-acquired pneumonia[*]

Pathogen		
Steptococcus pneumoniae	**9**	**(14)**
Hemophilus influnenzae	**7**	**(11)**
Klebsiella pneumoniae	**6**	**(9)**
Mycoplasma species	**2**	**(3)**
Chlamydia species	**2**	**(3)**
Legionella species	**2**	**(3)**
Brahamella catarrhalis	**1**	**(2)**
Escherichia coli	**1**	**(2)**
MRSA	**1**	**(2)**
Unkown pathogen	**33**	**(52)**
Anti-microbial agents		
Cephalosporins (3rd generation) + Non β-lactum agents [†]	**28**	**(44)**
Cephalosporins (3rd generation)	**8**	**(13)**
Ampicillin / Sulbactam	**8**	**(13)**
Cephalosporins (4th generation) + Non β-lactum agents [†]	**7**	**(11)**
Ampicillin / Sulbactam + Non β-lactum agents [†]	**5**	**(8)**
Piperacillin / Tazobactam	**2**	**(3)**
Carbapenem + Non β-lactum agents [†]	**2**	**(3)**
Cephalosporins (4th generation)	**1**	**(2)**
Piperacillin / Tazobactam + Non β-lactum agents [†]	**1**	**(2)**
Carbapenem	**0**	**(0)**
Others	**2**	**(3)**

*** Data are presented as number (percentage).**

[†] Non β-lactum agents include minocycline, fluoroquinolone, macrolide, and clindamycin

TABLE 3. Adrenal function in patients with community-acquired pneumonia

	median	range
ACTH (T0) *, pg/ml	**20**	**(5-188)**
Cortisol (T0) *, µg/dl	**21.3**	**(9.3-145.4)**
Cortisol (T60) †, µg/dl	**31.9**	**(16.8-147.0)**
Increase of cortisol secretion after cosyntropin administration, µg/dl	**14.3**	**(2.2-30.2)**

*** "T0" means just before cosyntropin administration**

† "T60" means 60 minutes after cosyntropin administration

Figure legends

Figure 1.

Correlation between adrenal function and severity of community-acquired pneumonia. The values of baseline concentration of serum ACTH (T0) (A), those of baseline concentration of serum cortisol (T0) (B), and increase in serum cortisol after cosyntropin stimulation (C) were correlated with the PORT scores in 64 hospitalized patients with community-acquired pneumonia, respectively. Spearman's rank correlation efficient.

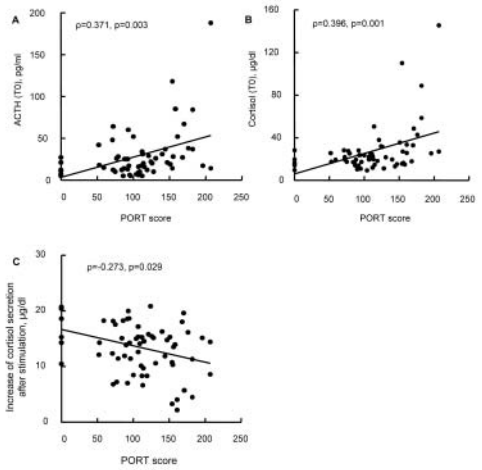

Figure 2.

Receiver Operator Curve analysis of baseline concentration of serum ACTH (T0) and the PORT score for predicting in-hospital mortality (A). The area under the ROC curve was 0.818 (95%CI: 0.694-0.942) for serum ACTH (T0) and 0.782 (95%CI:0.603-0.960) for the PORT score. The relation between specificity and the concentration of serum ACTH (T0) was depicted in (B).

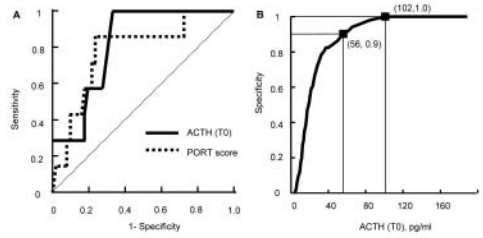

Figure 3.

Receiver Operator Curve analysis of baseline concentration of serum cortisol (T0) and the PORT score for predicting the length of hospital stay over 3 weeks (A). The area under the ROC curve was 0.818 (95%CI: 0.626-1.010) for serum cortisol, and 0.795 (95%CI: 0.559-1.030) for the PORT score. The relation between specificity and the concentration of serum ACTH (T0) was depicted in (B).