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Association of IL-6 in Serum with Endotoxin Translocation and Expression of Tight Junction Proteins in Colon from Patients with Severe Acute Pancreatitis *

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ABSTRACT: There is increasing evidence that severe acute pancreatitis (SAP) patients have high IL-6 levels in serum, and the low expression of tight junction proteins could increase endotoxin translocation (ET). Thus, we sought to investigate the correlation of IL -6 level in serum with endotoxin translocation (ET) and expression of tight junction (TJ) proteins in colon from severe acute pancreatitis patients. **Methods:** 50 severe acute pancreatitis patients were set as study objects. 12 of 50 patients for clinical course in the first 3 days with colonic involvement presented with severe abdominal distention, they were treated with adopt colonic irrigation and decompression with colonoscopy, and colonic mucosal tissue were obtained at the same time. All blood samples of the patients were extracted from their peripheral venous after treatment for the first ,3rd,7th,10th,14th day. 40 healthy individuals were set as control group. Serum IL-6 concentrations were determined by enzyme-linked immunosorbent assay (ELISA), levels of serum endotoxin were detected by limulus amebocyte lysate (LAL) assay, the expression of TJ proteins were determined by immunofluorescence and western blotting. **Results:** The levels of IL-6 and endotoxin in serum of SAP patients were higher than in healthy controls. However, the expressions of TJ proteins in SAP patients were lower than those in healthy controls. Compared with the late stage clinical course of SAP patients, the early stage clinical course of SAP patients had a significantly higher levels of endotoxin ($P<0.05$) and IL-6 ($P< 0.05$) in serum. The lower expression of TJ proteins in colonic mucosa had significantly ($r=0.735$, $P< 0.05$) associated with the higher levels of IL-6 in serum within 3 days clinical course of SAP. **Conclusions:** In our research, we found that the high levels of IL-6 in serum had closely relationship with high levels of endotoxin in serum and low expression of tight junction proteins in colonic mucosa. The levels of IL-6 in serum, as an index to evaluate the severity of severe acute pancreatitis, is associated with the clinical course of severe acute pancreatitis, and may the reason of endotoxin translocation.

Key words: Severe acute pancreatitis; Tight junction proteins; Colonoscopy; Endotoxin translocation; IL-6

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Introduction

Severe acute pancreatitis (SAP) develops in about 25% of patients with acute pancreatitis [1]. It is associated with a high morbidity and a mortality risk of up to 27%-45%, and the majority of deaths related to SAP are the result of infectious complications [2]. Bacteria translocation mainly from the gut is the most widely accepted mechanism in the pathogenesis of infected pancreatic necrosis [3]. The colon is one of the largest repository of bacteria and endotoxin, and also is the source of inflammatory mediators and cytokines in SAP, so much more attention should be paid to SAP patients with colonic involvement. Although, colonic irrigation with endoscope has applied to SAP patients with colonic involvement [4], few reports are performed using endoscopic biopsy for SAP patients. The intestinal mucosa barrier mainly determined by intestinal epithelial barrier and distribution of microbial flora, the intestinal epithelial barrier is composed of tight junction (TJ) between intestinal epithelial cells, the tight junction proteins form and regulate the paracellular pathway [5,6]. A functioning TJ is formed by multiple proteins, including Claudin proteins, Occludin proteins, Junction adhesion moleculars (JAMs), Zonula occludens proteins (ZOs). The claudin family of proteins is composed of at least 24 closely related transmembrane proteins, most of them are well characterized at the gene and protein levels [7]. Thus, claudins and occludin are considered to be the most prominent members in TJs [8]. Cytokines IL-6 produced by T cells and fibroblasts could down-regulated the expression of tight junction proteins, and reduce TJ proteins distribution in the membrane area of intestinal epithelium [9,10]. In our study, endoscopic biopsy had performed to the patients, and the association of high levels of IL-6 in serum with the low experssion of TJ proteins in colonic mucosa had been proved in our experiment.

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The mechanism of intestinal endotoxin translocation caused by SAP remains largely unknown. In humans, there is increasing evidence that the injury of intestinal barrier function is premise of endotoxin translocation [11]. In such cases, IL-6 could lower the expression of TJ proteins in colonic epithelium, lead to the gut barrier function injury, which is the main reason of intestinal endotoxin translocation.

Fifty severe acute pancreatitis patients were included in our study, colonoscopy was performed to the patients, and meanwhile colonic mucosa tissues were obtained. Eenzyme-linked immunosorbent assay (ELISA) was used to detect IL-6 in serum, limulus amebocyte lysate (LAL) assay was used to detect endotoxin, immunofluorescence and western blotting were used to detect the expression of tight junction proteins of colonic mucosa.

1 Information and Methods

1.1 General data

The present study involved 50 consecutive patients with SAP from July 2011 until June 2013 at the Affiliated Hospital of Medical College, Qingdao University and Jinlin Hospital, Nanjing University. Male and female SAP patients(≥ 18 and ≤ 70years of age) hospitalized within 24 hours of onset of symptoms were enrolled. The diagnostic criteria formulated for SAP at the Bangkok World Congress of Gastroenterology 2002 in Thailand adopted [12]. Patients with one of the following were included in the study: (i) local complications (pancreatic necrosis, pancreatic pseudocyst, pancreatic abscess), (ii) organ failure, (iii)APACHE-II score≥ 8, (iv)Ranson criteria≥ 3, (v) Bahhazar CT grading II or above. Patients with any of the following were excluded from the study: (i) concurrent sepsis or pancreatic infection or peripancreatic infection caused by a second disease,(ii) patients with acute or chronic gastrointestinal diseases, (iii) sent directly to the intensive care unit for multiorgan failure, (iv) post-encoscopic Retrograde Cholangio-Pancreatography or traumatic or operative pancreatitis, (v) pregnancy, malignancy, immunodeficiency or moribund patients regardless of cause within 48 hours prior to enrollment. The ethics committee of the hospital approved the study protocol. Informed consent was obtained from each patient, and informed consent was also obtained from each healthy individual. 12 of 50 patients of clinical course in the first 3 days with colonic involvement presented with severe abdominal distention, colonic irrigation and decompression with endoscope were treated to them, and colonic mucosal tissue were obtained. Meanwhile the peripheral venous blood were obtained at the same time. The twelve patients were done colonoscopy in the condition of monitoring beside the bed. All blood samples were obtained on the frist,3rd,7th,10th,14th day from each patient and healthy control.

1.2 Quantification of serum IL-6 levels

Eenzyme-linked immunosorbent assay (ELISA) was used to detect IL-6 in serum obtained from SAP patients and healthy controls using Human Quantikine kits (R&D Systems,Abingdon, UK), according to the manufacturer's protocol.

1.3 Quantification of serum endotoxin concentrations

The endotoxin assay based on a Limulus amebocyte extract with a chromogenic Limulus amebocyte lysate (LAL) assay (QCL-1000, Lonza Group Ltd.). Samples were diluted in pyrogen-free water and heated at 70 ℃ for 10 min to inactivate endotoxin-neutralizing agents that inhibit the activity of endotoxin in the LAL assay. Then, pyrosperse reagent (Lonza Group Ltd.), a metallo-modified polyanionic dispersant, was added to the test samples at a ratio of 1/200 (v/v) before LAL testing to minimize interference in the reaction. Internal control of recovery calculation was included in the assessment. All samples were tested in duplicate and results were accepted when the intra-assay CV was less than 10 %. The endotoxin content was expressed as endotoxin units (EU) per ml. Exhaustive care was taken to avoid environmental endotoxin contamination and all material used for sample preparation and the test was pyrogen-free.

1.4 Visualization of TJ proteins OC, CL−2, and ZO−2 by immunofluorescence

Immunofluorescent staining were carried out for OC, CL-2, and ZO-2 in specimens. After blocking of endogenous peroxidases for non-specific binding, slides were incubated in 1% bovine serum album (BSA) for 30 min. After washing in PBS, primary antibodies (rabbit anti-human CL-2 antibody: Zymed Laboratories, San Francisco, USA; rabbit anti-OC antibody: Santa Cruz Biotechnology, Santa Cruz, USA; mouse anti-ZO-2 antibody: BD, Heidelberg, Germany) were applied according to the dilutions advised by the manufacturers. Isotype staining assured specific staining results. Slides were then incubated with goat anti-rabbit Alexa546 or goat anti-mouse Alexa546 secondary antibody, respectively (Molecular Probes/Invitrogen, Karlsruhe, Germany). Nuclei were stained with 4', 6-diamidino-2-phenylindole (DAPI) with a mounting medium (Vectashield, Vertor Laboratories). Immunofluorescent-stained sections were captured (at 4 high-power fields) with a microscope at the indicated magnifications using fluorescent light (Axiovert, Zeiss, Goettingen, Germany).

1.5 Quantification of TJ proteins OC, CL−2, and ZO−2 by western blotting

Western blotting analyses were undertaken according to standard protocols using the following primary antibodies: rabbit anti-claudin-2 (Zymed), mouse anti-occludin (clone 19, 1:250 dilution; BD, San Diego, USA) and mouse anti-ZO-2 (clone 1, 1:250 dilution; BD). Membranes were blocked at room temperature for 1 h in Tris buffer saline containing 0.05 % Tween 20 (TBS-T) and 5 wt % non-fat dry milk. Nitrocellulose membranes were incubated with primary antibodies for 1h at room temperature under slight agitation. Specific staining was controlled using the corresponding isotypes. Equal loading was ensured by staining with mouse an-

ti-β-actin antibody (clone C4, 1:3,000 dilution; Chemicon, Temecula , USA). After washing, the according horseradish peroxidase (HRP)-conjugated secondary antibody (goat anti-rabbit IgG-HRP, 1:8,000; goat anti-mouse IgG-HRP,1:3,000 dilution; BD) was added and the membrane incubated for a further 1 h under gentle shaking. Proteins were detected using the ECL-Plus-western blotting detection system (Amersham Life Science,Braunschweig, Germany). Protein bands were quantified by densitometry using Image-Pro Plus 6.0 (Media Cybernetics, Maryland, USA).

1.6 Stastical analysis

Continuous variables are expressed as means ± SE，and categorical variables as frequency or percentages. Statistical differences in basal characteristics between groups were analyzed using the χ^2 test for categorical data and the two sample t-test for quantitative data. P <0.05 were considered to indicate statistical significance. All analyses were conducted using the SPSS software (ver. 18.0).

2 Results and analysis

2.1 Patients characteristics

Features of the SAP patients and healthy individuals are shown in Table 1. No significant difference was noted in gender, age (P＞0.05). Statistically significant differences were found in Ranson score and APACHE-II score between SAP patients and healthy control (P＜0.05).

Table 1 Characteristics of patients and healthy control

	SAP	healthy control	P
Gender (M/ F)	32/18	22/18	0.162[a]
Age (years)	58.0± 13.5[b]	56.5± 11.0	0.724[c]
Ranson score	4.2± 1.9	2.3± 1.1	＜0.05[c]
APACHE-II score	10.6± 1.2	5.5± 2.1	＜0.05

Note: HC: healthy control. a Pearson's x2-test, b mean ± SD (all such values)，c two-sample t-test.

2.2 The levels of IL-6 and endotoxin in different groups

Table 2 shows the levels of IL-6 and endotoxin in serum of 50 SAP patients and 40 healthy individuals. We found significantly higher levels of IL-6 and endotoxin in ealy stage(clinical course in 0~7day) of SAP patients than late stage (clinical course in 8~14day) of SAP patients (P<0.01). A relative correlation (r= 0.735, P＜0.05) between IL-6 and endotoxin in clinical course of SAP is shown in Figure 1.

Table 2 The serum IL-6 and endotoxin levels in patients and healthy control ($\bar{x}$± s, pg/mL)

	HC(n=40)					SAP(n=50)				
	1d	3d	7d	10d	14d	1d	3d	7d	10d	14d
IL-6	36.5± 12.3	37.3± 11.2	37.6± 12.6	35.8± 10.7	36.4± 11.9	120.4± 15.2	162.4± 17.1	170.8± 18.3	153.8± 21.6	110.3± 22.1
Endotoxin	4.08± 1.21	4.12± 1.26	5.02± 2.01	4.88± 1.96	4.66± 1.92	9.71± 2.24	14.12± 2.89	17.22± 3.09	12.16± 3.11	9.15± 3.04

Note: HC: healthy control. P＜0.05 SAP vs. HC. P＜0.05 ,SAP(≤ 7d) vs. SAP(＞7d).

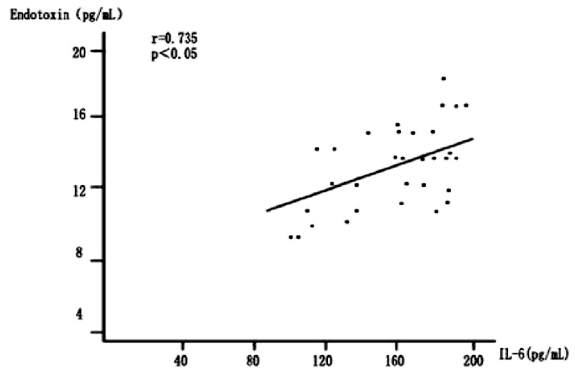

Fig.1 The relationship between IL-6 and endotoxin in SAP.

2.3 The levels of IL-6 in serum and TJ proteins OC, CL-2, and ZO-2 in different groups

Table 3 showed the levels of IL-6 in serum and TJ proteins OC, CL-2, and ZO-2 in colonic mucosa tissue with SAP patients of clinical course within 3days. Statistically significant differences were found higher levels of IL-6 and lower expression of TJ proteins between SAP patients and healthy controls (P<0.05). As seen in Figure 2, the tissues from SAP patients decreased levels of CL-2 could be detected by immuneofluorescence staining. The claudin-2 proteins were detected mainly under the epithelium cells and presented spot granular staining in epithelium of healthy patients, whereas much more spot granular staining existed in the whole epithelial cells of SAP patients. OC and ZO-2 accumulated in the entire mucosa, and was obviously decreased in SAP patients. And the western blot analyses confirmed these differences.

Table 3 The levels of IL-6 in serum and the expression of TJ proteins OC, CL-2, and ZO-2 in colonic mucosa tissue ($\bar{x}$± s, n%)

	HC(n=40)	SAP(n=12)
IL-6(pg/mL)	36.7± 11.8	150.6± 16.7
TJ proteins [(n)%]		
CL-2	0/40 (100%)	9/3 (25%)
OC	2/38 (95%)	10/2 (17%)
ZO-2	3/37 (93%)	11/1(8%)

Note: HC: healthy control. P＜0.05 IL-6 HC vs SAP, P＜0.05 CL-2,OC, ZO-2 HC vs SAP.

3 Discussion

In our study, the SAP patients with colonic involvement were

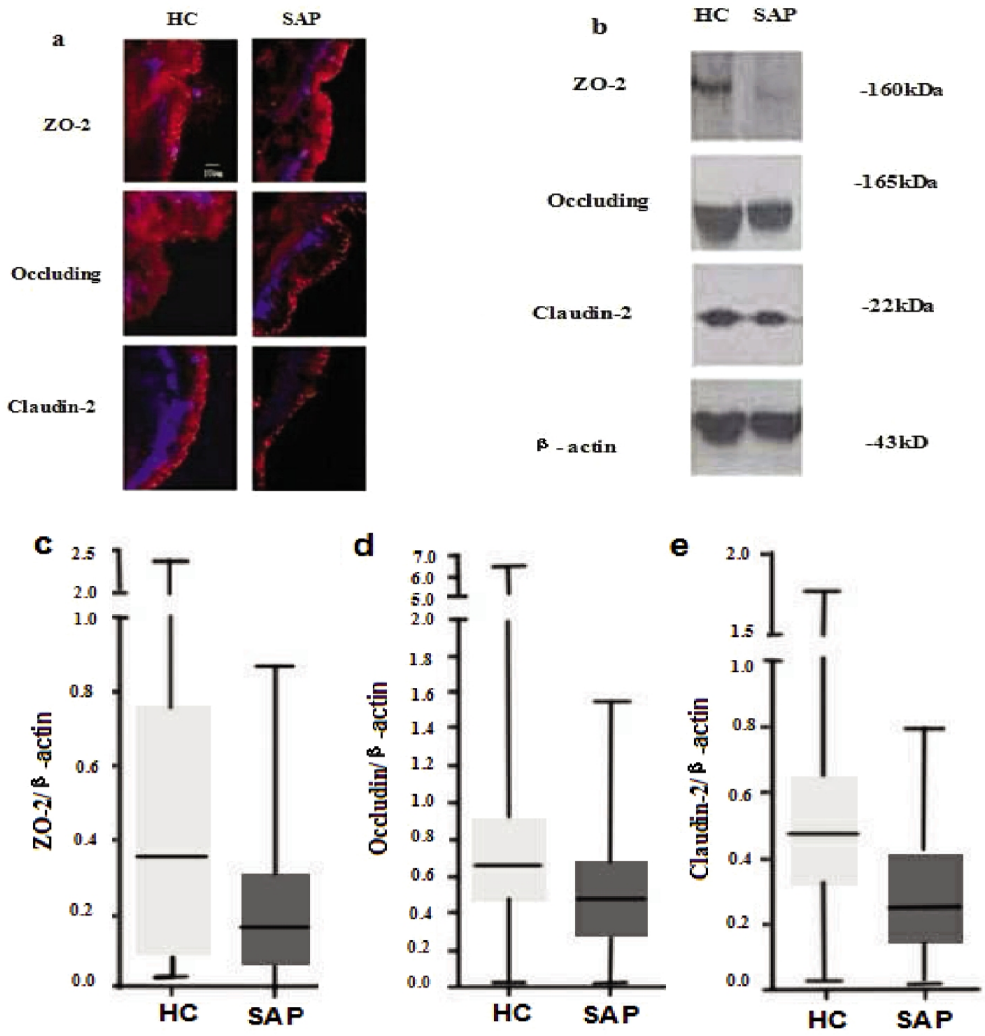

Fig.2 Localization of tight junction proteins in the colonic mucosa of SAP patients and healthy control. Representative photomicrographs show the distribution of zonula occludens-2 (ZO-2), occludin, and claudin-2 proteins in the colonic mucosa of SAP patients and healthy control (a). Expression of tight junction proteins in the colonic mucosa of SAP patients and healthy control. Representative immunoblots (b) and densitometric analyses of zonula occludens-2 (ZO-2) (c), occluding (d), and claudin-1 (e) in colonic mucosa of healthy control and SAP patients. Values are medians and interquartile ranges. c, $P < 0.05$; d, $P < 0.05$; e, $P < 0.05$.

treated with endoscope, and endoscopic biopsy had performed to them. It is found that the clinical course in the frist 3 days of SAP patients had lower expression of TJ proteins than healthy controls, but had higher levels of IL-6 than healthy controls. Further, patients in early stage of SAP had higher levels of IL-6 and endotoxin than late stage of SAP and healthy controls. Therefore, we considered that high levels of IL-6 in serum may contribute to endotoxin translocation from colon in SAP, and associate with the low expression of TJ proteins in colonic mucosa of SAP patients whose clinical course in the frist 3 days. A clinical trial defined the characteristic of bacteremia in patients with acute pancreatitis by 16S ribosomal RNA gene-based techniques [13], in such condition, we can speculate that the endotoxin is secreted by bacteria which transfers from the gut. To date, the mechanism of ET is not completely understood, some researches reported that bacterial translocation via the lymphatic pathway, and this phenomenon occurs in the earlier phases of SAP [14]. Besides, in SAP, waterfall-style release of inflammatory factors led to ischemia-reperfusion injury of gut mucosa which resulted in serious oxidative stress and severe apoptosis of gut mucosa [15], which lead to ET from gut. In our study, although we did not investigate alterations in intestinal microflora and endotoxin, it has been reported that acute pancreatitis had an intestinal bacterial overgrowth and translocation [16], the alterations of intestinal microflora could affect the expression of TJ proteins, increase the intestinal epithelial permeability, that is the main reason lead to ET, and inflammatory cytokines are also involved in the process above [17].

Considering that the patients enrolled in our study had no obvious exogenous infection, the inflammatory cytokines released in SAP patients might play an important role in the gut barrier function injury and ET. It is worth noting in our study that the severity of patients at an early stage of SAP were more serious than late stage, as reported that the initial management of severe acute pancreatitis is conservative, the previous a week conservative treat-

ment is crucial, but there are still some major controversies on conservative treatment, such as fluid therapy, antibiotic treatment, and nutrition [18]. At an early stage of SAP, it has high level of evidence that enteral feeding could reduce local and systemic infection than antibiotic prophylaxis[19]. A review reported[20], the organ failure of SAP is dynamic, in the first week of SAP predicts the clinical course and outcome. Therefore, elimination of cytokines such as IL-6 with continuous veno-venous hemofiltration (CVVH) are necessary in the early stage of SAP[21]. Otherwise, inflammatory cytokines could reduce the expression of TJ proteins, enlarge the intestinal permeability and cause ET, higher endotoxemia predicted poor outcome in severe acute pancreatitis[22].

There are some limitations to the present study. Currently, endoscopic biopsy for SAP patients has some certain risks, experienced endoscopic examination physicians are needed to performe the operation, techniques for the detection of TJ proteins in gut with SAP patients primarily include TJ proteins extraction from mucosa. Although immunofluorescence approach can lead false-positive results which the proteins of cytoplasm and cell nucleus also be detected and requires strict technology controls, it is a common method for detecting TJ proteins expression, as addressed by Magin et al[23]. Kasem and his colleagues used real-time polymerase chain reaction (PCR) to gene levels and proteins expression.This is an exact method, but is time-consuming. Certainly, better methods need to be explored in the future.

4 Conclusions

In summary, high levels of IL-6 in serum have closely associated with TJ proteins injury in SAP patients, which may contribute to the occurrence and development of ET. In future, reducing the levels of IL-6 in serum and using the intestinal mucosa protectant may be the necessary methods to reduce the riskes of ET.

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重症急性胰腺炎患者血清 IL-6 水平与内毒素移位及肠黏膜紧密连接蛋白表达关系的研究 *

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摘要 目的：大量研究表明重症急性胰腺炎（SAP）患者血清中高浓度 IL-6 和肠黏膜低表达的紧密连接蛋白可促进内毒素移位的发生。本文主要研究重症胰腺炎患者血清 IL-6 水平对内毒素移位和肠黏膜紧密连接蛋白表达的影响。**方法：**50 例重症胰腺炎患者，其中 12 例在患病早期因结肠受累合并腹胀，对 12 例结肠受累患者应用结肠镜行结肠灌洗进行腹腔减压，同时取结肠黏膜进行活组织检查。所有病人在治疗的第 3 天，第 7 天，第 10 天，第 14 天抽取外周静脉血。40 例健康志愿者作为对照组。应用 ELISA 方法检测血清 IL-6 水平，鲎试验（LAL）方法检测血清内毒素含量，应用免疫荧光和 Western blotting 方法检测肠黏膜紧密连接蛋白表达水平。**结果：**SAP 患者血清 IL-6 和内毒素含量明显高于健康对照组，而结肠黏膜紧密连接蛋白表达低于对照组；在临床治疗过程中，早期 SAP 患者血清 IL-6 和内毒素水平高于晚期（P 值均＜0.05）。SAP 早期血清高浓度的 IL-6 与结肠黏膜紧密连接蛋白的低表达具有相关性，差异有统计学意义（r=0.735，P＜0.05）。**结论：**血清 IL-6 水平可作为早期评价重症急性胰腺炎严重程度的一项指标，IL-6 水平与重症急性胰腺炎临床病程有相关性，可能导致肠道内毒素移位。

关键词：重症急性胰腺炎；紧密连接蛋白；结肠镜；内毒素移位；IL-6

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