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Serum matrix metalloproteinases MMP-9 and MMP-2 and tissue inhibitors TIMP-2 in necrotizing enterocolitis

Abstract

The analysis of the balance of elastase (MMP-2, MMP-9) and TIMP-4 was performed in order to determine their involvement in the pathogenesis of NEC. A progressive duration of NEC with sepsis is accompanied by increased serum concentrations of MMP-9, MMP-2 and TIMP-4. Increases in concentrations of MMP-2>503 ng/ml, MMP-9>812 ng/ml TIMP-4>1404 ng/ml can be regarded as statistically significant predictors of fatal outcome of NEC. The proposed method for determination of the outcomes of NEC in newborns is characterized by high sensitivity (94%) and specificity (87%).

Keywords: necrotizing enterocolitis, newborn, sepsis, matrix metalloproteinase MMP-9 matrix metalloproteinase MMP-2, tissue inhibitors of matrix metalloproteinase TIMP-2

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Introduction

Necrotizing enterocolitis (NEC) is a serious illness primarily in preterm newborns characterized by rapid coagulation necrosis of distal ileum, and in severe cases of the entire intestine. The spectrum of clinical manifestations is presented by reversible intestinal disorders to fulminant forms, accompanied by gangrene of the intestinal wall perforation, development of abdominal sepsis and septic shock.[1,2] One of priority directions in the study of NEC pathogenesis is a search of reliable molecular markers which help to identify the severity of the disease and to determine the prognosis and the selection of individual treatment strategies.[3] Currently, the prognosis of the duration of the disease is based on the use of standard criteria including clinical symptoms, laboratory parameters and morphological characteristics of the disease. Matrix metalloproteinases (MMPs), zinc endopeptidase are synthesized in a latent form and activated by proteolytic cleavage of the amino-terminal domain or conformational changes induced by oxidative stress and take a part in the degradation of collagen type IV, which is the main component of the basal membrane and it contributes to the destruction of gastrointestinal perforation.[4,5] Taking into consideration the complexity of the effects of the components of MMPs and TIMPs, their study as prognostic factors and course of NEC is relevant.

Purpose of the study is to study the role of matrix metalloproteinases MMP-9 and MMP-2 and **tissue** inhibitors TIMP-2 in newborns with NEC.

Materials and methods

The study was approved by the local medical ethics committee. The patients were divided into two groups. Group I (n=25) were defined as premature infants (≤ 37 completed weeks) without NEC, sepsis or septic shock, systemic inflammatory response syndrome. Group II (control group, n=30) included infants with proven NEC (Bell's stage III) who were treated in the intensive care unit of the University Medical center between September 2012 and June 2019. The distribution of gestational age, birth weight, and gender was similar in NEC and control groups.

Concentrations of elastase (MMP-9, MMP-2) and their tissue inhibitors of metalloproteinases (TIMP-2) in the blood plasma in group II were determined twice: in the occurrence of the first clinical presentation and 7 days after the surgery. In group II concentrations of elastase (MMP-9, MMP-2) and their tissue inhibitors of metalloproteinases (TIMP-2) in the blood plasma were determined once in the occurrence of the first clinical presentation. Blood was sampled by venipuncture and the serum harvested after centrifugation was stored at -20°C. Plasma enzyme concentration was quantified using a commercially kits for ELISA (Human Human MMP-9 Quantikine ELISA Kit, Human Human MMP-9 Quantikine ELISA Kit Human Human TIMR-1 Quantikine ELISA Kit, R & D Systems, USA) by ELISA analyzer ANTHOS 2020 (Austria). SPSS 17.0 software was used for statistical analysis with the methods of linear correlation and discriminant analyzes. All data were presented as mean±SD. The links between continuous variables were examined using Spearman rank correlation. Statistical differences between two groups were evaluated using unpaired Student's t-test or Kruskal-Wallis test. Differences were considered statistically significant at $P < 0.05$.

Results and discussion

According to the primary statistical processing all investigated parameters in patients in group II were significantly ($p < 0.01$) differed from control values**.** Significant differences ($p < 0.05$) were observed for MMP-2, TIMP-4 at all in patient of NEC. Ehe value of MMP-9 did not differ significantly between the groups. In patients with a fatal outcome average values of MMP-9 and TIMP-4 were higher than in survived patients by 2-times ($p < 0.01$) and a strong positive correlation between TIMP-4 and MMP-2 ($r = 0,81$; $p < 0.01$) are detected.

In patient with sepsis the production of MMP-9 and TIMP-4 was accompanied increased by 2.3-times (p <0.01) compared to those values in patients without signs of sepsis.

The deaths of patients with signs of sepsis were accompanied by a significant (p <0.01) increase in the average concentration of TIMP-4 (2085 ng/ml) and MMP-9 (1032 ng/ml). In patients without signs of lethal sepsis the average concentrations of TIMP-4 (1306 ng/ml) and MMP-9 (668 ng /ml) were elevated.

After operation in recovered patients the average concentrations of MMP-2 decrease by 1.5-times (p <0,01) and of TIMP-4 by 1.5 times (p <0,05), however, remained significantly higher than control values. The ROC analysis showed that the predictors of mortality in newborn with NEC were the following: TIMP-4 (AUC = 0,74, 95% CI = 0.62 to 0,97; P <0,001), MMP-2 (AUC = 0,95, 95% CI = 0.9 to 0,99; P <0,001), MMP-9 (AUC = 0,68, 95% CI = 0.52 to 0,84; P <0,003).

Optimal values for each predictor of mortality were: MMP-2> 503 ng/ml, MMP-9> 812 ng/ml, TIMP-4> 1404 ng/ml. Sensitivity of the test was 94%, specificity 87% and it proves the high quality of our proposed method for determining the basis of NEC.

Discussion

The analysis of the balance of elastase (MMP-2, MMP-9) and TIMP-4 in order to determine their involvement in the pathogenesis of NEC was performed. According to some investigations, in samples of removed intestinal tissue in the patients with NEC, the levels of expression of MMP-2, MMP-9 and TIMP-2 remained unchanged.[6] We have not found significant differences between the average concentrations of elastase and TIMP-4 in patients with NEC. High levels of MMP-9 and TIMP-4 in the blood serum were found in patients with sepsis and fatal outcome, which may be important for understanding the pathophysiology of sepsis in the patients with NEC. The role of MMP - 2, MMP -9 and TIMP -4 in sepsis remains unclear, but some studies indicate that MMP play a certain role in the migration of leukocytes from the blood in inflammation by MMP-mediated proteolysis of the basement membrane.[7] The development of endotoxemia might lead to the release of MMP-9, MMP-2 and TIMP-4, which explains the significant correlation differences between these parameters in patients with sepsis. Also, while MMP-9 is mainly released by activated leukocytes, the observed differences cannot be explained by the presence of leukocytosis, as the values were approximately the same in survived and not survived patients with NEC.[8]

Having analyzed the characteristics of ROC curve, we found out that serum levels of TIMP-4 and MMP-2 were good predictors of mortality in patients with NEC with high sensitivity and specificity. From a clinical point of view, a highly sensitive test may have overdiagnosis, but it helps to minimize the risk of missing the disease, which is important, for example, in determining the prognosis of NEC because of the high mortality in the development of complications.

Conclusion

A progressive duration of NEC with sepsis is accompanied by increased serum concentrations of MMP-9, MMP-2 and TIMP-4. Statistically significant predictors of fatal outcome of NEC can be regarded as an increase in the concentrations of MMP-2> 503 ng / ml, MMP-9> 812 ng / ml TIMP-4> 1404 ng / ml. The proposed method for determination of the outcomes of NEC in newborns is characterized by high sensitivity (94%) and specificity (87%).

Acknowledgments

None.

Conflicts of interest

None.

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