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急性缺血性脑卒中合并阻塞性睡眠呼吸暂停低通气综合征患者中性粒细胞/淋巴细胞比值、血小板/淋巴细胞比值的变化及短期预后

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【摘要】 目的 分析急性缺血性脑卒中合并阻塞性睡眠呼吸暂停低通气综合征(OSAHS)患者中性粒细胞/淋巴细胞比值(NLR)、血小板/淋巴细胞比值(PLR)及睡眠结构的改变和短期预后情况。**方法** 选取2021年1月至2022年3月于北京市大兴区人民医院神经内科住院的106例急性缺血性脑卒中患者为研究对象。对患者行多导睡眠图(PSG)监测, 根据呼吸暂停低通气指数将患者分为非OSAHS组(n=52)、轻度OSAHS组(n=24)及中重度OSAHS组(n=30)。比较3组患者血液中NLR、PLR水平及睡眠结构的改变, 并于出院3个月随访时采用Barthel指数和改良Rankin评分比较3组患者神经功能的差异。**结果** 3组患者血清NLR、PLR水平比较[1.90(1.60, 2.71)比2.30(1.70, 4.12)比2.35(1.67, 6.40)、(161.00 ± 74.10)比(207.10 ± 90.10)比(214.30 ± 96.60)], 差异有统计学意义(P < 0.05); 中重度OSAHS组患者NLR、PLR水平高于非OSAHS组, 差异有统计学意义(P < 0.05)。3组患者REM期比例、NREM 1期比例、NREM 3期比例、觉醒次数比较[(17.78 ± 6.13)%比(15.21 ± 5.29)%比(13.97 ± 5.03)%、(15.01 ± 8.62)%比(19.26 ± 10.93)%比(20.39 ± 9.14)%、(15.58 ± 9.55)%比(11.43 ± 5.49)%比(9.81 ± 5.86)%、4.00(3.00, 6.00)次比5.00(4.00, 6.00)次比6.00(5.00, 8.00)次], 差异有统计学意义(P < 0.05); 重度OSAHS组患者NREM 1期比例高于非OSAHS组, NREM 3期比例、REM期比例低于非OSAHS组, 觉醒次数多于非OSAHS组, 差异有统计学意义(P < 0.05)。3组患者出院3个月时的Barthel指数和改良Rankin评分比较[(87.40 ± 9.20)分比(83.54 ± 9.61)分比(82.67 ± 6.07)分、1.00(0, 2.00)分比2.00(0.25, 3.00)分比2.00(1.00, 3.00)分], 差异有统计学意义(P < 0.05); 轻度、中重度OSAHS组患者Barthel指数低于非OSAHS组, 改良Rankin评分高于非OSAHS组, 差异有统计学意义(P < 0.05)。**结论** 中重度OSAHS升高了患者的NLR及PLR水平, 增加了睡眠觉醒次数, 低氧促进的炎性反应及睡眠结构紊乱可能与急性缺血性脑卒中短期预后不良结局有关。

【关键词】 睡眠呼吸暂停, 阻塞性; 缺血性脑卒中; 短期预后; 中性粒细胞/淋巴细胞比值; 血小板/淋巴细胞比值

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Changes of neutrophil/lymphocyte ratio, platelet/lymphocyte ratio and short-term prognosis in ischemic stroke patients with obstructive sleep apnea hypopnea syndrome

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【Abstract】 Objective To analyze the changes of neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), sleep structure and short-term prognosis in patients with acute ischemic stroke and obstructive sleep apnea hypopnea syndrome (OSAHS). **Methods** From January 2021 to March 2022, a

total of 106 patients with acute ischemic stroke in the Department of Neurology of Beijing Daxing People's Hospital were selected as research subjects. All the patients were monitored by polysomnography (PSG). According to the apnea hypopnea index (AHI), the patients were divided into non OSAHS group (n=52), mild OSAHS group (n=24) and moderate to severe OSAHS group (n=30). The changes of NLR, PLR and PSG sleep parameters were compared among the three groups. The difference of neurological function among the three groups was compared by Barthel index and modified Rankin score at the 3-month follow-up after discharge. **Results** The differences in NLR and PLR level among the 3 groups were statistically significant [1.90 (1.60, 2.71) vs 2.30(1.70, 4.12) vs 2.35(1.67, 6.40), (161.00 ± 74.10) vs (207.10 ± 90.10) vs (214.30 ± 96.60)] (P < 0.05). The levels of NLR and PLR in moderate and severe OSAHS group were significantly higher than those in non OSAHS group, and the difference was statistically significant (P < 0.05). There were statistically significant differences in the proportions of REM phase, NREM phase 1, NREM phase 3 and awakening times among the three groups[(17.78 ± 6.13)% vs(15.21 ± 5.29)% vs (13.97 ± 5.03)%, (15.01 ± 8.62)% vs (19.26 ± 10.93)% vs(20.39 ± 9.14)%, (15.58 ± 9.55)% vs (11.43 ± 5.49)% vs (9.81 ± 5.86)%, 4.00(3.00, 6.00) vs 5.00 (4.00, 6.00) vs 6.00(5.00, 8.00)] (P<0.05). The proportion of NREM phase 1 in severe OSAHS group was higher than that in non OSAHS group, the proportion of NREM phase 3 and REM phase was lower than that in non OSAHS group, and the number of awakenings was higher than that in non OSAHS group, with statistical significance (P < 0.05). The Barthel index and the modified Rankin score of the three groups at the time of 3 months after discharge were statistically significant [(87.40 ± 9.20) vs (83.54 ± 9.61) vs (82.67 ± 6.07), 1.00(0, 2.00) vs 2.00(0.25, 3.00) vs 2.00(1.00, 3.00)] (P < 0.05). Barthel index of patients in mild, moderate and severe OSAHS group was lower than that in non OSAHS group, and the modified Rankin score was higher than that in non OSAHS group, the difference was statistically significant (P < 0.05). **Conclusions** Moderate and severe OSAHS increases the levels of NLR and PLR in patients with stroke, and increases the number of sleep awakenings. The inflammatory reaction promoted by hypoxia and sleep structure disorder may be related to the adverse short-term prognosis of acute ischemic stroke.

【**Key words**】 Sleep apnea, obstructive; Acute ischemic stroke; Short-term prognosis; Neutrophil/lymphocyte ratio; Platelet/ lymphocyte ratio

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阻塞性睡眠呼吸暂停低通气综合征(obstructive sleep apnea hypopnea syndrome, OSAHS)是一种以睡眠中反复出现上呼吸道阻塞为特征的睡眠障碍,男性发病率高于女性[1]。重度OSAHS常与高血压病、高脂血症、脑梗死、心肌梗死等疾病共存[2]。OSAHS是急性缺血性脑卒中的独立危险因素,可加重患者的脑缺氧情况,导致疾病发生进展。另有研究表明,OSAHS继发的炎性反应在心血管疾病的病理生理过程中起到重要作用,血液中中性粒细胞/淋巴细胞比值(neutrophil/lymphocyte ratio, NLR)及血小板/淋巴细胞比值(platelet/lymphocyte ratio, PLR)是相对稳定的炎性标志物,与心血管疾病的不良预后相关[3]。相关研究显示,NLR作为大血管闭塞卒中患者预后的炎性标志物,比传统炎性因子具有更好的预测能力[4-5]。缺血性脑卒中合并OSAHS患者存在的低氧血症能否促进血管内炎性反应,引起血液中PLR、NLR水平改变,以及是否会加重睡眠紊乱的相关研究较少,因此本研究对此进行探讨,现报道如下。

一、对象与方法

1.研究对象:选取2021年1月至2022年3月在北京市大兴区人民医院神经内科住院的106例急性缺血性脑卒中患者为研究对象。纳入标准:(1)发病时间≤3 d;(2)年龄18~80岁;(3)符合《中国急性缺血性脑卒中诊治指南2018》[6]中急性缺血性脑卒中的诊断标准;(4)入院后生命体征稳定,可配合完成多导睡眠图(polysomnography, PSG)检查;(5)患者或其家属自愿参与本研究并签署知情同意书。排除标准:(1)入院后接受连续气道正压通气(continuous positive airway pressure, CPAP)治疗或曾因OSAHS行口咽矫正器治疗;(2)合并意识障碍;(3)发病前改良Rankin评分≥2分;(4)合并严重的心、肝、肾等多器官功能衰竭;(5)合并支气管哮喘、慢性阻塞性肺疾病等原发性肺部疾病;(6)合并运动神经元病、格林-巴利综合征及重症肌无力等累及呼吸系统的疾病。本研究已通过北京市大兴区人民医院伦理委员会审批(伦理批号:20210617LLKYLX-1-29)。

2.研究方法:(1)收集一般资料。详细记录所有入组患者的年龄、性别、体重指数、既往病史等一般资料。(2)收集PSG数据。入组的急性缺血性脑卒中患者住院72 h内进行PSG检查(Nicolet, Natus公

司，美国），监测项目包括脑电图、下颌肌电图、热敏及压力式口鼻气流、胸腹运动、血氧饱和度、心电图、体位。记录呼吸暂停低通气指数（apnea hypopnea index，AHI）、总睡眠时间、睡眠效率、非快速眼球运动期（nonrapid eye movements，NREM）比例、快速眼球运动期（rapid eye movements，REM）比例、睡眠潜伏期、REM睡眠潜伏期、觉醒次数等情况，记录时间≥7 h。参照《美国睡眠医学学会睡眠及相关事件判读手册》标准分析数据[7]。入组患者行PSG时的注意事项：①检查前禁止饮咖啡、茶水、酒精等具有刺激作用的饮料；②禁服镇静安眠药物，以免加重睡眠呼吸暂停，干扰检查结果；③检查前尽量洗头、洗澡及刮胡子，减少电信号干扰；④保持心情平静，避免过分激动而影响睡眠。（3）检测NLR及PLR水平。入院第2天完成对入组患者的静脉血采集，采肘静脉血10 ml并计算NLR及PLR。（4）评估神经功能。在入院当天采用NIHSS对所有入组患者进行神经功能评定[8]，并于出院3个月随访时评价反映患者神经功能预后的Barthel指数及改良Rankin评分[9-10]，比较3组患者评分的差异。（5）OSAHS诊断及分组标准。参考成人阻塞性睡眠呼吸暂停基层诊疗指南（2018年）[11]，依据PSG结果中AHI的数值对入组患者进行分组。AHI＜5次/h纳入非OSAHS组，5～15次/h纳入轻度OSAHS组，AHI＞15次/h纳入中重度OSAHS组。

3.统计学方法：采用SPSS 23.0软件对研究数据进行统计学分析。对所有计量资料进行正态性检验，符合正态分布的计量资料采用均数±标准差（$\bar{x} \pm s$）描述，3组间比较采用单因素方差分析，两两比较采用LSD-t检验，比较前进行方差齐性检验；不符合正态分布的计量资料采用中位数和四分位数［$M(P_{25}, P_{75})$］描述，3组间比较采用Kruskal-Wallis H检验。计数资料采用频数、百分数（%）表示，组间比较采用 χ^2 检验。双侧检验，$P<0.05$ 为差异有统计学意义。

二、结果

1. 3组患者一般资料比较：106例患者中，非OSAHS组52例，轻度OSAHS组24例，中重度OSAHS组30例，共占50.9%（54/106）。中重度OSAHS组患者的体重指数高于非OSAHS组及轻度OSAHS组患者，差异有统计学意义（$P<0.05$）；3组患者年龄、性别、冠心病患病率、糖尿病患病率和高血压病患病率比较，差异均无统计学意义（$P>0.05$），见表1。

2. 3组患者血清NLR、PLR水平比较：3组患者血清NLR、PLR水平比较，差异有统计学意义（$P<0.05$）；中重度OSAHS组患者的血清NLR、PLR水平高于非OSAHS组，差异有统计学意义（$P<0.05$），见表2。

3. 3组患者睡眠参数比较：3组患者总睡眠时间、睡眠效率比较，差异无统计学意义（$P>0.05$）；3组患者REM期比例、NREM 1期比例、NREM 3期比例、觉醒次数比较，差异有统计学意义（$P<0.05$）。中重度OSAHS组患者NREM 1期比例高于非OSAHS组，NREM 3期比例、REM期比例低于非OSAHS组，觉醒次数多于非OSAHS组，差异均有统计学意义（$P<0.05$）。见表3。

4. 3组患者出院3个月时的神经功能比较：3组患者出院3个月时的Barthel指数和改良Rankin评分比较，差异有统计学意义（$P<0.05$）。轻度、中重度OSAHS组患者的改良Rankin评分高于非OSAHS组，Barthel指数低于非OSAHS组，差异有统计学意义（$P<0.05$）。见表4。

讨论 OSAHS是一种全身性疾病，与高血压病、冠心病及卒中密切相关。相关研究显示，72%的卒中患者存在OSAHS，且卒中后OSAHS的高患病

表1 3组急性缺血性脑卒中患者一般资料的比较

组别	例数	年龄（岁，$\bar{x} \pm s$）	男性［例（%）］	基础疾病［例（%）］			体重指数（kg/m^2，$\bar{x} \pm s$）	NIHSS评分（分，$\bar{x} \pm s$）
				冠心病	高血压病	糖尿病		
非OSAHS组	52	62.48±10.48	36(69.2)	16(30.7)	33(63.4)	14(26.9)	24.49±1.47	8.35±3.32
轻度OSAHS组	24	63.25±10.21	17(70.8)	8(33.3)	16(66.7)	7(29.1)	24.90±1.76	9.00±2.97
中重度OSAHS组	30	61.93±8.89	23(76.6)	14(46.7)	22(73.3)	13(43.3)	25.94±1.57[ab]	9.17±2.58
F/χ^2值		0.116	0.530	2.176	0.840	2.472	8.211	0.519
P值		0.891	0.767	0.337	0.657	0.291	＜0.001	0.596

注：[a]与非OSAHS组比较，$P<0.05$；[b]与轻度OSAHS组比较，$P<0.05$；OSAHS 阻塞性睡眠呼吸暂停低通气综合征；NIHSS 美国国立卫生研究院卒中量表

表2 3组急性缺血性脑卒中患者血清NLR、PLR水平比较

组别	例数	NLR[$M(P_{25}, P_{75})$]	PLR($\bar{x} \pm s$)
非OSAHS组	52	1.90(1.60, 2.71)	161.00 ± 74.10
轻度OSAHS组	24	2.30(1.70, 4.12)	207.10 ± 90.10
中重度OSAHS组	30	2.35(1.67, 6.40)[a]	214.30 ± 96.60[a]
H/*F*值		6.027	4.689
*P*值		0.049	0.011

注：[a]与非OSAHS组比较，$P<0.05$；NLR 中性粒细胞/淋巴细胞比值；PLR 血小板/淋巴细胞比值；OSAHS 阻塞性睡眠呼吸暂停低通气综合征

率会持续存在[12-13]。OSAHS的特征是患者睡眠期间上呼吸道塌陷、反复呼吸暂停、间歇性低氧血症和复氧，导致血液中二氧化碳分压升高及交感神经活动增加，继发氧化应激、炎性介质释放，引发慢性全身炎症。本研究结果显示，急性缺血性脑卒中患者合并OSAHS的比例达50.9%，合并中重度OSAHS患者的睡眠结构紊乱，血液中PLR及NLR水平升高，出院3个月时改良Rankin评分较高，而Barthel指数评分低于非OSAHS患者，提示短期预后较差。

Lux等[14]的研究表明，血液中NLR水平可预测缺血性脑卒中患者短期预后；Yu等[15]的研究表明，NLR与急性缺血性脑卒中患者的早期临床结局相关，高NLR水平组患者在出院时存在严重的神经功能缺损。Gong等[16]的研究表明，NLR、PLR水平与缺血性脑卒中患者早期神经功能恶化有关。NLR、PLR作为一种反映炎症反应的稳定指标，在中重度OSAHS患者中水平升高提示间歇性缺氧引发的炎症通路促进了动脉粥样硬化的发生和发展，加重卒中进展导致不良预后。本研究结果显示，中重度OSAHS组患者血清PLR、NLR水平高于非OSAHS组，与上述研究结果一致。

Gottlieb等[17]的研究表明，与非OSAHS患者比较，卒中合并OSAHS患者的总睡眠时间及觉醒时间的差异无统计学意义，但NREM的浅睡眠时间增加，深睡眠时间减少，觉醒指数增多。觉醒指数与卒中患者出院3个月时的改良Rankin评分呈正相关，睡眠结构紊乱和睡眠片段化可造成神经功能损伤，从而导致预后较差[18]。本研究结果显示，中重度OSAHS组患者存在睡眠结构紊乱，NREM 1期比例高于非OSAHS组患者，而REM及NREM 3期比例低于非OSAHS组患者，觉醒次数多于非OSAHS组患者，与上述研究结果一致。提示中重度OSHAS组患者与非OSAHS组患者相比，间歇性低氧血症介导的炎性反应及睡眠结构紊乱可能是导致缺血性脑卒中患者病情进展、预后不良的重要因素。

考虑到OSAHS的高发病率及其与卒中的双向关系，以及OSAHS是卒中发生的主要(和潜在的可改变的)危险因素，2021年美国心脏协会/美国卒中协会缺血性卒中二级预防指南建议对缺血性脑卒中或短暂性脑缺血发作患者进行OSAHS评估，有利于卒中患者OSAHS的筛查，提高OSAHS确诊率，并尽早进行有效干预[19]。相关研究表明，治疗OSAHS可以改善患者白天的睡眠情况、血压、与睡眠相关的生活质量和躯体功能[20]。

本研究存在不足之处：本研究纳入的样本量有限，未来需要进行大样本、多中心的研究，并进一步探讨卒中合并OSAHS患者炎性指标的动态变化及对长期预后的影响。

综上所述，中重度OSAHS与急性缺血性脑卒中患者血清中炎性因子的表达水平、睡眠结构紊乱及短期预后不良相关，临床医师需及时对卒中患者行PSG检查以发现OSAHS，进而为早期筛查和干预OSAHS提供治疗依据，进而改善患者的预后。

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作者贡献声明 研究设计、论文撰写为陈左然，研究实施、资料收集为周娟、范明鑫，论文修订为董立平，王铁军审校

表3 3组急性缺血性脑卒中患者PSG睡眠参数比较

组别	例数	总睡眠时间(min, $\bar{x} \pm s$)	睡眠效率(%, $\bar{x} \pm s$)	REM期比例(%, $\bar{x} \pm s$)	NREM 1期比例(%, $\bar{x} \pm s$)	NREM 2期比例(%, $\bar{x} \pm s$)	NREM 3期比例(%, $\bar{x} \pm s$)	觉醒次数[次, $M(P_{25}, P_{75})$]
非OSAHS组	52	406.36 ± 59.03	75.21 ± 4.92	17.78 ± 6.13	15.01 ± 8.62	51.46 ± 9.48	15.58 ± 9.55	4.00(3.00, 6.00)
轻度OSAHS组	24	402.70 ± 35.68	75.58 ± 4.42	15.21 ± 5.29	19.26 ± 10.93	53.63 ± 8.83	11.43 ± 5.49	5.00(4.00, 6.00)
中重度OSAHS组	30	399.44 ± 35.81	73.58 ± 5.51	13.97 ± 5.03[a]	20.39 ± 9.14[a]	55.96 ± 9.48	9.81 ± 5.86[a]	6.00(5.00, 8.00)[a]
F/*H*值		0.197	1.374	4.714	3.719	2.219	6.366	24.085
*P*值		0.822	0.258	0.011	0.028	0.114	0.002	<0.001

注：[a]与非OSAHS组比较，$P<0.05$；PSG 多导睡眠图；OSAHS 阻塞性睡眠呼吸暂停低通气综合征；REM 快速眼动睡眠期；NREM 非快速眼动睡眠期

表 4 3 组急性缺血性脑卒中患者出院 3 个月时的 Barthel 指数和改良 Rankin 评分(分)

组别	例数	Barthel 指数 ($\bar{x} \pm s$)	改良 Rankin 评分 [$M(P_{25}, P_{75})$]
非 OSAHS 组	52	87.40 ± 9.20	1.00(0, 2.00)
轻度 OSAHS 组	24	83.54 ± 9.61[a]	2.00(0.25, 3.00)[a]
中重度 OSAHS 组	30	82.67 ± 6.07[a]	2.00(1.00, 3.00)[a]
F/*H* 值		3.366	7.079
P 值		0.041	0.029

注：[a] 与非 OSAHS 组比较，$P < 0.05$；OSAHS 阻塞性睡眠呼吸暂停低通气综合征

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