

重症腺病毒肺炎患儿血清肝素结合蛋白和肿瘤坏死因子- α 表达水平及其对疾病预后评估价值研究

刘晓燕, 张小佛, 李 嘉, 余庆乐, 刘 麟 (长沙市中心医院儿科, 长沙 410004)

摘要: 目的 分析血清肝素结合蛋白 (heparin binding protein, HBP)、肿瘤坏死因子 (tumor necrosis factor, TNF)- α 与儿童重症腺病毒肺炎的关系及其对预后的评估价值。方法 收集长沙市中心医院儿童医学中心 2016 年 3 月~2020 年 8 月住院治疗的 232 例腺病毒肺炎患儿, 根据病情程度分为重症肺炎组 ($n=170$) 和非重症肺炎组 ($n=62$); 根据预后情况将重症腺病毒肺炎患儿分为预后良好组 ($n=116$) 和预后不良组 ($n=54$)。收集患儿病程、电解质紊乱、循环系统并发症等一般资料; 采用酶联免疫吸附 (ELISA) 法检测患儿血清 HBP 和 TNF- α 水平, 记录患者序贯器官功能衰竭评分 (SOFA) 和 Murray 肺损伤评分; 绘制受试者工作特征 (ROC) 曲线对比分析血清 HBP 和 TNF- α 水平与 SOFA, Murray 肺损伤评分对重症腺病毒肺炎患儿预后的预测价值; 采用多因素 Logistic 回归分析影响重症腺病毒肺炎患儿预后的因素。结果 与非重症肺炎组相比, 重症肺炎组血清 HBP (124.67 ± 32.84 ng/ml vs 40.79 ± 6.54 ng/ml), TNF- α (396.74 ± 53.71 pg/ml vs 263.95 ± 47.84 pg/ml) 水平及 SOFA (5.32 ± 1.36 分 vs 2.78 ± 0.56 分), Murray 肺损伤评分 (2.26 ± 0.49 分 vs 1.52 ± 0.29 分) 升高, 差异具有统计学意义 ($t=19.942, 17.141, 14.037, 11.027$, 均 $P < 0.05$)。与预后良好组相比, 预后不良组血清 HBP (160.61 ± 45.82 ng/ml vs 107.94 ± 32.87 ng/ml), TNF- α (432.44 ± 38.95 pg/ml vs 380.12 ± 35.41 pg/ml) 水平及电解质紊乱 (68.52% vs 33.62%)、循环系统并发症比例 (57.41% vs 22.41%)、SOFA (7.04 ± 1.95 分 vs 4.52 ± 1.23 分)、Murray 肺损伤评分 (2.76 ± 0.48 分 vs 2.02 ± 0.32 分) 较高, 差异具有统计学意义 ($t=8.539, 8.686, \chi^2=18.153, 20.245, t=10.232, 11.888$, 均 $P < 0.05$)。血清 HBP 和 TNF- α , 联合预测概率值及 SOFA, Murray 肺损伤评分预测重症腺病毒肺炎患儿预后的曲线下面积 (AUC) 分别为 0.778, 0.816, 0.939, 0.828 和 0.851, 特异度分别为 81.6%, 71.6%, 98.3%, 60.3% 和 81.9%, 敏感度分别为 63.5%, 81.5%, 76.4%, 90.7% 和 74.1%。HBP 和 TNF- α 是重症腺病毒肺炎患儿预后不良的独立危险因素 ($P < 0.05$)。结论 重症腺病毒肺炎患儿血清 HBP 和 TNF- α 水平相对较高, 且二者高水平可能与不良预后有关。

关键词: 重症腺病毒肺炎; 儿童; 肝素结合蛋白; 肿瘤坏死因子- α

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Study on the Expression Level of Serum Heparin Binding Protein and Tumor Necrosis Factor- α and Its Prognostic Value in Children with Severe *Adenovirus* Pneumonia

LIU Xiao-yan, ZHANG Xiao-fo, LI Jia, YU Qing-le, LIU Lin

(Department of Pediatrics, Changsha Central Hospital, Changsha 410004, China)

Abstract: Objective To analyze the relationship between serum heparin binding protein (HBP), tumor necrosis factor (TNF)- α and severe *Adenovirus* pneumonia in children and their prognostic evaluation value. **Methods** A total of 232 children with *Adenovirus* pneumonia who were hospitalized from March 2016 to August 2020 in the Children's Medical Center of Changsha Central Hospital were collected. According to the severity of the disease, they were divided into 170 cases of severe pneumonia and 62 cases of non-severe pneumonia. According to the prognosis, children with severe *Adenovirus* pneumonia were divided into a good prognosis group of 116 cases and a poor prognosis group of 54 cases. The general data were collected, including children's disease course, electrolyte disturbances, and circulatory system complications. Enzyme-linked immunosorbent assay (ELISA) was used to detect serum HBP and TNF- α levels in children, the sequential organ failure score (SOFA) and Murray lung injury score were recorded. Draw the receiver operating characteristic (ROC) curve and compare and analyze the serum HBP and TNF- α the value of serum level, SOFA and Murray lung injury score in predicting the prognosis of children with severe *Adenovirus* pneumonia. Multivariate Logistic regression was used to analyze the factors affecting the prognosis of

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作者简介: 刘晓燕 (1982-), 女, 硕士研究生, 副主任医师, 研究方向: 儿童重症医学, E-mail: a13450857974@126.com。

children with severe *Adenovirus* pneumonia. **Results** Compared with the non-severe pneumonia group, the severe pneumonia group had higher serum (124.67 ± 32.84 ng/ml vs 40.79 ± 6.54 ng/ml), TNF-α (396.74 ± 53.71 pg/ml vs 263.95 ± 47.84 pg/ml) levels and SOFA (5.32 ± 1.36 score vs 2.78 ± 0.56 score) and Murray lung injury score (2.26 ± 0.49 score vs 1.52 ± 0.29 score), and the differences were statistically significant ($t=19.942, 17.141, 14.037, 11.027$, all $P < 0.05$). Compared with the good prognosis group, the poor prognosis group had higher serum HBP (160.61 ± 45.82 ng/ml vs 107.94 ± 32.87 ng/ml), TNF-α (432.44 ± 38.95 pg/ml vs 380.12 ± 35.41 pg/ml) levels, proportions of electrolyte disturbances (68.52% vs 33.62%), circulatory complications (57.41% vs 22.41%) and SOFA (7.04 ± 1.95 score vs 4.52 ± 1.23 score) and Murray lung injury score (2.76 ± 0.48 score vs 2.02 ± 0.32 score), and the differences were statistically significant ($t=8.539, 8.686, \chi^2=18.153, 20.245, t=10.232, 11.888$, all $P < 0.05$). The area under the curve (AUC) of serum HBP, TNF-α, combined prediction probability value of the two and SOFA and Murray lung injury score for predicting the prognosis of children with severe *Adenovirus* pneumonia were 0.778, 0.816, 0.939, 0.828 and 0.851 respectively, with specificity of 81.6%, 71.6%, 98.3%, 60.3% and 81.9%, and the sensitivity of 63.5%, 81.5%, 76.4%, 90.7% and 74.1% respectively. HBP and TNF-α were independent risk factors for poor prognosis in children with severe *Adenovirus* pneumonia ($P < 0.05$). **Conclusion** The levels of serum HBP and TNF-α in children with severe *Adenovirus* pneumonia were relatively high, and the high levels of the two may be related to poor prognosis.

Keywords: severe *Adenovirus* pneumonia; children; heparin binding protein; tumor necrosis factor-α

腺病毒 (*Adenovirus*) 是引起儿童肺炎的重要病原, 婴幼儿免疫系统发育尚不成熟, 尤其是体液免疫功能不足, 因此易发生重症腺病毒肺炎, 可能会进一步发展为多器官功能衰竭^[1-3]。寻找与重症腺病毒肺炎有关的生物指标, 可为临床治疗提供导向。重症腺病毒肺炎的发病机制目前仍不十分明确, 但其可能与炎性因子介导的炎性反应有重要联系^[4]。肝素结合蛋白 (heparin binding protein, HBP) 是中性粒细胞被激活后释放的一种蛋白分子, 可调节炎症反应^[5]。肿瘤坏死因子 (tumor necrosis factor, TNF)-α 是体内炎症反应的关键启动因子, 可参与粒细胞激活^[6]。目前许多研究重点探讨了 HBP 和 TNF-α 等因子与腺病毒肺炎疾病严重程度的关系, 而本研究除了对比分析 HBP 和 TNF-α 在重症腺病毒肺炎患儿与非重症患儿中的表达差异, 还探究了 HBP 和 TNF-α 在重症腺病毒肺炎预后中的预测价值, 以期为重症腺病毒肺炎预后预测提供新的科学依据。

1 材料与方法

1.1 研究对象 收集长沙市中心医院儿童医学中心 2016 年 3 月 ~ 2020 年 8 月住院治疗的 232 例腺病毒肺炎患儿, 根据患儿病情程度将其分为重症肺炎组 ($n=170$) 和非重症肺炎组 ($n=62$), 其中重症肺炎组年龄 1 ~ 12 (5.13 ± 2.21) 岁, 男性 92 例, 女性 78 例; 非重症肺炎组年龄 1~12 (5.18 ± 2.30) 岁, 男性 35 例, 女性 27 例。重症肺炎组与非重症肺炎组年龄、性别比较, 差异无统计学意义 ($t/\chi^2=0.151, 0.100$, 均 $P > 0.05$)。同时收集患儿病程、消化系统并发症、肺不张、肺部实变、电解质紊乱、循环系统并发症等一般资料。本研究经医院临床伦理委员会审核通过, 符合《赫尔辛基宣言》, 患儿家长自愿参加, 并签署知情同意书。

纳入标准: ①患儿入院时经影像学检查确诊为肺炎, 入院后经肺泡灌洗液高通量基因检测证实为腺病毒感染, 符合《小儿肺炎临床诊疗》^[7]; ②患儿临床资料齐全, 且一个月内无激素、球蛋白、血液制品治疗史。排除标准: ①并发病毒性肺炎、支原体性肺炎、肺结核者; ②有免疫系统疾病史、血液系统疾病史者; ③有原发性心、肝、肾等重要器官功能障碍者。

1.2 仪器与试剂 HBP ELISA 试剂盒, TNF-α ELISA 试剂盒 (上海凡科维生物科技有限公司); DNA 提取试剂盒 (德国 QIAGEN 公司); Nextera XT DNA 样本准备试剂盒, Miseq 高通量测序仪及测序试剂盒 (美国 Illumina 公司); ELx808 型酶标仪 (美国 Lonza 公司)。

1.3 方法

1.3.1 高通量测序: 采集肺泡灌洗液用于病毒基因组提取, 依照试剂盒操作说明提取 DNA, 并将其溶解于 AE 缓冲液中, -20℃ 保存。测定并调整 DNA 浓度至 0.2 ng/μl, 分别取 1.0 ng DNA 依照 Nextera XT DNA 样本准备试剂盒说明书操作, 完成文库构建。依照美国 Illumina 公司提供的操作指南对文库进行上机测序, 以自带分析软件 Miseq Control Software 评价测序数据质量, 若 Q30 大于 85% 则进行进一步分析, NCBI 下载病原体基因组数据库后进行比对分析。

1.3.2 样品采集及保存: 采集腺病毒肺炎患儿入院 24 h 内清晨空腹静脉血, 室温放置 30 min, 3 000 r/min 离心 10 min, 收集上层血清, -80℃ 保存待测。

1.3.3 血清 HBP, TNF-α 水平检测: 采用酶联免疫吸附 (enzyme linked immunosorbent assay, ELISA) 法检测各组血清 HBP 和 TNF-α 水平, 均严格按照试剂盒及仪器说明书进行操作。

1.3.4 序贯器官功能衰竭评分 (sequential organ failure assessment, SOFA) 和 Murray 肺损伤评分:

基于心血管系统、凝血系统、肾脏系统、神经系统、呼吸系统、肝脏系统6个参数反映器官功能, 每项评分设定为0~4分, SOFA总分为各参数评分之和, 器官功能障碍越严重则评分越高。Murray肺损伤评分基于低氧血症、肺顺应性、呼吸末正压、胸部X线4个参数, 各参数评分设定为0~4分, Murray肺损伤评分=参数评分之和/参数数目之和, 肺损伤越严重则评分越高。

1.3.5 预后评估^[8]: 治疗一周后评估重症腺病毒肺炎患儿预后, 预后良好: 发热症状减轻或消退, 呼吸平稳、肺部无湿啰音或哮鸣音, 肺部阴影减轻或消失; 预后不良: 胸部影像学及症状体征无明显变化。根据预后情况将患儿分为预后良好组116例和预后不良组54例。

1.4 统计学分析 采用SPSS 25.0软件包统计分析数据, 计量资料以均数±标准差($\bar{x} \pm s$)表示, 行 t 检验; 计数资料以 $n(\%)$ 表示, 行 χ^2 检验; 绘制受试者工作特征(receiver operator characteristic, ROC)曲线对比分析血清HBP, TNF- α 水平与SOFA, Murray肺损伤评分对重症腺病毒肺炎患儿预后的预测价值; 采用多因素Logistic回归分析影响重症腺病毒肺炎患儿预后的因素。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 两组血清HBP, TNF- α 水平及SOFA, Murray肺损伤评分比较 见表1。重症肺炎组血清HBP, TNF- α 水平及SOFA, Murray肺损伤评分高于非重症肺炎组, 差异具有统计学意义(均 $P < 0.05$)。

表1 重症肺炎组、非重症肺炎组血清HBP, TNF- α 水平及SOFA, Murray肺损伤评分比较($\bar{x} \pm s$)

| 项目 | 非重症肺炎组 (n=62) | 重症肺炎组 (n=170) | t | P |
|-----------------------|------------------|------------------|--------|-------|
| HBP (ng/ml) | 40.79 ± 6.54 | 124.67 ± 32.84 | 19.942 | 0.000 |
| TNF- α (pg/ml) | 263.95 ± 47.84 | 396.74 ± 53.71 | 17.141 | 0.000 |
| SOFA (分) | 2.78 ± 0.56 | 5.32 ± 1.36 | 14.037 | 0.000 |
| Murray肺损伤评分(分) | 1.52 ± 0.29 | 2.26 ± 0.49 | 11.027 | 0.000 |

2.2 两组临床指标及血清HBP, TNF- α , SOFA, Murray肺损伤评分比较 见表2。预后良好组与预后不良组病程、年龄、性别、消化系统并发症、肺不张、肺部实变比较, 差异均无统计学意义(均 $P > 0.05$)。预后不良组HBP, TNF- α , SOFA, Murray肺损伤评分及电解质紊乱、循环系统并发症比例高于预后良好组, 差异均有统计学意义(均 $P < 0.05$)。

表2 不同预后组临床指标及血清HBP, TNF- α , SOFA, Murray肺损伤评分比较($\bar{x} \pm s, n(\%)$)

| 类别 | 预后良好组 (n=116) | 预后不良组 (n=54) | t/χ^2 | P |
|-----------------------|------------------|-----------------|------------|-------|
| 病程(天) | 12.62 ± 3.19 | 12.59 ± 3.29 | 0.057 | 0.955 |
| 年龄≤5岁 | 79 (68.10) | 36 (66.67) | 0.035 | 0.852 |
| 男性 | 65 (56.03) | 27 (50.00) | 0.540 | 0.462 |
| 电解质紊乱 | 39 (33.62) | 37 (68.52) | 18.153 | 0.000 |
| 消化系统并发症 | 28 (24.14) | 14 (25.93) | 0.063 | 0.801 |
| 循环系统并发症 | 26 (22.41) | 31 (57.41) | 20.245 | 0.000 |
| 肺不张 | 18 (15.52) | 8 (14.81) | 0.014 | 0.906 |
| 肺部实变 | 52 (44.83) | 24 (44.44) | 0.002 | 0.963 |
| HBP (ng/ml) | 107.94 ± 32.87 | 160.61 ± 45.82 | 8.539 | 0.000 |
| TNF- α (pg/ml) | 380.12 ± 35.41 | 432.44 ± 38.95 | 8.686 | 0.000 |
| SOFA (分) | 4.52 ± 1.23 | 7.04 ± 1.95 | 10.232 | 0.000 |
| Murray肺损伤评分(分) | 2.02 ± 0.32 | 2.76 ± 0.48 | 11.888 | 0.000 |

2.3 重症腺病毒肺炎患儿预后预测价值分析 见图1。以血清HBP, TNF- α , 联合预测概率值及SOFA, Murray肺损伤评分为检验变量, 以重症腺病毒肺炎患儿是否预后不良为状态变量绘制ROC曲线, 结果显示, 血清HBP, TNF- α 和联合预测概率值及SOFA, Murray肺损伤评分预测重症腺病毒肺炎患儿预后的曲线下面积(area under curve, AUC)分别为0.778 (95%CI: 0.695 ~ 0.861), 0.816 (95%CI: 0.748 ~ 0.884), 0.939 (95%CI: 0.857 ~ 0.962), 0.828 (95%CI: 0.761 ~ 0.895)和0.851 (95%CI: 0.790 ~ 0.913), 特异度分别为81.6%, 71.6%, 98.3%, 60.3%和81.9%, 敏感度分别为63.5%, 81.5%, 76.4%, 90.7%和74.1%, 其中联合预测AUC高于HBP, TNF- α , SOFA, Murray肺损伤评分单独预测AUC, 差异有统计学意义($Z=3.224, 2.783, 2.557, 2.141$, 均 $P < 0.05$)。

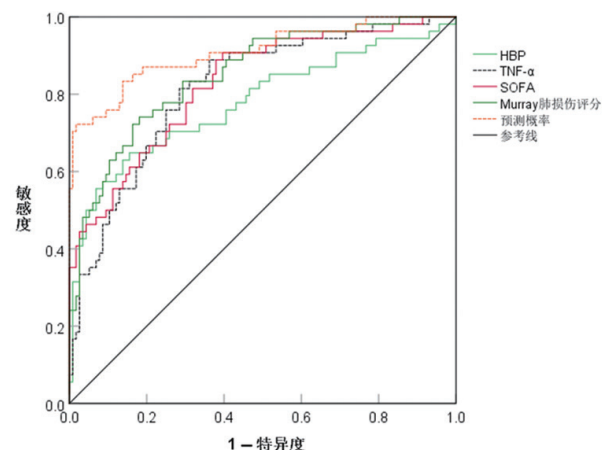


图1 血清HBP, TNF- α , SOFA, Murray肺损伤评分预测重症腺病毒肺炎患儿预后的ROC曲线

2.4 重症腺病毒肺炎患儿预后的多因素 Logistic 回归分析 见表3。将重症腺病毒肺炎患儿是否预后不良作为因变量,以 HBP, TNF- α , 年龄、电解质紊乱、循环系统并发症、SOFA, Murray 肺损伤

评分为自变量进行 Logistic 回归分析,结果显示, HBP, TNF- α 是重症腺病毒肺炎患儿预后不良的独立危险因素(均 $P < 0.05$)。

表3 重症腺病毒肺炎患儿预后的多因素 Logistic 回归分析

| 因素 | B | SE | Wald | OR | 95%CI | P |
|---------------|-------|-------|--------|-------|---------------|-------|
| HBP | 0.891 | 0.262 | 11.559 | 2.437 | 1.458 ~ 4.073 | 0.001 |
| TNF- α | 0.873 | 0.276 | 10.014 | 2.395 | 1.394 ~ 4.114 | 0.002 |
| 年龄 | 0.113 | 0.209 | 0.294 | 1.120 | 0.744 ~ 1.687 | 0.588 |
| 电解质紊乱 | 0.111 | 0.109 | 1.030 | 1.117 | 0.902 ~ 1.383 | 0.310 |
| 循环系统并发症 | 0.137 | 0.132 | 1.080 | 1.147 | 0.886 ~ 1.486 | 0.299 |
| SOFA | 0.133 | 0.246 | 0.291 | 1.142 | 0.705 ~ 1.850 | 0.589 |
| Murray 肺损伤评分 | 0.112 | 0.107 | 1.104 | 1.119 | 0.907 ~ 1.380 | 0.293 |

3 讨论

腺病毒可引发婴幼儿致死性肺炎,它是一种最初由人腺样体细胞中分离得到的 DNA 病毒^[9-10]。人体感染腺病毒后会激发体内炎症反应,引发淋巴细胞亚群和细胞因子异常,甚至可能造成全身炎症反应综合征^[11-12]。因此,早期评估病情并及时干预,对降低腺病毒肺炎患儿死亡率至关重要。

HBP 是中性粒细胞分泌的一种重要颗粒蛋白,具有杀菌、趋化作用,可激活单核细胞及巨噬细胞,进而导致相关炎性介质大量释放^[13-14]。PAULSSON 等^[15]研究表明, HBP 在呼吸机相关性肺炎患者肺泡灌洗液中高表达,本研究结果中 HBP 表达趋势与上述研究一致。范江花等^[16]研究结果表明,重症腺病毒肺炎患儿血清 HBP 水平高于非重症患儿,与本研究结果同样具有一致性。基于既往研究分析 HBP 可能通过增加毛细血管通透性造成血管渗漏,引起组织低灌注及肺水肿,进而出现肺损伤。TNF- α 是反映炎症状态的敏感指标,机体内发生感染时,其表达水平异常升高^[17]。本研究结果显示,重症腺病毒肺炎患儿血清 TNF- α 表达水平升高,与既往研究结论相符^[18]。李建成等^[19]研究结果同样显示 TNF- α 在腺病毒肺炎患儿血浆及肺泡灌洗液中均增高。基于既往研究推测:腺病毒感染初期时体内炎症反应被激发, TNF- α 表达水平随之升高参与中性粒细胞激活,被激活的中性粒细胞大量释放 HBP 并进一步激活巨噬细胞,释放 TNF- α 等炎性介质,引发炎症级联反应。研究显示,炎症因子表达水平越高,体内免疫抑制程度越明显,患者病情越重^[20]。表明炎症因子差异表达对判断疾病进展及预后有重要作用。初步推测 HBP, TNF- α 可能在重症腺病毒肺炎疾病发展进程中发挥重要作用,且能作为重症腺病毒肺炎预后评估的重要参考

指标。

研究显示, SOFA, Murray 肺损伤评分在肺损伤患者预后中有较高的评估价值^[21]。而本研究中 HBP, TNF- α 联合后的预后评估价值高于 SOFA, Murray 肺损伤评分,进一步表明 HBP, TNF- α 在临床实践中具有较高的辅助应用价值,当临床 HBP, TNF- α 检测水平异常升高时,重症腺病毒肺炎患儿预后不良发生风险可能较高。依据多因素分析结果进一步推测:重症腺病毒肺炎患儿体内炎症反应相对强烈,且伴随 HBP, TNF- α 表达异常升高,二者表达上调可进一步介导患儿体内炎症相关的病理生理过程,造成循环系统损害,不利于患儿预后。

综上所述,腺病毒所致的儿童重症肺炎发生时,患儿血清 HBP, TNF- α 表达水平升高。临床检测 HBP, TNF- α 两指标水平变化可能有利于监测重症腺病毒肺炎患儿预后,提高治疗效果,临床可予以重视。然而本研究的局限性在于:①收集的样本量不充足,可能会对结果造成一定偏倚;②未能进行长期随访观察,监测重症腺病毒肺炎患儿可能出现的后遗症;③因本研究旨在探讨 HBP, TNF- α 在重症腺病毒肺炎预后中的价值,未对高通量基因检测数据进行相关研究,且未将包括血细胞检测在内的其他指标和影响因素纳入本研究,今后将进一步深入探讨。

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