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儿童细菌性脓毒症中富含组氨酸糖蛋白血浆浓度及其诊断价值

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[摘　要]　**目的：**探讨血浆富含组氨酸糖蛋白(histidine-rich glycoprotein，HRG)、降钙素原(procalcitonin，PCT)和C反应蛋白(C-reactive protein，CRP)浓度在儿童细菌性脓毒症中的诊断价值。**方法：**收集2018年1月至12月于武汉市金银潭医院传染病科住院就诊的60例细菌性脓毒症患儿为观察组，同期年龄和性别相匹配的60例健康儿童为对照组。检测并比较观察组治疗前后血浆HRG，PCT和CRP浓度差异，并与对照组进行比较，受试者工作特征(receiver operating characteristic，ROC)曲线分析三者诊断效能。**结果：**治疗前，观察组血浆HRG浓度显著低于对照组[(28.7±11.3) μg/mL vs (53.0±21.0) μg/mL，P<0.001]；治疗后，HRG浓度升至(38.6±9.7) μg/mL。观察组血浆PCT [(10.9±4.6) μg/L vs (0.5±0.2) μg/L，P<0.01]和CRP [(19.4±6.5) mg/L vs (0.2±0.3) mg/L，P<0.05]浓度均显著高于对照组。治疗后PCT和CRP浓度均较治疗前显著下降(P<0.05)。当截断值为33.2 μg/mL时，血浆HRG浓度诊断脓毒症ROC曲线下面积(area under the curve，AUC)为0.910 (95% CI 0.840~0.940，P<0.001)，优于PCT (AUC 0.754)和CRP (AUC 0.654)。三种标志物联合应用可提高诊断效能，其敏感度和特异度分别为94.6%和96.8%。治疗前血浆HRG与PCT浓度显著正相关(r=0.76，P<0.001)。**结论：**细菌性脓毒症患儿血浆HRG浓度显著下降，PCT和CRP浓度显著升高，HRG对细菌性脓毒症患儿诊断效能优于PCT和CRP，是细菌性脓毒症的潜在诊断标志物。

[关键词]　富含组氨酸糖蛋白；脓毒症；细菌感染；诊断价值

Plasmic concentration of histidine-rich glycoprotein in pediatric bacterial sepsis and its diagnosis value

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Abstract　**Objective:** To investigate the diagnosis value of plasma histidine-rich glycoprotein (HRG), procalcitonin (PCT) and C-reactive protein (CRP) concentrations in pediatric bacterial sepsis. **Methods:** Sixty pediatric patients diagnosed with bacterial sepsis admitted to the Infectious Disease Department of Jinyintan Hospital of Wuhan from January 2018 to December 2018 were enrolled as an observation group. Sixty healthy children with matched age and sex were selected as a control group. Plasma concentrations of HRG, PCT and CRP before and after treatment in the observation group were detected and compared with those in the control group. The receiver

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operating characteristic (ROC) curve was used to analyze the diagnosis efficacy of the three markers. **Results:** Before the treatment, plasma concentration of HRG in the observation group was significantly lower than that in the control group [(28.7±11.3) μg/mL vs (53.0±21.0) μg/mL, $P<0.001$]. After the treatment, HRG concentration increased to (38.6±9.7) μg/mL. Plasma concentrations of PCT [(10.9±4.6) μg/L vs (0.5±0.2) μg/L, $P<0.01$] and CRP [(19.4±6.5) mg/L vs (0.2±0.3) mg/L, $P<0.05$] were significantly higher in the observation group than those in the control group. When the cut-off value was 33.2 μg/mL, the area under the ROC curve (AUC) for sepsis diagnosis by HRG plasma concentration was 0.910 (95% CI 0.840–0.940, $P<0.001$), superior to those of PCT (AUC 0.754) and CRP (AUC 0.654). Combined application of the three markers significantly improved the diagnosis efficacy, with diagnostic sensitivity and specificity of 94.6% and 96.8%, respectively. Before the treatment, there was significant positive correlation between plasma concentrations of HRG and PCT (r=0.76, $P<0.001$). **Conclusion:** In children with bacterial sepsis, plasma concentration of HRG is significantly decreased while concentrations of PCT and CRP are significantly increased. The diagnosis efficacy of HRG is superior to those of PCT and CRP and could be a potential marker for the diagnosis of bacterial sepsis.

Keywords histidine-rich glycoprotein; sepsis; bacterial infection; diagnosis value

儿童细菌性脓毒症感染发病急骤、病情变化快，病死率高达23.3%~47.4%[1]。目前，脓毒症早期诊断标志物特异性均较差，研究新的细菌性脓毒症早期诊断分子标志物对提高细菌性脓毒症的诊治水平具有重要意义[2]。肝脏产生的富含组氨酸糖蛋白(histidine-rich glycoprotein，HRG)是一种多结构域蛋白质，能与多种配体相互作用，参与凝血、免疫反应、血管生成调节等多种生理和病理功能[3]。研究[4-5]报道在体外和体内实验中均发现其与细菌和真菌引起感染密切相关，在宿主防御机制中起保护作用。降钙素原(procalcitonin，PCT)和传统C反应蛋白(C-reaction protein，CRP)是细菌感染非特异性指标，但其诊断特异性较差[6]。本研究通过测定和比较HRG，PCT和CRP在细菌性脓毒症患儿血浆中的浓度，并采用受试者工作特征(receiver operating characteristic curve，ROC)曲线比较三者在细菌性脓毒症中的诊断价值，阐明HRG在患儿细菌性脓毒症中的诊断效能。

1 对象与方法

1.1 对象

观察组选取2018年1月至12月武汉市金银潭医院收治的细菌性脓毒症患儿共60例，男36例，女24例，年龄(8.5±1.2)岁，病程(6.1±4.1) d。对照组选取年龄匹配的60例健康儿童，其中男40例，女20例，年龄(6.7±2.5)岁。观察组和对照组年龄和性别差异无统计学意义($P>0.05$)，具有可比性。本研究征得患儿家属同意，经武汉市金银潭医院医学伦理委员会批准实施。

1.2 纳入和剔除标准

纳入标准：1)符合中华医学会急诊学分会儿科组制定的儿童脓毒症诊断标准[7]；2)临床病例检查和检验、治疗完整。剔除标准：1)有自身免疫性疾病、恶性肿瘤以及严重创伤的患儿；2)有心、肝、肾功能严重不全的患儿。

1.3 治疗方法及检测指标

入院后根据血培养和药敏结果给予相应的补液，抗感染，纠酸等支持对症治疗。于治疗前和治疗2周后抽取观察组和对照组清晨空腹静脉血5 mL，检测HRG，PCT及CRP血浆浓度。采用免疫比浊法检测CRP和PCT浓度。采用ELISA法(试剂盒由美国Biocompare公司提供，货号ABIN2637516)测量血浆中HRG浓度，最低测量值为0.5 μg/mL，组间和组内变异系数为8.4%和3.2%。

1.4 统计学处理

采用SPSS 20.0软件行数据分析。计量资料采用均数±标准差($\bar{x}\pm s$)表示，治疗前后两者参数比较采用配对t检验，治疗前后和对照组比较采用t检验。ROC曲线分析HRG，PCT和CRP血浆浓度对脓毒症的诊断价值，并进行Spearman相关性分析，以$P<0.05$为差异有统计学意义。

2 结果

2.1 两组血浆 HRG，PCT 和 CRP 浓度比较

治疗前，观察组HRG浓度显著低于对照组，PCT和CRP浓度均显著高于对照组，差异有统计学意义(均P<0.05)；治疗后，观察组HRG浓度显著高于治疗前(P<0.001)，PCT和CRP浓度均低于治疗前，差异有统计学意义(均P<0.05)，但仍高于对照组，差异有统计学意义(均P<0.05，表1)。

2.2 HRG，PCT 和 CRP 血浆浓度对脓毒症的诊断价值

ROC曲线显示：当截断值为33.2 μg/mL时，血浆HRG浓度诊断脓毒症的ROC曲线下面积(area under the curve，AUC)为0.910 (95% CI 0.840~0.940，P<0.001)，敏感性和特异性分别为92.1%和93.6%；当截断值为0.5 μg/L时，PCT诊断脓毒症的ROC曲线AUC为0.754 (95% CI 0.740~0.830，P<0.001)；截断值为8.0 mg/L时，CRP诊断脓毒症的ROC曲线AUC为0.654 (95% CI 0.640~0.710，P<0.05；图1)。

3种标志物各自和联合检测的敏感度和特异度见表2。CRP对细菌性脓毒症患儿诊断效力最低，HRG最高。当3种联合应用时，诊断效能明显提高，特异度为96.8%，敏感度为94.6%，准确度为95.7%。

2.3 HRG，PCT 和 CRP 三者相关性

Spearman相关性分析显示：治疗前血浆HRG浓度与PCT显著正相关(r=0.76，P<0.001)，与CRP无显著相关性(r=0.36，P=0.061)，PCT与CRP无显著相关性(r=0.41，P=0.079；图2)。

表1 观察组和对照组血浆HRG，PCT及CRP浓度比较(n=60，$\bar{x} \pm s$)

Table 1 Comparison of plasma concentrations of HRG, PCT and CRP in the observation and control group (n=60, $\bar{x} \pm s$)

组别	HRG/(μg·mL^{-1})	PCT/(μg·L^{-1})	CRP/(mg·L^{-1})
观察组			
治疗前	28.7 ± 11.3*	10.9 ± 4.6*	19.4 ± 6.5*
治疗后	38.6 ± 9.7#	4.8 ± 1.7#	7.6 ± 2.3#
对照组	53.0 ± 21.0	0.5 ± 0.2	0.8 ± 0.3

与对照组比较，*P<0.05；与治疗前比较，#P<0.05。

Compared with observation group, *P<0.05; compared with treatment before, #P<0.05.

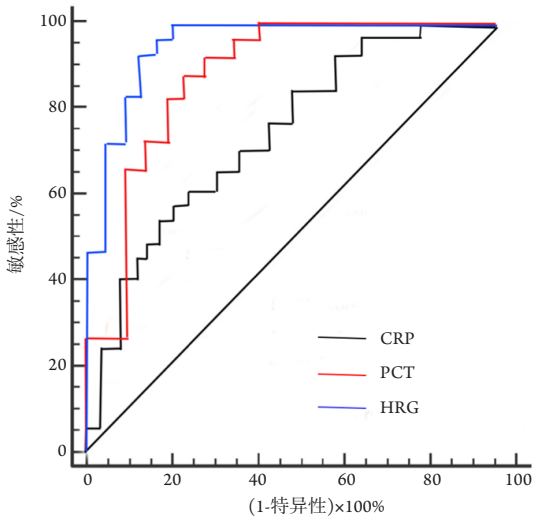

图1 HRG，PCT和CRP诊断脓毒症的ROC曲线

Figure 1 ROC curves for the diagnosis of sepsis by plasma concentrations of HRG, PCT and CRP

表2 HRG，PCT和CRP血浆浓度及其联合应用对细菌性脓毒症的诊断效能

Table 2 Diagnosis efficacy of plasma concentrations of HRG, PCT and CRP and their combined application for bacterial sepsis

参数	敏感度/%	特异度/%	阳性预测值/%	阴性预测值/%	准确度/%
CRP	67.8	70.9	69.5	69.2	69.3
PCT	76.7	81.1	80.7	77.2	78.9
HRG	92.1	93.6	95.3	93.5	96.3
联合应用	94.6	96.8	96.7	94.7	95.7

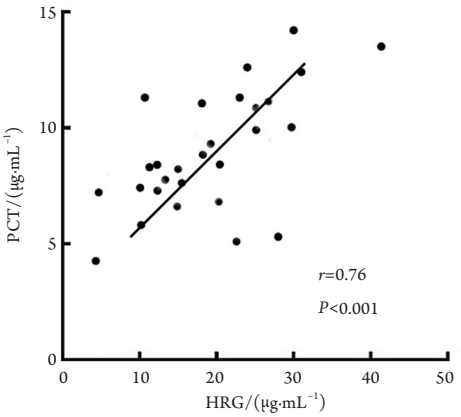

图2 患儿血浆HRG与PCT浓度相关性

Figure 2 Correlation between plasma concentrations of HRG and PCT in children with bacterial sepsis

3 讨论

未得到有效控制的细菌感染在儿童中极易导致全身性炎症性反应性疾病，称为脓毒症[8]。常规诊断是依据临床症状和血常规来确诊，但往往缺乏特异性，需要发现新的早期诊断标志物，以提升脓毒症的诊治水平[9-10]。HRG是由肝合成的，分子质量约75 kD的多肽单链蛋白，人类HRG基因位于38号染色体上的3q28~q29位置，预计编码507个氨基酸的多结构域蛋白。最近研究[11]发现：HRG也存在于巨噬细胞、单核细胞、血小板和巨核细胞表面。正常状态下血浆HRG浓度相对较高，为60~110 μg/mL，在肝功能不全患者和接受皮质类固醇治疗者中，血浆HRG浓度下降[12]。孕期特别是先兆子痫患者血浆HRG浓度进一步下降，且具有早期诊断先兆子痫的价值[13]。PCT是含有116个氨基酸糖的降钙素前肽。在炎症和应激下，肝肾PCT合成和释放增加，导致其血清浓度显著升高[14-15]。CRP是由肝在急性炎性反应及应激状态下合成和释放的急性相蛋白，是常规的急性期炎症非特异性标志物。CRP水平高于100 mg/L表示机体存在严重炎性病变[16]。

本研究发现：在儿童脓毒血症患者中，HRG血浆浓度显著低于健康对照组，且治疗后回归正常水平，提示HRG可反映机体感染状态。目前有关重症和感染患者血浆HRG浓度的文献报道有限。Kuroda等[17]报道在危重ICU患者中，全身炎症反应综合征(systemic inflammatory response syndrome，SIRS)患者血浆HRG浓度显著下降，且诊断价值优于PCT，其结果与本研究一致。儿童脓毒症血浆HRG降低原因尚不清楚。在动物实验[18]中，脓毒症小鼠血浆中HRG迅速减少，并导致免疫血栓形成，急性呼吸窘迫综合征(acute respiratory distress syndrome，ARDS)和血管内凝血(disseminated intravascular coagulation，DIC)生理过程，提示在脓毒血症患者中，血浆HRG可能参与了细菌感染所致的炎症级联反应而大量消耗。同时，本研究发现：儿童脓毒症血浆PCT和传统CRP浓度均显著高于对照组，治疗后显著下降，提示儿童脓毒症细菌感染患者体内PCT和CRP均显著增高，而HRG显著下降，三者均可作为脓毒症细菌感染的指标。

本研究发现治疗前血浆HRG浓度诊断儿童脓毒症的ROC曲线AUC高于PCT和CRP，当截断值为33.2 μg/mL时，其诊断敏感性和特异性分别为92.1%和93.6%，均高于PCT和CRP，提示在儿童细菌感染脓毒症患者中，其诊断效能优于后两者。进一步分析可见：HRG浓度与PCT呈显著正相关，与CRP无显著相关性，考虑到CRP非细菌感染特异性标志物，提示前两者对细菌感染诊断存在一定程度的特异性。同时本研究将三者联合使用，其诊断敏感度、特异度、阳性预测值、阴性预测值及准确度均明显升高。因此，HRG，PCT和CRP联合使用有助于对脓毒症细菌感染进行早期准确诊断。

本研究尚存在不足之处：首先，相较于成人血浆HRG变化范围较大，目前尚缺乏有关正常儿童循环中HRG浓度范围的报道；其次，本研究为单中心研究，纳入病例数目较少，需要多中心大样本病例验证本研究结果；最后，儿童脓毒症细菌感染者循环中HRG降低的原因有待于进一步研究。

综上，细菌性脓毒症患儿血浆HRG浓度显著升高，PCT和CRP浓度显著降低，HRG对儿童细菌性脓毒症诊断效能优于PCT和CRP，是细菌性脓毒症诊断的潜在标志物。

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