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INTERLEUKIN IL-6 PROGNOSTIC MARKER OF EARLY DIAGNOSIS OF EXCERING CHRONIC PANCREATITIS

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✓ ***Resume***

We conducted a single-center, open-label, randomized, prospective study to evaluate the role of pro-inflammatory cytokines in the pathogenesis of acute pancreatitis. The significance of serum levels of interleukin-2-R and interleukin-6 in predicting the outcome of acute pancreatitis was evaluated. Acute necrotizing pancreatitis is a serious illness with high morbidity and mortality. This non-infectious destruction of the pancreatic parenchyma rapidly induces an inflammatory response at the site of injury. The difference between acute pancreatitis and other diseases of the gastrointestinal tract is its tendency to a sharp transition from a localized process to a generalized systemic inflammatory response.

Key words: pancreas, acute pancreatitis, pathogenesis, necrosis, randomized study, interleukin, pro-inflammatory

ИНТЕРЛЕЙКИН IL-6 ПРОГНОСТИЧЕСКИЙ МАРКЕР РАННЕЙ ДИАГНОСТИКИ ОБОСТРЕНИЯ ХРОНИЧЕСКОГО ПАНКРЕАТИТА

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✓ ***Резюме***

Мы провели одноцентровое, открытое, рандомизированное, проспективное исследование для оценки роли провоспалительных цитокинов в патогенезе острого панкреатита. Оценивались значение сывороточных уровней фактора интерлейкина-2-R и интерлейкина-6 в прогнозировании исхода острого панкреатита. Острый некротический панкреатит - тяжелое заболевание с высокой заболеваемостью и смертностью. Это неинфекционное разрушение паренхимы поджелудочной железы быстро вызывает воспалительную реакцию в месте повреждения. Отличием острого панкреатита от других заболеваний желудочно-кишечного тракта, является его склонность к резкому переходу от локализованного процесса к генерализованной системной воспалительной реакции.

Ключевые слова: поджелудочная железа, острый панкреатит, патогенез, некроз, интерлейкин, провоспалительный, цитокин.

SURUNKALI PANKREATIT QO'ZISH DAVRINING ERTA DIAGNOSTIKASIDA INTERLEYKIN IL-6 MARKERI

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O'tkir pankreatit patogenezida yallig'lanishni kuchaytiradigan sitokinlarning rolini baholash uchun bitta markazli, ochiq yorliqli, randomizatsiyalangan, istiqbolli tadqiqot o'tkazdik. O'tkir pankreatitning natijasini taxmin qilishda interleykin-2-R va interleykin-6 darajasining ahamiyati baholandi. O'tkir nekrozlangan pankreatit yuqori darajada kasallanish va o'limga olib keladigan jiddiy kasallikdir. Oshqozon osi bezi parenximasining bu yuqumli bo'lmagan halokati shikastlanish joyida tezda

yallig'lanish reaktsiyasini keltirib chiqaradi. O'tkir pankreatit va oshqozon-ichak traktining boshqa kasalliklari o'rtasidagi farq shundaki, uning lokalizatsiya qilingan jarayondan umumiy tizimli yallig'lanish reaktsiyasiga keskin o'tish tendentsiyasi.

Kalit so'zlari: oshqozon osi bezi, o'tkir pankreatit, patogenez, nekroz, sitokin, interleykin

Relevance

Acute necrotizing pancreatitis is a serious illness with high morbidity and mortality. This non-infectious destruction of the pancreatic parenchyma rapidly induces an inflammatory response at the site of injury. The difference between acute pancreatitis and other diseases of the gastrointestinal tract is its tendency to a sharp transition from a localized process to a generalized systemic inflammatory response. Ultimately, it is this abrupt transition that is responsible for most of the development and prognosis of the disease [1,2].

Nearly all patients with even mild pancreatitis will exhibit some systemic manifestations such as fever, tachycardia, hypovolemia, tachypnea, and hypoxia, with up to 12% of them manifesting respiratory failure, shock, or even multisystem organ failure (MOSF). Unsurprisingly, much of pancreatitis research has focused on identifying inducers of this systemic disease, which is now known to include the potent cytokines interleukin-1 (IL-1), IL-2, IL-6, tumor necrosis factor-a (TNF- a), etc. Cytokines have been shown to play a key role in multiple organ dysfunction, the leading cause of death in severe acute pancreatitis.

The inability to correctly identify acute necrotizing pancreatitis at admission using only clinical information has led to the development of a number of more objective means of assessing severity, including the Ranson and Glasgow and Acute Physiology and Chronic Health Evaluation (APACHE II) systems and many individual serum parameters [1 –6]. Concentrations of serum mediators of the acute phase protein response, cytokines, were considered faster predictors of prognosis. Although the exact mechanisms triggering the inflammatory and necrotic process are not fully understood, it is generally accepted that activated leukocytes play an important role in the pathogenesis of acute pancreatitis (7, 8). Despite the fact that there is a huge amount of data on the role of cytokines in the development of the systemic inflammatory process in acute pancreatitis, the predictive reliability and temporal dynamics of these latter in acute pancreatitis are not completely clear

The aim of this study was to evaluate the role of IL-II R, IL-6 in the prognosis of acute pancreatitis by serially determining serum concentrations within 1 week after hospitalization. We also compared the predictive values of the APACHE II diagnostic tool (9) with cytokine levels.

Material and methods

For this study, seventeen randomly selected patients with acute pancreatitis were recruited among 28 admitted to the gastroenterology department at the RSCEMP clinic from 01.2019 to 06.2019. The diagnosis of acute pancreatitis was based on the presence of abdominal pain associated with serum amylase and lipase levels more than three times the upper limit of normal (normal amylase <180 IU / L, lipase <190 IU / L). Abdominal diseases with similar clinical manifestations, such as perforated peptic ulcer disease and intestinal obstruction, were excluded. The study included only patients who had an acute pancreatitis attack within 24 hours. Patients with traumatic pancreatitis, acute pancreatitis caused by surgery or endoscopic intubation, and patients with diabetic ketoacidosis, non-ketotic hyperosmolar syndrome, or pregnancy were excluded.

The control group were randomly selected 7 patients, for the same period receiving treatment, with a subacute course of pancreatitis, did not require treatment in intensive care.

Methods: Serum samples for determination of IL-2R and IL-6 were collected on the day of hospitalization (day 1), the morning of the third day, and the morning of the fifth day of hospitalization. Sera for cytokine determination were stored at -80 ° C prior to assay. Appropriate laboratory and physiological data were recorded on days 1, 2 and 3 to allow the APACHE II score to be calculated [3,16]. Weights for age and chronic health were added for the final assessment. Abdominal ultrasound in each case was performed within 72 hours of admission. In the study, severe seizure was defined as a) local complications (necrosis, abscess, or pseudocyst); b) systemic complications (acute respiratory failure, renal failure, heart failure or

sepsis); or 3) death [6,17]. Patients were followed up prospectively until discharge or death.

Determination of cytokines

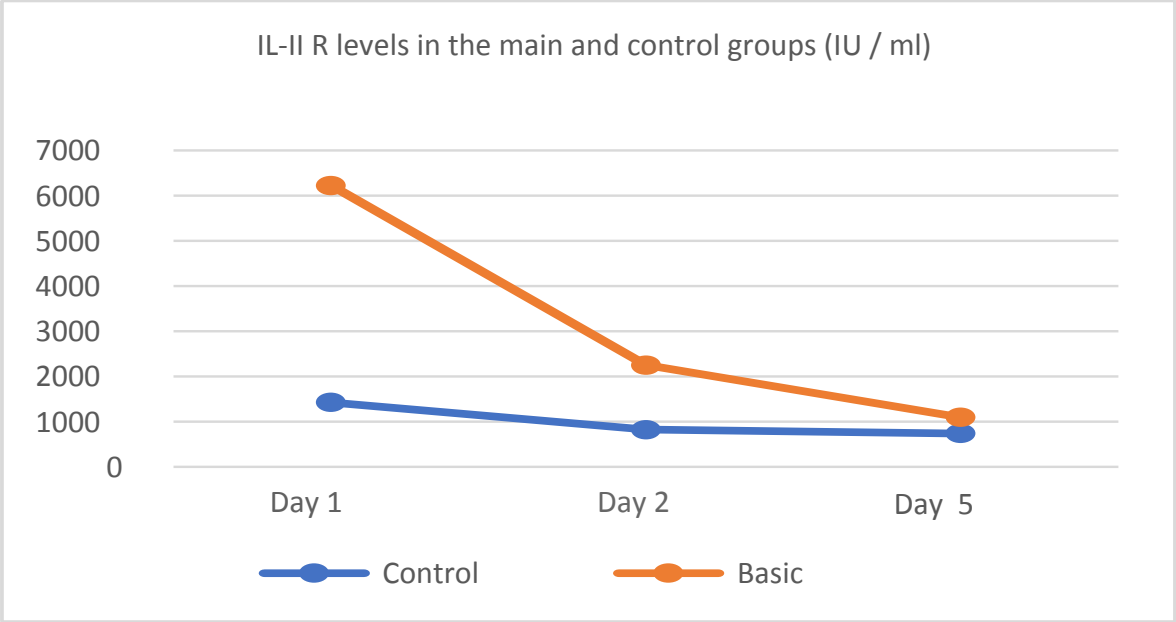
Serum IL-2R and IL-6 levels were determined using commercial enzyme-linked immunosorbent assay (ELISA) kits.

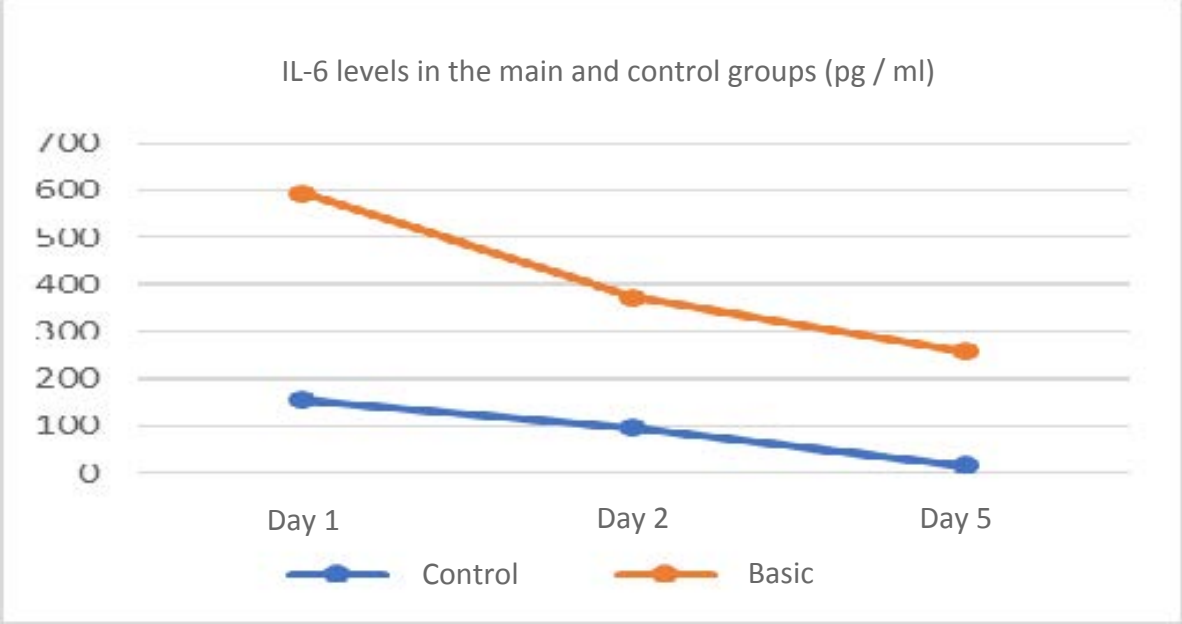
Statistical analysis

Data were expressed as mean ± standard error of the mean. The Mann-Whitney U test was used for statistical analysis. Correlation between serum markers was assessed using linear regression analysis. A p-value <0.05 was determined to be statistically significant.

Result and discussion

The main group included 14 men and 3 women, whose average age was 51.2 ± 14.9 years (from 33 to 88 years) who developed serious complications (eight cases of pancreatic necrosis, three cases of abscess, three cases of pseudocyst, and three deaths), while the control group with seven patients (five males, two females, whose average age was 48.3 ± 17.3) with a subacute course recovered without complications. Serum IL-II R, IL-6 levels on days 1, 3, and 5 of the study and control groups are shown in Charts 1 and 2, respectively.





Serum concentrations of IL-2R and IL-6 on days 1, 3 and 5 were significantly higher in patients from the main group than in patients from the control group. The mean peak IL-2R and IL-6 were reached on the first day. Peak serum concentrations (mean values) of IL-II R and IL-6 were 7500 IU / ml and 522 pg / ml, respectively, in fatal patients. APACHE II indices in the main group were significantly higher than in the control group on days 1 and 2 (day 1: 11.9 ± 1.3 versus 5.8 ± 0.8, p <0.0005; day 2: 12.0 ± 1.2 versus 5.1 ± 0.5, p <0.0001).

Table № 1. Comparison of interleukin levels with the APACHE II diagnostic tool

		Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
IL-II R	Day 1	72	87	76	85	82
	Day 3	56	78	63	80	74
IL-6	Day 1	89	87	80	93	88
	Day 3	50	97	90	78	80
APACHE II	Day 1	72	72	59	82	72
	Day 3	56	91	77	78	78

The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of IL-II R, IL-6 and APACHE II indicators for predicting the severity of pancreatitis on days 1 and 2 are equal shown in Table 1. On day 1, serum IL-6 had a higher sensitivity and accuracy compared to IL-II R. The correlation between the pro-inflammatory cytokines IL-II R, IL-6 on days 1 and 3 was r-0.32 (P <0.05) and r-0.53 (P <0.0005), respectively. Although serum amylase and lipase levels play a huge role in the pathogenesis of acute pancreatitis, we did not observe a significant difference in serum levels of amylase (2738 ± 621 versus 2601 ± 296 IU / L) or lipase (5521 ± 1123 versus 4352 ± 699 IU / L) between the main and control groups.

In the early 1990s, the appearance of inflammatory cytokines in the blood serum in animals with experimentally induced pancreatitis was clarified. Since then, many studies have been carried out that determined the activity of certain cytokines in the pathogenesis of acute pancreatitis. Contrary to the above, the pathogenesis of acute pancreatitis has not yet been fully understood, although there are many theories, such as the theory of the inflammatory factor, the theory of intestinal bacterial translocation, impaired microcirculation, the theory of self-digestion by trypsin, and the theory of oxidative stress (10). It is generally believed that a large number of pancreatic enzymes are activated in the patient's body due to various etiological factors, which leads to edema and necrosis of the pancreas and surrounding tissues [11]. Late diagnosis and initiation of treatment can cause complications with various symptoms and impairment of the function of other organs. Often, the development of a violation of the intestinal immune barrier due to acute pancreatitis leads to the release of a large number of bacteria and endotoxins, which primarily migrate to the liver, causing liver damage, which facilitates the development of high endotoxemia and hyperinflammatory process. Pathogenic factors in the future can overcome the liver barrier and enter the systemic circulation, causing sepsis and other serious complications. To date, it is not a discovery to reveal the activity of IL-6 in the blood serum, as well as IL-II R. Although our study had a number of shortcomings in the form of a study in one center and a small number of participants (due to the high cost of studies), we tried to find available and sensitive methods for early diagnosis of acute pancreatitis. According to the available literature, we knew that the increased secretion of proinflammatory cytokines by activated monocytes and mononuclear phagocytes is of great importance for this process. Among other things, we have demonstrated that patients with severe

pancreatitis had much higher serum IL-6 and IL-II R values than patients with mild forms of the disease [12, 15].

Early prediction of the severity of acute pancreatitis is important for adequate treatment. Serum markers such as CRP, polymorphonuclear granulocyte elastase, antiproteases, and IL-6 have been reported to be useful indicators of the severity of acute pancreatitis (4-6, 9-11). In the present study, we have shown once again that serum IL-6 is an early marker (1 day after admission). The sensitivity, specificity and accuracy of predicting severe course were 89%, 87% and 88%.

The predictive power of serum IL-II R on the first day was not as good as that of serum IL-6 (82% versus 88% in terms of accuracy).

We also knew that in fatal patients, the most markedly elevated IL-6 concentrations were on days 1 and 2, and they increased continuously on day 7 (9, 10). The levels of proinflammatory cytokines in the blood serum in our mortality cases were noticeably higher than in other patients with severe pancreatitis (2–5 times higher than the average statistical values). Due to the small number of cases, it was not possible to assess the correlation of serum cytokine concentrations and death.

The study showed that the level of IL-6 in the blood serum has the best value for the early assessment of the severity of acute pancreatitis among the pro-inflammatory cytokines. We recommend that serum IL-6 levels be measured on the day of hospitalization in all patients with acute pancreatitis.

Conclusion

Among the proinflammatory cytokines, interleukin-6 turned out to be the most sensitive parameter for the early prognosis of acute pancreatitis.

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