C-REACTIVE PROTEIN (CRP) AND ITS PREDICTIVE ROLE

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Abstract: *The early diagnosis of pancreatic necrosis is particularly important for the establishment of the subsequent therapeutic management. Recent studies show that pancreatic necrosis occurs in the first 48-72 hours from the onset of acute pancreatitis.(1) Therefore, markers for pancreatic necrosis reaching a maximum concentration in serum or urine within the first 24-48 hours are searched for. The most studied are CRP PMN elastase, TNF factor, interleukin-6, α1-antitrypsin, trypsinogen, TAP (trypsinogen activating peptide), and serum amyloid pancreatic ribonuclease.(2) While CRP is available in all laboratories, the other markers are not available in the clinic and occur only in the clinical trails regarding their efficacy.(3,1,4)*

Cuvinte cheie: *proteina C reactivă, necroza pancreatică*

Rezumat: *Diagnosticul precoce al necrozei pancreatice, este deosebit de important, pentru stabi-lirea conduitei terapeutice ulterioare. Studiile recente prezintă rezultate în care necroza pan-creatică apare în primele 48-72 de ore de la debutul pancreatitei acute.(1) Astfel se caută markeri pentru necroza pancreatică care ating concentraţii maxime în ser sau urină în primele 24-48 de ore. Cei mai studiaţi sunt PCR, PMN elastaza, factorul TNF, interleukina-6, α1-antitripsina, tripsinogenul, TAP (peptida activatoare a tripsinogenului), amiloidul seric şi ribonucleaza pancreatică (2). În timp ce proteina C reactivă este disponibilă în toate labora-toarele, ceilalţi markeri nu sunt disponibili în clinică şi apar doar în studii clinice privind eficacitatea lor.(3,1,4)*

INTRODUCTION

C-reactive protein (CRP) is a nonspecific mediator of inflammation produced in hepatocytes. Elevations of serum C-reactive protein occur in trauma, inflammations, keeping, infections or neoplastic pathology. CRP production is stimulated by interleukin 1 and 6. IL-6 is considered to be a primary mediator of the acute phase reactive substances, such as CRP; the maximum level of CRP and IL-6 occurs 12 hours before the occurrence of the maximum level of CRP, indicating the possibility that early diagnosis can be made by measuring IL-6, as this mediator predicts the possible development of the inflammatory disease evolution to a severe stage.(5)

In acute pancreatitis (AP), C-reactive protein is considered to be a useful indicator for assessing severity only 48 hours after the onset of the illness. Maximum blood levels occur at 72 hours after the onset of pancreatitis. In literature and in our study, the mean maximum CPR value appears on day 3 of hospitalization in the group with severe pancreatitis.(6)

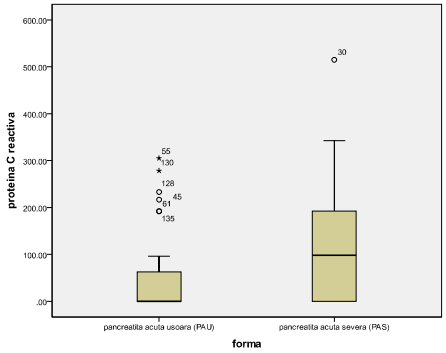
PURPOSE

The study aimed at C-reactive protein values and at the early prediction of severe pancreatitis. Determining the severity of AP is difficult in the early phase after onset and we often encounter difficulties in taking decisions to initiate the intensive therapy in the early phase. We determined the values of C-reactive protein (CRP) and we compare them with the severity of acute pancreatitis, respectively to determine the relationship between the C-reactive protein and pancreatic necrosis and the assessment of the prognostic value of CRP in the early diagnosis of pancreatic necrosis. It is therefore a real need to have a simple and cheap method that can accurately assess the severity of AP. The combination of CRP and leukocytosis has a good predictive value for infection, being very useful in detecting bacterial infection, being superior to the number of leukocytes taken separately.

METHODS

The study was conducted on a sample of 35 patients with acute pancreatitis admitted to the Clinical County Hospital of Sibiu – I Surgery Clinic between January 2010 and December 2013. They were divided according to the severity of pancreatitis in two groups: group I included patients with severe pancreatitis and group II, patients with mild pancreatitis. The patients were included in the two groups after performing CT or after setting the intraoperative diagnosis, adopting the same attitude as that encountered in the literature.(7)

Figure no. 1. C-reactive protein in PAU and PAS



CRP levels decreased to 1.0 0.4, and 0.3 mg / dl in

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severe cases. These 35 patients were admitted within 24 hours after the onset of pancreatitis and CRP was measured after admission, between Day 1 and Day 9.

Mild to moderate cases had CRP levels below 0.2 mg / dl. 19 of the cases were hospitalized 7 days after onset, and 16 cases were admitted within 24 hours of the onset. In the present study, we measured serum CRP levels in patients with AP using the quantitative and semi-quantitative CRP testing in the laboratory within the Clinical County Hospital of Sibiu.

Mean C-reactive protein values were compared between groups using the unpaired t test. The difference was statistically significant ($p = 0.019 < 0.05$).

RESULTS

Men predominate in both groups. The average age in both groups was almost the same. In the case of biliary etiology, there has been found a high incidence of PAU up to the age of 60 years old and over this age, there is an increase in the number of cases of PAS ($p = 0.501$). The etiologic factor for severe pancreatitis with necrosis was gallstone.

Figure no. 2. Statistical correlation of CRP in case of biliary and alcohol etiology

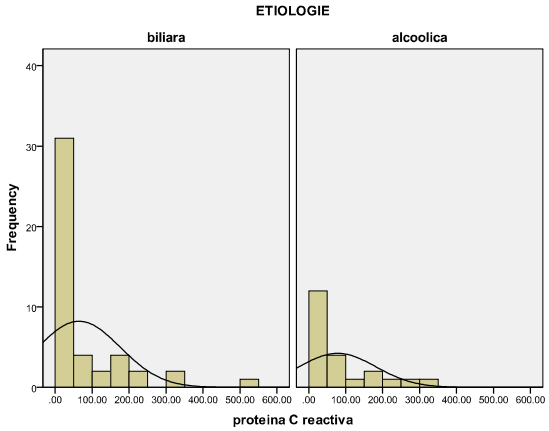

Table no. 1 - Sensibility, specificity, positive and negative predictive values of CRP

CRP (mg/dl) value	Sensibility (%)	Specificity (%)	VPP (%)	VPN (%)
100	76	76	57	90
120	77	77	58	89
140	84	79	64	92
150	92	96	69	97

It has been seen from the above table that the specificity and sensitivity optimal values are at a cut-off value of 150 mg / dl, values also found in other studies.(8)

The best cut-off value was at 150 mg / dl. Our study on the early prediction of severe pancreatitis confirmed that the CRP can be considered a marker of pancreatic necrosis with peak values detected in the serum after 72 hours. Both in literature and in our study, it has been observed that the highest value of CRP in severe pancreatitis is on the third day of hospitalization. It should however be noted that even from the first day, the mean CRP concentrations differ statistically between the two groups. The only explanation of this phenomenon is the late presentation of the patients.

It has not been reached any consensus on the cut-off value for testing CPR regarding pancreatic necrosis. The value varies widely between 120 and 210 mg / dl as shown by several authors.(9,1,410) The smaller is the cut-off value, the more increased sensitivity and accuracy are.

On the other hand, the higher cut-off value is, it is associated with an increased specificity and positive predictive value. One must determine what is most important for the clinical aspect: to assign patients with edematous pancreatitis in the group with necrotic pancreatitis or the vice versa.(8) The chosen cut-off value should establish the diagnosis of pancreatic necrosis with the highest accuracy, without paying special attention to false positive results.(11)

DISCUSSIONS

In 2002, Imamtjra et al. (12) published a study on the significance of measuring high-sensitivity C-reactive protein (hs CRP) in acute pancreatitis.

Japanese study findings. Measurement of hs-CRP is a simple and cheap method. Hs-CRP levels were significantly increased in the early phase of severe AP suggesting that hs-CRP is an early indicator of AP progression towards worsening.

Although PA is a benign condition, it often develops severely and mortality is still high. A survey conducted by the Untreatable Disease Research Committee of the Ministry of Health and Welfare of Japan (MHW) revealed a mortality of 275 in the patients with severe AP. Renal, circulatory, respiratory, cardiac failure are common causes of death within 2 weeks from the onset of severe AP.

Since determining the severity of AP is difficult in the early phase after the onset, we encounter difficulties in taking decisions in order to initiate intensive therapy during the early phase.

It is therefore urgently needed a simple and cheap method that can accurately assess the severity of AP. Measurement of serum CRP as a marker of systemic inflammation reaction is a simple and cheap method. In the above-mentioned study, serum CRP levels were measured in the patients with AP, using the hs CRP test. 10 hospitalized patients with severe AP and 10 patients with mild to moderate PA were diagnosed according to the criteria for assessing the severity of AP established by the Untreatable Disease Research Committee of the Ministry of Health and Welfare of Japan (MHW) and of chronic health evaluation (APACHE II). Blood samples were centrifuged at admission 3000rpm for 10 min. Supernatants were placed at 80 ° C.

CRP levels were determined using latex agglutination immunoassay. Hs-CRP levels were measured using a nephelometer with N-latex, according to the immunonephelometric assays with increased particle for C-reactive protein, serum amyloid, mannose-binding lectin in human serum. Interleukin -6 IL-6 was measured by enzyme immunoassay method. The significance of differences was determined by Scheffe's Multiple Contrast after the analysis of single variance. Levels difference of 5% or less was considered to have statistical significance.

CRP is an indicator of systemic inflammation reaction and an increase in CRP is known to be a predictive factor for the incidence of risk of cardiovascular problems. The relation between hs-CRP and high density lipoprotein / total cholesterol HDL is reported to be useful predictors for the risk of cardiovascular issues. It was also reported that the final result of severe AP can be measured by assessing the acute phase protein CRP.

The Japanese authors still believe that CRP is not suitable for assessing the severity of AP or to predict progression to severe condition because the maximum CRP values occurs 24-48 hours after the onset of pancreatitis. Therefore, they launched hypothesis according to which hs-CRP levels in severe AP were higher than in the patients with moderate to mild forms of pancreatitis, when those levels were

measured in the early phase, 24-48 hours after the onset. Therefore, -hs-CRP levels were measured using serum from the patients with acute pancreatitis. CRP is known to be a sensitive acute phase protein produced by the liver upon the inflammatory stimulation produced by cytokines.

In AP, macrophages can stimulate cell-mediated immunity through the activation of lymphocytes and releasing the cytokines derived from T IL-6, IL-1 cells and the tumour necrosis factor. It has also been hypothesized that this increase of CRP may partly be due to the pancreatic tissue and the production from the inflammation site.

The average level of hs-CRP was of 222760/32197 ng / ml in the patients with severe AP and of 22798/8216 ng / ml in the patients with mild to moderate pancreatitis with markedly greater levels in severe cases. Although the severe cases had lower CRP levels when they were measured immediately after the onset, hs-CRP levels were higher then. Mild to moderate pancreatitis had levels of hs-CPR of 1800 and 55400 ng / ml, respectively, compared with those seen in the severe cases. When the highest limit was more than 83400ng / ml on admission, ROC analysis was performed, the sensitivity and specificity of the patients included in the study were of 90% and 100%, respectively, while the positive predictive values were of 100%, 90.9% respectively.

Taking into account these results, the evolution to a severe condition is evident when hs-CRP levels exceed 83400ng / ml in the early phase of acute pancreatitis, demonstrating that measuring hs-CRP can be used as a simple and cheap method. Hs-CRP levels were found to increase significantly in the early phase of severe pancreatitis, suggesting that hs-CRP could serve as an early indicator of the evolution of AP in a severe condition. Since the hs-CRP levels in the early phase after the onset of AP can be measured only in a small number of patients as in the present study, the reason of the dissociation of CRP and hs-CRP remains incomprehensible and should be clarified in the future.

The combination of CRP and leukocytosis has a good predictive value for infection, and it is useful in detecting bacterial infection, being superior to the number of leukocytes.

CONCLUSIONS

Our study shows that CRP test is the best method for the detection of pancreatic necrosis at cut-off values of 150 mg / dl, with a specificity of 92% and an accuracy of 96%.

The results show that the CPR values increase significantly in the early stages of necrotic pancreatitis. It is a prognostic marker of pancreatic necrosis with the highest sensitivity and accuracy at a cut-off value of 150 mg / dl. Patients with values below 150 mg / dl are unlikely to evolve towards pancreatic necrosis.

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