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急性脑梗死患者血清 RBP、NLR、PTX3 水平与颈动脉粥样硬化斑块稳定性的关系研究*

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摘要 目的:探讨急性脑梗死(ACI)患者血清视黄醇结合蛋白(RBP)、中性粒细胞与淋巴细胞比值(NLR)、内正五聚蛋白 3(PTX3)水平与颈动脉粥样硬化斑块稳定性的关系。**方法:**收集我院 2017 年 1 月~2019 年 1 月收治的 300 例 ACI 患者,根据颈动脉粥样硬化斑块超声结果分为稳定斑块组($n=173$)和不稳定斑块组($n=127$),另选同期在我院体检中心进行健康体检的志愿者 100 例为对照组。对 ACI 患者和对照组进行 RBP、NLR、PTX3、血脂指标的检测,并进行组间统计学对比。采用 Pearson 检验对 ACI 患者的 RBP、NLR、PTX3 与血脂指标的相关性进行分析。**结果:**三组受试者性别、年龄、体质指数(BMI)、吸烟史、饮酒史等基础资料对比无显著性差异($P>0.05$)。稳定斑块组、不稳定斑块组患者的 RBP、NLR、PTX3 水平均高于对照组,且不稳定斑块组上述指标水平高于稳定斑块组($P<0.05$)。稳定斑块组、不稳定斑块组患者的总胆固醇(TC)、甘油三酯(TG)、低密度脂蛋白(LDL-C)、纤维蛋白原(FIB)水平均高于对照组,且不稳定斑块组上述指标水平高于稳定斑块组($P<0.05$)。经 Pearson 检验分析,ACI 患者的 RBP、NLR、PTX3 水平与 TC、TG、LDL-C、FIB 均呈正相关性($P<0.05$)。**结论:**在 ACI 患者中 RBP、NLR、PTX3 水平较高,并与患者的颈动脉粥样硬化斑块的稳定性有紧密的关联性。初步推测 RBP、NLR、PTX3 可能参与颈动脉粥样硬化斑块的形成,进而影响 ACI 疾病的发生发展过程。

关键词:急性脑梗死;颈动脉粥样硬化斑块;视黄醇结合蛋白;中性粒细胞与淋巴细胞比值;内正五聚蛋白 3;相关性

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Relationship between the Levels of RBP, NLR, PTX3 and the Stability of Carotid Atherosclerotic Plaque in Patients with Acute Cerebral Infarction*

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ABSTRACT Objective: To investigate the relationship between the level of serum retinol binding protein (RBP), the ratio of neutrophils to lymphocytes (NLR), the endopentamerin 3 (PTX3) and the stability of carotid atherosclerotic plaque in patients with acute cerebral infarction (ACI). **Methods:** 300 patients with ACI who were admitted to our hospital from January 2017 to January 2019 were enrolled in this study. According to the results of carotid atherosclerotic plaque ultrasound, they were divided into stable plaque group ($n=173$) and unstable plaque group ($n=127$). Another 100 volunteers who had physical examination in the physical examination center of our hospital at the same time were selected as the control group. The RBP, NLR, PTX3 and blood lipid indexes of patients with ACI and control group were detected, and the statistical comparison between groups was made. Pearson test was used to analyze the correlation between RBP, NLR, PTX3 and blood lipid indexes in patients with ACI. **Results:** There was no significant difference in gender, age, body mass index (BMI), smoking history and drinking history among the three groups ($P>0.05$). The levels of RBP, NLR and PTX3 in stable plaque group and unstable plaque group were higher than those in control group, and the levels of the above indexes in unstable plaque group were higher than those in stable plaque group ($P<0.05$). The levels of total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL-C) and fibrinogen (FIB) in stable plaque group and unstable plaque group were higher than those in the control group. The levels of the above indexes in the unstable plaque group were higher than those in the stable plaque group ($P<0.05$). According to Pearson test, the levels of RBP, NLR and PTX3 in patients with ACI were positively correlated with TC, TG, LDL-C and FIB ($P<0.05$). **Conclusion:** The levels of RBP, NLR and PTX3 are higher in patients with ACI, and they are closely related to the stability of carotid atherosclerotic plaque. It is preliminarily speculated that RBP, NLR and PTX3 may be involved in the formation of carotid atherosclerotic plaque, and then affect the occurrence and development of ACI disease.

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Key words: Acute cerebral infarction; Carotid atherosclerotic plaque; Retinol binding protein; Ratio of neutrophils to lymphocytes; Endo pentamerin 3; Correlation

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前言

急性脑梗死(Acute cerebral infarction, ACI)是颅脑内部血流突然中断后导致的脑组织坏死,在临床上又称之为急性缺血性脑卒中,并伴随着神经元、星形胶质细胞、胶质细胞的损伤,是导致患者出现致残、致死的严重心脑血管疾病之一,严重威胁患者的生命健康和生活质量,其发病主要与颈动脉粥样硬化斑块的形成及血栓栓塞性物质存在密切关联^[1-3]。目前,对于ACI的发病机制尚未完全明确,其中以动脉粥样硬化斑块形成成为主要的病理基础,相关报道显示炎症反应、脂质代谢异常、高血压、糖尿病、肥胖等多重因素均可影响颈动脉粥样硬化斑块的形成及斑块形成的稳定性,并进一步参与到ACI的发病过程中^[4-6]。血清视黄醇结合蛋白(Retinol binding protein, RBP)是由肝脏组织合成的一种维生素转运蛋白,广泛分布于机体各组织中,相关报道显示RBP能够加重脂质代谢紊乱、促进炎症反应的发生等,进而推测可能参与颈动脉粥样硬化斑块发生发展甚至影响斑块的稳定性^[7,8]。中性粒细胞与淋巴细胞比值(Ratio of neutrophils to lymphocytes, NLR)、内正五聚蛋白3(Endo-n-pentamerin 3, PTX3)均为反应机体炎症反应状态的重要指标,是否与颈动脉粥样硬化斑块形成及稳定性有关联尚未有深入的报道阐述^[9,10]。基于此本研究以ACI患者为目标人群,对其实施RBP、NLR、PTX3水平检测,并分析探讨与颈动脉粥样硬化斑块形成稳定性的关系,报告如下。

1 资料与方法

1.1 一般资料

收集我院2017年1月~2019年1月收治的300例ACI患者,纳入标准:①患者经头颅CT、血管造影检查确诊为ACI,符合《中国急性缺血性脑卒中诊治指南2014》中的相关诊断标准^[11];②患者均在发病后的24h入住本院;③患者基础资

料、临床检查资料完整无缺项;④研究开展取得患者家属的知情同意,研究方案经本院伦理学委员会批准。排除标准:①患者并发其他心脑血管疾病;②严重的心肝肾功能不全患者;③有活动性出血、凝血功能障碍患者;④长期服用抗凝药物的患者;⑤原发性高脂血症患者。患者入院后进行彩色多普勒超声检查,根据颈动脉粥样硬化斑块超声结果分为稳定斑块组(n=173)和不稳定斑块组(n=127),另选同期在我院体检中心进行健康体检的志愿者100例为对照组,受试者各项检测指标正常,无脑梗死病史。

1.2 研究方法

采集ACI患者、对照组的空腹静脉血约5 mL,采用Byc310型高速离心机(济南鑫贝西生物技术有限公司)进行离心分离得到血清样本,采用酶联免疫吸附试验法检测患者的RBP、NLR、PTX3指标水平,检测仪器为MR-96A型多功能酶标仪(深圳迈瑞医疗科技有限公司),采用AU5800型全自动生化分析仪(美国贝克曼公司)检测患者的血脂指标,包括甘油三酯(triglyceride, TG)、总胆固醇(total cholesterol, TC)、低密度脂蛋白(Low density lipoprotein, LDL-C)、纤维蛋白原(Fibrinogen, FIB),检测试剂盒均购置于上海罗氏诊断试剂公司,操作步骤按仪器操作规程和试剂盒说明书要求进行。

1.3 统计学分析

采用SPSS 21.0进行数据处理与分析,计量资料以($\bar{x} \pm s$)表示,两组间比较采用t检验,三组间对比采用F检验,计数资料采用[n(%)],实施 χ^2 检验,相关性分析采用Pearson检验,检验水准 $\alpha=0.05$ 。

2 结果

2.1 三组受试者一般资料对比

三组受试者性别、年龄、体质指数(Body mass index, BMI)、吸烟史、饮酒史等基础资料对比无显著性差异($P>0.05$),见表1。

表1 三组受试者一般资料对比($\bar{x} \pm s$)

Table 1 Comparison of general data of three groups of subjects($\bar{x} \pm s$)

Groups	n	Gender		Age(years)	BMI(kg/m ²)	Smoking history		Drinking history	
		Male	Female			Yes	No	Yes	No
Unstable plaque group	127	67	60	54.39 $\pm$ 8.23	22.73 $\pm$ 2.03	9	118	18	109
Stable plaque group	173	93	80	54.98 $\pm$ 8.67	22.12 $\pm$ 2.15	13	160	27	146
Control group	100	56	44	55.67 $\pm$ 8.81	22.93 $\pm$ 2.24	5	95	13	87
F/ χ^2		0.244		1.128	0.696	0.670		0.363	
P		0.885		0.260	0.487	0.715		0.834	

2.2 三组受试者RBP、NLR、PTX3水平对比

稳定斑块组、不稳定斑块组患者的RBP、NLR、PTX3水平均高于对照组,且不稳定斑块组上述指标水平高于稳定斑块组($P<0.05$),见表2。

2.3 三组受试者血脂指标水平对比

稳定斑块组、不稳定斑块组患者的TC、TG、LDL-C、FIB水平均高于对照组,且不稳定斑块组上述指标水平高于稳定斑块组($P<0.05$),见表3。

表 2 三组受试者 RBP、NLR、PTX3 水平对比($\bar{x} \pm s$)

Table 2 Comparison of levels of RBP, NLR and PTX3 in three groups of subjects($\bar{x} \pm s$)

Groups	n	RBP (mg/L)	NLR (%)	PTX3 ($\mu\text{g/L}$)
Unstable plaque group	127	74.23 $\pm$ 7.89* [#]	184.89 $\pm$ 21.54* [#]	16.23 $\pm$ 2.98* [#]
Stable plaque group	173	56.89 $\pm$ 6.36*	153.12 $\pm$ 18.65*	11.87 $\pm$ 2.65*
Control group	100	38.82 $\pm$ 5.93	101.32 $\pm$ 11.52	6.78 $\pm$ 1.03
F	-	37.332	35.041	30.306
P	-	0.000	0.000	0.000

Note: comparison with the control group, * $P<0.05$; comparison with the stable plaque group, [#] $P<0.05$.

表 3 三组受试者血脂指标水平对比($\bar{x} \pm s$)

Table 3 Comparison of serum lipids in three groups of subjects($\bar{x} \pm s$)

Groups	n	TC(mmol/L)	TG(mmol/L)	LDL-C(mmol/L)	FIB(g/L)
Unstable plaque group	127	7.98 $\pm$ 1.23* [#]	4.89 $\pm$ 1.03* [#]	5.87 $\pm$ 1.03* [#]	6.62 $\pm$ 1.24* [#]
Stable plaque group	173	6.21 $\pm$ 1.06*	3.12 $\pm$ 0.97*	4.36 $\pm$ 0.97*	5.13 $\pm$ 1.09*
Control group	100	4.25 $\pm$ 0.89	1.43 $\pm$ 0.57	2.53 $\pm$ 0.83	3.03 $\pm$ 0.86
F	-	25.514	30.145	26.375	24.652
P	-	0.000	0.000	0.000	0.000

Note: comparison with the control group, * $P<0.05$; comparison with the stable plaque group, [#] $P<0.05$.

2.4 相关性分析

与 TC、TG、LDL-C、FIB 均呈正相关性($P<0.05$),见表 4。

经 Pearson 检验分析,ACI 患者的 RBP、NLR、PTX3 水平

表 4 相关性分析

Table 4 Correlation analysis

Indexes	RBP		NLR		PTX3	
	r	P	r	P	r	P
TC	0.512	0.000	0.494	0.003	0.507	0.000
TG	0.498	0.002	0.503	0.001	0.483	0.009
LDL-C	0.487	0.007	0.490	0.004	0.496	0.002
FIB	0.491	0.004	0.484	0.009	0.505	0.001

3 讨论

ACI 的发病机制较为复杂,目前主流的观点认为与颈动脉粥样硬化斑块的形成以及脑内血栓栓塞性物质的出现,导致的脑内动脉血管的堵塞或严重狭窄,致使患者的脑内组织出现缺血缺氧等,进而诱发患者脑组织的出现缺血坏死,引发一系列的临床症状^[12-14]。颈动脉粥样硬化斑块的形成及破裂是 ACI 发病的最主要病理特征,据流行病学调查显示约 80% 的 ACI 患者超声检查显示有不同程度大小的颈动脉粥样硬化斑块的存在^[15]。颈动脉粥样硬化斑块形成是由多种因素所致,主要涉及血管重塑、血管壁表面情况、炎性反应、血液黏稠度、脂质代谢指标异常、局部机械力学等^[16,17]。患者的颈动脉粥样硬化斑块可分为稳定性斑块、不稳定性斑块两种,经过生理和病理检查分析发现,稳定性斑块的炎性细胞少且细胞的纤维壁较厚,因此在未受到其他因素的影响时结构上不易破裂;而不稳定性斑块中的炎性细胞浸润较多,炎性细胞的质地较软、细胞纤维壁较

薄、具有脆性大,同时基底处有大量的新生微血管,易出现破裂,进而影响 ACI 的发病和病情进展,因此对于 ACI 病情的防治主要的一点是密切观察和预防不稳定性颈动脉粥样硬化斑块的形成^[18-20]。通过对影响颈动脉粥样硬化斑块稳定性的因素的分析探讨,对于颈动脉粥样硬化斑块的形成及 ACI 的防治有着重要作用。

本研究结果显示,在 ACI 患者中 RBP、NLR、PTX3 水平较高,并随着患者颈动脉粥样硬化斑块的稳定性改变而进一步提高,进一步推测 RBP、NLR、PTX3 与颈动脉粥样硬化斑块的形成及稳定性的改变有一定的关联,这与既往的临床报道结果基本一致^[21,22]。RBP 具有促进胰岛素抵抗,加重脂质代谢功能紊乱等作用,同时还可激活机体的氧化应激反应,合成分泌大量的炎性物质导致血管的炎性损伤,促进颈动脉粥样硬化斑块的形成和进展^[23-25]。NLR 是一种新型的炎性反应标志物,中性粒细胞分泌炎性介质参与急性组织损伤,可通过蛋白水解酶释放花生四烯酸衍物、氧化应激指标形成,使得颈动脉粥样硬化斑

块更脆弱,活化的中性粒细胞粘附于内皮细胞表面造成内皮功能紊乱,进一步增加炎症因子对于粥样硬化斑块稳定性的影响^[26-28]。PTX3 是一种炎症标志物蛋白,可反映机体的炎症反应状态,通过抑制血管内促纤维细胞因子释放,促使斑块纤维壁逐渐变薄,并且还可诱导血管内血管的高凝状态,进而导致不稳定性颈动脉粥样硬化斑块的形成^[29,30]。在各项血脂指标对比中,ACI 患者的 TC、TG、LDL-C、FIB 水平均高于对照组,且不稳定斑块组 TC、TG、LDL-C、FIB 水平均高于稳定斑块组,表明脂质代谢紊乱、血液的高凝态是颈动脉粥样硬化斑块形成的基础原因。在相关性分析中,ACI 患者的 RBP、NLR、PTX3 水平与 TC、TG、LDL-C、FIB 均呈正相关性,表明 RBP、NLR、PTX3 均参与颈动脉粥样硬化斑块的形成和进展过程中,并且可能是不稳定性斑块形成的主要诱因。

综上所述,在 ACI 患者中 RBP、NLR、PTX3 水平较高,并与患者的颈动脉粥样硬化斑块的稳定性密切相关。初步推测 RBP、NLR、PTX3 可能参与颈动脉粥样硬化斑块的形成,进而影响 ACI 疾病的发生发展过程。因此,可通过对患者 RBP、NLR、PTX3 指标水平的监测,可以及时准确的发现不稳定性的颈动脉粥样硬化斑块,进而采取积极有效的治疗干预措施,避免 ACI 疾病的进一步恶化。

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综上所述,过表达 miR-382-3p 可通过下调 RASA1 促进软骨细胞增殖,抑制 LPS 诱导的软骨细胞凋亡。

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