

miR-151a-3p 在急性脑梗死患者血清中的表达及与炎症因子的相关性研究

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【摘要】 目的 探讨急性脑梗死(ACI)患者外周血微小RNA(miRNA)表达的临床意义及与炎症因子的相关性,为其在ACI诊断和治疗方面提供新的依据及思路。方法 采用回顾性研究方法,选择2004年4月至7月武汉大学人民医院神经内科收治的114例首次发病且病程为2~14 d的ACI患者临床资料,以同期年龄、性别相匹配的58例健康体检者为健康组。记录ACI患者的脑梗死危险因素,以及所有研究对象的血清miR-151a-3p、白细胞介素(IL-6、IL-8)、C-反应蛋白(CRP)、肿瘤坏死因子- α (TNF- α)水平。分析血清miR-151a-3p水平与脑梗死面积和分型、梗死原因及炎症因子的关系;并分析不同miR-151a-3p表达水平ACI患者的10年存活率。结果 114例ACI患者中男性59例,女性55例;年龄48~63岁,平均(55.0±6.7)岁;大梗死25例,中梗死26例,小梗死53例,腔隙性梗死10例。按改良急性卒中治疗低分子肝素试验(TOAST)分型,动脉粥样硬化性血栓形成性脑梗死(AT)92例,心源性脑栓塞(CE)10例,小动脉闭塞性脑梗死(SAD)12例。排除脑梗死危险因素对miRNA表达水平的影响后,ACI组血清miR-151a-3p表达水平明显高于健康组($2^{-\Delta\Delta Ct}$: 2.28±1.85比1.27±0.98, $P<0.01$);大梗死组、中梗死组、小梗死组和腔隙性梗死组血清miR-151a-3p表达水平均高于健康组($2^{-\Delta\Delta Ct}$: 1.78±1.02、1.92±1.11、2.22±1.54、2.61±1.82比1.27±0.98,均 $P<0.05$),不同梗死面积组间比较差异无统计学意义;AT组、CE组血清miR-151a-3p表达水平较健康组明显升高($2^{-\Delta\Delta Ct}$: 2.01±1.45、1.99±0.89比1.27±0.98,均 $P<0.05$),而SAD组与健康组比较差异无统计学意义($2^{-\Delta\Delta Ct}$: 1.72±0.30比1.27±0.98, $P>0.05$)。ACI组血清IL-6、IL-8、CRP和TNF- α 水平均明显高于健康组[IL-6(ng/L): 45.21±14.33比39.70±13.15, IL-8(μ g/L): 29.12±14.92比22.50±10.12, CRP(mg/L): 6.61±3.02比5.40±2.75, TNF- α (ng/L): 65.20±16.14比55.70±14.35,均 $P<0.05$]。相关性分析显示,ACI患者血清miR-151a-3p与IL-6、IL-8、CRP、TNF- α 均呈显著正相关(R^2 值分别为0.092、0.055、0.034、0.036,均 $P<0.05$)。miR-151a-3p低表达组患者10年存活率较miR-151a-3p高表达组明显升高[以1.27±0.98为界值,48.57%(17/35)比34.18%(27/79), log-rank=3.411, $P=0.045$]。结论 血清miR-151a-3p水平可提示脑梗死的发病及进展,有可能作为诊断ACI的潜在生物学标志物。

【关键词】 微小RNA-151a-3p; 脑梗死,急性; 炎症因子

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The expression of serum miR-151a-3p in patients with acute cerebral infarction and its correlation with pro-inflammatory factors Chang Hong, Lu Zuneng

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【Abstract】 Objective To investigate the clinical significance of serum microRNA-151a-3p (miR-151a-3p) expression in peripheral blood of patients with acute cerebral infarction (ACI), and to analyze the correlation between miR-151a-3p and related inflammatory factors, in order to obtain new evidence and ideas in the diagnosis and treatment of ACI. **Methods** A retrospective analysis was conducted. The clinical data of patients with ACI admitted to Department of Neurology of People's Hospital of Wuhan University from April to July in 2004 were enrolled. 114 ACI patients with first onset and duration of 2-14 days served as the research objects, and in the same period 58 healthy persons with matched age, and gender served as healthy control group. The risk factors of cerebral infarction

in ACI patients and levels of serum miR-151a-3p, interleukins (IL-6, IL-8), C-reactive protein (CRP), tumor necrosis factor- α (TNF- α) in all the subjects were completely recorded. The correlation between serum miR-151a-3p and the area and type of cerebral infarction, the causes of infarction as well as the inflammatory cytokines was analyzed. The correlation of 10-year survival rate of patients with different expression levels of miR-151a-3p in patients with ACI was analyzed. **Results** A total of 114 patients with ACI were enrolled, with 59 male, 55 female, and age ranged 48-63 years with a mean of (55.0 ± 6.7) years. Large infarction was found in 25 cases, middle sized infarction in 26 cases, small infarction in 53 cases, and lacunar infarction in 10 cases. According to the modified Trial of Org 10172 in acute stroke treatment (TOAST), the patients were classified as thrombotic cerebral infarction (AT) 92 cases, embolism (CE) from cardiac origin 10 cases, and small arterial occlusive cerebral infarction (SAD) 12 cases. After eliminating the influence of cerebral infarction risk factors on the expression level of miRNAs, and compared with that of healthy control group, the level of serum miR-151a-3p expression was significantly increased in ACI group ($2^{-\Delta\Delta Ct}$: 2.28 ± 1.85 vs. 1.27 ± 0.98 , $P < 0.01$); the levels of serum miR-151a-3p in large, middle, small, lacunar infarction groups were markedly up-regulated ($2^{-\Delta\Delta Ct}$: 1.78 ± 1.02 , 1.92 ± 1.11 , 2.22 ± 1.54 , 2.61 ± 1.82 vs. 1.27 ± 0.98 , all $P < 0.05$) with no significant difference among different infarction groups. The serum miR-151a-3p expression in AT and CE groups was significantly higher than that of the healthy control group ($2^{-\Delta\Delta Ct}$: 2.01 ± 1.45 , 1.99 ± 0.89 vs. 1.27 ± 0.98 , both $P < 0.05$), but no significant difference was found between SAD group and healthy control group ($2^{-\Delta\Delta Ct}$: 1.72 ± 0.30 vs. 1.27 ± 0.98 , $P > 0.05$). The levels of serum IL-6, IL-8, CRP and TNF- α in ACI group were all higher than those of healthy control group [IL-6 (ng/L): 45.21 ± 14.33 vs. 39.70 ± 13.15 , IL-8 (μ g/L): 29.12 ± 14.92 vs. 22.50 ± 10.12 , CRP (mg/L): 6.61 ± 3.02 vs. 5.40 ± 2.75 , TNF- α (ng/L): 65.20 ± 16.14 vs. 55.70 ± 14.35 , all $P < 0.05$]. In addition, higher expression of serum pro-inflammatory mediators IL-6, IL-8, CRP and TNF- α were positively correlated with miR-151a-3p (R^2 value were 0.092, 0.055, 0.034, 0.036, all $P < 0.05$). Ten-year survival rate was higher in patients with low expression of miR-151a-3p [with 1.27 ± 1.98 as the boundary, 48.57% (17/35) vs. 34.18% (27/79), log-rank = 3.411, $P = 0.045$]. **Conclusions** Up-regulated serum miR-151a-3p may be involved in the pathophysiology of ACI. Therefore, miR-151a-3p may be used as a reference to predict the severity of neurological deficit in clinic.

【Key words】 microRNA-151a-3p; Acute cerebral infarction; Inflammatory factor

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脑梗死是一种发病率、致残率、病死率均较高的疾病,且发病年龄呈年轻化趋势^[1]。寻找能早期诊断急性脑梗死(ACI)的血液标志物,对识别病因、指导早期临床个体化治疗、预测病情变化和预后都具有重要的临床意义及应用价值^[2]。微小RNA(miRNA)是基因表达调控主要因子之一,参与生物体细胞增殖、分化、凋亡、代谢等生物学过程^[3]。外周血 miRNA 具有不易降解且检测方法敏感、准确等特点,成为临床疾病潜在的诊断、病情鉴别的新型标志物^[4]。本研究通过回顾性分析本院 10 年间收治的 ACI 患者血清 miR-151a-3p 和相关炎症因子的表达变化及其相关性,以期为临床 ACI 诊疗提供指导。

1 资料与方法

1.1 研究对象的选择:采用回顾性研究方法。选择 2004 年 4 月至 7 月本院神经内科收治的首次发病的 ACI 患者为研究对象,病程为 2~14 d,诊断符合文献[5]标准,且经头颅 CT 或磁共振成像(MRI)证实,全部患者为临床首次发作或既往曾有脑梗死发作史、但未遗留后遗症,发病 72 h 内就诊。以同期

在本院门诊进行体检的年龄、性别相匹配的非脑梗死者为健康组。

1.2 伦理学:本研究符合医学伦理学标准,经医院伦理委员会批准,所有治疗均取得过研究对象的知情同意。

1.3 病例分组

1.3.1 按脑梗死面积分组:参照影像学分型方法^[6],以梗死灶最大径作为测量标准,将脑梗死分为大梗死、中梗死、小梗死、腔隙性梗死、多发性梗死。

1.3.2 按照改良急性卒中治疗低分子肝素试验(TOAST)分型分组:根据心脏病病史、心电图、心脏彩超、磁共振血管成像及颈部血管彩超等结果,参照改良 TOAST 分型方法^[7]分为动脉粥样硬化性血栓形成性脑梗死(AT)、心源性脑栓塞(CE)、小动脉闭塞性脑梗死(SAD)、其他原因所致脑梗死(SOE)、不明原因脑梗死(SUE)。

1.3.3 按血清 miR-151a-3p 水平分组:以健康者 miR-151a-3p 表达水平为基准将 ACI 患者分为低、高表达组。

1.4 观察指标:记录研究对象的性别、年龄;脑梗

死危险因素,包括高血压、糖尿病、高血脂、冠心病、心房颤动(房颤)、吸烟史、饮酒史及脑血管病家族史等;血清 miR-151a-3p 表达值〔采用实时定量反转录-聚合酶链反应(qRT-PCR)检测〕;血清炎症因子白细胞介素(IL-6、IL-8)、C-反应蛋白(CRP)、肿瘤坏死因子-α(TNF-α)水平〔采用酶联免疫吸附试验(ELISA)检测〕;10年生存情况。

1.5 统计学分析:使用 SPSS 12.0 软件进行数据处理,计量资料以均数 ± 标准差($\bar{x} \pm s$)表示,组间比较采用 *t* 检验;采用 Kaplan-Meier 法绘制 10 年生存曲线;*P* < 0.05 为差异有统计学意义。

2 结果

2.1 各组临床资料比较:共入选 ACI 组患者 114 例,其中男性 59 例,女性 55 例;年龄 48 ~ 63 岁,平均(55.0 ± 6.7)岁;脑梗死面积:大梗死 25 例,中梗死 26 例,小梗死 53 例,腔隙性梗死 10 例,多发性梗死 0 例;改良 TOAST 分型:AT 92 例,CE 10 例,SAD 12 例。健康组 58 例,其中男性 29 例,女性 29 例;年龄 49 ~ 64 岁,平均(56.0 ± 5.7)岁。两组性别和年龄差异无统计学意义(均 *P* > 0.05),说明基线资料均衡,具有可比性。

2.2 ACI 患者血清 miR-151a-3p 表达及相关危险因素分析

2.2.1 ACI 组与健康组比较(图 1A):ACI 组血清 miR-151a-3p 表达水平明显高于健康组,差异有统计学意义(*P* < 0.01)。

2.2.2 脑梗死危险因素对 miRNA 水平的影响:ACI 患者 miR-151a-3p 表达水平在高血压与非高血压人群、糖尿病与非糖尿人群、房颤与非房颤人群、高血脂与非高血脂人群之间差异均无统计学意义(均 *P* > 0.05)。

2.2.3 不同脑梗死面积组比较(图 1B):大梗死组、中梗死组、小梗死组和腔隙性梗死组患者血清 miR-151a-3p 表达水平均高于健康组(均 *P* < 0.05);而不同面积梗死组之间差异无统计学意义(均 *P* > 0.05)。

2.2.4 不同分型梗死组比较(图 1C):与健康组比较,SAD 组血清 miR-151a-3p 表达水平无明显升高(*P* > 0.05),而 AT 组、CE 组血清 miR-151a-3p 表达水平明显升高(均 *P* < 0.05)。

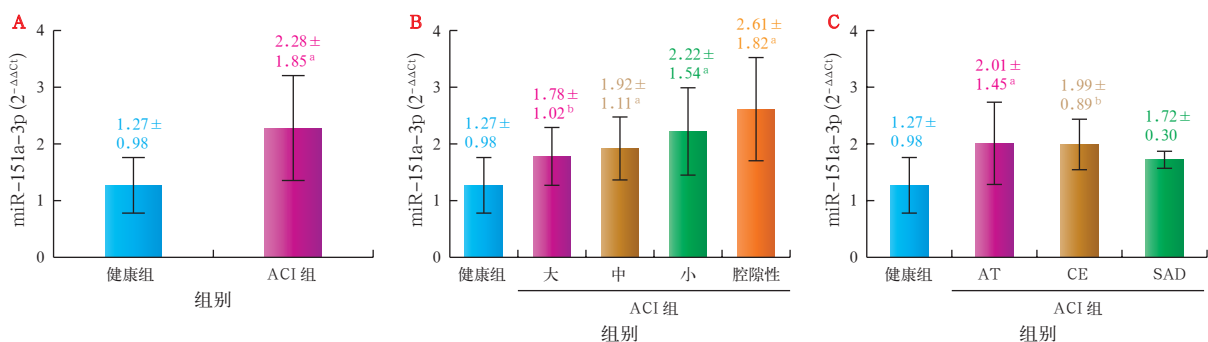
2.3 ACI 组与健康组血清炎症因子水平比较(表 1):ACI 组血清 IL-6、IL-8、CRP 和 TNF-α 水平均明显高于健康组(均 *P* < 0.05)。

组别	例数(例)	IL-6(ng/L)	IL-8(μg/L)	CRP(mg/L)	TNF-α(ng/L)
健康组	58	39.70 ± 13.15	22.50 ± 10.12	5.40 ± 2.75	55.70 ± 14.35
ACI 组	114	45.21 ± 14.33 ^a	29.12 ± 14.92 ^b	6.61 ± 3.02 ^a	65.20 ± 16.14 ^b

注:ACI 为急性脑梗死,IL-6、IL-8 为白细胞介素-6 和 8,CRP 为 C-反应蛋白,TNF-α 为肿瘤坏死因子-α;与健康组比较,^a*P* < 0.05,^b*P* < 0.01

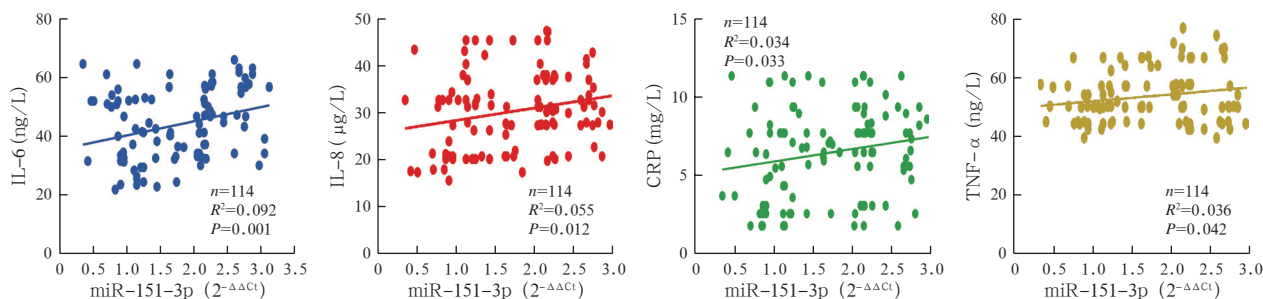
2.4 ACI 患者血清 miR-151a-3p 与炎症因子的相关性分析(图 2):血清 miR-151a-3p 与 IL-6、IL-8、CRP、TNF-α 均呈显著正相关(均 *P* < 0.05)。

2.5 ACI 患者 miR-151a-3p 表达水平与存活率的关系(图 3):以健康组血清 miR-151a-3p 表达水平 1.27 ± 0.98 作为 ACI 患者高、低表达组分组的分界值,高表达 miR-151a-3p 组患者 10 年存活率明显低于 miR-151a-3p 低表达组〔34.18% (27/79) 比 48.57% (17/35), log-rank = 3.411, *P* = 0.045〕。进一步证明了 miR-151a-3p 低表达的 ACI 患者 10 年存活率较高。



注:A 为 ACI 组与健康组比较,B 为不同梗死面积组与健康组比较,C 为不同脑梗死分型组与健康组比较;AT 为动脉粥样硬化性血栓形成性脑梗死,CE 为心源性脑栓塞,SAD 为小动脉闭塞性脑梗死;与健康组比较,^a*P* < 0.01,^b*P* < 0.05

图 1 急性脑梗死(ACI)组与健康组血清微小 RNA-151a-3p(miR-151a-3p)表达水平比较



注: miR-151a-3p 为微小 RNA-151a-3p, IL-6、IL-8 为白细胞介素 -6 和 8, CRP 为 C-反应蛋白, TNF-α 为肿瘤坏死因子-α

图2 急性脑梗死患者血清 miR-151a-3p 表达与血清炎症因子水平的相关性分析

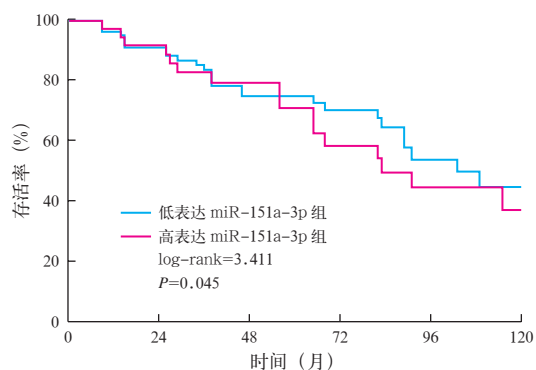


图3 不同血清微小 RNA-151a-3p(miR-151a-3p) 表达水平急性脑梗死患者 10 年生存曲线

3 讨论

ACI 是由于供应脑部血液的动脉出现粥样硬化和血栓形成,使管腔狭窄甚至闭塞,最终导致局灶性急性脑供血不足而发病^[8]。研究显示,miRNA 在神经系统发育和功能上起重要作用^[9],有人推测 miRNA 可能会像其他物质一样从破碎的组织细胞或凋亡细胞中被动漏出,也可能从受损组织细胞主动分泌进入血循环,而后者被认为是主要方式^[10]。临床研究发现,脑梗死患者外周血中 miRNA 存在差异性表达^[11-12]。Jeyaseelan 等^[13]测定大鼠脑组织 miRNA 表达时发现,脑缺血后 24 h 脑组织 miRNA 表达谱即发生特异性改变,且在缺血脑组织中高表达的一些 miRNA 可在血液中被检测到,并与脑缺血损伤标志物基质金属蛋白酶-9(MMP-9)表达变化一致。Liu 等^[14]研究发现,缺血性卒中成年大鼠脑组织和血液中的 miR-298、miR-155、miR-362-3p 表达均上调或下调了 2 倍以上。Zeng 等^[15]发现,急性缺血性脑卒中患者外周血 miR-210 表达水平较对照组显著下降,尤其在发病后 7 d 和 14 d 变化更为明显,预后好组显著高于预后差组,研究者认为外周血 miR-210 是缺血性脑卒中临床诊断和预后的一种新生物标志物。Zhao 等^[16]研究显示,miR-23a-3p

能够减弱脑梗死小鼠的氧化应激损伤。本研究发现,miR-151a-3p 在 ACI 患者血清中高表达,且在一定程度上可反映脑梗死的进展和病因情况。

有研究显示:炎症是 ACI 的关键因素^[17];IL-1、TNF、细胞间黏附分子-1(ICAM-1)、CRP 等炎症因子均参与了 ACI 的发生发展^[18-19];脑梗死患者血清中 TNF-α、IL-2、ICAM-1 和转化生长因子-β1(TGF-β1)等水平明显升高,可促进炎症反应及血管斑块的形成,且其水平与病情严重程度及梗死面积相关^[20-21]。本研究发现,ACI 患者血清 IL-6、IL-8、CRP 及 TNF-α 均表现出较高的水平,说明其炎症状态较为明显;相关性分析也显示,miR-151a-3p 与 IL-6、IL-8、CRP 及 TNF-α 均呈正相关;10 年生存曲线分析显示,miR-151a-3p 低表达能够提高 ACI 患者的存活率。所有这些都从临床实践的角度证明了血清 miR-151a-3p 表达水平对 ACI 的诊断和病情判断具有重要作用。

综上,本研究表明血清 miR-151a-3p 可能作为 ACI 的一种潜在生物学标志物用于临床诊断和病情判断。由于本研究例数少,其结论的推广有待大样本的前瞻性临床研究证实。

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• 科研新闻速递 •

一项有关脓毒症确诊后第1天及第3天弥散性血管内凝血评分的前瞻性观察研究

有关弥散性血管内凝血(DIC)评分在脓毒症患者中的作用尚无系统研究,为此,最近韩国学者进行了一项前瞻性观察研究,旨在了解脓毒症确诊后第1天(24 h内)和第3天(48~72 h)DIC的发病情况。DIC参照国际血栓和止血协会(ISTH)的诊断标准。该研究从381例筛选对象中共纳入了219例患者,脓毒症确诊后第1天和第3天DIC发病率分别为27.9%和30.1%。与未合并肺炎的患者相比,合并肺炎的脓毒症患者第1天DIC发病率相对较低,但其院内病死率较高。尽管第1天和第3天DIC评分与患者院内病死率没有明显相关性,但DIC评分的变化趋势与患者病死率明显相关[优势比(OR)=1.862, 95%可信区间(95%CI)=1.061~3.266]。第3天DIC评分较第1天DIC评分更能准确预测院内病死率($P<0.001$),尤其是在未合并肺炎的脓毒症患者。然而DIC评分在目前现有预后评分的基础上并不能提高对脓毒症患者死亡的预测能力。因此,研究人员据此得出结论:合并肺炎的脓毒症患者第1天DIC发病率较低,但其病死率更高。

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