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学龄前儿童细菌性腹泻的病原学特征及 PCT、CD64 和 sTREM-1 测定的临床意义 *

张锡波¹ 叶旭鑫¹ 何慧君¹ 张凤宜¹ 何天文² 吴志锋¹

(1 南方医科大学附属东莞市人民医院检验科 广东 东莞 523039; 2 广东省妇幼保健院番禺院区医学遗传中心 广东 广州 511400)

摘要 目的:分析学龄前儿童细菌性腹泻的病原学特征及血清中降钙素原(PCT)、中性粒细胞分化群64(CD64)和髓样细胞触发受体-1(sTREM-1)检测的临床意义。**方法:**选择2017年1月~2018年3月南方医科大学附属东莞市人民医院收治的214例学龄前感染性腹泻患儿为研究对象,包括细菌性腹泻(细菌组,n=101)和病毒性腹泻(病毒组,n=113),以同期入院行儿童保健的113例健康学龄前儿童为对照组。统计细菌组患儿的病原菌种类,比较两组腹泻患儿与对照组儿童血清PCT、CD64和sTREM-1水平的差异、三种血清学指标的阳性率及三种指标对细菌性腹泻患儿的诊断效能。**结果:**101例细菌性腹泻患儿粪便培养的细菌菌株中,共培养菌株213株,大肠埃希菌、志贺菌属和沙门菌属阳性率最高,分别占41.78%、23.01%和15.96%;细菌组的血清PCT、CD64和sTREM-1水平及阳性率均高于病毒组和对照组,且病毒组的sTREM-1水平高于对照组($P<0.05$);三种指标的灵敏度、特异度、阳性预测值和阴性预测值比较,差异无统计学意义($P>0.05$)。**结论:**学龄前儿童细菌性腹泻的致病菌主要为革兰阴性菌,PCT、CD64和sTREM-1均可作为判断细菌性腹泻的早期敏感指标。

关键词:细菌性腹泻;病原;降钙素原;中性粒细胞分化群64;髓样细胞触发受体-1;学龄前

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Etiology Characteristics and Clinical Significance of PCT, CD64 and sTREM-1 in Preschool Children with Bacterial Diarrhea*

ZHANG Xi-bo¹, YE Xu-xin¹, HE Hui-jun¹, ZHANG Feng-yi¹, HE Tian-wen², WU Zhi-feng¹

(1 Department of Laboratory, Dongguan People's Hospital Affiliated to Southern Medical University, Dongguan, Guangdong, 523039, China; 2 Panyu Medical Heredity Center, Guangdong Maternal and Child Health Hospital, Guangzhou, Guangdong, 511400, China)

ABSTRACT Objective: To analyze the etiology characteristics and the clinical significance of serum procalcitonin (PCT), cluster of differentiation 64 (CD64) and soluble triggering receptors expressed on myeloid cells-1 (sTREM-1) in preschool children with bacterial diarrhea. **Methods:** 214 children with infectious diarrhea who were admitted to Dongguan People's Hospital Affiliated to Southern Medical University from January 2017 to March 2018 were selected as research subjects. It included bacterial diarrhea (bacterial group, n=101) and viral diarrhea (viral group, n=113), and 113 healthy school age children who were admitted to hospital during the same period were selected as control group. The types of pathogens in the bacterial group were counted, and the differences of serum PCT, CD64 and sTREM-1 levels between the two groups of diarrhea children and the control group were compared, and the positive rates of three serological indicators and the diagnostic efficacy of the three indicators for children with bacterial diarrhea were also compared. **Results:** Among the 101 Bacterial diarrhea in children, 213 bacterial strains were cultured in feces. The positive rates of Escherichia coli, Shigella and Salmonella were the highest, accounting for 41.78%, 23.01% and 15.96% respectively. The levels and positive rates of serum PCT, CD64 index and sTREM-1 in bacterial group were higher than those in viral group and control group, and the sTREM-1 level in viral group was higher than those in control group ($P<0.05$). The sensitivity, specificity, positive predictive value and negative predictive value of the three indexes were compared, the differences were not statistically significant ($P>0.05$). **Conclusion:** The main pathogens in preschool children with bacterial diarrhea are Gram-negative bacteria. The PCT, CD64 index and sTREM-1 could be used as early sensitive indicators for judging bacterial diarrhea.

Key words: Bacterial diarrhea; Etiology; Procalcitonin; Cluster of differentiation 64; Soluble triggering receptors expressed on myeloid cells-1; Preschool children

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前言

感染性腹泻是儿童多见的,以腹泻为主要表现的一种消化道传染病。根据致病微生物种类的不同,可分为细菌性腹泻、病

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作者简介:张锡波(1984-),男,本科,主管技师,研究方向:临床医学检验,E-mail: zhangxibo369@163.com

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毒性腹泻、真菌性腹泻等^[1,2]。学龄前儿童因其免疫低下、卫生习惯不良等因素的影响,已成为该病的易感及好发人群。通常该病在接受抗菌抗病毒等治疗后均可得到明显改善,而近年来致病菌往往因未得到针对性的治疗,导致延误治疗的最佳时期,从而使病情进一步发展和恶化,轻者影响患儿的正常生长发育,重者导致患儿死亡。目前临床中对病原菌的判断主要依靠病原体培养和检测方法,但该方法耗时长,具有滞后性,因此,探寻感染性腹泻的早期生物标志物成为目前研究的重要方向^[3-5]。降钙素原(Procalcitonin, PCT)是一种主要由甲状腺C细胞和外周单核细胞分泌的降钙素前体物质,在正常生理状态时水平很低,但在发生脓毒症、创伤、急慢性肺炎时显著升高,为早期感染的重要指标^[6,7]。中性粒细胞分化群64(Cluster of differentiation 64, CD64)是免疫球蛋白的Fc段受体,其表达受细胞因子的调控,在体液免疫和细胞免疫中发挥桥梁作用,近年来已成为诊断感染性疾病的新指标。髓样细胞触发受体-1(Soluble triggering receptors expressed on myeloid cells, sTREM-1)是一种免疫球蛋白超家族受体,有研究发现^[8],sTREM-1可利用特殊细胞信号激活炎症介质,放大炎症过程。本研究通过分析学龄前细菌性腹泻儿童血清PCT、CD64和

sTREM-1检测的临床价值,期望为探索细菌性腹泻的早期判断指标提供依据。

1 资料与方法

1.1 研究对象

选择2017年1月~2018年3月于南方医科大学附属东莞市人民医院住院治疗的214例学龄前感染性腹泻患儿为研究对象,纳入标准:(1)患儿的症状和体征均符合《儿童腹泻病诊断治疗原则的专家共识》中腹泻病的诊断标准^[9];(2)患儿年龄在3~6岁之间;(3)在东莞市人民医院首诊,且临床资料完整者;(4)对研究和治疗方案配合者;(5)确诊为感染性腹泻者;(6)所有对象的监护人均签署知情同意书。排除标准:(1)因饮食不良、病毒、物理刺激等其他原因所致的腹泻者;(2)入院前接受过抗感染治疗者;(3)合并呼吸系统、消化系统等其他系统的感染患儿;(4)同时合并细菌感染和病毒感染的患儿。根据细菌培养和病毒血清学检测的结果,可分为细菌性腹泻(细菌组,n=101)和病毒性腹泻(病毒组,n=113)。选择同期入院行儿童保健的113例健康学龄前儿童为对照组。三组儿童基本资料比较无差异($P>0.05$),具有可比性。见表1。

表1 三组儿童基本资料比较

Table 1 Comparison of basic data of children in three groups

Groups	Gender (male/female)	Age (year)	Course of disease(d)
Bacteriological group(n=101)	56/45	4.42±1.06	5.21±1.54
Virus group(n=113)	61/52	4.27±1.47	5.46±1.62
Control group(n=113)	59/54	4.16±1.52	-
F/ χ^2 /t	0.226	0.787	-1.153
P	0.893	0.456	0.250

1.2 研究方法

1.2.1 菌种鉴定 查阅细菌组患儿的病例资料,记录各患儿的病原菌种类。病原菌的检测方法为:取治疗前的粪便样本,2h内送检验科微生物室进行病原菌检验,操作过程严格遵照《全国临床检验操作规程》^[10]进行,即:挑取新鲜粪便标本粘液脓血部分,接种于麦康凯和SS琼脂平板中,35°C培养箱中培养18~24h后,在Microscan WalkAway-40全自动微生物分析仪中进行菌种的鉴定,革兰阳性菌和革兰阴性菌为仪器配套。

1.2.2 血清PCT、CD64和sTREM-1测定 细菌组和病毒组儿童入院当天在未进行任何治疗前、对照组在行儿童保健当天,抽取外周静脉血3管,其中1管2mL储存于EDTA抗凝管中用于CD64的检测,另2管各3mL,促凝后均以3500 r/min离心10 min,取上清冻存于-20°C冰箱中,用于PCT和sTREM-1的测定。(1)PCT的测定:采用酶联免疫分析方法对PCT水平进行测定,所用仪器和试剂均为梅里埃mini VIDAS系列,阳性标准为:PCT≥0.5 μg/L;(2)中性粒细胞表面CD64的检测:取2mL EDTA抗凝管中的全血样品,50 μL全血加入20 μL CD64PE/CD45PerCP抗体(购于美国BD公司),混匀,置于暗处放置1小时,后加入2mL FACS溶血剂,再于暗处放置20分钟后,利用FACS Calibur型流式细胞仪(美国BD)上进

行检测,所用试剂为中性粒细胞CD64专用定量检测试剂。计算每1万个细胞中的CD64的平均荧光强度(Mean fluorescence intensity, MFI),阳性标准为:CD64>3.5MFI;(3)sTREM-1的测定:采用上海沪峰生物科技有限公司的试剂盒,利用双抗体夹心酶联免疫吸附法进行检测。阳性标准为:sTREM-1>24.45 pg/mL。

1.3 观察指标

统计细菌组粪便样品中各病原菌的分布特征,比较三组儿童血清中PCT、CD64和sTREM-1水平及三种血清学指标的阳性率,分析三种指标对细菌性腹泻患儿的诊断效能,包括灵敏度、特异度、阳性预测值和阴性预测值,其中灵敏度=真阳性/(真阳性+假阴性)×100%,特异度=真阴性/(假阳性+真阴性)×100%,阳性预测值=真阳性/(真阳性+假阳性)×100%,阴性预测值=真阴性/(假阴性+真阴性)×100%。

1.4 统计学分析

本研究数据在SPSS 21.0统计软件中进行整理和分析。计量资料以均数±标准差($\bar{x} \pm s$)表示,三组样本均数比较采用F检验,两两比较采用LSD-t检验;计数资料以率(%)表示,采取 χ^2 检验。以 $P<0.05$ 代表差异具有显著性。

2 结果

2.1 细菌组患儿的病原学分布

101 例细菌组粪便培养的细菌菌株中, 共培养菌株 213 株, 其中大肠埃希菌、志贺菌属和沙门菌属阳性率最高, 分别占 41.78%、23.01% 和 15.96%, 其次为肠球菌属和变形杆菌属, 分别占 8.45% 和 6.57%, 见表 2。

表 2 细菌组儿童的病原学分布
Table 2 Etiology distribution of children in bacterial group

Pathogenic bacteria		Number of positive strains	Positive rate(%)
Gram-negative bacteria	Shigella	49	23.01
	<i>Escherichia coli</i>	89	41.78
	Salmonella	34	15.96
	Klebsiella	5	2.35
	<i>Pseudomonas aeruginosa</i>	3	1.41
	Proteus	14	6.57
Gram-positive bacteria	<i>Enterococcus</i>	18	8.45
Fungus	<i>Candida albicans</i>	1	0.47
	Total	213	100.00

2.2 三组儿童血清中 PCT、CD64 和 sTREM-1 的水平比较

由表 3 可知, 细菌组的血清 PCT、CD64 和 sTREM-1 水平均高于病毒组和对照组, 且病毒组的 sTREM-1 水平高于对照组, 差异均有统计学意义($P<0.05$)。

表 3 三组儿童血清中 PCT、CD64 和 sTREM-1 的水平比较($\bar{x}\pm s$)

Table 3 Comparison of serum PCT, CD64 and sTREM-1 levels of children in three groups ($\bar{x}\pm s$)

Groups	PCT($\mu\text{g/L}$)	CD64(MFI)	sTREM-1(pg/mL)
Bacteriological group(n=101)	8.01± 3.17	15.21± 5.22	56.97± 7.51
Virus group(n=113)	0.06± 0.01*	3.13± 1.25*	22.16± 4.82**
Control group(n=113)	0.04± 0.01*	2.92± 0.91*	15.28± 2.47*
F	73.013	62.608	48.714
P	0.000	0.000	0.000

Note: compared with the bacterial group, * $P<0.05$; compared with the control group, ** $P<0.05$.

2.3 三组儿童血清学指标阳性率比较

由表 4 可知, 细菌组的 PCT、CD64 和 sTREM-1 的阳性率均显著高于病毒组和对照组($P<0.05$); 而病毒组和对照组对比, 差异无统计学意义($P>0.05$)。

表 4 三组儿童血清学指标阳性率比较[n(%)]

Table 4 Comparison of positive rates of serological indicators of children in three groups[n(%)]

Groups	PCT positive	CD64 positive	sTREM-1 positive
Bacteriological group(n=101)	86(85.15)	89(88.12)	91(90.10)
Virus group(n=113)	18(15.93)*	19(16.81)*	26(23.01)*
control group(n=113)	14(12.39)*	13(11.50)*	18(15.93)*
χ^2	52.830	64.483	44.823
P	0.000	0.000	0.000

Note: compared with the bacterial group, * $P<0.05$.

2.4 三种指标对细菌性感染患儿的诊断效能比较

由表 5 可知, 三种指标的灵敏度、特异度、阳性预测值与阴性预测值对比, 差异均无统计学意义($P>0.05$)。

3 讨论

细菌性腹泻为儿科的常见病和多发病, 占儿童腹泻病的

30%左右, 且以 5 岁以下儿童最为多见, 占 90%以上^[11]。及时明确细菌性腹泻的病原菌种类, 将对采取有效的治疗方法、控制病情进展具有重要意义。病原菌的培养与检测是临床中检测微生物种类的基本方法^[12,13]。本次研究发现, 在 101 例细菌组儿童的病菌株中, 大肠埃希菌、志贺菌属和沙门菌属为最主要的流行菌株, 占 80%以上。这与尚艳等人^[14]的检测结果基本相符。提

表 5 三种指标对细菌性感染患儿的诊断效能比较

Table 5 Comparison of diagnostic effectiveness of three indicators for children with bacterial infection

Testing items	Sensitivity	Specificity	Positive predictive value	Negative predictive value
PCT	82.56%(71/86)	73.33%(11/15)	94.67%(71/75)	42.31%(11/26)
CD64	87.64%(78/89)	83.33%(10/12)	97.50%(78/80)	47.62%(10/21)
sTREM-1	85.71%(78/91)	80.00%(8/10)	97.50%(78/80)	38.10%(8/21)
χ^2	0.919	0.888	3.637	0.421
P	0.632	0.641	0.162	0.810

示革兰氏阴性菌为主要致病菌，在细菌性腹泻患儿的治疗中，应以这类病菌的抗感染治疗为主。

然而临床中往往需在病菌检出之前及早进行相关治疗，以防止病情的延误。而该法的检测步骤较为复杂，具有明显滞后性，故探寻更为迅速的检测手段成为临床工作的重要课题。PCT 为一种无激素活性的降钙素前体物质，为临床中检测炎症性疾病的较敏感指标，其水平不会因体内应激反应、缺氧等因素而发生改变，而在发生脓毒症等全身系统性感染时，因细菌内毒素及细胞因子对神经内分泌细胞的促进而大量分泌^[15-17]。CD64 为一种免疫反应指标，正常情况下 CD64 呈低水平表达，而在机体发生免疫功能活化时快速上升，特异性识别免疫球蛋白 G 的 Fc 段，发挥相应抗感染及调节机体免疫的功能^[18,19]，且其水平变化情况会因病原体种类和过敏原的不同有所差异，因此有研究认为其在细菌和病毒感染方面具有一定的鉴别能力。sTREM-1 是一种免疫球蛋白超家族成员的细胞膜受体，可在 CD14 单核细胞和中性粒细胞中选择性表达，虽其确切来源不甚明确，但已证实其在感染早期即可释放入体液且表达上调^[20,21]。研究显示，sTREM-1 可诱导中性粒细胞和单核细胞分泌肿瘤坏死因子 -α、白细胞介素 -1β 等促炎症因子，其还可诱发钙离子转移，磷酸化细胞表面信号相关激酶及磷脂酶 C 络氨酸，从而发挥介导感染性休克、扩大炎症反应等作用^[22-24]。有研究发现，PCT、CD64 指数和 sTREM-1 等指标均与各类感染性疾病的发生发展密切相关^[25,26]，但其在细菌性腹泻中的诊断作用和价值仍有待进一步的确定。本次研究发现，细菌组的血清 PCT、CD64 和 sTREM-1 水平及阳性率均高于病毒组和对照组，且病毒组的 sTREM-1 水平高于对照组 ($P<0.05$)。提示 PCT、CD64 和 sTREM-1 的水平及阳性率上升可能与细菌性腹泻的发生发展有关，可作为细菌性腹泻的诊断指标。这与以往相关研究结果^[27-29]具有一致性。其原因可能在于机体在受到细菌入侵和繁殖等刺激后，可导致各类免疫细胞的活化及细菌内毒素和细胞因子的分泌，从而进一步引起 PCT、CD64 和 sTREM-1 的大量释放。

进一步对 PCT、CD64 和 sTREM-1 三种指标在诊断细菌性腹泻的灵敏度、特异度等诊断效能指标进行研究，结果发现，三种指标的诊断效能较高，但阴性预测值不太理想，且三者比较均无统计学差异 ($P>0.05$)。提示 PCT、CD64 和 sTREM-1 水平对于细菌性腹泻的诊断和预警具有一定的临床价值，这与杨芳^[30]的研究基本相符。但是，本研究的对比仍停留在分析三种指标的单独诊断效能，在今后的研究中，将考虑三种指标联合或其中两者联合对疾病的诊断效能。

综上所述，学龄前儿童细菌性腹泻的致病菌主要为革兰阴性细菌，PCT、CD64 和 sTREM-1 均可作为判断细菌性腹泻的早期敏感指标，对三种血清学指标进行监测，有助于对患儿的病情程度和预后进行判断。

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