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耐药大环内酯类肺炎支原体肺炎患儿外周血 HMGB1 表达与预后转归的关系 *

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摘要 目的: 探讨耐药大环内酯类肺炎支原体 (Mycoplasma pneumoniae,MP) 肺炎患儿外周血高迁移率族蛋白 B1 (high mobility group protein B1,HMGB1)表达与预后转归的关系。**方法:**2017 年 1 月 -2019 年 12 月选择在新疆维吾尔自治区人民医院诊治的耐药大环内酯类肺炎支原体肺炎患儿 78 例、非耐药大环内酯类肺炎支原体肺炎患儿 78 例与健康儿童 78 例分别作为耐药组、非耐药组与对照组,检测三组外周血 HMGB1 表达水平,调查耐药组患儿的急性生理与慢性健康(Acute Physiology and Chronic Health Evaluation,APACHEⅡ)评分与随访预后并进行相关性分析。**结果:**耐药组、非耐药组的血清 HMGB1 水平高于对照组(P<0.05),耐药组高于非耐药组(P<0.05)。随着入院时间的增加,耐药组患儿的 APACHEⅡ评分逐渐降低,对比差异有统计学意义(P<0.05)。随访到 2020 年 5 月 1 日,耐药组患儿死亡 2 例,死亡率为 2.6 %。在耐药组中,Pearson 相关分析显示外周血 HMGB1 与 APACHEⅡ评分、发热持续时间、住院时间、肺部病变个数存在相关性(P<0.05)。受试者工作特征(receiver operating characteristic,ROC)曲线分析显示外周血 HMGB1、APACHEⅡ评分预测患儿死亡的最大截面积为 0.872(95 %CI:0.729-0.878)和 0.889(95 %CI:0.813-0.941)。**结论:**耐药大环内酯类肺炎支原体肺炎患儿外周血 HMGB1 呈现高表达状况,与患儿的 APACHEⅡ评分呈现正相关性,以上结果有助于预测患儿的随访预后,并为进一步明确该病的发生机制提供一定的借鉴。

关键词:耐药大环内酯类;肺炎支原体肺炎;小儿;高迁移率族蛋白 B1;急性生理与慢性健康评分;相关性

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The Relationship between the Expression of HMGB1 in Peripheral Blood and Prognosis of Children with Drug-resistant Macrolide-type Mycoplasma Pneumoniae*

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ABSTRACT Objective: To investigate the relationship between the expression of high mobility group protein B1 (HMGB1) and the prognosis of children with drug-resistant Mycoplasma pneumoniae (MP) pneumonia. **Methods:** From January 2017 to December 2019, 78 cases of children with drug-resistant macrolide Mycoplasma pneumoniae pneumonia, 78 cases of children with non-drug-resistant macrolide mycoplasma pneumoniae pneumonia and 78 cases of healthy children were selected for diagnosis and treatment in People's Hospital of Xinjiang Uygur Autonomous Region were selected as drug-resistant group, non-drug-resistant group and control group. The expression levels of HMGB1 in the peripheral blood of the three groups were detected, and were to investigate the Acute Physiology and Chronic Health Evaluation (APACHEⅡ) score and followed-up prognosis of children in the drug-resistant group and given correlation analysis. **Results:** The serum HMGB1 levels in the drug-resistant group and non-resistant group were higher than those in the control group (P<0.05), and the drug-resistant group were higher than the non-resistant group (P<0.05). With the increased of admission time, the APACHEⅡ scores of children in the drug-resistant group were gradually decreased, and the difference were statistically significant (P<0.05). Followed-up until May 1, 2020, there were 2 children in the drug-resistant group died, with the mortality rate of 2.6 %. In the drug resistance group, Pearson correlation analysis showed that peripheral blood HMGB1 were correlated with APACHEⅡ score, duration of fever, length of hospitalization, and number of lung lesions (P<0.05). Receiver operating characteristic(ROC) curve analysis showed that the maximum cross-sectional area predicted by the peripheral blood HMGB1 and APACHEⅡ scores were 0.872 (95 %CI: 0.729-0.878) and 0.889 (95 %CI: 0.813-0.941). **Conclusion:** Peripheral blood HMGB1 are highly expressed in children with drug-resistant macrolide Mycoplasma pneumoniae pneumonia, which are positively correlated with the children's APACHE Ⅱ score, and can also predict the follow-up prognosis of the children. The above results are helpful to predict the follow-up prognosis of children, and provide a certain

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reference for further clarifying the occurrence mechanism of the disease.

Key words: Drug-resistant macrolides; Mycoplasma pneumoniae pneumonia; children; High mobility group protein B1; Acute physiology and chronic health scores; Correlation

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MP 肺炎支原体是可以在无细胞培养体系中生存的最小的微生物之一，也为儿童常见社区获得性肺炎的主要病原体之一[1]，还可引起溶血性贫血、脑炎、心肌炎、肾炎等，当前已经严重影响到儿童的身心健康[2,3]。由于肺炎支原体缺乏细胞壁，使其对 β- 内酰胺类、万古霉素药物天然耐药。而随着大环内酯类药物长期广泛的临床应用，当前已出现大量的耐药大环内酯类肺炎支原体肺炎患儿，肺炎支原体菌株明显增加[4,5]。耐药大环内酯类肺炎支原体肺炎患儿的病程比较长，在临床上可表现为呼吸困难、进行性低氧血症等，并且病情发展迅速，有一定的致死率[6]。大环内酯类药物的结合位点位于 23S rRNA 结构域，当 23S rRNA 结构域的核苷酸发生点突变、移位突变等会降低抗生素和核糖体之间的亲和力，导致肺炎支原体产生耐药性[7]。但由于肺炎支原体临床分离困难及工作量大，耐药大环内酯类肺炎支原体的具体耐药性机制尚未得到明确阐述[8,9]。现代研究表明肺炎发生与机体的局部炎症反应及免疫调控存在相关性，HMGB1 是一种重要的炎症介质，可由免疫细胞主动分泌或坏死细胞被动释放至细胞外[10,11]。HMGB1 参与了肺炎的进程，且与机体恶性肿瘤、肺损伤、脓毒症等疾病存在相关性。并且其出现时间晚，发病后其表达水平才上升，不过具有一定的稳定性[12-14]。本文具体探讨了耐药大环内酯类肺炎支原体肺炎患儿外周血 HMGB1 表达与预后转归的关系，希望为明确该病的发生机制提供一定的借鉴。

1 资料与方法

1.1 研究对象

2017 年 1 月 -2019 年 12 月选择在新疆维吾尔自治区人民医院诊治的耐药大环内酯类肺炎支原体肺炎患儿 78 例、非耐药大环内酯类肺炎支原体肺炎患儿 78 例与健康儿童 78 例分别作为耐药组、非耐药组与对照组。纳入标准：耐药组、非耐药组都符合肺炎支原体肺炎的诊断标准，X 线或 CT 检查显示肺部出现新浸润影；对照组经体征、血液学与影像学检查都为健康状态；年龄 3-12 岁；患儿的监护人知情同意此次研究；研究得到本院院伦理委员会的批准。排除标准：伴有先天性心脏疾病和其他的严重疾病患儿；不同意此次治疗或者中途停止治疗的患儿；免疫缺陷和混合感染患儿；伴有其他影响血清 HMGB1 水平的入选者；先天性呼吸器官发育异常者；严重营养不良者。

三组的性别、年龄、体重、身高等对比差异无统计学意义(P>0.05)，耐药组的发热持续时间、住院时间、肺部病变个数高于非耐药组(P<0.05)。见表 1。

表 1 三组一般资料对比

Table 1 Comparison of three sets of general information

Group	n	Gender (M/F)	Age (years)	Weight (kg)	Height (cm)	Fever duration (d)	Hospitalization time (d)	Number of lung lesions
Resistance group	78	40/38	7.41±0.26	30.18±1.33	128.72±12.75	8.82±1.43	9.11±0.32	3.33±0.14
Non-resistant group	78	39/39	7.45±0.33	30.25±2.74	129.00±13.15	4.58±0.24	4.76±0.14	1.63±0.22
Control group	78	41/37	7.43±0.28	30.33±3.14	128.61±12.47	-	-	-
χ^2/F/t		0.103	0.089	0.214	0.413	8.999	8.472	13.744
P		0.950	0.923	0.878	0.687	0.001	0.003	0.000

1.2 血清 HMGB1 表达检测

采集所有入选者的静脉外周血 2-3 mL，2500 rpm/min 离心 10 min，离心半径 8 cm，取上层血清保存于 -70 ℃冰箱。采用酶联免疫法检测血清 HMGB 水平，检测试剂盒购自武汉三鹰公司(批号 20848214)，所有操作步骤严格遵循试剂盒说明书。

1.3 APACHEⅡ评分与预后调查

采用 APACHEⅡ评分对耐药组患儿进行病情评定，分别与入院第 1 d、第 3 d 与第 5 d 进行评定，分值范围为 0-71 分，分值越高，表明患儿病情越严重。同时耐药组患儿随访到 2020 年 5 月 1 日，记录患儿死亡与存活情况。

1.4 统计方法

统计软件为 SPSS22.00 软件，计量资料采取($\bar{x}\pm s$)表示(t 检验和方差分析)；计数数据采用(%)表示(χ^2 检验)。以 ROC 曲线分析诊断价值，相关性采用 Pearson 相关分析，检验水准为 α=0.05。

2 结果

2.1 血清 HMGB1 水平对比

耐药组、非耐药组的血清 HMGB1 水平均显著高于对照组，耐药组也显著高于非耐药组(P<0.05)。见表 2。

2.2 APACHEⅡ评分对比

随着入院时间的增加，耐药组患儿的 APACHEⅡ评分逐渐降低，对比差异有统计学意义(P<0.05)。见表 3。

2.3 预后转归情况

随访到 2020 年 5 月 1 日，耐药组患儿死亡 2 例，死亡率为 2.6 %。

2.4 相关性分析

在耐药组中，Pearson 相关分析显示外周血 HMGB1 与 APACHEⅡ评分、发热持续时间、住院时间、肺部病变个数存在相关性(P<0.05)。见表 4。

表 2 三组血清 HMGB1 水平对比(ng/mL，$\bar{x}\pm s$)

Table 2 Comparison of serum HMGB1 levels in three groups(ng/mL, $\bar{x}\pm s$)

Groups	n	HMGB1
Resistance group	78	14.22±2.18*#
Non-resistant group	78	6.38±0.11*
Control group	78	1.72±0.28
F		89.144
P		0.000

Note: Compared with the control group, *P<0.05; Compared with the non-resistant group, #P<0.05.

表 3 三组入院不同时间点的 APACHEⅡ评分对比(分，$\bar{x}\pm s$)

Table 3 Comparison of APACHEⅡ scores of three groups at different time points of admission (score, $\bar{x}\pm s$)

Time point	n	APACHEⅡ score
Admission d 1	78	47.25±3.81
Admission d 3	78	40.87±4.18
Admission d 7	78	35.24±4.44
F		12.742
P		0.000

表 4 耐药大环内酯类肺炎支原体肺炎患儿外周血 HMGB1 表达与临床指标的相关性(n=78)

Table 4 Correlation between peripheral blood HMGB1 expression and clinical indexes in children with mycoplasma pneumoniae pneumonia(n=78)

Index	APACHEⅡ score	Fever duration	LOS	Number of pulmonary lesions
r	0.672	0.475	0.511	0.655
P	0.000	0.015	0.010	0.000

2.5 诊断价值分析

在耐药组中，ROC 曲线分析显示外周血 HMGB1、APACHEⅡ评分预测患儿死亡的最大截面积为 0.872(95 %CI：0.729-0.878)和 0.889(95 %CI：0.813-0.941)。

3 讨论

肺炎支原体肺炎是严重危害小儿健康的一种疾病，其死亡率占感染性疾病的前列[15]。肺炎支原体是引发肺炎的主要病原体之一，研究显示：部分肺炎患儿常存在多个病原体的感染，故易出现耐药性，因此对于临床诊治要求较高[16]。肺炎支原体无细胞壁，对青霉素等作用于细胞壁的抗生素天然耐药[17]。大环内酯类为临床上治疗肺炎支原体肺炎的主要乃至首选药物，不过由于各种因素的影响，大环内酯类药物的滥用比较突出，使得耐药大环内酯类肺炎支原体肺炎患儿也越来越多，特别是不规则使用大环内酯类药物与耐药菌株的产生呈正相关性，也使得患儿的预后变差[18]。大环内酯类药物是临床放线菌属细菌的次级代谢产物，代表药物包括阿奇霉素、红霉素、克拉霉素等，可抑制核糖体上的蛋白质合成。大环内酯类药物的耐药菌株产生的主要机制为 23S rRNA 基因突变，结构特征以 14-16 元环大环内酯为母核，糖苷键和 1-3 分子糖相连接[19]。

现代研究表明耐药大环内酯类肺炎支原体肺炎患儿除了具有呼吸系统症状外还可引起其他系统功能异常，特别是肺炎支原体会破坏肺泡上皮细胞、毛细血管内皮细胞，可刺激 β 细胞产生大量的 IgM 和 IgG 抗体，引发弥漫性肺间质和肺泡水肿，造成重症肺炎的发生，恶化患儿的病情，在一定情况下可导致患儿死亡[20,21]。HMGB1 为代表的细胞因子参与了肺部感染的进程，其多在发病 24h 后出现增长，主要由活化的自然杀伤细胞、巨噬细胞、单核细胞、成熟树突细胞分泌，具有分泌达峰时间短、分泌持续时间长等[22]。HMGB1 可作用于免疫细胞、内皮细胞的表面受体，破坏上皮屏障，使细胞释放多种细胞因子，使炎症加重[23]。本研究显示耐药组、非耐药组的血清 HMGB1 水平高于对照组(P<0.05)，耐药组高于非耐药组(P<0.05)，结合 Sekiguchi F 等研究分析：HMGB1 可作用于免疫细胞、内皮细胞的表面受体，破坏上皮屏障，使细胞释放多种细胞因子，使炎症加重，因此耐药大环内酯类肺炎支原体肺炎患儿多伴随有外周血 HMGB1 的高表达。

肺炎支原体感染的临床症状除了出现肺部症状外，还可引起肺外多系统并发症，包括以血液系统、胃肠系统、皮肤系统受累等，部分患儿可引起多器官功能障碍综合征等[24]。大环内酯类药物可抑制核糖体 50S 大亚基的组装，从而抑制细菌蛋白质的合成；并且其能结合于转肽酶中心与肽输出通道狭窄之间的部分，导致细胞内有功能的核糖体数量下降，抑制新生肽链的延伸，阻碍蛋白质的合成，从而发挥抑菌作用[25]。不过随着大环内酯类药物的广泛使用，肺炎支原体的耐药性在临床上

越来越普遍。本研究显示随着入院时间的增加,耐药组患儿的APACHEⅡ评分逐渐降低,对比差异有统计学意义(P<0.05);随访到2020年5月1日,耐药组患儿死亡2例,死亡率为2.6%。有研究报道大环内酯类药物治疗耐药肺炎支原体感染退热时间显著延长,提示耐药大环内酯类肺炎支原体感染可导致患儿病程迁延[26-28]。

许多耐药大环内酯类肺炎支原体肺炎患儿多存在肺部基础性疾病,其免疫功能相对紊乱[29,30]。本研究Pearson相关分析显示耐药大环内酯类肺炎支原体肺炎患儿的外周血HMGB1与APACHEⅡ评分、发热持续时间、住院时间、肺部病变个数存在相关性(P<0.05)。结合相关研究分析其原因在于:HMGB1可由活化细胞主动分泌进入外周循环或细胞外,放大机体的炎症反应,从而造成患儿肺组织损伤[31,32]。另外,也有研究显示脓毒症患者的血清HMGB1水平与APACHEⅡ评分成正相关性,HMGB1的水平越高,病情越重,患儿的预后越差,与本研究结果一致[33-35]。本研究也存在一定的不足,没有调查非耐药大环内酯类肺炎支原体肺炎患儿的预后,纳入患儿的数量比较少,将在后续研究中进行探讨。

总之,耐药大环内酯类肺炎支原体肺炎患儿外周血HMGB1呈现高表达状况,并与患儿的APACHEⅡ评分呈现正相关性,因此监测该指标水平变化有助于预测患儿的随访预后情况。

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