The association of serum total cortisol and pneumonia severity index

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ABSTRACT

الأهداف: دراسة العلاقة بين مدى حدة الالتهاب الرئوي ومعدل مصل الكورتيزول في الدم وذلك في مجموعة من المرضى المصريين.

الطريقة: لقد تضمنت الدراسة كافة المرضى المُصابين بالالتهاب الرئوي المُكتسب داخل المجتمع (CAP) والذين دخلوا مستشفى جامعة المنصورة، المنصورة، مصر خلال الفترة من مارس 2008م إلى ديسمبر 2008م. وبالمقابل استبعدت الدراسة المرضى المصابين بأحد الأمراض التالية: الإيدز (HIV)، ضعف الجهاز المناعي، المرض الكولاجيني الوعائي، التهاب الرئة الخلالي، الداء الرئوي المسد المزمن (COPD)، الربو الذي يتطلب جرعة مقدارها 10 ملغرام من بريدنيسولون (prednisolone) يومياً على الأقل، ورم خبيث نشط، فشل القلب الاحتقاني (CHF)، تشمع الكبد، أوالمسببات الأخرى لمرض نقص البروتين في الدم والصدمة الانتانية. اعتمد قياس مدى حدة الالتهاب الرئوي على مؤشر حدة الالتهاب الرئوي (PSI) الذي يستخدم معايير بورت (PORT)، في حين تم قياس معدل الكورتيزول العام في المستشفى وذلك باستخدام اختبار المناعة إليزا (ELISA).

النتائج: جمعت الدراسة الحالية 23 مريضاً مُصاباً بالالتهاب الرئوي المُكتسب داخل المجتمع، وكان عددهم 14 ذكراً و9 إناث ويتراوح معدل أعمارهم ما بين 16.7±47 عاماً. ارتبط معدل الكورتيزول العام (387.91±483.11 نانومول/لتر) بعلاقة طردية مع حدة الالتهاب الرئوي التي قاسها مؤشر حدة الالتهاب الرئوي (p=0.012, R=0.576). هذه بالإضافة إلى ارتباطه بعلاقة عكسية واضحة مع ضغط الأوكسجين في الدم (p=0.035, R=-0.500)، ونسبة امتصاص الأوكسجين في الدم (p=0.029, R=0.450)، وكذلك معدل بيكربونات الدم (p=0.03, R=0.266)، كما أنه يرتبط بعلاقة طردية مع مدى عمل الرئتين (p=0.041).

خاتمة: لقد ارتبط معدل الكوتيزول العام بعلاقة طردية واضحة مع مدى حدة الالتهاب الرئوي المكتسب داخل المجتمع والتي عينها مؤشر (PSI) وذلك باستخدام معايير بورت (PORT) في الدراسة التي تناولت المرضى. إن قياس واحد لمعدل الكورتيزول في الدم قد تكون معلومة مفيدة كباقي العوامل العشرين المتغيرة والتي يتم إدراجها في جدول مؤشر حدة الالتهاب الرئوي.

Objectives: To study the relation between severity of pneumonia and serum cortisol level in a cohort of Egyptian patients.

Methods: All consecutive adult patients with community acquired pneumonia (CAP) admitted to Mansoura University Hospital, Mansoura, Egypt between March 2008 and December 2008 were considered for study inclusion. Exclusion criteria were patients with HIV infection, impaired immune systems, collagen vascular disease, interstitial pneumonia, chronic obstructive pulmonary disease (COPD), asthma requiring 10 mg of prednisolone at least daily, active malignant neoplasm, congestive heart failure (CHF), liver cirrhosis, or other causes of hypoproteinemia and septic shock. Pneumonia severity was scored at hospital admission according to pneumonia severity index (PSI) using the PORT criteria. The serum total cortisol was measured at hospital admission using ELISA.

Results: The present study comprised 23 adult patients with CAP: 14 male and 9 females with a mean age of 47±16.7 years. Total serum cortisol (mean 483.11±387.91 nmol/L) was positively correlated (p=0.012, R=0.576) with pneumonia severity as assessed by the PSI. Moreover, the total serum cortisol levels showed significantly negative correlation with arterial oxygen tension (R=-0.500, p=0.035), oxygen saturation % (R=0.450, p=0.029), and bicarbonate level (R=0.266, p=0.03), as well as a significant positive correlation with the extent of lung involvement (p=0.041).

Conclusion: Total serum cortisol showed a significantly positive correlation with the severity of CAP assessed by the PORT index (PSI) in our study population. A single measurement of total serum cortisol may provide helpful information as the complex 20-variables, which are used in pneumonia severity index.

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Pneumonia is a syndrome caused by acute infection usually bacterial, characterized by clinical and/or radiological signs of consolidation of part or parts of one or both lungs.[1] Despite advances in antimicrobial therapy, community acquired pneumonia (CAP) remains a serious illness and is considerably a main cause of mortality and morbidity. Community acquired pneumonia is the most frequent cause of death from infection in developed countries.[2] Corticosteroids promote anti-inflammatory activity in several ways. They are highly effective in controlling airway inflammation in asthma.[3] In a study conducted by Confalonieri et al,[4] low dose hydrocortisone infusion was found to hasten resolution of pneumonia and to prevent the development of sepsis related complications. Cortisol is transported in blood in 3 forms: free cortisol, cortisol bound to proteins, as well as cortisol metabolites. Free cortisol, which is only found in small quantities in the plasma (5-10%), represents the active form. The 2 main binding proteins are the cortisol-binding protein (CBG) and albumin. The cortisol plasma concentration follows a diurnal rhythm with its peak concentration between 7 and 8 am each day and a minimum concentration. This diurnal cycle is lost in cases of an infection.[5-7] These effects are due to increased production of corticotrophin releasing hormone and corticotropin and reduction of negative feed back from cortisone.[8] Stimulation of the hypothalamic-pituitary-adrenal axis in this context is caused by circulating cytokines, among other factors.[9] Several studies have been conducted on the cortisol level as an indicator of severity and prognosis in severe sepsis and septic shock.[10-12] Cortisol has been studied in a limited number of studies as a treatment modality along with antibiotics and other measures in severe pneumonia,[5,12] and as a marker of severity and as a predictor of the prognosis.[11] Christ-Crain et al,[10] and Gotoh et al[14] found that serum cortisol was positively correlated with CAP severity, and the later study disclosed that not only serum cortisol, but also adrenocorticotropic hormone (ACTH) were increased in CAP in relation to severity. This study was carried out to study any relation between severity of pneumonia and serum cortisol level in Egyptian patients.

Methods. This study was conducted at Mansoura University Hospital, Mansoura, Egypt. Inclusion criteria comprised all CAP patients consecutively hospitalized in the general medical wards between September 2007 and February 2008. The diagnosis of CAP was based on clinical signs and symptoms of lower respiratory tract infections. Radiographic abnormalities consistent with infection were neither preexisting nor caused by any other previous conditions. We excluded patients with the following conditions: HIV infection, impaired immune systems, collagen vascular disease, interstitial pneumonia, COPD, asthma requiring 10 mg of prednisolone at least daily, active malignant neoplasm, congestive heart failure (CHF), liver cirrhosis, or other causes of hypoproteinemia and septic shock. We scored the PSI and classified study patients into risk class I-V using the PORT criteria.[13] The local ethics committee approved this study protocol, and informed consent was obtained from all patients or their representatives. All patients were subjected to the following: full medical history, physical examination, chest x-ray (posteroanterior and lateral views), complete blood count, sputum examination by gram stain culture and sensitivity, arterial blood gases, urea, creatinine, electrolytes, serum glutamic oxaloacetic transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), bilirubin, 2 sets of blood culture if the temperature more than 38°C, serological tests if suspicion of viral or bacterial pneumonia, in addition to pleural fluid analysis and culture in cases with para pneumonic effusion.

Measurement of cortisol. Blood was collected for cortisol and placed on ice. Samples were allowed to clot and then were separated and placed in plastic vials for analysis. The samples were taken to the lab, and measurement was carried out using an enzyme immune assay kit (EIA). Serum samples and standards were added to the antibody-coated plates, enzyme conjugate solution was then added and the mixture was shaken and incubated at room temperature for one hour to remove all the unbound materials. The plate was then washed 4 times. Bound enzyme conjugate was detected by the addition of a substrate, which generated optimal color after 10 minutes. Results were obtained by measuring and comparing the absorbance of wells containing samples with wells containing standards, using a micro plate reader at 450 nm with blank subs traction at 650 nm. The inter-assay coefficient of variance at 49 nmol per liter was 10%, at 411 it was 5.3%, and at 729 it was 9.1%. The intra-assay coefficient of variance at 50 nmol per liter was 6.9%, at 250 it was 4.3%, and at 750 was 6.5%. The calculated sensitivity of the assay was 25 nmol per liter.

The statistical analysis was carried out using Excel and the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 10. The results were expressed as mean ± standard deviation. For quantitative data, Student t-test was used for comparison between 2 groups, and one-way ANOVA test for comparison between more than 2 groups. For qualitative data (frequency and proportion) Chi-square test was used. To determine association between variables, the correlation coefficient test was used. $P<0.05$ were considered statistically significant.

Results. The present study comprised 23 adult patients with CAP: 14 male and 9 females with a mean

age 47±16.7 years. The mean and SD of vital signs and the laboratory parameters in the study population are summarized in **Table 1**. **Table 2** shows the mean and SD of total cortisol level in patients with CAP (483.11 ± 387.91 nmol/L). We found a significant positive correlation between total cortisol, and the extent of lung lobes involved in patients with CAP (p=0.041) (**Table 3**). We also found that serum total cortisol has a significant positive correlation (p=0.012, R=0.576) with CAP severity classified according to PSI score (**Table 3**). There is also a significant negative correlation between partial pressure of oxygen (PaO_2) (p=0.35), oxygen saturation % (p=0.29), and bicarbonate ion (HCO3) (p=0.003) reflecting a high degree of respiratory distress. Also, we found no significant correlation with age, temperature, pulse rate, blood pressure, white blood count, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, bilirubin, blood glucose, urea, or creatinine.

Discussion. The present study revealed that serum total cortisol has a significant positive correlation with CAP severity classified according to PSI score. This finding is supported by Christ-Crain et al,[10] and Gotoh et al[14] who found that serum cortisol was positively correlated with CAP severity and the later study disclosed that not only serum cortisol, but also ACTH were increased in CAP in relation to severity. This may be explained by the high cortisol levels reflecting the high degree of stress.[10] The effects of cortisol are directed toward the acute provision of energy protection against excessive inflammation, and improvement in hemodynamic status,[16,17] therefore, appropriate activation of the hypothalamic-pituitary-adrenal axis during illness is essential for survival, and parallels the degree of stress.

In this study it was found that there is a significant negative correlation between PaO_2, oxygen saturation %,

Table 1 - The mean and SD of vital signs and laboratory parameters in the study population.

Parameters	Mean ± SD
Pulse, bpm	109.44 ± 13.58
RR, breaths/min	27.72 ± 4.07
Temperature, ^{0}C	38.13 ± 1.01
Systolic BP, mm Hg	118.44 ± 31.15
Diastolic BP, mm Hg	71.38 ± 18.53
Sodium plasma, mmol/L	137.22 ± 6.75
Potassium plasma, mmol/L	4.07 ± 0.45
Urea plasma, mmol/L	6.56 ± 2.57
Plasma creatinine µmol/L	105.33 ± 28.15
SGOT, U/L	39.44 ± 27.37
SGPT, U/L	42.94 ± 41.97
Bilirubin plasma, µmol/L	17.00 ± 19.76
Blood glucose, mmol/L	8.16 ± 5.36
PaO_2, kpa	10.15 ± 2.16
$PaCO_2$,kpa	4.29 ± 1.02
Oxygen saturation	93.50 ± 4.54
HCO3, mmol/L	22.80 ± 2.81
pH	7.41 ± 5.49
Serum total cortisol, nmol/L	483.11 ± 387.91

RR - respiratory rate, BP - blood pressure, PaO_2 - arterial oxygen tension $PaCO_2$- arterial CO_2 tension, HCO3 - bicarbonate level, WBC - White blood cells, SGOT - serum glutamic oxalacetic transaminase, SGPT - serum glutamic pyruvate transaminase

Table 2 - Comparison of cortisol levels among patients according to the extent of lung involvement

Lung involvement	Patients number	Mean total serum cortisol, nmol/L	SD	*P*-value
Lobar	14	289.50	±232.63	0.041
Multilobular	5	429.25	±218.76	
Broncho-pneumonia	4	573.33	±451.62	

*statistical significance: p<0.05

Table 3 - The correlation between cortisol level and the degree of pneumonia severity, age and physical findings variables among patients with CAP.

Parameter	R	p	Significance
PSI index	0.576	0.012	S†
Age	0.017	0.94	NS*
Physical findings			
Pulse rate	0.164	0.516	NS*
Temperture	0.003	0.99	NS*
RR	0.001	0.99	NS*
Diast. BP	0.361	0.141	NS*
Syst.BP	0.354	0.149	NS*
WBC	0.452	0.059	NS*
Urea	0.546	0.022	S†
Creatinine	0.626	0.005	S‡
SGOT	0.406	0.094	NS
SGPT	0.046	0.856	NS
Bilirubin	0.161	0.523	NS
Glucose	0.159	0.528	NS
Sodium	0.292	0.235	NS
PaO_2	-0.500	0.035	S*
Oxygen saturation	-0.450	0.029	S*
$PaCO_2$	0.266	0.286	NS*
PH	0.144	0.569	NS
HCO3	-0.667	0.003	S‡

*Non-significant p>0.05, †significant p<0.05, ‡highly significant p<0.01
RR - respiratory rate, BP - blood pressure, PaO_2 - arterial oxygen tension $PaCO_2$- arterial CO_2 tension, HCO3=bicarbonate level, WBC - White blood cells, SGOT - serum glutamic oxalacetic transaminase, SGPT - serum glutamic pyruvate transaminase

and HCO3 reflecting a high degree of respiratory distress. The decline of the later might reflect lactic acidosis from tissue hypoxia causing more inflammatory cytokine release, for example, IL6, from the inflamed lung tissue, which directly or indirectly stimulates ACTH and cortisol synthesis.[18] This is also explained by our finding of a significant positive correlation between total cortisol and the extent of lung lobes involved in patients with CAP.

In this study, we measured serum total rather than free serum cortisol concentrations, but as concluded by Christ-Crain et al,[10] free cortisol was no better than total cortisol as a predictor of severity of CAP. Serum free cortisol is reported to be a more precise marker in patients with hypoproteinemia, especially in patients with serum albumin less than 2.5 g/dl,[19] so in the present study patients with hypoproteinemia and or hypoalbuminemia were excluded. Total and free serum cortisol levels were positively correlated with PSI scores. On multivariate analysis, the prognostic power of the total serum cortisol level was equal to the PSI score.[10] These findings suggest that a single measure of total serum cortisol on presentation is as accurate as the clinically derived PSI for assessing severity of CAP.

The study has methodological limitations, including measurement of the cortisol level once, on presentation, rather than at the same time of the day for all patients. During acute infective illness, the circadian rhythm of cortisol is usually lost.[15] However, if the results are reproducible, this would indicate that a single blood test on initial evaluation could be used to determine CAP severity and assist in management, including the decision of whether hospital admission is warranted. Other limitations are small sample size, no cut-off value to classify patients with CAP according to the severity, and evaluation of pituitary adrenal reserve was not carried out to rule out undiagnosed subtle adrenal failure in those patients.

In conclusion, serum total cortisol has a significant positive correlation with severity of CAP and according to our data, simple measurement of total cortisol provides additional information for CAP severity as the complex 20-variables, which are used in pneumonia severity index. However, it is recommended that cortisol level in patients with CAP should be investigated in a larger population aiming at estimating a cut-off value to classify patients with CAP according to the severity of illness, which may dictate further management plans.

References

1. Seaton D. Pneumonia. In: Seaton A, Seaton D, Leitch AG, editors. Crofton and Douglas Respiratory Diseases. 5th ed. Oxford (UK): Blackwell Scientific Publications; 2000. p. 356.
2. Health and Welfare Statistics Association of Japan Annual Report of National Health and Hygiene in Japan. ***Kouseinoshihyou*** 2004; 51:382–385. Japanese
3. National Institutes of Health/National Heart Lung, Blood Institute (2002) Global Initiative for Asthma. Global strategy for asthma management and prevention. NIH Publ 02–3659
4. Confalonieri M, Urbino R, Potena A, Piattella M, Parigi P, Puccio G, et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. ***Am J Respir Crit Care Med*** 2005; 171: 242-248.
5. Franchimont D, Kino T, Galon J, Meduri GU, Chrousos G. Glucocorticoids and inflammation revisited: the state of the art. NIH clinical staff conference. ***Neuroimmunomodulation*** 2002-2003; 10: 247-260.
6. Beishuizen A, Thijs LG, Haanen C, Vermes I. Macrophage migration inhibitory factor and hypothalamo-pituitary-adrenal function during critical illness. ***J Clin Endocrinol Metab*** 2001; 86: 2811-2816.
7. Oppert M, Reinicke A, Gräf KJ, Barckow D, Frei U, Eckardt KU. Plasma cortisol levels before and during "low-dose" hydrocortisone therapy and their relationship to hemodynamic improvement in patients with septic shock. ***Intensive Care Med*** 2000; 26: 1747-1755.
8. Maqbool M, Shah ZA, Wani FA, Wahid A, Parveen S, Nazir A. Prevalence of occult adrenal insufficiency and the prognostic value of a short corticotropin stimulation test in patients with septic shock. ***Indian J Crit Care Med*** 2009; 13: 85-91.
9. Annane D. Glucocorticoids in the treatment of severe sepsis and septic shock. ***Curr Opin Crit Care*** 2005; 11: 449-453.
10. Christ-Crain M, Stolz D, Jutla S, Couppis O, Müller C, Bingisser R, et al. Free and total cortisol levels as predictors of severity and outcome in community-acquired pneumonia. ***Am J Respir Crit Care Med*** 2007; 176: 913-920.
11. Salluh JI, Póvoa P, Soares M, Castro-Faria-Neto HC, Bozza FA, Bozza PT. The role of corticosteroids in severe community-acquired pneumonia: a systematic review. ***Crit Care*** 2008; 12: R76.
12. España PP, Capelastegui A, Gorordo I, Esteban C, Oribe M, Ortega M, et al. Development and validation of a clinical prediction rule for severe community-acquired pneumonia. ***Am J Respir Crit Care Med*** 2006; 174: 1249-1256.
13. Müller B, Harbarth S, Stolz D, Bingisser R, Mueller C, Leuppi J, et al. Diagnostic and prognostic accuracy of clinical and laboratory parameters in community-acquired pneumonia. ***BMC Infect Dis*** 2007; 7: 10.
14. Gotoh S, Nishimura N, Takahashi O, Shiratsuka H, Horinouchi H, Ono H, et al. Adrenal function in patients with community-acquired pneumonia. ***Eur Respir J*** 2008; 31: 1268-1273.
15. Singanayagam A, Chalmers JD, Hill AT. Severity assessment in community-acquired pneumonia: a review. ***QJM*** 2009; 102: 379-388.
16. Marik PE, Kiminyo K, Zaloga GP. Adrenal insufficiency in critically ill patients with human immunodeficiency virus. ***Crit Care Med*** 2002; 30: 1267-1273.
17. Annane D, Meduri GU, Marik P. Critical illness-related corticosteroid insufficiency and community-acquired pneumonia: back to the future! ***Eur Respir J*** 2008; 31: 1150-1152.
18. American Thoracic Society. Guidelines for the Management of Adults with Community-acquired Pneumonia. ***Am J Respir Crit Care Med*** 2001; 163; 1730-1754.
19. Hamrahian AH, Oseni TS, Arafah BM. Measurements of serum free cortisol in critically ill patients. ***N Engl J Med*** 2004; 350: 1629-1638.