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重症急性胰腺炎患者血清炎性因子含量与全身靶器官损伤的关系研究

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[摘要] **目的:** 研究重症急性胰腺炎(SAP)患者血清炎性因子含量与全身靶器官损伤的关系。**方法:** 选择在本院诊断为重症急性胰腺炎的85例患者作为SAP组, 选择同期体检的100例健康志愿者作为对照组, 检测血清中炎性因子、肝功能损伤指标、肾功能损伤指标、肠黏膜屏障功指标及尿液中肾功能损伤指标。**结果:** SAP组血清中PCT、TNF- α 、CRP、HMGB-1、ALT、AST、TBIL、BUN、Scr、CysC、DAO、D-乳酸、Occludin、ZO-1的含量及尿液中NGAL、KIM-1的含量均显著高于对照组; SAP患者血清中PCT、TNF- α 、CRP、HMGB-1含量与血清中ALT、AST、TBIL、BUN、Scr、CysC、DAO、D-乳酸、Occludin、ZO-1含量及尿液中NGAL、KIM-1含量呈正相关。**结论:** SAP患者血清中炎性因子的异常释放会引起肝功能、肾功能、肠黏膜屏障功能损伤。

[关键词] 重症急性胰腺炎; 炎性因子; 肝功能; 肾功能; 肠黏膜屏障

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Study on the relationship between serum inflammatory factors and systemic target organ damage in patients with severe acute pancreatitis

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View from specialist: It is creative, and of certain scientific and educational value.

[ABSTRACT] **Objective:** To study the relationship between serum inflammatory factor levels and systemic target organ damage in patients with severe acute pancreatitis. **Methods:** A total of 85 patients who were diagnosed with severe acute pancreatitis in the Second Affiliated Hospital of Xi'an Jiaotong University between June 2013 and August 2016 were enrolled in SAP group, and 100 healthy volunteers who received physical examination during the same period were enrolled in control group. Then serum inflammatory factors, liver function injury indexes, renal function injury indexes and intestinal mucosal barrier function indexes as well as urine renal function injury indexes were determined. **Results:** Serum PCT, TNF- α , CRP, HMGB-1, ALT, AST, TBIL, BUN, Scr, CysC, DAO, D-lactate, Occludin and ZO-1 levels as well as urine NGAL and KIM-1 levels of SAP group were significantly higher than those of control group; serum PCT, TNF- α , CRP and HMGB-1 levels of patients with SAP were positively correlated with serum ALT, AST, TBIL, BUN, Scr, CysC, DAO, D-lactate, Occludin and ZO-1 levels as well as urine NGAL and KIM-1 levels. **Conclusions:** Abnormal release of inflammatory factors in serum of SAP patients can cause the injury of liver function, renal function and intestinal mucosal barrier function.

[KEY WORDS] Severe acute pancreatitis; Inflammatory factor; Liver function; Renal function; Intestinal mucosal barrier

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重症急性胰腺炎(SAP)是临床上常见的危急重症,病情进展迅速、并发症发生率高、预后较差^[1,2]。在SAP的病情发展变化过程中,炎症反应的激活不仅会造成胰腺局部坏死,还会引起全身炎症反应的级联激活并造成全身炎症反应综合征(SIRS)的发生,造成多种炎症因子大量释放。SIRS的发生及病程进展会增加多器官功能衰竭综合征的发生风险,引起肾脏、肝脏、肠黏膜等靶器官的损伤^[3,4]。目前,关于全身炎症反应激活与SAP患者靶器官损伤的关系受到了越来越多的关注,为了明确炎症反应过程中炎症因子的释放与靶器官损伤程度的关系,我们在下列研究中分析了SAP患者血清炎症因子含量与靶器官肾脏、肝脏、肠黏膜损伤的关系。

1 资料与方法

1.1 一般资料

选择2013年6月~2016年8月期间在西安交通大学第二附属医院诊断为重症急性胰腺炎的85例患者作为研究的SAP组,所有患者均结合临床症状、实验室检查及影像学检查诊断为重症急性胰腺炎,入院时APACHE-II评分 ≥ 8 分。选择同期在西安交通大学第二附属医院体检的100例健康志愿者作为对照组,均体健且既往无胰腺疾病病史。SAP组中男性56例,女性29例,年龄37~55岁;对照组中男性63例,女性37例,年龄35~53岁。两组受试者一般资料的比较无显著性差异($P>0.05$)。

1.2 方法

1.2.1 临床标本采集方法 两组受试者均采集外周静脉血5 mL,SAP组患者在入院时采集、对照组志愿者在体检时采集,室温静置后凝血,离心并分离上层血清后转移入新的1.5 mL EP管中,放置在-80℃低温冰箱保存;SAP组患者入院时留取留取清洁中段尿50 mL,对照组志愿者体检时留取留取清洁中段尿,离心后取上层血清样本并保存。

1.2.2 临床指标检测方法 采用酶联免疫吸附试剂盒测定PCT、TNF- α 、CRP、HMGB-1、CysC、DAO、D-乳酸、Occludin、ZO-1的含量,采用全自动生化分析仪测定ALT、AST、TBIL、BUN、Scr含量。取尿液标本,采用酶联免疫吸附试剂盒测定NGAL、KIM-1含量。

1.3 统计学处理

采用SPSS21.0对两组间的数据进行采用 t 检验,对两资料间的相关性进行Pearson检验, $P<0.05$ 为差异有统计学意义。

2 结果

2.1 血清中炎症因子的含量

SAP组血清中PCT、TNF- α 、CRP、HMGB-1的含量均显著高于对照组。SAP组和对照组血清中PCT、TNF- α 、CRP、HMGB-1含量的差异有统计学意义($P<0.05$)。见表1。

表1 血清中PCT、TNF- α 、CRP、HMGB-1的含量($\bar{x}\pm s$)

组别	<i>n</i>	PCT	TNF- α	CRP	HMGB-1
		($\mu\text{g/L}$)	($\mu\text{g/L}$)	(mg/L)	($\mu\text{g/L}$)
SAP组	85	13.41 \pm 1.95	154.28 \pm 22.18	65.41 \pm 8.94	112.37 \pm 16.84
对照组	100	0.29 \pm 0.04	10.38 \pm 1.68	2.57 \pm 0.35	7.58 \pm 0.93
<i>t</i>		74.812	33.282	29.282	37.513
<i>P</i>		<0.05	<0.05	<0.05	<0.05

2.2 血清中肝功能损伤指标

SAP组血清中ALT、AST、TBIL的含量均显著高于对照组。SAP组和对照组血清中ALT、AST、TBIL含量两两比较的差异有统计学意义($P<0.05$)。Pearson检验显示:SAP患者血清中PCT、TNF- α 、CRP、HMGB-1的含量与血清中ALT、AST、TBIL的含量呈相关性关系。见表2。

表2 两组受试者血清中肝功能损伤指标的含量($\bar{x}\pm s$)

组别	<i>n</i>	ALT	AST	TBIL
		(U/L)	(U/L)	($\mu\text{mol/L}$)
SAP组	85	84.41 \pm 10.25	93.18 \pm 11.26	57.48 \pm 8.31
对照组	100	22.12 \pm 3.51	16.48 \pm 2.41	15.49 \pm 2.32
<i>t</i>		26.839	32.198	22.185
<i>P</i>		<0.05	<0.05	<0.05

2.3 血清中肾功能损伤指标

SAP组血清中BUN、Scr、CysC的含量及尿液中NGAL、KIM-1的含量均显著高于对照组。SAP组和对照组血清中BUN、Scr、CysC含量及尿液中NGAL、KIM-1含量两两比较的差异有统计学意义($P<0.05$)。Pearson检验显示:SAP患者血清中PCT、TNF- α 、CRP、HMGB-1的含量与血清中BUN、Scr、CysC含量及尿液中NGAL、KIM-1含量呈相关性关系。见表3。

表3 两组受试者血清中肾功能损伤指标的含量($\bar{x}\pm s$)

组别	<i>n</i>	血清			尿液	
		BUN	Scr	CysC	NGAL	KIM-1
		(mmol/L)	($\mu\text{mol/L}$)	(mg/L)	($\mu\text{g/gCr}$)	(ng/gCr)
SAP组	85	14.58 \pm 1.91	203.52 \pm 28.54	1.83 \pm 0.25	19.31 \pm 2.52	147.68 \pm 20.29
对照组	100	7.52 \pm 0.93	85.41 \pm 9.35	0.77 \pm 0.11	6.53 \pm 0.91	68.65 \pm 8.39
<i>t</i>		10.382	14.282	15.309	17.482	12.485
<i>P</i>		<0.05	<0.05	<0.05	<0.05	<0.05

2.4 血清中肠黏膜屏障功能损伤指标

SAP组血清中DAO、D-乳酸、Occludin、ZO-1的含量均显著高于对照组。SAP组和对照组血清中DAO、D-乳酸、Occludin、ZO-1含量两两比较的差异有统计学意义($P<0.05$)。Pearson检验显示:SAP患者血清中PCT、TNF- α 、CRP、HMGB-1的含量与血清中DAO、D-乳酸、Occludin、ZO-1的含量呈相关性关系。见表4。

表4 两组受试者血清中肠黏膜屏障功能损伤指标的含量($\bar{x}\pm s$)

组别	<i>n</i>	DAO	D-乳酸	Occludin	ZO-1
		(U/L)	(mg/L)	($\mu\text{g/L}$)	($\mu\text{g/L}$)
SAP组	85	6.59 \pm 0.89	2.25 \pm 0.35	29.58 \pm 3.52	42.16 \pm 6.74
对照组	100	1.42 \pm 0.19	0.57 \pm 0.09	9.38 \pm 1.03	13.29 \pm 1.85
<i>t</i>		32.918	27.584	22.191	29.497
<i>P</i>		<0.05	<0.05	<0.05	<0.05

3 讨论

全身炎症反应激活是造成 SAP 患者病情发展变化重要的病理环节,炎症反应激活所造成的炎症因子大量分泌不仅会造成胰腺炎局部损伤程度的加重,还会引起全身多个靶器官的损伤^[5,6]。PCT 是降钙素的前体物质,在炎症反应激活的过程中,多个脏器内巨噬细胞受到内毒素的刺激会大量合成 PCT^[7];TNF- α 是由单核巨噬细胞分泌产生的炎症因子,不仅与组织的炎症损伤有关,还能介导炎症的级联放大^[8];CRP 由肝细胞在促炎介质的作用下分泌和释放,是反应炎症反应程度的急性时相反应蛋白^[9];HMGB-1 是一类由单核巨噬细胞、树突状细胞分泌的晚期炎症介质,能够破坏上皮屏障、引起组织损伤^[10]。为了明确全身炎症反应激活与 SAP 患者靶器官损伤的关系,我们首先通过分析 SAP 患者血清中炎症因子的含量来反应全身炎症反应的程度,由两组间血清中炎症因子含量的比较可知:SAP 组患者血清中 PCT、TNF- α 、CRP、HMGB-1 的含量均显著高于对照组。这就说明炎症因子 PCT、TNF- α 、CRP、HMGB-1 的大量释放与 SAP 的发生、发展密切相关。SAP 患者体内炎症因子的大量释放会造成炎症反应的级联放大激活,病情进一步发展会导致全身炎症反应综合征的发生并增加多器官功能衰竭综合征的发生风险。肝脏是 SAP 病情发展变化过程中常见受累的靶器官,炎症因子在肝脏内浸润会引起肝细胞损伤、破裂,一方面导致肝细胞内的转氨酶 ALT、AST 释放进入血液循环,另一方面影响胆红素的代谢并造成 TBIL 含量升高^[11]。我们通过分析 SAP 患者血清中肝功能损伤指标的含量可知:SAP 组患者血清中 ALT、AST、TBIL 的含量均显著高于对照组。这就说明 SAP 患者存在不同程度的肝功能损伤。进一步分析肝功能损伤指标与炎症因子含量的相关性可知:SAP 患者血清中 PCT、TNF- α 、CRP、HMGB-1 的含量与血清中 ALT、AST、TBIL 的含量呈相关性关系。这就证实 SAP 患者体内大量合成和分泌的炎症因子 PCT、TNF- α 、CRP、HMGB-1 会造成肝功能损伤。

SAP 的病情发展会增加急性肾损伤的发生风险。肌酐和尿素氮是体内蛋白质代谢的副产物,经由肾小球滤过并排泄,炎症反应所致肾脏损伤会影响肌酐和尿素氮的排泄,进而造成 BUN 和 Scr 的升高^[12];CysC 是能够自由通过肾小球的小分子物质,肾小球滤过功能损伤会影响 CysC 排泄并造成 CysC 含量升高^[13];NGAL 和 KIM-1 是近端小管合成和分泌的蛋白,炎症反应所致肾小管损害会造成尿液中 NGAL 和 KIM-1 含量升高^[14]。我们通过分析 SAP 患者血清及尿液中肾功能损伤指标的含量可知:SAP 组患者血清中 BUN、Scr、CysC 的含量及尿

液中 NGAL、KIM-1 的含量均显著高于对照组。这就说明 SAP 患者存在不同程度的肾功能损伤。进一步分析肾功能损伤指标与炎症因子含量的相关性可知:SAP 患者血清中 PCT、TNF- α 、CRP、HMGB-1 的含量与血清中 BUN、Scr、CysC 的含量及尿液中 NGAL、KIM-1 的含量呈相关性关系。这就证实 SAP 患者体内大量合成和分泌的炎症因子 PCT、TNF- α 、CRP、HMGB-1 不仅会造成肝功能损伤,还会引起肾功能损伤。

肠道是微生物聚集的部位,生理状态下肠黏膜屏障功能对维持肠道内病原菌的平衡具有重要价值。SAP 患者体内炎症因子的大量释放会造成肠黏膜上皮细胞损伤、细胞间紧密连接破坏,同时也会引起菌群异位、内毒素大量释放并加重炎症反应^[15]。DAO 是在肠黏膜上皮细胞内参与核酸、蛋白质合成代谢的催化酶,炎症因子对肠黏膜上皮细胞的损伤会造成 DAO 大量释放进入血液循环;D-乳酸是肠道内微生物发酵的产物,在肠黏膜屏障的保护下极少吸收入血,炎症因子对肠黏膜屏障功能的损伤会造成 D-乳酸吸收入血增多;Occludin 和 ZO-1 是两种紧密连接蛋白,对维持肠黏膜上皮细胞间的紧密连接以及肠黏膜屏障的完整性具有重要价值,炎症因子对细胞间紧密连接的破坏会造成 Occludin 和 ZO-1 释放入血^[16,17]。我们通过分析 SAP 患者血清中肠黏膜功能损伤指标的含量可知:SAP 组患者血清中 DAO、D-乳酸、Occludin、ZO-1 的含量均显著高于对照组且与 PCT、TNF- α 、CRP、HMGB-1 的含量呈正相关。这就证实 SAP 患者体内大量合成和分泌的炎症因子 PCT、TNF- α 、CRP、HMGB-1 会造成肠黏膜屏障功能损伤。

SAP 患者血清中炎症因子 PCT、TNF- α 、CRP、HMGB-1 的异常释放会引起全身炎症反应激活,进而通过炎症反应来造成肝脏、肾脏、肠黏膜等靶器官功能发生损伤。

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