·临床研究·

慢性阻塞性肺病对急性脑梗死患者预后的影响

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【摘要】 **目的** 探讨慢性阻塞性肺病对急性脑梗死患者预后的影响。**方法** 采用美国国立卫生研究院卒中量表(NIHSS)和Barthel指数(BI)对慢性阻塞性肺病合并急性脑梗死(COPD组)患者发病不同阶段(入院时、治疗第14和28天)神经功能缺损程度和日常生活活动能力进行评分,与单纯急性脑梗死(对照组)患者进行比较,评价其预后。**结果** 治疗前两组一般情况、NIHSS和BI评分差异均无统计学意义($P>0.05$)。治疗第14天时,COPD组患者NIHSS评分升高[(9.47±3.43)分]、BI评分降低[(33.83±15.68)分],但与对照组[NIHSS评分:(8.37±3.50)分,BI评分:(37.83±17.25)分]比较差异无统计学意义($P=0.224$,0.351)。治疗第28天时,COPD组患者NIHSS评分[(6.93±2.59)分]高于、BI评分[(54.00±15.45)分]低于对照组[NIHSS评分:(5.43±2.13)分,BI评分:(65.67±16.33)分],差异具有统计学意义($P=0.017$,0.006)。**结论** 慢性阻塞性肺病合并急性脑梗死患者发病后预后不良可能与病程中始终存在的系统性炎症和氧化应激有关。

【关键词】 脑梗死; 肺疾病,慢性阻塞性; 预后

The effect of chronic obstructive pulmonary disease on the prognosis of patients with acute cerebral infarction

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【**Abstract**】 **Objective** To observe the effect of chronic obstructive pulmonary disease (COPD) on the prognosis of patients with acute cerebral infarction. **Methods** A total of 60 acute cerebral infarction patients were diagnosed by CT or MRI. According to whether the patients were suffering from COPD or not, they were divided into COPD group (N = 30) or control group (N = 30). The neurological deficit was evaluated by National Institutes of Health Stroke Scale (NIHSS), and the ability of daily life was evaluated by Barthel Index (BI) on patients in both groups at admission, and 14 and 28 d after treatment. The prognosis of patients was evaluated and compared between 2 groups. **Results** There were no significant differences between 2 groups in the general data, NIHSS and BI scores before treatment ($P>0.05$, for all). After 14 d of treatment, the NIHSS score (9.47 ± 3.43) was slightly higher, BI score (33.83 ± 15.68) was slightly lower in COPD group, but compared with those in control group (NIHSS score: 8.37 ± 3.50, BI score: 37.83 ± 17.25), there were no significant differences ($P=0.224$, 0.351, respectively). After 28 d of treatment, the NIHSS score in COPD group (6.93 ± 2.59) was significantly higher than that in control group (5.43 ± 2.13, $P=0.017$), and BI score in COPD group (54.00 ± 15.45) was significantly lower than that in control group (65.67 ± 16.33, $P=0.006$). **Conclusions** The prognosis of patients with acute cerebral infarction was affected by COPD, which may be related to the existence of systemic inflammation and oxidative stress in COPD patients.

【**Key words**】 Brain infarction; Pulmonary disease, chronic obstructive; Prognosis

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慢性阻塞性肺病(COPD)是以进行性、不完全可逆性气流受限为特点的慢性呼吸系统疾病,主要累及肺部,亦可引起全身(或称肺外)器官或组织的不良反应[1];由于患者长期处于慢性炎症状态,可伴随血液高凝状态和血管壁损害,此为继发脑梗死的危险因素[2]。据文献报道,慢性阻塞性肺病患者病程中的炎症反应是缺血性脑损伤的重要病理生理学机制之一,不仅参与其发生发展,且与病情严重程度和危及生命的并发症相关[3];而且持续存在的炎症反应、氧化应激和高凝状态等均是影响患者预后的危险因素[4]。鉴于此,笔者采用美国国立卫生研究院卒中量表(NIHSS)和Barthel指数(BI)[5]对河北省唐山市乐亭县中医医院内科近年诊断与治疗的30例慢性阻塞性肺病合并急性脑梗死患者进行神经功能缺损程度评价,旨在探讨慢性阻塞性肺病对急性脑梗死患者预后的影响。

对象与方法

一、观察对象

1. 纳入标准 (1)为首次发病且未经治疗的脑梗死患者,符合1995年第四届全国脑血管病学术会议制定的诊断标准,并经头部CT或MRI证实。(2)年龄<80岁。(3)发病6~48 h就诊。

2. 排除标准 (1)头部CT或MRI显示颅内出血患者。(2)慢性阻塞性肺病伴发肺性脑病、呼吸衰竭、消化道出血、严重肝肾功能障碍、出血性疾病或血液病患者。

3. 一般资料 选择2013年6月–2014年10月在我院内科住院治疗的急性脑梗死患者60例,根据中华医学会修订的《慢性阻塞性肺疾病诊疗指南(2013年修订版)》[6]筛查出慢性阻塞性肺病合并急性脑梗死患者30例(COPD组),其余30例无慢性阻塞性肺病的脑梗死患者为对照组。(1)COPD组:男性18例,女性12例;年龄45~75岁,平均(61.97±7.54)岁。梗死灶部位分别位于基底节(12例)、丘脑(4例)、脑叶(6例)或其他部位(8例);病程6.50~45.00 h,中位病程11.50 h;既往高血压15例、糖尿病9例和高脂血症15例。(2)对照组:男性16例,女性14例;年龄46~79岁,平均(63.07±8.31)岁。梗死灶分别位于基底节(13例)、丘脑(6例)、脑叶(6例)或其他部位(5例);病程6~47 h,中位病程12 h;既往患高血压14例、糖尿病10例、高脂血症16例。两组患者性别、年龄、病程、梗死灶部位、既往史等项资料比较,差异无统计学意义(均$P>0.05$,表1)。

表1 COPD组与对照组患者一般资料的比较
Table 1. Comparison of general data between 2 groups

Item	Control (N = 30)	COPD (N = 30)	Statistical value	*P* value
Sex [case (%)]			0.271	0.795
Male	16 (53.33)	18 (60.00)		
Female	14 (46.67)	12 (40.00)		
Age ($\bar{x}\pm s$, year)	63.07±8.31	61.97±7.54	-0.537	0.593
Duration [M (P_{25}, P_{75}), h]	12.00 (9.00, 15.25)	11.50 (8.75, 15.25)	-0.393	0.694
Infarct site [case (%)]			1.132	0.769
Basal ganglia	13 (43.33)	12 (40.00)		
Thalamus	6 (20.00)	4 (13.33)		
Lobes	6 (20.00)	6 (20.00)		
Others	5 (16.67)	8 (26.67)		
Hypertension [case (%)]	14 (46.67)	15 (50.00)	0.067	1.000
Diabetes mellitus [case (%)]	10 (33.33)	9 (30.00)	0.077	1.000
Hyperlipidemia [case (%)]	16 (53.33)	15 (50.00)	0.067	1.000

t test for comparison of age, Mann-Whitney *U* test for comparison of duration, and χ^2 test for comparison of others。COPD, chronic obstructive pulmonary disease,慢性阻塞性肺病

二、评价方法

1. 药物治疗 两组患者入院后均进行为期28 d的综合治疗,包括甘露醇减轻脑水肿、阿司匹林抗血小板聚集、胞二磷胆碱营养神经细胞、低分子肝素抗凝,以及硝苯地平、格列吡嗪和阿托伐他汀控制血压、血糖和血脂水平。对于COPD组有咳嗽、咳痰、喘息症状的患者则以头孢呋辛钠、氨茶碱、氨溴索进行抗感染、止咳、平喘、祛痰治疗。

2. 预后评价 两组患者均于入院时,以及治疗第14和28天时行NIHSS和BI评分。(1)NIHSS评分:总评分42分,其中0~4分为无和(或)轻微神经功能缺损;5~20分为中度神经功能缺损;21~42分为重度神经功能缺损。(2)BI评分:总评分100分,其中>60分者为良好,日常生活与活动基本自理;40~60分为中度功能障碍,日常生活需他人帮助;20~40分为重度功能障碍,日常生活不能够完全自理;<20分为完全残疾,日常生活与活动需依赖他人。

三、统计分析方法

采用SPSS 19.0统计软件进行数据处理与分析。呈正态分布的计量资料以均数±标准差($\bar{x}\pm s$)表示,行两独立样本的*t*检验;两组患者NIHSS和BI评分的比较采用两因素多水平重复测量设计的方

表2 COPD组与对照组患者治疗前后NIHSS和BI评分的比较($\bar{x} \pm s$,评分)

Table 2. Comparison of NIHSS and BI scores before and after treatment between 2 groups ($\bar{x} \pm s$, score)

Group	N	NIHSS			BI		
		0 d	14 d	28 d	0 d	14 d	28 d
Control	30	14.40 ± 4.36	8.37 ± 3.50	5.43 ± 2.13	29.33 ± 11.72	37.83 ± 17.25	65.67 ± 16.33
COPD	30	14.27 ± 4.49	9.47 ± 3.43	6.93 ± 2.59	29.80 ± 11.72	33.83 ± 15.68	54.00 ± 15.45

COPD,chronic obstructive pulmonary disease,慢性阻塞性肺病;NIHSS,National Institutes of Health Stroke Scale,美国国立卫生研究院卒中量表;BI,Barthel Index,Barthel指数。The same for tables below

表3 COPD组与对照组患者治疗前后NIHSS和BI评分的重复测量设计的方差分析表

Table 3. ANOVA for repeated measurement design for NIHSS and BI scores before and after treatment between 2 groups

Source of variation	*SS*	df	*MS*	*F* value	*P* value	Source of variation	*SS*	df	*MS*	*F* value	*P* value
NIHSS						BI					
Treatment	30.422	1	30.422	4.542	0.049	Treatment	1 150.139	1	1 150.139	5.227	0.023
Time	2064.678	2	1032.339	83.209	0.000	Time	30 602.500	2	15 301.250	69.541	0.000
Treatment × time	21.744	2	10.872	0.876	0.418	Treatment × time	1 135.278	2	567.639	2.580	0.079
Error between groups	1905.489	58	32.802			Error between groups	33 606.944	58	579.430		
Error within group	211.817	58	3.652			Error within group	2 550.417	58	43.973		

表4 COPD组与对照组患者同一时间点NIHSS和BI评分的组间比较

Table 4. Paired comparison of NIHSS and BI scores of the same time points between 2 groups

Paired comparison	0 d		14 d		28 d	
	q value	*P* value	*q* value	*P* value	*q* value	*P* value
NIHSS	0.014	0.908	1.512	0.224	6.019	0.017
BI	0.028	0.868	0.883	0.351	8.079	0.006

表5 COPD组与对照组患者不同时间点NIHSS和BI评分的两两比较

Table 5. Paired comparison of NIHSS and BI scores of different time points within group

Paired comparison	Control		COPD		Paired comparison	Control		COPD	
	q value	*P* value	*q* value	*P* value		*q* value	*P* value	*q* value	*P* value
NIHSS					BI				
0 d∶14 d	18.853	0.000	16.382	0.000	0 d∶14 d	-5.982	0.000	-4.251	0.000
0 d∶28 d	16.363	0.000	16.975	0.000	0 d∶28 d	-23.127	0.000	-13.113	0.000
14 d∶28 d	7.598	0.000	10.424	0.000	14 d∶28 d	-14.664	0.000	-10.395	0.000

差分析,两两比较行SNK-q检验;呈非正态分布的计量资料以中位数和四分位数间距[$M(P_{25}, P_{75})$]表示,行Mann-Whitney U检验。计数资料以相对数构成比(%)或率(%)表示,采用χ^2检验。以$P \leqslant 0.05$为差异具有统计学意义。

结　果

两组患者入院时神经功能缺损程度比较,NIHSS和BI评分差异无统计学意义(均$P > 0.05$,表2~4)。治疗第14天时,两组NIHSS评分略有下降、BI评分略有升高,但组间差异无统计学意义(均$P > 0.05$);治疗第28天时,COPD组患者NIHSS评分高于($P = 0.017$)、Barthel评分低于($P = 0.006$)对照组,且组间差异有统计学意义(表2~4)。两组患者治疗第14和28天时与入院时比较,NIHSS评分均下降($P = 0.000$)、BI评分均升高($P = 0.000$);治疗第28天与治疗第14天比较,亦为NIHSS评分下降($P = 0.000$)、BI评分升高($P = 0.000$),差异有统计学意义(表2,3,5)。

讨　论

慢性阻塞性肺病主要指慢性阻塞性支气管炎

并发阻塞性肺气肿，其病理学机制和临床表现不仅限于肺部炎症和呼吸道重塑，而是全身慢性炎症性疾病[1,7]。由于慢性阻塞性肺病患者长期慢性缺氧和(或)二氧化碳潴留、异常炎症反应可导致多器官和组织损伤，因此对该病的认识已从局限于肺部疾病转向于全身疾病，其高黏血症和低氧血症为脑梗死危险因素的观点已为共识[8]。慢性阻塞性肺病是一种炎性疾病，包括呼吸道炎症和全身系统性炎症，在急性加重期系统性炎性因子表达水平明显升高，即使在病情稳定期，其系统性炎性因子表达水平亦高于正常人群。其中，肺泡巨噬细胞分泌的基质金属蛋白酶(MMPs)是调节细胞外基质降解与合成的主要酶类，参与炎症反应和组织重建，有研究显示，慢性阻塞性肺病患者急性发作期和缓解期血清MMP-9表达水平均明显高于正常人群[9]。脑缺血-再灌注损伤使肺泡巨噬细胞对基质金属蛋白酶的分泌增加，破坏血-脑屏障，促进脑水肿形成及炎性细胞浸润，加速神经细胞死亡，致使缺血性脑损伤进一步加重[10]。另外，肿瘤坏死因子-α(TNF-α)的参与诱导血管内皮细胞功能紊乱，亦是缺血-再灌注损伤的重要病理学过程[11]，且在缺血性损伤的不同阶段发挥作用，最终导致神经细胞死亡[12]。系统性炎症在慢性阻塞性肺病和脑梗死的发生发展过程中具有重要作用，可使脑梗死患者病情进展甚至恶化[13-14]。大量临床观察证实，脑梗死患者血清炎性因子水平明显升高，发病数小时内其血清C-反应蛋白(CRP)、白细胞介素-6(IL-6)、纤维蛋白原和TNF-α等炎性因子水平即明显升高，至1～2周方逐渐下降[15-17]。其中，IL-6和CRP可以通过激活补体系统和凝血纤溶系统加重缺血程度；纤维蛋白原则促使纤维蛋白原分子之间，以及与其他蛋白质分子之间的相互作用，使细胞凝聚性增强、纤维蛋白原形成、血液凝固时间缩短，继而增加血液黏稠度使之具备潜在形成血栓的可能[18-19]。故而推测慢性阻塞性肺病与缺血性脑损伤可能存在共同的炎症损伤机制。对本组慢性阻塞性肺病合并急性脑梗死患者预后的评价显示，虽然COPD组患者与对照组患者所接受的治疗措施相同，但急性期后(发病第14天时)COPD组患者则呈现NIHSS评分升高、BI评分降低之趋势，这种趋势虽未达到统计学差异，但提示慢性阻塞性肺病合并急性脑梗死患者近期神经功能缺损程度有所改善；至发病第28天时，COPD组患者则表现为NIHSS评分明显升高、BI评分明显降低，且组间差异具有统计学意义。表明慢性阻塞性肺病合并急性脑梗死患者虽经治疗，其神经功能和预后仍不如单纯急性脑梗死患者。尹忠平等[20]的临床观察结果显示，慢性阻塞性肺病合并急性脑梗死患者的治疗有效率为53.26%(49/92)，明显低于单纯急性脑梗死患者的70%(42/60，$P<0.05$)；朱祖福等[21]报告36例慢性阻塞性肺病合并急性脑梗死患者的临床疗效，结果显示，与30例单纯急性脑梗死患者相比，其治疗总有效率(44%)明显低于对照组(70%，$P<0.01$)。

综上所述，慢性阻塞性肺病与急性脑梗死存在共同的炎症损伤机制，慢性阻塞性肺病合并急性脑梗死患者在发病急性期血液循环中的炎性因子水平显著升高，导致炎性细胞活化、氧化负荷增加，使其缺血性脑损伤进一步加重，从而影响患者预后，具体机制有待深入研究。对本组患者的观察提示：持续存在的炎症反应对慢性阻塞性肺病合并急性脑梗死患者的预后具有重要影响，及时对病程中炎性介质的干预治疗可能为急性脑梗死患者的治疗开辟新途径，由于本研究样本较小，对此类患者长期预后的评价尚待大样本临床证据。

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Cellular therapy for stroke and neural trauma has gained worldwide attention during the last decade and has shown some promising results. Various cells, including neural stem cells, bone marrow stem cells, endothelial progenitor cells, and many others have had protective or regenerative effects in animal models. The proposed book will address recent research on all relevant cell types. In addition, it will provide information on cell isolation and culture skills, transplantation methods, and neurological functional evaluations. This is the first book to focus on cellular therapy for stroke and other CNS injuries.

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