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· 临床研究 ·

呼吸道病毒感染与慢性阻塞性肺疾病急性加重的关系*

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摘要 目的:探讨呼吸道病毒与慢性阻塞性肺疾病急性加重(AECOPD)的相关性,以期能为 AECOPD 的诊治提供参考。**方法:**选取 200 例 AECOPD 患者为研究对象,检测患者肺功能,用 Luminex xMAP 多重分析技术平台,采集患者咽拭子建立多重 PCR 检测技术,对鼻病毒(RHV)、呼吸道合胞病毒(RSV)、流感病毒 A(INF-A)、流感病毒 B(INF-B)、副流感病毒(PIV)、腺病毒(ADV)进行检测。**结果:**200 例患者肺功能分级 I 级 25 例,II 级 62 例,III 级 96 例,IV 级 17 例,其构成比分别为 17.50%、31.00%、48.00%、8.50%;咽拭子共检出呼吸道病毒 116 株,检出率为 58.00%,其中 RHV11 株、RSV36 株、INF-A37 株、INF-B19 株、PIV10 株、ADV3 株,检出率分别为 5.5%、18.00%、18.50%、9.50%、5.00%、1.50%;肺功能分级 I 级患者病毒检出率为 20.00%,II 级为 48.39%,III 级为 69.79%,IV 级为 82.35%,病毒检出率在不同肺功能 AECOPD 患者中比较差异具有统计学意义($P<0.05$);肺功能分级与病毒检出率直线相关分析结果显示随着肺功能分级的严重程度增加患者咽拭子呼吸道病毒检出率明显呈现增高趋势,两者直接具有正相关($r=0.67$, $P<0.05$)。**结论:**COPD 患者病情加重与病毒关系密切相关,病毒感染可能参与了 COPD 患者的病程进展。

关键词:呼吸道病毒;慢性阻塞性肺疾病;感染

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The Relation between Respiratory Virus Infection and Acute Exacerbation of Chronic Obstructive Pulmonary Disease*

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ABSTRACT Objective: To investigate the relation between the respiratory viruses and chronic obstructive pulmonary diseases acute exacerbation (AECOPD), and to provide reference for the diagnosis and treatment of AECOPD. **Methods:** 200 cases of patients with AECOPD were selected as the research object, patients' lung function were detected, and with Luminex xMAP multiple analysis technology platform, patients throat swab collected were subjected to the multiple PCR detection. Virus, namely rhinovirus (RHV), respiratory syncytial virus (RSV), influenza virus A (INF - A), influenza virus B (INF) B, parainfluenza (PIV) and adenovirus (ADV) were detected. **Results:** According to pulmonary function, 200 cases of in patients consist of 25 cases of class I, 62 cases of class II, 96 cases of class III and 17 cases of class IV, the constituent ratio were 17.50%, 31.00%, 48.00%, 8.50% respectively; 116 strains of respiratory viruses were detected in the throat swabs, with a detection rate of 58.00%, including 11 seedlings of RHV, 37 INF - A, 36 RSV, 10 PIV, 19 INF - B, and 3 ADV, the detection rate were 5.5%, 18.00%, 18.50%, 9.50%, 5.00% and 1.50% respectively; The virus detection rate was 20.00% in lung function class I patients, 48.39% in class II, 69.79% in class III, and 82.35% in class IV, virus detection rate in patients with AECOPD of different lung functions presenting statistically significant difference ($P<0.05$); Linear correlation analysis of lung function grading and virus detection rates showed that the respiratory virus detection rates increased with the severity of lung function gradings, showing a direct positive correlation ($r=0.67$, $P<0.05$). **Conclusion:** Disease progression in patients with COPD is closely related to the viruses and virus infection may be involved in the progression of COPD.

Key words: Respiratory viruses; Chronic obstructive pulmonary disease; Infection

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前言

慢性阻塞性肺疾病^[1,2](Chronic obstructive pulmonary disease, COPD)是呼吸内科常见疾病,主要为气流受限为特征的慢性疾病^[3],COPD的病死率较高,虽然近年死亡率有所下降^[4],但是COPD的容易恶化和病情反复仍然对患者的生活质量带来了较大影响,导致患者生活质量下降^[5]。传统上认为COPD急性加重(AECOPD)主要是由于细菌感染所致^[6],但是随着研究的深入人们发现呼吸道病毒感染与AECOPD的发生关系也极为密切^[7]。因此,我院在2010年1月-2011年12月期间对收治的AECOPD患者采用Luminex xMAP (flexible multi-analyte profiling)多重分析技术平台,建立多重PCR检测技术,对鼻病毒(RHV)、呼吸道合胞病毒(RSV)、流感病毒A(INF-A)、流感病毒B(INF-B)、副流感病毒(PIV)、腺病毒(ADV)进行了检测,旨在探讨呼吸道病毒感染与AECOPD之间的相关性,以期能为AECOPD的诊治提供参考,现将结果报告如下。

1 资料与方法

1.1 研究对象

选取2010年1月-2011年12月期间收治的AECOPD患者200例为研究对象,AECOPD的诊断依据2011年中华人民共和国卫生部制定的相关诊断标准^[8],入选对象要求排除支气管哮喘、肺结核、肺癌、肺间质疾病等引起肺功能下降所致的疾病,无严重的其他重要脏器功能障碍存在,无近期使用过糖皮质激素及茶碱类药物史,无急慢性其他炎症性疾病及免疫系统疾病。200例患者其中男性146例,女性54例,年龄43-88岁,平均68.52±11.58岁。

1.2 方法

1.2.1 肺功能测定方法^[9]要求在入院确诊后尚未进行任何药物治疗前进行检测,肺功能检测仪器为德国耶格公司生产的肺功能检测仪,患者先要求静坐,先吸入舒张剂万托林400 μg,在

15min后进行复查,重复对肺功能相关指标进行检测3次,最后取平均值,肺功能的检测指标包括:第1秒用力呼出量(FEV1)、用力肺活量(FVC)、肺活量(VC)、小气道功能测定(V25%,V50%)。AECOPD根据FEV1分为四级,FEV1≥80%为I级,50%≤FEV1<80%为II级,≤30%FEV1<50%为III级,FEV1<30%为IV级。

1.2.2 咽拭子采集方法 患者在进行肺功能检测后进行咽拭子采集,先嘱患者用生理盐水进行漱口,用了将气管深部痰液咳出,吐出第一口痰液后,无菌咽拭子在咽部进行擦拭,然后置于无菌试管内送检,-80℃下保存待检。

1.2.3 呼吸道病毒检测方法^[10] 病毒检测应用Luminex xMAP多功能数据分析技术平台,病毒核酸提取DNA、RNA提取试剂盒均购自Qiagen公司,建立多重PCR检测技术,参考相关文献^[11]将取得的咽拭子标本先进行PCR引物扩增,然后将PCR引物与探针微球杂交,后与Luminex xMAP多功能数据分析技术平台分析检测数据结果。

1.3 统计学方法

用SPSS17.0统计学软件对数据进行统计分析,计数资料采用率表示进行卡方检验,相关性分析采用直线相关分析,检验值P<0.05为差异具有统计学意义。

2 结果

2.1 AECOPD患者肺功能分级

通过检测,200例患者肺功能分级I级25例,II级62例,I-II级96例,IV级17例,其构成比分别为17.50%、31.00%、48.00%、8.50%。

2.2 AECOPD患者咽拭子标本呼吸道病毒检测结果

200例患者的咽拭子共检出呼吸道病毒116株,检出率为58.00%,其中RHV11株、RSV36株、INF-A37株、INF-B19株、PIV10株、ADV3株,检出率分别为5.5%、18.00%、18.50%、9.50%、5.00%、1.50%,详见表1。

表1 AECOPD患者咽拭子标本呼吸道病毒检测结果(n=200)

Table 1 The detection result of respiratory viruses in throat swab specimen of AECOPD patients(n=200)

病毒 Virus	株数 n	检出率(%) Detection rate(%)
RHV	11	5.5
RSV	36	18.00
INF-A	37	18.50
INF-B	19	9.50
PIV	10	5.00
ADV	3	1.50
合计 Totals	116	58.00

2.3 不同肺功能 AECOPD 患者咽拭子标本呼吸道病毒检测结果

将不同肺功能的AECOPD患者病毒检出率进行比较,肺功能分级I级患者病毒检出率为20.00%,II级为48.39%,III级为69.79%,IV级为82.35%,病毒检出率在不同肺功能AE-

COPD患者中比较差异具有统计学意义(P<0.05),详见表2。

2.4 AECOPD 患者肺功能分级与呼吸道病毒检出率的相关性分析

对肺功能分级与病毒检出率进行直线相关分析,结果显示随着肺功能分级的严重程度增加患者咽拭子呼吸道病毒检

出率明显呈现增高趋势,两者直接具有正相关($r=0.67, P<0.05$)。

表 2 不同肺功能 AECOPD 患者咽拭子标本呼吸道病毒检测结果

Table 2 The results of respiratory viruses detection in throat swab specimen of different AECOPD patients

肺功能分级 Lung function class	n	检出病毒 Detected Virus		未检出病毒 Not Detected Virus	
		株数 n	检出率(%) Detection Rate(%)	株数 n	检出率(%) Detection Rate(%)
I 级 Class I	25	5	20.00	20	80.00
II 级 Class II	62	30	48.39	32	51.61
III 级 Class III	96	67	69.79	29	30.21
IV 级 Class IV	17	14	82.35	3	17.65
χ^2			26.79		26.79
P			<0.05		<0.05

3 讨论

COPD 的概念^[10,11]最早是与二十世纪 60 年代提出的,其发病以气流受限为临床特征,为不完全可逆,发病机制主要有蛋白酶和抗蛋白酶学说、氧化损伤假说、免疫失衡及炎症假说、感染假说,以上学说被认为可能并不是独立一个因素即可致病,而是多学说可能共同有参与^[12,13]。近年来随着病毒检测技术的提高,呼吸道病毒感染在 COPD 发病中的作用被逐渐重视,2011 年卫生部颁布的《慢性阻塞性肺疾病诊疗规范》对病毒及细菌感染单独做了强调^[14,15]。

引起 AECOPD 的病毒以呼吸道病毒为主,常见的病毒有 RHV、RSV、INF-A、INF-B、PIV、ADV 等^[16],而大多数 AECOPD 患者同时合并有细菌感染,因此细菌感染与病毒感染可能共同感染引起了协同作用,导致患者病情发展或加重。研究发现 AECOPD 患者病毒感染后会对支气管炎粘膜上皮细胞造成一定程度的损伤,并且患者在存在病毒感染时 CD^{3+} 、 CD^{4+} 、 CD^{4+}/CD^{8+} 等均会有所下降,表明病毒感染可能也引起是患者免疫功能紊乱,因此出现 T 淋巴细胞亚群变化^[17,18]。还有学者研究发现 RSV 病毒感染后患者会启动免疫反应从而释放大量的炎症因子,患者气道反应更为严重,因此病毒感染明显加快了患者的病情进展^[19]。病毒感染除了直接损失气道外,还会造成不同程度的一氧化氮及内皮细胞源性舒张因子产生的减少,导致气道狭窄发生,因此加重病情。有研究显示呼吸道感染后导致气道感觉神经纤维暴露,降解缓激肽的能力下降,因此影响到胆碱能反应性的出现增高,引起气道进一步狭窄加重^[20]。我院采用 Luminex xMAP 多重分析技术平台,建立多重 PCR 检测技术对 AECOPD 患者呼吸道病毒感染情况进行了检测,结果显示呼吸道病毒的检出率为 58.00%,其中 RHV、RSV、INF-A、INF-B19 株、PIV、ADV 的检出率分别为 5.5%、18.00%、18.50%、9.50%、5.00%、1.50%,患者主要以 RSV、INF 病毒感染多见,分析患者肺功能与病毒检出率之间的关系,在肺功能分级 I 级的 AECOPD 患者中病毒检出率为 20.00%,II 级为 48.39%,III 级为 69.79%,IV 级为 82.35%,可以看出随着患者肺功能下降程度加重患者病毒检出率明显增高,两者之间相关性分析也证实确实存在正相关,表明呼吸道感染在 COPD 患者病情发展及急性加重中可能参与了期进程,而这一研究结

果在相关临床报道中也被大多数学者所支持。

综上所述,COPD 患者病情加重与呼吸道感染关系密切,病毒感染可能参与了 COPD 患者的病程进展,对 AE-COPD 患者检测呼吸道病毒如确实存在病毒感染应进行相应的抗病毒治疗,对于患者病情缓解具有一定意义。

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