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炎症性肠病患者的肠道菌群分布与血清 TNF- α 与 IL-6 水平的相关性

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摘要 目的:探讨炎症性肠病患者的肠道菌群分布与血清肿瘤坏死因子- α (TNF- α)与白介素-6(IL-6)水平的相关性。**方法:**选择我院收治的 172 例炎症性肠病患者作为观察组, 同期选择在我院经询问病史及体格检查无消化道疾病的 172 例患者作为对照组, 检测两组肠道菌群的分布与血清 TNF- α 与 IL-6 水平, 并分析炎症性肠病患者肠道菌群分布与血清 TNF- α 与 IL-6 水平的相关性。**结果:**观察组的肠球菌、粪肠球菌和大肠埃希杆菌含量明显高于对照组, 而双歧杆菌含量明显低于对照组($P<0.05$)。观察组的血清 TNF- α 与 IL-6 值分别为 0.98 ± 0.54 ng/mL 和 0.98 ± 0.38 pg/mL, 都明显高于对照组的 0.61 ± 0.37 ng/mL 和 0.55 ± 0.34 pg/mL($P<0.05$)。观察组的双歧杆菌含量与 TNF- α 与 IL-6 呈现明显负相关性($P<0.05$), 而肠球菌、粪肠球菌、大肠埃希杆菌含量与 TNF- α 与 IL-6 都呈现明显正相关性($P<0.05$)。**结论:**炎症性肠病患者存在益生菌含量减少、有害菌含量增加的现象, 这可能与患者血清促炎因子过量表达有关, 二者的共同作用可促进炎症性肠病的发生及进展。

关键词:炎症性肠病; 肿瘤坏死因子- α ; 白介素-6; 肠道菌群

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Correlation of the Intestinal Flora Distribution with the Serum TNF- α and IL-6 Levels in the Inflammatory Bowel Disease

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ABSTRACT Objective: To investigate the correlation of intestinal flora distribution with the serum levels of TNF- α and IL-6 in the inflammatory bowel disease. **Methods:** 172 patients with inflammatory bowel disease in our hospital were selected as the observation group, and 172 patients without digestive tract disease history and positive physical examination results were selected as the control group. The intestinal flora distribution and serum levels of TNF- α and IL-6 were detected and the correlation of them were analyzed. **Results:** The contents of *Enterococcus*, *Fecal streptococcus*, *Escherichia coli* in the observation group were significantly higher than those in the control group, while the *Bacillus* content of control group was significantly lower than that of the control group ($P<0.05$). The serum levels of TNF- α and IL-6 in the observation group were 0.98 ± 0.54 pg/mL and 0.98 ± 0.38 ng/mL respectively, which were significantly higher than those in the control group (0.61 ± 0.37 ng/mL and 0.55 ± 0.34 pg/mL) ($P<0.05$). The *Bacillus* showed significantly negative correlation with the serum TNF- α and IL-6 levels in the observation group ($P<0.05$), and the *Enterococcus*, *Fecal streptococcus*, *Escherichia coli* showed significantly positive correlation with the serum TNF- α and IL-6 levels ($P<0.05$). **Conclusion:** The increase of *Enterococcus*, *Fecal streptococcus*, *Escherichia coli* and decrease of *Bacillus* were observed in the patients with inflammatory bowel disease, which could be related to the over-expression of serum TNF- α and IL-6. Both changes could promote the occurrence and development of inflammatory bowel disease.

Key words: Inflammatory bowel disease; TNF- α ; IL-6; Intestinal flora

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前言

炎症性肠病(inflammatory bowel disease, IBD)是一类病因和发病机制尚不十分清楚的肠道炎症性疾病, 包括溃疡性结肠

炎(ulcerative colitis, UC)、克罗恩病(crohn disease, CD)等, 当前我国的发病人数明显增加^[1,2]。现代研究表明炎症性肠病的发病因素较多, 包括肠道菌群分布、遗传因素、环境因素、免疫异常等, 其中以肠道菌群与疾病发生发展的关系最为密切^[3,4]。人

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类正常肠道菌群包括需氧菌、厌氧菌以及兼性厌氧菌,由 30 属 500 种构成,是一个极为复杂的微生态系统。当前研究指出肠道菌群失衡会参与各种消化道疾病的发生发展,肠道菌群失衡和机体免疫功能低下可导致肠道细菌移位,继而进入机体循环,激发全身炎症反应,诱发严重并发症的发生^[5,6]。而当肠道菌群紊乱时,肠黏膜细胞之间通透性增高,致使肠黏膜屏障功能减弱,大量内毒素可易位进入门脉系统,释放包括肿瘤坏死因子 α (TNF- α) 在内的多种炎性因子,对肠道进行攻击^[7,8];此外炎症因子也可导致一氧化氮合成酶(iNOS)活性增强,松懈上皮细胞间的紧密连接,加重肠道炎症反应^[9,10]。本研究主要探讨了炎症性肠病患者的炎性指标与肠道菌群结构变化的相关性,现报道如下。

1 资料与方法

1.1 研究对象

选择 2014 年 2 月到 2016 年 5 月在我院就诊的 172 例炎症性肠病患者作为观察组,本组患者符合中华医学会消化病学分会制定的相关诊断标准,其中溃疡性结肠炎 100 例,克罗恩病 72 例。同期选择在我院经询问病史及体格检查无消化道疾病的 172 例患者作为对照组。两组都排除有感染及使用胃肠道动力药、抗生素、微生态调节剂及其他可影响肠道菌群制剂的患者,研究都得到患者的知情同意与医院伦理委员会的批准。观察组中,男 100 例,女 72 例;年龄最小 24 岁,最大 89 岁,平均年龄 49.22 ± 2.85 岁;平均体重指数为 22.84 ± 2.11 kg/m²;平均血糖为 5.26 ± 1.34 mmol/L。对照组中,男 96 例,女 76 例;年龄最小 23 岁,最大 88 岁,平均年龄 49.11 ± 3.19 岁;平均体重

指数为 22.76 ± 1.83 kg/m²;平均血糖为 5.21 ± 1.24 mmol/L。两组的性别、年龄、体重指数、血糖等对比差异无明显统计学意义 ($P > 0.05$),具有可比性。

1.2 肠道菌群检测

取新鲜粪便 0.5 g,按 10 倍系列稀释法将所获粪便标本稀释后,分别用 MRS 琼脂培养基培养乳酸杆菌,双歧杆菌 BS 培养基 250 培养双歧杆菌,肠球菌培养基培养粪肠球菌,麦康凯琼脂板培养大肠埃希杆菌。乳酸杆菌和双歧杆菌在 37℃ 温箱中厌氧培养 72 h,大肠埃希杆菌和粪肠球菌在 37℃ 温箱中需氧培养 24 h 和 48 h。使用半自动微生物鉴定系统(法国梅里埃公司生产)进行细菌鉴定。结果以每克粪便湿重中菌落形成单位的对数值表示(log CFU/g)。

1.3 炎性指标测定

两组的血炎性指标检测由我院检验科自动生化分析仪完成,取患者的空腹静脉血,4℃、3000 rpm 离心 15 min,取上层血清,采用 ELISA 法测定 TNF- α 与 IL-6 的含量。

1.4 统计学分析

采用 SPSS 20.00 软件进行数据分析,计量数据以均数 $\pm$ 标准差表示,计数数据以百分比表示,对比采用 t 检验或 χ^2 分析,相关性采用 Pearson 相关检验分析。以 $P < 0.05$ 为差异具有统计学意义。

2 结果

2.1 两组肠道菌群分布比较

观察组肠球菌、粪肠球菌和大肠埃希杆菌含量明显高于对照组,而双歧杆菌含量明显低于对照组($P < 0.05$)。见表 1。

表 1 两组肠道菌群分布对比(log CFU/g, 均数 $\pm$ 标准差)

Table 1 Comparison of the distribution of intestinal flora between two groups (log CFU/g, $\bar{x} \pm s$)

Groups	n	<i>Enterococcus</i>	<i>Enterococcus faecalis</i>	<i>Escherichia coli</i>	<i>Bifidobacterium</i>
Observation group	172	7.34 ± 1.24	8.76 ± 1.44	7.45 ± 1.23	7.13 ± 1.28
Control group	172	6.52 ± 1.11	7.42 ± 1.42	6.92 ± 1.63	8.83 ± 1.23
P		< 0.05	< 0.05	< 0.05	< 0.05

2.2 两组血清 TNF- α 与 IL-6 水平的比较

观察组血清 TNF- α 与 IL-6 水平分别为 0.98 ± 0.54 ng/mL

和 0.98 ± 0.38 pg/mL,均明显高于对照组的 0.61 ± 0.37 ng/mL 和 0.55 ± 0.34 pg/mL($P < 0.05$)。见表 2。

表 2 两组血清 TNF- α 与 IL-6 水平的比较(均数 $\pm$ 标准差)

Table 2 Comparison of the serum TNF- α and IL-6 between two groups ($\bar{x} \pm s$)

Groups	n	TNF- α (ng/mL)	IL-6 (pg/mL)
Observation group	172	0.98 ± 0.54	0.98 ± 0.38
Control group	172	0.61 ± 0.37	0.55 ± 0.34
P		< 0.05	< 0.05

2.3 炎症性肠病患者肠道菌群分布与血清 TNF- α 与 IL-6 水平的相关性

观察组中,Pearson 相关检验显示双歧杆菌含量与 TNF- α 与 IL-6 呈明显负相关($P < 0.05$),而肠球菌、粪肠球菌、大肠埃希

杆菌含量与 TNF- α 与 IL-6 呈现明显正相关($P < 0.05$)。见表 3。

3 讨论

炎症性肠病是我国常见的消化道疾病,严重危害人民健

表 3 炎症性肠病患者肠道菌群分布与血清 TNF- α 与 IL-6 水平的相关性(n=172)Table 3 Correlation of the distribution of intestinal flora with serum TNF- α and IL-6 levels of patients with inflammatory bowel disease(n=172)

Items	TNF- α		IL-6	
	r	P	r	P
<i>Bifidobacterium</i>	-0.401	<0.05	-0.378	<0.05
<i>Enterococcus</i>	0.371	<0.05	0.389	<0.05
<i>Enterococcus faecalis</i>	0.321	<0.05	0.414	<0.05
<i>Escherichia coli</i>	0.382	<0.05	0.298	<0.05

康,其具体的病因和发病机制尚不完全清楚。我国目前虽然尚无炎症性肠病的全国性大规模流行病学调查资料,但地区性流行病学调查显示我国炎症性肠病的患病率有上升趋势^[11,12]。

正常成人肠道内含有近 500 种细菌,大肠内每克粪便中含有 1011 个微生物,主要是由厌氧菌、兼性厌氧菌和需氧菌等组成。其中,双歧杆菌是一种人体必需的细菌,具有免疫调节及营养作用^[13];肠球菌是一种条件致病菌,当肠道菌群紊乱/平衡失调时,就会对人体有害;大肠埃希杆菌的长期定植的机会少,一旦数量超出正常范围则致病。有研究报道炎症性肠病的发生与肠道微生态关系密切,肠道菌群失调在炎症性肠病发生发展中的作用越来越受到重视^[14]。本研究显示观察组的肠球菌、粪肠球菌和大肠埃希杆菌含量明显高于对照组,而双歧杆菌含量明显低于对照组,表明炎症性肠病患者体内存在明显的肠道菌群失调,主要表现为益生菌含量减少,而有害菌含量增加。

在炎症性肠病的致病因素中,肠黏膜通透性改变、小肠细菌增殖与易位等所致的内毒素血症等在炎症性肠病的发病中起着重要的作用^[15,16]。炎症因子具有调节细胞功能、维持生理平衡等作用,IL-6 能够激活转录激活因子,诱导抗凋亡因子的生成,可通过诱导纤维蛋白原启动凝血因子,在肠道黏膜异常堆积,使炎症反应不断加重^[17]。TNF- α 可在受损的肠黏膜中大量表达,并且其病变范围越大、病变越严重,TNF- α 水平越高^[18]。本研究显示炎症性肠病患者的血清 TNF- α 与 IL-6 水平分别为 0.98 ± 0.54 ng/mL 和 0.98 ± 0.38 pg/mL,都明显高于对照组,说明 TNF- α 与 IL-6 水平可能与炎症性肠病的发生有关。

肠道细菌还参与维生素的合成、钙镁铁等离子代谢,短链脂肪酸产生,促进肠上皮细胞的生长和分化等过程。肠道菌群可以活化肠上皮细胞表面的多种病原相关性分子模式,下游信号传导通路,引起上皮细胞分泌抗炎物质^[19,20]。本研究结果显示炎症性肠病患者的双歧杆菌含量与 TNF- α 与 IL-6 呈现明显负相关性,而肠球菌、粪肠球菌、大肠埃希杆菌含量与 TNF- α 与 IL-6 都呈现明显正相关性,提示菌群的改变可能影响了体内炎症因子的产生和分泌。

综上所述,炎症性肠病患者存在益生菌含量减少、有害菌含量增加的现象,这可能与患者血清促炎因子过量表达有关,二者的共同作用可促进炎症性肠病的发生及进展。

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