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血清 25-羟维生素 D 水平与脓毒症患者凝血功能、炎症因子及预后的关系*

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摘要 目的:探讨血清 25-羟维生素 D(25-OH-VitD)水平与脓毒症患者凝血功能、炎症因子及预后的相关性。**方法:**选取 2016 年 5 月-2017 年 12 月期间山东省立医院收治的脓毒症患者 68 例为研究组,根据研究组患儿血清 25-OH-VitD 水平将其分为三组:缺乏组(<20 ng/mL)6 例、不足组(20-29.9 ng/mL)19 例、充足组(≥ 30 ng/mL)43 例,再根据研究组患儿 28d 后转归情况分为好转组 56 例与恶化组 12 例。另选取同时期在山东省立医院进行体检的健康儿童 46 例为对照组,检测并比较各组实验室指标,并分析血清 25-OH-VitD 与 C 反应蛋白(CRP)、白介素-2R(IL-2R)、白介素-6(IL-6)、降钙素原(PCT)、凝血酶原时间(PT)、活化部分凝血活酶时间(APTT)的相关性,对脓毒症患者预后的独立影响因素进行 Logistic 回归分析。**结果:**缺乏组、不足组、充足组患儿 CRP、IL-2R、IL-6、PCT、PT、APTT 水平均明显高于对照组($P<0.05$),其中 CRP、IL-2R、IL-6、PCT 随着 25-OH-VitD 水平的降低而升高($P<0.05$)。与恶化组对比,好转组患儿血清 25-OH-VitD 水平明显升高,CRP、IL-2R、IL-6、PCT 水平明显降低($P<0.05$)。经 Pearson 相关性分析显示,脓毒症患者血清 25-OH-VitD 均与 CRP、IL-2R、IL-6、PCT 呈负相关($P<0.05$),与 PT、APTT 无关($P>0.05$)。经 Logistic 回归分析显示,血清 25-OH-VitD 是脓毒症患者预后的独立影响因素($P<0.05$)。**结论:**血清 25-OH-VitD 与脓毒症患者炎症因子密切相关,与凝血功能指标无关,且血清 25-OH-VitD 是其预后的独立影响因素。

关键词:脓毒症;25-羟维生素 D;凝血功能;预后;炎症因子;相关性

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The Relationship between Serum 25-hydroxyvitamin D Level and Coagulation Function, in Inflammatory Factors and Prognosis in Children with Sepsis*

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ABSTRACT Objective: To investigate the correlation between serum 25-hydroxyvitamin D (25-OH-VitD), coagulation function, inflammatory factors and prognosis in children with sepsis. **Methods:** 68 children with sepsis who were treated in Shandong Provincial Hospital from May 2016 to December 2017 were selected as the study group. According to the serum 25-OH-VitD level of the children in the study group, it was divided into three groups: 6 cases of lack group (<20 ng/mL), 19 cases of insufficient group (20-29.9 ng/mL), 43 cases of adequate group (more than 30 ng/mL). According to the prognosis of 28d in the study group, the patients was divided into 56 cases in the improvement group and 12 cases in the worsening group. 46 healthy children selected for physical examination in Shandong Provincial Hospital in the same period as the control group. The laboratory indexes of each group were detected and compared. The correlation between serum 25-OH-VitD, C reactive protein (CRP), interleukin-2R (IL-2R), interleukin-6 (IL-6), procalcitonin (PCT), prothrombin time (PT), activated partial thromboplastin time (APTT) were analyzed. Logistic regression analysis was conducted on the independent prognostic factors of children with sepsis. **Results:** The levels of CRP, IL-2R, IL-6, PCT, PT and APTT in the lack group, the insufficient group and the adequate group were all significantly higher than those of the control group ($P<0.05$). CRP, IL-2R, IL-6 and PCT increased with the decrease of 25-OH-VitD level ($P<0.05$). Compared with the worsening group, the serum 25-OH-VitD level of the children in the improvement group was significantly increased, and the levels of CRP, IL-2R, IL-6 and PCT were significantly decreased ($P<0.05$). The Pearson correlation analysis showed that the serum 25-OH-VitD of children with sepsis was negatively correlated with CRP, IL-2R, IL-6 and PCT ($P<0.05$), it has no correlation with PT and APTT ($P>0.05$). Logistic regression analysis showed that serum 25-OH-VitD was independent factor affecting the prognosis of children with sepsis ($P<0.05$). **Conclusion:** Serum 25-OH-VitD is closely

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related to inflammatory factors in children with sepsis, it is not related to the indexes of coagulation function, and serum 25-OH-VitD is an independent prognostic factor.

Key words: Sepsis; 25-hydroxyvitamin D; Coagulation function; Prognosis; Inflammatory factor; Correlation

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前言

脓毒症是一种感染性疾病,近年来其发病率呈逐年升高的趋势,且病死率较高,脓毒症患儿的病死率高达 21.9%^[1,2]。脓毒症的发病机制较为复杂,其预后可能受多种复杂因素的影响^[3,4]。近年来,随着临床学者对维生素 D 的深入研究,其不仅能够调节钙磷代谢,还能够对多种细胞因子和免疫细胞产生影响,进而抑制适应性免疫应答和调控固有免疫,最终影响脓毒症的发生与发展^[5-7]。目前,国际上已经将血清 25-羟维生素 D (25-hydroxy-vitamin D, 25-OH-VitD) 指定为监测和衡量机体维生素 D 含量的有效指标^[8],据国外相关研究显示,25-OH-VitD 的缺乏是影响脓毒症患儿预后的危险因素,可能会增加脓毒症患儿的病死率^[9,10]。目前,国内关于 25-OH-VitD 对脓毒症患儿预后影响的相关研究还需进一步加强,本研究主要是对血清 25-OH-VitD 水平与脓毒症患儿凝血功能、炎症因子等指标及预后的相关性进行探讨,旨在为脓毒症患儿的防治提供新的方向,现作如下报道。

1 资料与方法

1.1 一般资料

选取 2016 年 5 月-2017 年 12 月期间山东省立医院收治的脓毒症患儿 68 例为研究组,纳入标准:(1)均符合中国中西医结合学会急救医学专业委员会、《中国中西医结合急救杂志》编辑委员会制定的《脓毒症中西医结合诊治专家共识》中有关脓毒症诊断标准^[11];(2)非手术外伤者;(3)在抢救室存活时间>24h;(4)患儿家属对本研究知情同意,并签署知情同意书。排除标准:(1)近期服用过影响维生素 D 代谢的药物;(2)伴有甲状旁腺疾病患儿;(3)伴有先天性免疫缺陷患儿;(4)伴有先天性代谢性疾病的患儿。研究组男 42 例,女 26 例,年龄 4-15 岁,平均(10.87±2.14)岁,体重 15-52kg,平均(32.42±4.18)kg,其中革兰阴性菌感染 28 例,革兰阳性菌感染 30 例,真菌感染 10 例。另选取同时期在山东省立医院进行健康体检儿童 46 例为对照组,男 28 例,女 18 例,年龄 3-13 岁,平均(9.55±1.98)岁,体重 14-48 kg,平均(31.89±5.17) kg。研究组与对照组在性别、

年龄、体重方面对比无统计学差异($P>0.05$),均衡可比。本研究通过山东省立医院伦理委员会批准。

1.2 方法

对照组在体检时、研究组在入院 24h 内抽取静脉血 5 mL,应用离心机(美国 Beckman 公司)以 3000 r/min 的转速离心 10 min,离心半径为 10 cm,收集血清,-29℃ 保存待检,25-OH-VitD 水平采用电化学发光法检测,试剂盒由德国罗氏公司提供,C 反应蛋白(C reactive protein, CRP)、白介素-2R(interleukin-2R, IL-2R)、白介素-6(interleukin-6, IL-6)采用酶联免疫吸附法检测,试剂盒由上海歌凡生物科技公司提供,降钙素原(procalcitonin, PCT)水平采用酶联荧光法检测,试剂盒由法国 Bio Merieux 公司提供,严格按照试剂盒说明书进行操作。凝血酶原时间(prothrombin time, PT)、活化部分凝血活酶时间(activated partial thromboplastin time, APTT)应用 PUZS-300X 全自动生化分析仪(北京普朗)检测。根据研究组患儿血清 25-OH-VitD 水平将其分为三组:缺乏组(<20 ng/mL)6 例、不足组(20-29.9 ng/mL)19 例、充足组(≥ 30 ng/mL)43 例。记录研究组住院患儿 28d 转归情况,未满 28d 出院者采用电话随访进行记录,根据 28d 后转归情况分为好转组 56 例与恶化组 12 例。

1.3 统计学方法

采用 SPSS19.0 统计学软件,计量资料以($\bar{x}\pm s$)的形式表示,实施 t 检验,计数资料以%表示,实施 χ^2 检验,采用 Pearson 相关性分析方法分析脓毒症患儿血清 25-OH-VitD 与炎症因子和凝血功能的相关性,脓毒症患儿预后的独立影响因素采用 Logistic 回归分析,检验水准设置为 $\alpha=0.05$ 。

2 结果

2.1 研究组不同 25-OH-VitD 水平患儿与对照组炎症因子和凝血功能水平对比

缺乏组、不足组、充足组患儿 CRP、IL-2R、IL-6、PCT、PT、APTT 水平均明显高于对照组($P<0.05$),其中 CRP、IL-2R、IL-6、PCT 随着 25-OH-VitD 水平的降低而升高($P<0.05$),缺乏组、不足组、充足组患儿之间 PT、APTT 两两对比无统计学差异($P>0.05$),见表 1。

表 1 研究组不同 25-OH-VitD 水平患儿与对照组炎症因子和凝血功能水平对比($\bar{x}\pm s$)

Table 1 Comparison of inflammatory factors and coagulation function between children with different levels of 25-OH-VitD and control group($\bar{x}\pm s$)

Groups	n	CRP(mg/L)	IL-2R(ng/L)	IL-6(ng/L)	PCT(μ g/L)	PT(s)	APTT(s)
Lack group	6	102.76±15.43 ^{*#}	9.24±0.18 ^{*#}	25.95±4.33 ^{*#}	82.33±9.16 ^{*#}	23.14±8.72 [*]	49.72±11.98 [*]
Insufficient group	19	68.97±7.69 [#]	7.59±0.32 [#]	19.58±3.49 [#]	59.72±7.84 [#]	22.15±9.14 [*]	47.93±11.54 [*]
Adequate group	43	43.12±5.42 [*]	5.08±0.23 [*]	11.86±2.65 [*]	22.37±4.52 [*]	21.98±8.43 [*]	46.54.12±10.29 [*]
Control group	46	8.87±1.49	2.74±0.18	4.52±1.33	1.54±0.21	12.54±3.47	26.78±7.32

Note: compared with the control group, ^{*} $P<0.05$; compared with the adequate group, [#] $P<0.05$; compared with the insufficient group, ^{*} $P<0.05$.

2.2 好转组与恶化组 25-OH-VitD、炎症因子和凝血功能水平对比 高,CRP、IL-2R、IL-6、PCT 水平明显降低 ($P<0.05$), 两组患儿 PT、APTT 水平对比无统计学差异($P>0.05$),见表 2。

与恶化组对比, 好转组患儿血清 25-OH-VitD 水平明显升

表 2 好转组与恶化组 25-OH-VitD、炎症因子和凝血功能水平对比($\bar{x}\pm s$)

Table 2 Comparison of 25-OH-VitD, inflammatory factors and coagulation function between the improvement group and the worsening group($\bar{x}\pm s$)

Groups	n	25-OH-VitD(ng/mL)	CRP(mg/L)	IL-2R(ng/L)	IL-6(ng/L)	PCT(ug/L)	PT(s)	APTT(s)
Improvement group	56	37.12± 5.77	58.92± 11.98	6.45± 0.35	13.68± 4.29	59.72± 7.45	22.53± 6.12	47.32± 11.45
Worsening group	12	17.33± 3.85	89.33± 15.87	8.89± 0.42	24.19± 5.63	70.49± 10.43	24.13± 8.45	49.16± 10.58
t		12.986	10.763	18.918	14.419	15.872	0.766	0.129
P		0.008	0.014	0.001	0.006	0.003	0.446	0.672

2.3 脓毒症患儿血清 25-OH-VitD 与炎症因子和凝血功能相关性分析 均与 CRP、IL-2R、IL-6、PCT 呈负相关($P<0.05$),而与 PT、APTT 无关($P>0.05$)。见表 3。

经 Pearson 相关性分析显示,脓毒症患儿血清 25-OH-VitD

表 3 脓毒症患儿血清 25-OH-VitD 与炎症因子和凝血功能相关性分析

Table 3 Correlation analysis of serum 25-OH-VitD and inflammatory factors and coagulation function in children with sepsis

Indexes	25-OH-VitD	
	r	P
CRP	-0.289	0.001
IL-2R	-0.412	0.007
IL-6	-0.628	0.011
PCT	-0.597	0.009
PT	0.120	0.084
APTT	0.253	0.068

2.4 Logistic 回归分析脓毒症患儿预后的独立影响因素 量纳入 Logistic 回归分析模型,结果显示,血清 25-OH-VitD 是脓毒症患儿预后的独立影响因素($P<0.05$),见表 4。

以脓毒症患儿好转或恶化为因变量,以结果 2.2 中差异有统计学意义的指标 25-OH-VitD、CRP、IL-2R、IL-6、PCT 为自变

表 4 Logistic 回归分析脓毒症患儿预后的独立影响因素

Table 4 Logistic regression analysis of independent prognostic factors in children with sepsis

Factor	β	P	Wald χ^2 value	OR value	95%CI
25-OH-VitD	-0.083	0.013	7.529	4.194	1.878-10.459
CRP	0.001	0.378	0.914	1.052	0.974-1.267
IL-2R	0.297	0.512	0.732	1.314	0.682-4.533
IL-6	0.412	0.408	0.382	1.297	0.714-4.276
PCT	0.068	0.439	0.415	0.998	0.615-4.678

3 讨论

脓毒症在儿童中的发病率较高主要是因为儿童的免疫系统发育不完善,当发生细菌感染后,机体对外界的抵抗能力较弱,因此导致儿童脓毒症的发病率呈逐年上升的趋势^[12,13]。儿童脓毒症由于其具有较高的病死率,是临床治疗危重症较为棘手的难题^[14,15]。当病原体入侵患儿身体后则可引发一系列动态、连

续的宿主反应,早期诊断脓毒症,及时对患儿采用抗生素及液体复苏治疗,可将脓毒症病情控制在初始阶段,防止其发展为脓毒性休克、严重脓毒症^[16-18]。因此寻求一种能够预测脓毒症患儿病情的方法,对改善脓毒症患儿预后具有重要的临床意义。近年来,国内外较多研究显示维生素 D 水平影响着脓毒症的发生与发展,维生素 D 是一种类固醇衍生物,是人体必需的营养元素,在体内可经 25-羟化酶转化为 25-OH-VitD,与免疫细

胞表面的维生素 D 受体相结合进而发挥免疫调节作用, 通过调节细胞增殖与分化来参与脓毒症的发生与发展^[19-21]。

CRP、IL-2R、IL-6 均是可有效反映机体炎症反应状态的有效指标, PCT 是一种蛋白质, 可有效反映全身炎症反应的活跃度, PT、APTT 是反映机体凝血功能的有效指标。本研究结果显示, 脓毒症患者血清炎症因子和凝血功能水平高于健康儿童 ($P < 0.05$), 且炎症因子水平随着脓毒症患者血清 25-OH-VitD 水平的下降而升高 ($P < 0.05$)。分析其原因主要是因为脓毒症患者受细菌感染后, 病情发展迅速, 机体处于炎症反应状态, 同时也会发生器官功能障碍, 因此炎症因子水平会较健康儿童高, 凝血功能也会随之发生异常^[22-24]。当机体内维生素 D 缺乏时, 机体内免疫细胞会发生障碍, 致使巨噬细胞的吞噬和趋化功能异常, T 淋巴细胞的细胞免疫也无法正常发挥, 而此时, 如果病原体侵入机体, 将相应受体激活, 并扩大信号, 将信号传至细胞核, 最终致使炎症介质呈瀑布样释放, 同时由于机体的免疫功能不能够有效的发挥抵抗作用, 而使炎症因子的水平急剧增高^[25-27]。在对不同转归脓毒症患者各指标分析中显示, 与恶化组对比, 好转组患者血清 25-OH-VitD 水平明显升高, 炎症因子水平明显降低, 可能是随着血清 25-OH-VitD 水平的降低, 机体免疫功能下降, 脓毒症患者的感染程度可能逐渐加重, 炎症反应加剧^[28, 29]。在相关性分析中显示, 脓毒症患者血清 25-OH-VitD 均与 CRP、IL-2R、IL-6、PCT 呈负相关 ($P < 0.05$), 而与 PT、APTT 无关 ($P > 0.05$), 进一步说明了血清 25-OH-VitD 水平对免疫细胞发挥正常功能具有重要的作用。经 Logistic 回归分析显示, 血清 25-OH-VitD 是脓毒症患者预后的独立影响因素, 充足的 25-OH-VitD 是脓毒症患者预后的保护影响因素, 可有效改善患者预后, 可能是 25-OH-VitD 与机体免疫功能及炎症因子存在显著相关性, 当 25-OH-VitD 水平上升时, 机体免疫功能提高, 炎症反应减轻, 使得患者病情好转, 预后得到改善^[30]。

综上所述, 血清 25-OH-VitD 是脓毒症患者预后的独立影响因素, 其与患者炎症因子水平呈负相关, 与凝血功能指标无明显相关性, 检测血清 25-OH-VitD 水平有助于评估患者病情及预后。

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