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血清 MMP-9 水平与急性脑梗死溶栓后出血转化的相关性及其预测意义 *

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摘要 目的:研究血清基质金属蛋白酶-9(MMP-9)水平与急性脑梗死(ACI)溶栓后出血转化(HT)的相关性及其预测意义。**方法:**选择2014年2月到2017年6月在承德医学院附属医院神经内科诊治的ACI患者130例作为研究对象。根据患者是否存在溶栓后HT将其分成HT组(65例)和NHT组(65例),两组均根据患者的实际病情给予个性化的治疗,对比两组患者实验室指标、血清MMP-9水平、美国国立卫生研究院卒中量表(NIHSS)评分,随访6个月后,记录死亡人数及Barthel指数,并分析患者血清MMP-9水平与其NIHSS评分、Barthel指数、低密度脂蛋白胆固醇(LDL-C)及总胆固醇(TC)水平的相关性。**结果:**HT组LDL-C及TC水平均低于NHT组($P<0.05$)。HT组患者在溶栓前、溶栓后3d、溶栓后7d的血清MMP-9水平、NIHSS评分均高于NHT组($P<0.05$)。随访6个月后,HT组的死亡率高于NHT组,而Barthel指数低于NHT组($P<0.05$)。根据Spearman法分析相关性发现,患者血清MMP-9水平与其NIHSS评分呈正相关,而与Barthel指数、LDL-C及TC水平呈负相关($P<0.05$)。**结论:**血清MMP-9水平与ACI溶栓后HT具有紧密的关联,有助于更好地预测患者的病情及预后,临床上可考虑在治疗ACI溶栓后HT时监测MMP-9水平,从而获得更加精准的辅助性数据参考。

关键词:基质金属蛋白酶-9;急性脑梗死;溶栓;出血转化;相关性;预测意义

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Correlation Between Serum MMP-9 Level and Hemorrhage Transformation after Thrombolysis in Acute Cerebral Infarction and its Predictive Significance*

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ABSTRACT Objective: To study the correlation between serum matrix metalloproteinase-9 (MMP-9) level and hemorrhage transformation (HT) after thrombolysis in acute cerebral infarction (ACI) and its predictive significance. **Methods:** 130 patients with ACI who were treated in the Department of Neurology of the Affiliated Hospital of Chengde Medical College from February 2014 to June 2017 were selected as the subjects. According to whether the patients had HT after thrombolysis, they were divided into HT group (65 cases) and NHT group (65 cases), and the two groups were given individualized treatment according to the actual condition of the patient. The laboratory indexes, serum MMP-9 level, National Institutes of Health Stroke Scale (NIHSS) score were compared between the two groups. 6 months after follow-up, the number of deaths and the Barthel index were recorded, and the correlation between serum MMP-9 level and NIHSS score, Barthel index, low density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) level were analyzed. **Results:** The levels of LDL-C and TC in the HT group were significantly lower than the NHT group ($P<0.05$). The serum MMP-9 level in the HT group before thrombolysis, 3 d after thrombolysis, 7 d after thrombolysis were higher than that in NHT group ($P<0.05$). At 6 months after follow-up, the mortality rate of HT group was higher than that in NHT group, but the Barthel index was lower than that in NHT group ($P<0.05$). According to the correlation analysis of Spearman method, it was found that serum MMP-9 level was positively correlated with NIHSS score, but it was negatively correlated with Barthel index, LDL-C and TC levels ($P<0.05$). **Conclusion:** Serum MMP-9 level is closely related to HT after thrombolysis in patients with ACI. It helps to better predict the patient's condition and prognosis. It can be considered in clinical treatment of HT after thrombolysis in ACI to monitor MMP-9 level, so as to get more accurate auxiliary data reference.

Key words: Matrix metalloproteinase-9; Acute cerebral infarction; Thrombolysis; Hemorrhage transformation; Correlation; Predictive significance

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前言

急性脑梗死(Acute cerebral infarction, ACI)是神经内科的常见病及多发病,由于此病患者预后较差,因此被认为是人类健康的杀手^[1]。溶栓疗法是治疗 ACI 的重要手段,但是患者在溶栓后可能会出现出血转化(Hemorrhagic transformation, HT)等情况,这将进一步加重患者的病情,严重者甚至导致死亡^[23]。血清基质金属蛋白酶-9(Matrix metalloproteinase-9, MMP-9)作为一种锌依赖蛋白性水解酶,其可降解机体的基底细胞层,与脑水肿具有较强的联系^[45]。近年来,国外有报道指出,MMP-9与 ACI 的发生及发展具有一定的关联^[67]。因此,分析 MMP-9 与 ACI 溶栓后 HT 之间关系,对于患者的诊治具有积极的作用^[8]。本文通过分析血清 MMP-9 水平与 ACI 溶栓后 HT 的相关性以及其预测意义,旨在为临床治疗提供数据支持,现报道如下。

1 资料和方法

1.1 临床资料

选择 2014 年 2 月到 2017 年 6 月在承德医学院附属医院神经内科诊治的 ACI 患者 130 例作为研究对象。纳入标准:(1)患者均满足我国第四届脑血管病会议中制定的《脑血管病诊断要点》当中关于 ACI 的诊断标准^[9];(2)年龄 >50 岁;(3)初次发病者;(4)有溶栓治疗的适应症者;(5)患者或家属均对此次研究知情同意并签署知情同意书。排除标准:(1)有心血管疾病者;(2)有恶性肿瘤者;(3)有血液疾病者;(4)有免疫类疾病或感染性疾病者。根据患者是否存在溶栓后 HT 将其分成 HT 组(65 例)和 NHT 组(65 例),其中 HT 组男性 45 例,女性 20 例;年龄 52-77 岁,平均(61.54±1.39)岁;梗死体积 3-14 cm³,平均(8.24±1.89)cm³;合并症:高血压 38 例,糖尿病 17 例,高脂血症 27 例。NHT 组男性 47 例,女性 18 例;年龄 54-76 岁,平均(60.89±1.53)岁;梗死体积 4-13 cm³,平均(7.91±1.94)cm³;合并症:高血压 34 例,糖尿病 16 例,高脂血症 30 例。两组的上述资料相比,差异无统计学意义(P>0.05)。此次研究已经获得了医院伦理委员会批准同意。

1.2 方法

1.2.1 治疗方法 两组均根据患者的实际病情给予个性化的治疗,主要措施包含静脉溶栓和抗血小板的聚集,并应用抗凝和脑保护剂,以及他汀类药物。HT 组在确诊后,应立刻停止静脉溶栓和抗凝治疗,不再服用抗血小板的聚集、扩张血管、改善微循环的药物,适时给予降压及控制血糖等处理。

1.2.2 HT 的判断标准 患者在发病后首次进行影像学检查时未见出血灶,但入院治疗 7d 时复查其头颅 CT 显示存在以下 HT 情况:出血型脑梗死或脑实质出血,具体表现为梗死边缘存在小点状出血或梗死区内存在片状出血或存在血肿及占位效应。

1.3 观察指标

两组患者均在入院后第 2 d 采集其空腹静脉血 4 mL,给予 10 min 3000 r/min 的离心后提取血清,应用购自日本日立公司的 7180 型全自动生化反应分析仪及配套试剂测定低密度脂蛋白胆固醇(Low-density lipoprotein cholesterol, LDL-C)、高密度脂蛋白胆固醇(High-density lipoprotein cholesterol, HDL-C)、总胆固醇(Total Cholesterol, TC)、甘油三酯(Glycerin trilaurate, TG)、超敏 C-反应蛋白(Hypersensitive C-reactive protein, hs-CRP)、同型半胱氨酸(Homocysteine, Hcy),相关操作严格按照试剂盒说明书进行。分别采集两组患者在溶栓前、溶栓后 3 d 及溶栓后 7 d 的晨间空腹静脉血 3 mL,给予 15 min 3000 r/min 的离心后提取血清,应用酶联免疫法检测血清 MMP-9 的水平,试剂盒购自武汉博士德公司,操作严格按照试剂盒说明书进行。根据美国国立卫生研究院卒中量表(National Institutes of Health Stroke Scale, NIHSS)^[10]对两组患者溶栓前、溶栓后 3d 及溶栓后 7 d 的神经功能进行评分。此量表共有 11 个条目,总分为 42 分,分值越高则表示患者的神经损伤越严重。通过门诊复查的方式随访 6 个月,应用 Barthel 指数量表^[11]对患者预后生活情况进行评价,其中 Barthel 指数总分为 100 分,分值越高,表示患者的日常生活能力也越好,记录死亡人数。分析患者血清 MMP-9 水平与其 NIHSS 评分、Barthel 指数、LDL-C 及 TC 水平的相关性。

1.4 统计学方法

通过 SPSS21.0 统计软件实施处理分析,死亡率、性别比例等计数资料用(%)表示,其比较采用 χ^2 检验。实验室指标、MMP-9 水平、NIHSS 评分等计量资料用($\bar{x} \pm s$)表示,其比较采用 t 检验。各指标与 MMP-9 水平的相关性分析应用 Spearman 法进行评价,检验标准设置为 $\alpha=0.05$ 。

2 结果

2.1 两组实验室指标的对比

HT 组 LDL-C 及 TC 水平均低于 NHT 组(P<0.05);两组患者 HDL-C、TG、hs-CRP 及 Hcy 水平相比,差异无统计学意义(P>0.05),见表 1。

表 1 两组实验室指标的对比($\bar{x} \pm s$)

Table 1 Comparison of laboratory indicators of two groups ($\bar{x} \pm s$)

Groups	n	LDL-C (mmol/L)	HDL-C (mmol/L)	TC(mmol/L)	TG(mmol/L)	hs-CRP(mg/L)	Hcy(μ mol/L)
HT group	65	2.19± 0.63	1.43± 0.41	3.69± 0.96	1.46± 0.67	1.19± 0.56	8.86± 1.21
NHT group	65	2.73± 0.52	1.38± 0.53	4.47± 1.32	1.59± 0.81	1.24± 0.63	9.15± 1.17
t	-	6.067	0.769	3.467	0.766	0.578	1.389
P	-	0.000	0.443	0.001	0.445	0.564	0.167

2.2 两组血清 MMP-9 水平对比

两组患者在溶栓前、溶栓后 7 d 的血清 MMP-9 水平均低

于溶栓后 3 d(P<0.05);HT 组患者在溶栓前、溶栓后 3 d、溶栓后 7 d 的血清 MMP-9 水平均高于 NHT 组(P<0.05),见表 2。

表 2 两组血清 MMP-9 水平对比($\mu\text{g/L}$, $\bar{x} \pm s$)

Table 2 Comparison of serum MMP-9 level in two groups ($\mu\text{g/L}$, $\bar{x} \pm s$)

Groups	n	Before thrombolytic	3 d after thrombolysis	7 d after thrombolysis
HT group	65	325.69 $\pm$ 98.17*	427.54 $\pm$ 126.39	346.72 $\pm$ 101.68*
NHT group	65	236.71 $\pm$ 87.65*	322.75 $\pm$ 106.27	236.14 $\pm$ 93.49*
t	-	5.451	5.116	18.887
P	-	0.000	0.000	0.000

Note: compared with 3d after thrombolysis, *P<0.05.

2.3 两组 NIHSS 评分的对比

HT 组患者在溶栓前、溶栓后 7 d 的 NIHSS 评分低于溶栓后 3 d, NHT 组溶栓后 3 d 的 NIHSS 评分低于溶栓前, 但高于

溶栓后 7 d (P<0.05); HT 组患者在溶栓前、溶栓后 3 d、溶栓后 7 d 的 NIHSS 评分均高于 NHT 组 (P<0.05), 见表 3。

表 3 两组 NIHSS 评分的对比(分, $\bar{x} \pm s$)

Table 3 Comparison of NIHSS scores in two groups (scores, $\bar{x} \pm s$)

Groups	n	Before thrombolytic	3 d after thrombolysis	7 d after thrombolysis
HT group	65	15.26 $\pm$ 4.87*	17.63 $\pm$ 5.19	13.98 $\pm$ 4.32*
NHT group	65	8.86 $\pm$ 3.45*	7.32 $\pm$ 3.53	6.15 $\pm$ 2.37*
t	-	8.646	13.243	12.812
P	-	0.000	0.000	0.000

Note: compared with 3 d after thrombolysis, *P<0.05.

2.4 两组临床预后有关指标的对比

随访 6 个月后, HT 组共有 7 例 (10.77%) 患者因继发性多脏器衰竭而死亡, 剩余 58 例患者的 Barthel 指数为 (43.74 $\pm$ 15.62) 分, NHT 组共有 1 例 (1.53%) 患者因肺癌死亡, 剩余 64 例患者的 Barthel 指数为 (81.36 $\pm$ 12.69) 分, HT 组的死亡率高于 NHT 组 ($\chi^2=4.795$, P=0.029), 而 Barthel 指数低于 NHT 组 (t=19.077, P=0.000)。

2.5 患者血清 MMP-9 水平与其 NIHSS 评分、Barthel 指数、LDL-C 及 TC 水平的相关性分析

根据 Spearman 法分析相关性发现, 患者血清 MMP-9 水平与其 NIHSS 评分呈正相关 (r=0.693, P=0.000), 而与 Barthel 指数、LDL-C 及 TC 水平呈负相关 (r=-0.576, -0.621, -0.605; P=0.003, 0.001, 0.002)。

3 讨论

ACI 在临床上的发病率较高, 且具有相对较高的致残率以及致死率, 因此早期对 ACI 患者进行积极有效的治疗十分必要^[12,13]。溶栓治疗是针对 ACI 患者的一种常用治疗措施, 但其也会使患者机体的凝血功能减弱, 而引起溶栓后 HT 症状^[14-16]。MMP-9 属于一种生化标记物, 其对脑血管类疾病具有一定的指示性作用^[17,18]。对于 ACI 患者而言, 进行溶栓治疗后发生 HT 症状打破了患者的颅内脑血管的生化代谢平衡, 因此监测 MMP-9 意义重大, 并可对患者的预后产生较好的评估价值^[19-21]。

本研究结果显示, HT 组 LDL-C 及 TC 水平均低于 NHT 组 (P<0.05), 这提示了低血脂可能会增加 ACI 患者产生 HT 的风险。分析原因, 可能与 LDL-C 及 TC 的生化机制有关。具体而言, TC 属于细胞膜脂质的一种重要成分, 其对于保持细胞膜的完整性及流动性具有重要的作用, 适量的 TC 对于脑组织中小

血管壁的完整性存在重要的意义, 而低水平的 TC 则可能导致颅内血管自身中层平滑肌有关细胞膜的机构及功能发生变化, 破坏了脑组织中小血管壁的完整性而增大了 HT 的发生风险^[22,23]。而低水平的 LDL-C 则可能通过血管内脂质水平的异常而影响细胞结构, 最终间接地诱发 HT^[24,25]。同时, HT 组患者在溶栓前、溶栓后 3 d、溶栓后 7 d 的血清 MMP-9 水平、NIHSS 评分均高于 NHT 组 (P<0.05), 这提示了 HT 组的血清 MMP-9 水平及 NIHSS 评分明显升高。可能的原因是 MMP-9 能够通过自身的过度表达及高活性地降解颅内微血管的基底膜而破坏了血脑屏障的完整性, 进而参与到 HT 的发生及演变进程^[26,27]。此外, HT 组的死亡率高于 NHT 组, 而 Barthel 指数低于 NHT 组 (P<0.05), 这提示了 HT 组患者的预后相对较差, 原因主要是因为 ACI 患者发生溶栓后 HT 的病情往往更重, 治疗难度增大, 对患者的预后也具有较大影响^[28-30]。最后, 本研究根据 Spearman 法分析相关性发现, 患者血清 MMP-9 水平与其 NIHSS 评分呈正相关, 而与 Barthel 指数、LDL-C 及 TC 水平均呈负相关 (P<0.05), 这也再次证实了 ACI 患者的血清 MMP-9 水平与其预后及血脂水平均具有紧密联系。因此可考虑通过监测血清 MMP-9 水平以较好地评估及预测患者的病情, 改善预后情况。

综上所述, 血清 MMP-9 参与到 ACI 溶栓后 HT 的形成过程中, 其与患者的 NIHSS 评分呈正相关, 而与 Barthel 指数、LDL-C 及 TC 水平均呈负相关, 临床上可通过监测 MMP-9 水平, 从而更好地评估及预测患者的病情及预后。

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