

急性胰腺炎患者胃肠动力障碍及其与细胞因子的关系

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【摘要】 目的 分析急性胰腺炎(AP)患者胃肠动力障碍及其与细胞因子表达之间的关系。方法 选取上海市宝山区仁和医院消化科2017年3月至2019年6月收治的59例AP患者为研究组,依照病情严重程度将其分为轻症(MAP)35例,中重症(MSAP)20例,重症(SAP)4例;同期选取健康体检者30例作为对照组。于发病就诊后第1天、第7天静脉取血,测定血小板生成因子(TPO)、白介素-1(IL-1)、白介素-6(IL-6)、白介素-8(IL-8)、白介素-10(IL-10)、肿瘤坏死因子(TNF)水平,并与对照组进行比较。结果 MAP组、MSAP组、SAP组患者入院第1天、第7天的TPO水平明显高于对照组,SAP组明显高于MAP、MSAP组,MSAP组又明显高于MAP组,差异均有统计学意义($P<0.05$);MAP组、MSAP组、SAP组患者入院第1天的TPO水平明显高于第7天,差异均有统计学意义($P<0.05$);SAP组、MSAP组、MAP组患者入院第1天的TNF水平明显高于对照组,SAP组明显高于MAP组、MSAP组,MSAP组明显高于MAP组,差异均有统计学意义($P<0.05$);MAP组患者入院第7天的TNF水平与对照组比较差异无统计学意义($P>0.05$),而MSAP及SAP组第7天的TNF水平明显高于对照组,SAP组明显高于MSAP组,差异均有统计学意义($P<0.05$);SAP组、MSAP组、MAP组患者入院第7天的TNF水平明显低于第1天,差异均有统计学意义($P<0.05$);MAP组、MSAP组、SAP组患者入院第1天、第7天的血清IL-1、IL-6、IL-8、IL-10水平明显高于对照组,差异均有统计学意义($P<0.05$);MSAP组、SAP组患者入院第1天、第7天的血清IL-1、IL-6、IL-8、IL-10水平明显高于MAP组,而SAP组明显高于MSAP组,差异均有统计学意义($P<0.05$);MAP组、MSAP组、SAP组入院第7天的血清IL-1、IL-6、IL-8、IL-10水平明显低于第1天,差异均有统计学意义($P<0.05$);SAP组、SMAP组与MAP组患者腹部前后径与横径比值比较,以及SAP组与SMAP组的比值比较,差异均具有统计学意义($P<0.05$)。结论 胃肠动力障碍可能与细胞因子异常表达存在相关性,表现为TPO、IL-1、IL-6、IL-8、IL-10及TNF水平异常升高,且增幅越大病情越重。

【关键词】 急性胰腺炎;胃肠动力障碍;细胞因子;异常表达;相关性

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Gastrointestinal motility disorder in patients with acute pancreatitis and its relationship with cytokines. ZUO Yan¹, LIU Yi², ZHANG Qiu-qin¹. 1. Department of Gastroenterology, Renhe Hospital, Baoshan District, Shanghai 200431, CHINA; 2. Department of Gastroenterology, Huashan Hospital Affiliated to Fudan University, Shanghai 200040, CHINA

【Abstract】 Objective To analyze the relationship between gastrointestinal motility disorder and cytokine expression in patients with acute pancreatitis (AP). **Methods** A total of 59 AP patients admitted to Department of Gastroenterology, Renhe Hospital, Baoshan District, Shanghai from March 2017 to June 2019 were selected as the research group. According to the severity of the disease, they were divided into 35 cases of mild disease (MAP) and 20 cases of moderate severe disease (MSAP), 4 cases of severe disease (SAP); 30 healthy persons were selected as the control group during the same period. Blood was taken intravenously on the 1st and 7th days after the onset of treatment, and the determination of thrombopoietin (TPO), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8) and interleukin-10 (IL-10) and tumor necrosis factor (TNF) levels were compared with the control group. **Results** The TPO levels of the MAP, MSAP and SAP groups on the 1st and 7th day were significantly higher than those of the control group; the TPO levels of the SAP group were significantly higher than those of the MAP and MSAP groups; the TPO level of the MSAP was significantly higher than that of the MAP group, and all above differences were statistically significant (all $P<0.05$). The TPO levels of MAP, MSAP, and SAP groups on the 1st day were significantly higher than that on the 7th day, and the differences were statistically significant (all $P<0.05$). The TNF levels of SAP, MSAP, and MAP groups on the 1st day were higher than that of the control group; the SAP group was higher than the MAP group and the MSAP group, and the MSAP group was higher than that of the MAP group, and all above differences were statistically significant (all $P<0.05$). There was no significant difference in TNF levels between the MAP group and the control group on the 7th day ($P>0.05$). The TNF levels on the 7th day in the MSAP and SAP groups were lower than those in the control group, and the SAP group were higher than the MSAP group, with statistically significant differences (all $P<0.05$). The levels of TNF on the

7th day in SAP, MSAP, and MAP groups were higher than that on the 1st day, and the differences were statistically significant (all $P < 0.05$). Serum IL-1, IL-6, IL-8, and IL-10 levels of patients in the MAP group, MSAP group, and SAP group on the 1st and 7th days of admission were significantly higher than those in the control group, and the differences were statistically significant (all $P < 0.05$). The serum levels of IL-1, IL-6, IL-8, and IL-10 of patients in the MSAP group and SAP group were significantly higher than those of the MAP group on the 1st and 7th days of admission, while the SAP group was significantly higher than that of the MSAP group, and the differences were statistically significant (all $P < 0.05$). The serum levels of IL-1, IL-6, IL-8, and IL-10 on the 7th day of admission in the MAP group, MSAP group, and SAP group were significantly lower than that on the 1st day, and all above differences are statistically significant (all $P < 0.05$). The difference in the ratio of the anteroposterior diameter to the transverse diameter of the abdomen among of the SAP group, SMAP group and MAP group was statistically significant ($P < 0.05$), and the difference in the ratio between SAP group and SMAP group was also statistically significant ($P < 0.05$). **Conclusion** The gastrointestinal motility disorder may be related to the abnormal expression of cytokines, which is manifested by increased levels of TPO, IL-1, IL-6, IL-8, IL-10 and TNF, and the greater the increase, the more severe the disease.

【Key words】 Acute pancreatitis; Gastrointestinal motility disorder; Cytokine; Abnormal expression; Correlation

急性胰腺炎(acute pancreatitis, AP)为临床常见危重症之一,常由大量饮酒或暴饮暴食诱发,可导致多器官功能障碍,以胃肠道功能障碍最为常见,主要表现为腹胀和排气排便次数的减少^[1];同时胃肠道蠕动障碍会造成小肠内细菌因繁殖过快而脱落,增大发生细菌感染、病情加重的风险^[2]。长时间胃肠蠕动减慢会导致胃肠功能衰竭,进而引起多脏器衰竭甚至出现腹腔间隔室综合征(abdominal compartment syndrome, ACS),危及患者生命安全^[3]。重症急性胰腺炎(severe acute pancreatitis, SAP)并发ACS患者的死亡率高达50%~70%。在AP治疗的前瞻性研究中发现,患者血小板生成因子(thrombopoietin, TPO)、白介素-1(interleukin-1, IL-1)、白介素-6(interleukin-6, IL-6)、白介素-8(interleukin-8, IL-8)、白介素-10(interleukin-10, IL-10)、肿瘤坏死因子(tumor necrosis factor, TNF)的水平及腹部前后径与横径比值与胃肠动力相关,分析其规律可用于指导AP的治疗,并为防止腹内高压(intra-abdominal hypertension, IAH)及ACS的发生提供理论依据。

1 资料与方法

1.1 一般资料 选取上海市宝山区仁和医院消化科2017年3月至2019年6月收治的59例AP患者为研究组,其中男性43例,女性16例;年龄27~74岁,平均(41.34±8.76)岁;胆源性24例,高脂血症10例,酒精性8例,暴饮暴食4例,病因不明13例。将59例AP患者根据Ranson评分和CT分级分为重症(SAP)、中重症(MSAP)、轻症(MAP)三组^[4]。其中MAP组35例,MSAP组20例,SAP组4例。另外选取健康体检者30例作为对照组,其中男性19例,女性11例;年龄18~67岁,平均(40.15±8.85)岁。两组受检者的性别和年龄比较差异均无统计学意义($P > 0.05$),具有可比性。本研究经医院伦理委员会审查同意。

1.2 入选标准 ①结合临床表现、生化及影像学

检查,AP诊断明确;②均在发病24 h内院就诊;③期间未给予吗丁啉、莫沙必利片、伊托必利片等促胃动力药物治疗;④签署知情同意书。

1.3 排除标准 ①合并其他引起肠道疾病的器质性疾病者,如肝硬化、消化道恶性肿瘤、消化道溃疡、溃疡性肠炎、克罗恩病、慢性便秘等消化道疾病;②合并引起肠道动力障碍的基础性疾病者,如甲状腺功能减退(亢进)、风湿免疫病、糖尿病、精神疾病等全身综合性疾病;③SAP置管患者。

1.4 方法 对照组于第1天晨起空腹采外周静脉血3 mL,AP患者于入院后第1天、第7天晨起空腹采外周静脉血3 mL,以3 000 r/min的速度离心15 min,至-80℃下保存,采用双抗体ABC-ELISA法测定TPO、IL-1、IL-6、IL-8、IL-10、TNF的水平;采用CE32排螺旋CT扫描机的CT图像检测入组AP患者第1天、第7天的腹部前后径与横径的比值。

1.5 统计学方法 应用SPSS17.0软件分析数据,计量资料符合正态分布,以均数±标准差($\bar{x} \pm s$)表示,组间两两比较采用 t 检验,以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 四组受检者的血清TPO水平比较 MAP组、MSAP组和SAP组患者第1天、第7天的TPO水平明显高于对照组,SAP组明显高于MAP组、MSAP组,MSAP组又明显高于MAP组,差异均具有统计意义($P < 0.05$);MAP组、MSAP组、SAP组第1天的TPO水平明显高于第7天,差异具有统计意义($P < 0.05$),见表1。

表1 四组受检者的血清TPO水平比较($\bar{x} \pm s$, ng/L)

| 组别 | 例数 | 第1天 | 第7天 | t 值 | P 值 |
|-------|----|------------------------------|-----------------------------|--------|-------|
| MAP组 | 35 | 201.65±56.76 ^a | 80.53±19.79 ^a | 11.921 | 0.001 |
| MSAP组 | 20 | 300.54±88.49 ^{ab} | 130.76±37.96 ^{ab} | 7.885 | 0.001 |
| SAP组 | 4 | 401.24±102.76 ^{abc} | 150.32±41.26 ^{abc} | 4.532 | 0.004 |
| 对照组 | 30 | 66.45±18.98 | 67.12±19.01 | 0.300 | 0.756 |

注:与对照组比较,^a $P < 0.05$;与MAP组比较,^b $P < 0.05$;与MSAP组比较,^c $P < 0.05$ 。

2.2 四组受检者的血清 TNF 水平比较 SAP 组、MSAP 组和 MAP 组患者第 1 天的 TNF 水平明显高于对照组, SAP 组明显高于 MAP 组、MSAP 组, MSAP 组又明显高于 MAP 组, 差异均具有统计学意义 ($P < 0.05$)。MAP 组与对照组第 7 天的 TNF 水平比较差异无统计学意义 ($t=1.756, P=0.084$), 但 MSAP 组和 SAP 组第 7 天的 TNF 水平明显高于对照组, SAP 组明显高于 MSAP 组, 差异均具有统计学意义 ($P < 0.05$); SAP、MSAP、MAP 组第 7 天的 TNF 水平低于第 1 天, 差异均具有统计学意义 ($P < 0.05$), 见表 2。

表 2 四组受检者的血清 TNF 的测定比较 ($\bar{x} \pm s, \text{ng/L}$)

| 组别 | 例数 | 第 1 天 | 第 7 天 | <i>t</i> 值 | <i>P</i> 值 |
|------|----|--------------------------|---------------------------|------------|------------|
| MAP | 35 | 12.98±2.45 ^a | 8.71±0.96 | 9.420 | 0.001 |
| MSAP | 20 | 16.45±4.76 ^{ab} | 8.34±1.31 ^b | 7.346 | 0.001 |
| SAP | 4 | 25.03±5.61 ^{ab} | 10.78±1.67 ^{abc} | 4.833 | 0.003 |
| 对照组 | 30 | 8.20±1.05 | 8.27±1.06 | 0.257 | 0.798 |

注: 与对照组比较, ^a $P < 0.05$; 与 MAP 组比较, ^b $P < 0.05$; 与 MSAP 组比较, ^c $P < 0.05$ 。

2.3 四组受检者的 IL-1、IL-6、IL-8、IL-10 水平比较 MAP 组、MSAP 组、SAP 组患者入院第 1 天、第 7 天的血清 IL-1、IL-6、IL-8、IL-10 水平明显高于对照组, MSAP 组、SAP 组明显高于 MAP 组, SAP 组又明显高于 MSAP 组, 差异均具有统计学意义 ($P < 0.05$); MAP 组、MSAP 组、SAP 组入院第 7 天的血清 IL-1、IL-6、IL-8、IL-10 水平均低于第 1 天, 差异均具有统计学意义 ($P < 0.05$), 见表 3。

2.4 三组患者的腹部前后径与横径比值比较 SAP 组、SMAP 组与 MAP 组患者的腹部前后径与横径比值分别为 $0.031 1 \pm 0.004 7$ 、 $0.021 4 \pm 0.002 7$ 、 $0.015 2 \pm 0.001 6$, SAP 组、SMAP 组患者的腹部前后径与横径的比值均大于 MAP 组, 差异均具有统计学意义 ($t_1=1.667, P_1=0.014; t_2=1.997, P_2=0.001$), SAP 组患者的腹部前后径与横径的比值大于 SMAP 组, 差异具有统计学意义 ($t=1.996, P=0.001$)。

表 3 四组受检者的 IL-1、IL-6、IL-8、IL-10 水平比较 ($\bar{x} \pm s, \text{ng/L}$)

| 组别 | 例数 | 时间(d) | IL-1 | IL-6 | IL-8 | IL-10 |
|--------|----|------------|----------------------------|----------------------------|------------------------------|----------------------------|
| MAP 组 | 35 | 1 | 42.76±9.92 ^a | 35.51±7.69 ^a | 283.16±69.32 ^a | 72.45±21.34 ^a |
| | | 7 | 27.98±7.21 ^a | 11.59±3.14 ^a | 93.17±25.56 ^a | 43.19±12.01 ^a |
| | | <i>t</i> 值 | 7.111 | 17.037 | 15.213 | 7.069 |
| | | <i>P</i> 值 | 0.002 | 0.001 | 0.001 | 0.001 |
| MSAP 组 | 20 | 1 | 48.45±11.24 ^{ab} | 55.43±14.35 ^{ab} | 320.16±88.89 ^{ab} | 80.25±22.34 ^{ab} |
| | | 7 | 31.76±8.25 ^{ab} | 30.21±8.75 ^{ab} | 85.64±21.54 ^{abc} | 43.19±11.01 ^{ab} |
| | | <i>t</i> 值 | 7.082 | 8.877 | 15.169 | 8.803 |
| | | <i>P</i> 值 | 0.002 | 0.001 | 0.001 | 0.001 |
| SAP 组 | 4 | 1 | 58.35±14.32 ^{abc} | 78.69±21.57 ^{abc} | 363.98±100.22 ^{abc} | 97.75±22.43 ^{abc} |
| | | 7 | 38.26±9.52 ^{abc} | 53.58±11.67 ^{abc} | 84.87±14.78 ^{abc} | 43.81±12.63 ^{abc} |
| | | <i>t</i> 值 | 6.939 | 4.822 | 16.300 | 12.397 |
| | | <i>P</i> 值 | 0.002 | 0.002 | 0.001 | 0.001 |
| 对照组 | 30 | 1 | 21.39±6.28 | 7.25±2.43 | 49.50±11.04 | 35.48±6.90 |

注: 与对照组比较, ^a $P < 0.05$; 与 MAP 组比较, ^b $P < 0.05$; 与 MSAP 组比较, ^c $P < 0.05$ 。

3 讨论

AP 是胰腺组织因各种原因发生自身消化进而引发全身炎症反应的综合征^[5], 其基本致病机理是免疫细胞大量激活过度产生释放炎症因子, 造成血液处于高细胞因子状态, 血管通透性得到增加, 液体渗出引发间质水肿和有效循环血量减少, 导致肠黏膜发生缺血缺氧, 同时炎症介质可直接损害黏膜保护屏障, 造成胃肠动力障碍^[6]。

AP 患者在疾病的发生进展过程中常有并发症出现, 严重的并发症甚至危及患者生命安全。部分 AP 患者会出现胃肠动力障碍, 但其发生机制尚不清楚。LI 等^[8]认为, 胃肠动力主要受到神经及内分泌系统的调节, 发生 AP 时, 神经递质、炎症介质产生过多, 肠道细菌繁殖过度, 巨噬细胞功能障碍, 腹腔积液形成, 多种因素干预可能使肠道平滑肌细胞的收缩功能受损,

或间接作用于胃肠蠕动相关神经回路, 从而导致胃肠动力障碍。

相关研究发现, 当迷走神经被阻断后, 胃的电生理活动随之停止, 小肠的周期性活动未受到影响, 说明迷走神经在胃肠动力的调节中具有重要作用^[9]。AP 时, 应激反应兴奋交感神经、抑制迷走神经活动, 造成胃肠蠕动减慢。同时, 胃肠动力也受肠神经系统的调节。AP 产生的炎症介质及其造成的肠道中大量渗出液体均会对胃肠黏膜产生刺激作用, 使 NO 生成过多, NO 具有舒张平滑肌的作用, 大量的 NO 促进胃肠道平滑肌松弛, 进而出现胃肠蠕动减慢^[10]。目前认为 AP 对胃肠动力的影响与以下因素有关: ① 相关文献^[11]指出, 肠道内的细菌增长与小肠的移动性复合运动周期的长短具有相关性, 周期越长, 细菌增长越快。AP 时, 肠道细菌过度繁殖, 释放大量内毒素, 刺激机体引发

胃肠动力障碍。② AP时,患者长期处于禁食水状态,肠黏膜摄入能量不足引起胃肠蠕动减慢^[12]。③ SAP时,患者渗出大量液体,引发肠黏膜水肿,胃肠蠕动减慢。④ AP时释放大量炎性因子,形成高细胞因子血症。相关研究发现TNF- α 在一定程度上参与了AP特别是SAP的胃肠动力障碍,TNF- α 升高会造成肠黏膜缺血再灌注的损伤,加重肠黏膜的氧化应激反应,促进细胞凋亡脱落^[13]。⑤ AP时产生大量炎性介质,严重时导致肠黏膜发生缺血、缺氧及酸中毒,有效血容量减少、大量氧自由基及缺血再灌注对肠黏膜产生的损伤都会促进胃肠动力障碍的发生^[14-15]。本研究,通过对合并胃肠动力障碍的AP患者细胞因子水平及腹部前后径与横径的比值的测量,分析两者相互关系,探讨AP患者胃肠动力障碍的发生机制及临床意义。

目前认为IL-1、IL-6、IL-8、IL-10及TNF等细胞因子与AP的发生及发展相关,AP在发生1h内即可产生大量IL-1、IL-6、TNF,其水平与胰腺炎症的严重程度呈相关性^[16]。促炎-抗炎理论认为,有害刺激可激活具有保护作用的促炎机制,但在促炎因子释放的同时抗炎机制也启动,用于调节炎症反应^[17]。目前认为TNF- α 、IL-1 β 、IL-6、IL-8等为促炎因子,IL-4、IL-10、IL-12等为抗炎因子,维持两者动态平衡可促进AP患者康复并防止MAP发展为MSAP或SAP^[18]。AP治疗的关键在于迅速达到促炎与抗炎的动态平衡,通过对两者尤其是IL-6及IL-10的检测,可起到预测胰腺炎预后和所需治疗时间的作用,有效弥补了早期血清学指标的不足,同时加强对炎性因子的检测对SIRS早期发现和治疗以及预防SIRS的发生,有重要意义^[19-20]。

TPO是一种可有效促进骨髓生成血小板的糖蛋白,主要在肝脏和肾脏中合成^[21]。编码TPO前155个氨基酸的基因位于3号染色体的长臂(q26.3-27),和EPO具有高度同源性。血小板主要由巨核细胞分化形成,TPO具有促进这一过程的作用,同时具有增加巨核细胞体积和增强血小板特异性抗原表达的功能^[22-23]。但是,TPO的受体c-Mpl(CD110)被人为敲除后,其仍然具有造血功能,表明TPO可能通过多种途径发挥造血功能。血小板数量与TPO水平呈负反比关系,血小板数量的减少会刺激机体生成大量TPO,通过对未分化的骨髓细胞的诱导,促使其分化为巨核细胞。已有研究发现,在血液病、脓毒血症等多种疾病中TPO存在异常表达,其水平均高于常人,在脓毒血症患者中,病情越重的患者TPO水平越高,可能是高水平的TPO促进血小板活化,进而参与到多器官的损伤过程^[24-25]。但是目前尚无TPO在AP发生及

病程进展中作用的报道,对是否存在血小板依赖与非依赖的损伤途径尚不明确。

TNF是一种重要的炎性因子,常参与组织的病理损伤,其表达水平可间接反应体内炎症反应的轻重程度^[26]。TNF主要由活化的单核/巨噬细胞产生,具有抑制、杀灭肿瘤细胞和促进中性粒细胞吞噬的作用;能够增强肝细胞的蛋白合成能力,提升机体免疫力,通过引起发热起到抗感染的作用;诱导髓样细胞分化为巨噬细胞,提升细胞增殖和分化能力^[27]。

合并胃肠动力障碍的AP患者常表现为肠鸣音减弱、腹痛腹胀、排气排便减少,少数患者出现恶心、呕吐等症状。SAP患者并发胃肠动力障碍时,蠕动功能严重受损,肠管内积气随着排便排气次数的减少逐渐增多,加之胰腺的不断渗出,患者腹内压急剧升高,腹胀明显,此时腹部前后径增大。腹部前后径与横径的比值变化可用于判断胃肠动力情况,作为防止腹内高压症发生的重要参考之一。

本研究发现,SAP组、SMAP组患者的腹部前后径与横径的比值均大于MAP组,差异均具有统计学意义($P<0.05$),SAP组患者的腹部前后径与横径的比值大于SMAP组,差异具有统计学意义($P<0.05$)。说明腹部前后径与横径的比值变化与AP患者胃肠动力障碍轻重有关,同时SAP治疗前后比值的变化最大,提示SAP病情最重,即发生腹内压的风险较高。

综上所述,AP患者腹部前后径与腹横径比值的增加与肠腔内积气、积液有关,提示存在胃肠蠕动减慢,病情越重,胃肠动力障碍越重。同时AP患者存在细胞因子表达异常,表现为血清TPO、IL-1、IL-6、IL-8、IL-10、TNF水平升高,且病情越重,升高幅度越大。

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