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腔隙性脑梗死伴脑白质病变患者血清 miR-146a 和 NSE 水平与 MoCA 评分的关系研究*

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摘要 目的:研究腔隙性脑梗死(LI)伴脑白质病变(WML)患者血清 miR-146a 和神经元特异性烯醇化酶(NSE)水平与蒙特利尔认知评估量表(MoCA)评分的关系。**方法:**纳入我院从 2017 年 3 月~2019 年 3 月收治的 LI 伴 WML 患者 108 例进行研究,记作 LI 伴 WML 组。另取同期收治的单纯 WML 患者与单纯 LI 患者各 100 例,分别记作 WML 组与 LI 组,再取同期于我院进行体检的健康人员 100 例作为对照组。比较四组人员的血清 miR-146a 和 NSE 水平、MoCA 评分,并作相关性分析。**结果:**LI 伴 WML 组、WML 组、LI 组血清 miR-146a 相对表达量均低于对照组,而 LI 伴 WML 组血清 miR-146a 相对表达量又显著低于 WML 组、LI 组(均 $P<0.05$);LI 伴 WML 组、WML 组、LI 组血清 NSE 水平均显著高于对照组,且 LI 伴 WML 组血清 NSE 水平均显著高于 WML 组、LI 组(均 $P<0.05$)。LI 伴 WML 组 MoCA 总分显著低于 WML 组与 LI 组,且 WML 组与 LI 组 MoCA 总分显著低于对照组(均 $P<0.05$)。经 Pearson 相关性分析可得:LI 伴 WML 组患者血清 miR-146a 相对表达量与 MoCA 总分呈正相关关系($P<0.05$),而血清 NSE 水平与 MoCA 总分呈负相关关系($P<0.05$)。**结论:**LI 伴 WML 患者的血清 miR-146a 水平存在明显低表达,而 NSE 水平存在明显高表达,并与 MoCA 评分相关,两者可能在认知功能损伤的发生、发展过程中起着至关重要的作用。

关键词:腔隙性脑梗死;脑白质病变;miR-146a;神经元特异性烯醇化酶;蒙特利尔认知评估量表

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Relationship between Serum miR-146a and NSE Levels and MoCA Score in Patients with Lacunar Infarction with Leukoencephalopathy*

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ABSTRACT Objective: To study the relationship between serum miR-146a and neuron-specific enolase (NSE) levels and Montreal cognitive assessment scale (MoCA) scores in patients with lacunar cerebral infarction (LI) with leukoencephalopathy (WML). **Methods:** 108 patients with LI and WML who were admitted to our hospital from March 2017 to March 2019 were included in the study, and were recorded as the LI with WML group. In addition, 100 cases of WML patients and 100 cases of LI patients who were admitted at the same time were recorded as WML group and LI group, and 100 cases of healthy people who underwent physical examination in our hospital at the same time were taken as the control group. Serum miR-146a and NSE levels and MoCA scores of the four groups were compared, and the correlation was analyzed. **Results:** The relative expression of serum miR-146a in the LI with WML group, WML group and LI group were lower than that in the control group, while the relative expression of serum miR-146a in the LI with WML group were significantly lower than that in the WML group and LI group (all $P<0.05$). The serum NSE level of the LI with WML group, WML group and LI group were significantly higher than that in the control group, and the serum NSE level of the LI with WML group were significantly higher than that in the WML group and LI group (all $P<0.05$). The total MoCA score of the LI with WML group were significantly lower than that in the WML group and LI group, and the total MoCA score of the WML group and the LI group were significantly lower than that in the control group (all $P<0.05$). Pearson correlation analysis showed that the relative expression of serum miR-146a in the LI with WML group was positively correlated with the total MoCA score ($P<0.05$), while the serum NSE level was negatively correlated with the total MoCA score ($P<0.05$). **Conclusion:** Serum miR-146a level in LI with WML patients is significantly lower, while the serum NSE level is significantly higher, and they are correlated with MoCA score, which may play a crucial role in the occurrence and development of cognitive impairment.

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前言

腔隙性脑梗死(Lacunar cerebral infarction, LI)在神经科临床上多见,其主要病因为颅内穿支动脉病变或(和)颅内小动脉闭塞、痉挛、狭窄,继而引起动脉阻滞缺血及坏死^[1,2]。脑白质病变(Leukoencephalopathy, WML)则是指半卵圆中心亦或是脑室周围白质区域出现弥漫性或对称性点状、片状异常变化^[3,4]。近年来临床上已有大量研究证实,LI与WML均会对患者的认知功能造成不同程度的损害,其中WML更是会增加脑血管疾病发生的风险^[5,6]。目前,关于LI伴WML对认知功能影响的相关研究并不多见,其所涉及的一系列分子机制仍未完全明确^[7,8]。随着近年来相关研究的日益深入,越来越多的学者发现微小RNA(miRNA)可能在多种神经系统疾病的发生、发展过程中发挥着至关重要的作用,可能具有调控认知功能受损以及学习记忆障碍等病理过程的作用^[9,10]。鉴于此,本文通过研究LI伴WML患者血清miR-146a和神经元特异性烯醇化酶(Neuron-specific ene purification enzyme, NSE)水平与蒙特利尔认知评估量表(Montreal cognitive assessment scale, MoCA)评分的关系,旨在为LI伴WML患者的临床诊治提供新的靶点与思路。现作以下报道。

1 资料与方法

1.1 一般资料

纳入我院从2017年3月~2019年3月收治的LI伴WML患者108例进行研究,记作LI伴WML组。另取同期收治的单纯WML与单纯LI患者各100例,记作WML组与LI组。纳入标准:(1)LI伴WML、单纯LI、单纯WML患者均经头颅MR检查确诊;(2)入院前均未接受任何可能改善认知功能的措施治疗;(3)均为老年人;(4)病历治疗完整。排除标准:(1)既往有认知功能异常史者;(2)合并大面积脑梗死或(和)脑梗死者;(3)伴有其他可能对认知功能障碍影响的疾病者;(4)正接受其他研究者。再取同期于我院进行体检的认知功能无异常的健康人员100例作为对照组。纳入人员及其家属签署了知情同意书,医院伦理委员会已批准。

1.2 研究方法

(1)标本采集:所有患者均于入院后第2d清晨进行采血,对照组人员体检当日清晨进行采血,所有患者及对照组人员处于空腹状态下,采集肘静脉血5 mL,放入EDTA抗凝管内实施抗凝处理,随后以3000 r/min作为离心条件,实施时长为10 min的离心处理,获取血清保存在-80℃冰箱中备用。(2)血清miR-146a和NSE水平的检测:其中血清miR-146a表达检测方式为荧光实时定量PCR法。首先以RNA提取试剂盒(购自美国Sigma-Aldrich)完成血清总RNA的提取,然后借助反转录试剂盒(购自日本Takara)完成逆转录。其中miR-146a扩增引物由上海生工生物工程股份有限公司合成,上游引物序列为

5,-GTTTACCTACTCGTCTCTGGTAC-3,,下游引物序列为5,-CCTTATCCCAATACGTGTCGACATCAT-3,,以 β -actin作为内参,其上游引物序列为5,-TGACGAGACCTCTATGCC-GACTC-3,,下游引物序列为5,-ACTTCTCATCGTACTCCC-CTG-3,,采用ABI PCR System7300扩增仪完成PCR反应,按照基因特异性引物分析miR-146a的表达,以 $2^{-\Delta\Delta C_T}$ 计算miR-146a相对表达量。PCR反应体系:5 μ L的十倍缓冲液,4 μ L的2.5mmol/L dNTP,0.5 μ L的Tap酶,2.5 μ L的Pmix,上游引物与下游引物个1 μ L,ddH₂O为36 μ L。PCR反应条件:94℃预变性120s,94℃变性25s,60℃退火35s,72℃延伸20s,共31个循环。NSE检测方式为酶联免疫吸附法,具体操作务必以试剂盒说明书为准,相关试剂盒购自上海酶联生物科技有限公司。(3)认知功能评价主要是借助MoCA完成:内容涵盖视空间与执行、命名、注意力、语言、抽象思维、延迟回忆、定向力,总分30分,得分越高代表认知功能越佳^[11]。

1.3 统计学方法

数据的分析借助SPSS20.0软件完成,计数和(或)计量资料以[n(%)]和($\bar{x} \pm s$)表示,予以 χ^2 和(或)t检验。多组间对比差异予以单因素方差分析。LI伴WML组患者血清miR-146a、NSE水平与MoCA评分的关系予以Pearson相关性分析。 $P < 0.05$ 表示差异有统计学意义。

2 结果

2.1 四组基线资料对比

四组人员各项基线资料对比差异无统计学意义(均 $P > 0.05$),见表1。

2.2 四组血清miR-146a与NSE水平对比

LI伴WML组、WML组、LI组血清miR-146a相对表达量均低于对照组,而LI伴WML组血清miR-146a相对表达量又显著低于WML组、LI组($P < 0.05$);LI伴WML组、WML组、LI组血清NSE水平均显著高于对照组,且LI伴WML组NSE水平显著高于WML组、LI组(均 $P < 0.05$),见表2。

2.3 四组人员MoCA评分对比

各组视空间与执行、命名、注意力、语言、抽象思维、延迟回忆、定向力评分以及MoCA总分整体比较差异有统计学意义(均 $P < 0.05$),LI伴WML组MoCA总分显著低于WML组与LI组,且WML组与LI组MoCA总分均显著低于对照组(均 $P < 0.05$),见表3。

2.4 LI伴WML组患者血清miR-146a、NSE水平与MoCA评分的相关性分析

经Pearson相关性分析可得:LI伴WML组患者血清miR-146a相对表达量与MoCA总分呈正相关关系($r=0.571$, $P=0.000$),而血清NSE水平与MoCA总分呈负相关关系($r=-0.406$, $P=0.001$)。

3 讨论

表 1 四组基线资料对比

Table 1 Comparison of four groups of baseline data

Baseline data	LI with WML group (n=108)	WML group (n=100)	LI group(n=100)	Control group (n=100)	χ^2/F	<i>P</i>
Age(years)	71.42±3.71	72.04±3.19	71.94±3.78	72.19±3.24	1.340	0.509
Gender (Male/Female)	58/50	53/47	54/46	52/48	0.204	0.604
Education time (years)	7.52±2.39	7.66±2.41	7.68±2.48	7.41±2.56	1.284	0.533
Smoking	59(54.63%)	50(50.00%)	51(51.00%)	51(51.00%)	0.156	0.802
Drinking	62(57.41%)	57(57.00%)	56(56.00%)	54(54.00%)	0.124	0.912
Hypertension	68(62.96%)	62(62.00%)	63(63.00%)	61(61.00%)	0.177	0.769
Diabetes mellitus	45(41.67%)	41(41.00%)	42(42.00%)	40(40.00%)	0.184	0.625
Hyperlipemia	11(10.19%)	9(9.00%)	10(10.00%)	9(9.00%)	0.145	0.874

表 2 四组血清 miR-146a 与 NSE 水平对比($\bar{x}\pm s$)Table 2 Comparison of serum miR-146a and NSE levels in four groups($\bar{x}\pm s$)

Groups	n	Relative expression of miR-146a	NSE(ng/ml)
LI with WML group	108	0.80±0.41 [#]	13.24±3.77 [#]
WML group	100	1.24±0.49 ^{#*}	10.23±2.01 ^{#*}
LI group	100	1.26±0.54 ^{#*}	10.20±2.05 ^{#*}
Control group	100	2.02±0.53	6.68±1.41
F	-	31.494	43.282
<i>P</i>	-	0.000	0.000

Note: Compared with the control group, [#]*P*<0.05; compared with the LI with WML group, ^{*}*P*<0.05.

表 3 四组人员 MoCA 评分对比(分, $\bar{x}\pm s$)Table 3 Comparison of MoCA scores in four groups(scores, $\bar{x}\pm s$)

MoCA scores	LI with WML group (n=108)	WML group (n=100)	LI group(n=100)	Control group (n=100)	F	<i>P</i>
Visual space and execution	3.79±0.82	4.42±1.13	4.37±1.07	5.71±0.24	24.382	0.000
Nominate	2.52±0.22	2.80±0.20	2.77±0.21	2.80±0.13	16.011	0.000
Attention	3.59±0.42	4.12±0.40	5.39±0.34	5.52±0.27	234.824	0.000
Language	1.80±0.16	2.04±0.23	2.01±0.25	2.80±0.16	115.235	0.000
Abstract thinking	1.67±0.32	1.84±0.17	1.83±0.15	1.88±0.21	8.015	0.000
Delayed memory	2.91±0.39	3.44±0.27	3.45±0.30	3.41±0.21	22.185	0.000
Directive force	5.66±0.52	5.71±0.14	5.72±0.18	5.80±0.10	0.875	0.401
Total MoCA score	21.71±3.50 [#]	24.34±4.02 [#]	24.87±3.50 ^{#*}	28.02±1.17	20.844	0.000

Note: Compared with the control group, [#]*P*<0.05; compared with the LI with WML group, ^{*}*P*<0.05.

迄今为止,关于 WML 的具体发病机制仍处于探索阶段,不少学者推测其可能与脑小血管病变有关,可导致认知功能出现一定程度的下降,继而引发一系列相关症状^[12-14]。小动脉病变导致基底节、丘脑的 LI 与侧脑室周围和半卵圆中心发生 WML,从而阻断皮层和白质两者的环路联系,进一步促使信息传递发生障碍,继而导致认知功能障碍的发生,最终促使患者出现记忆力减退以及理解、判断、计算能力的不同程度下降

等^[15-17]。此外,LI 的发病机制可能与高血压引起的微小动脉壁的脂性透明病性、血流动力学异常以及大脑中动脉与基底动脉的动脉粥样硬化相关,可能引发不同程度的认知功能障碍。随着研究的日益深入,大量研究证实 miRNA 可能在大脑发育以及神经元分化的过程中起着至关重要的作用,继而影响学习记忆以及认知功能^[18]。已有研究报道证实^[19,20],血清 miR-146a 在系统性红斑狼疮以及银屑病患者的中均存在明显异常表达,可能

参与了上述两种基本的发生、发展过程。

本研究结果发现:LI 伴 WML 组、WML 组、LI 组血清 miR-146a 相对表达量均低于对照组,而 LI 伴 WML 组血清 miR-146a 相对表达量最低;LI 伴 WML 组、WML 组、LI 组血清 NSE 水平均显著高于对照组,且 LI 伴 WML 组 NSE 水平最高(均 $P < 0.05$)。刘明等人的研究报道发现^[21]:脑梗死患者的血清 miR-146a 存在明显低表达,且和疾病严重程度密切相关。而王薇等人的研究结果显示^[22]:脑梗死患者血清 NSE 存在明显高表达,与认知障碍关系密切。这提示了血清 miR-146a、NSE 均可能参与了 LI 伴 WML 发生、发展过程。分析原因,笔者认为 miR-146a 可通过增加细胞周期蛋白依赖性激酶活性,从而促进细胞的增殖,进一步导致血管内壁增粗狭窄;与此同时,miR-146a 可通过对细胞金属基质酶的分泌产生抑制作用,进一步削弱其对 EMC 的降解作用,从而促使细胞和 EMC 的聚集增强;此外,miR-146a 可通过激活淋巴细胞、中性粒细胞以及内皮细胞等,继而形成高凝状态以及纤溶亢进,进一步引起血液粘滞性和凝固性的增强,从而促使其处于高凝或血栓前状态,最终促进了疾病的发生、进展^[23-25]。NSE 则是广泛存在于大脑神经元以及神经内分泌细胞的一种特异性酶,在正常状况下,仅微表达于血液中,一旦神经细胞发生缺血、损伤,则可能导致细胞膜的完整性被破坏,进一步促使 NSE 释放入脑脊液,并于血脑屏障遭受破坏后进入血液循环^[26,27]。此外,LI 伴 WML 组 MoCA 总分显著低于 WML 组与 LI 组,且 WML 组与 LI 组 MoCA 总分均显著低于对照组(均 $P < 0.05$)。吴小杨等人的研究结果也显示^[28]:LI 合并 WML 患者除定向力外的各项 MoCA 评分均显著低于健康对照组,且 MoCA 总分、视空间与执行、抽象思维评分均显著低于 WML 组与 LI 组。另外,经 Pearson 相关性分析可得:LI 伴 WML 组患者血清 miR-146a 相对表达量与 MoCA 总分呈正相关关系,而血清 NSE 水平与 MoCA 总分呈负相关关系(均 $P < 0.05$)。这充分说明了血清 miR-146a、NSE 与 LI 伴 WML 患者认知功能密切相关。临床工作中可能通过对上述两项指标进行检测,并为临床治疗方案的制定提供参考依据^[29,30]。

综上所述,LI 伴 WML 患者血清 miR-146a 和 NSE 水平均存在异常表达,且两者和患者认知功能损伤的发生、发展存在密切相关。

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