血清 PDGF 及 SDF-1 水平与急性脑梗死患者脑侧支循环建立的相关性研究

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摘 要：目的 探讨血清血小板源性生长因子（platelet-derived growth factor，PDGF）及基质细胞衍生因子-1（stromal-derived factor-1，SDF-1）水平与急性脑梗死患者脑侧支循环建立的相关性。**方法** 选择2017年3月～2019年3月在陕西省核工业二一五医院神经内科住院治疗的82例急性脑梗死患者作为研究对象，依据脑血管造影检查对患者脑侧支循环状态的评估分级分为侧支循环良好组（Fine collateral circulation，FCC组）50例和侧支循环不良组（poor collateral circulation，PCC组）32例，选择35例同期体检健康者作为对照组。采用罗氏MODULARP800全自动生化分析仪检测空腹血糖、血清总胆固醇（total cholesterol，TC）及三酰甘油（triglyceride，TG）水平。血清PDGF及SDF-1水平采用酶联免疫吸附法检测，通过磁共振成像（magnetic resonance imaging，MRI）检查得到患者的梗死体积，依据美国国立卫生研究院卒中量表（National Institutes of Health Stroke Scale Score，NIHSS）评价患者入院时的神经功能状态（NIHSS评分），比较分析以上指标的变化与急性脑梗死后脑侧支循环建立的相关性。**结果** 在对照组、FCC组和PCC组中，血清PDGF（pg/ml）和SDF-1（pg/ml）水平分别为163.20±33.19，127.21±27.32，62.37±13.56和596.32±102.37，965.29±323.17，1 231.37±423.67。FCC组和PCC组的SDF-1水平与对照组比较明显增加，其中PCC组SDF-1水平增高更显著，差异均有统计学意义（$F=98.67$，$P=0.000$）。FCC组和PCC组的PDGF水平与对照组比较明显降低，其中PCC组的PDGF水平降低更显著，差异有统计学意义（$F=65.23$，$P=0.000$）。在对照组、FCC组和PCC组中，收缩压（mmHg）、空腹血糖（mmol/ml）、TC（mmol/ml）及TG（mmol/ml）水平分别为118.23±13.46，147.06±15.19，153.79±16.57；4.92±0.97，6.33±1.10，6.51±1.23；4.23±0.57，4.49±0.67，4.46±0.70和1.29±0.37，1.33±0.36，1.42±0.41。在FCC组和PCC组中，NHISS评分（分）和梗死体积（cm^3）分别为11.49±5.27，26.75±9.37和6.39±5.03，11.07±7.96。FCC组和PCC组的收缩压和空腹血糖水平与对照组比较显著增加，差异有统计学意义（$F=69.32$，29.26，均$P=0.000$），而FCC组和PCC组间的收缩压和空腹血糖水平比较差异无统计学意义（$P>0.05$）。对照组、FCC组和PCC组间的TC和TG水平比较差异无统计学意义（$F=0.37$～0.97，均$P=1.000$）。PCC组的NHISS评分及梗死体积显著高于FCC组（$t=43.20$～63.27，均$P=0.000$）。在FCC组和PCC组中，血清PDGF和SDF-1水平呈负相关性（$r=-0.802$，-0.826，均$P<0.01$）。在PCC组和FCC组中，PDGF水平分别与NHISS评分和梗死体积呈负相关性，而SDF-1水平分别与NHISS评分和梗死体积呈正相关性（$r_{PDGF}=-0.839$，-0.847，均$P<0.01$；$r_{SDF-1}=0.818$，0.837，均$P<0.01$）。**结论** 分析PDGF和SDF-1与急性脑梗死患者脑侧支循环建立的相关性可以预测侧支循环的发生，评价脑梗死的病情进展，并为脑梗死的诊治研究提供新的线索。

关键词：急性脑梗死；脑侧支循环；美国国立卫生研究院卒中量表（NIHSS）评分；梗死体积；血小板源性生长因子；基质细胞衍生因子-1

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Study on the Correlation between Levels of MMP-9 and SDF-1 in Serum and the Establishment of Cerebral Collateral Circulation in Patients with Acute Cerebral Infarction

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Abstract: Objective To investigate the correlation between levels (platelet-derived growth factor, PDGF) and stromal-de-

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rived factor-1 (SDF-1) in serum and the establishment of collateral circulation in patients with acute cerebral infarction. **Methods** 82 patients with acute ischemic stroke hospitalized in Department of Neurology in 215 Hospital of Nuclear Industry of Shaanxi Province from March 2017 to March 2019 were selected as the study subjects. According to the evaluation classification of cerebral collateral circulationby by cerebral angiography, the patients were divided into two groups: fine collateral circulation (FCC,50 cases) group and poor collateral circulation (PCC,32 cases) group, 35 healthy subjects were enrolled in the control group. The levels of fasting blood glucose, total cholesterol (TC) and triglyceride (TG) were measured by Roche modularp800 automatic biochemical analyzer. Serum levels of PDGF and SDF-1 were detected by ELISA. The infarct volume was obtained by magnetic resonance imaging (MRI). The NIHSS score was evaluated by the National Institutes of Health Stroke Scale (NIHSS). The correlation between the changes of the above indexes and the establishment of cerebral collateral circulation after acute cerebral infarction was compared and analyzed. **Results** The serum levels of PDGF(pg/ml) and SDF-1(pg/ml) in the control group, FCC group and PCC group were 163.20 ± 33.19, 127.21 ± 27.32, 62.37 ± 13.56 and 596.32 ± 102.37, 965.29 ± 323.17, 1 231.37 ± 423.67, respectively. Compared with the control group, the levels of SDF-1 and PDGF in FCC group and PCC group increased significantly, while the levels of PDGF decreased significantly. The levels of SDF-1 and PDGF in PCC group increased or decreased more significantly(F = 65.23, 98.67, all P = 0.000). In the control group, FCC group and PCC group, the levels of systolic systolic blood pressure (mmHg), fasting blood glucose (mmol/ml), TC (mmol/ml) and TG (mmol/ml) were 118.23 ± 13.46, 147.06 ± 15.19 and 153.79 ± 16.57, 4.92 ± 0.97, 6.33 ± 1.10 and 6.51 ± 1.23, 4.23 ± 0.57, 4.49 ± 0.67, 4.46 ± 0.70 and 1.29 ± 0.37, 1.33 ± 0.36, 1.42 ± 0.41, resperctively. In FCC and PCC groups, NIHSS score(points) and infarct volume (cm^3) were 11.49 ± 5.27, 26.75 ± 9.37 and 6.39 ± 5.03, 11.07 ± 7.96, respectively. The levels of systolic blood pressure and fasting blood glucose increased significantly in FCC group and PCC group compared with in the control group, the difference was statistically significant (F = 69.32, 29.26, all P = 0.000), which between FCC Group and PCC group were not statistically significant (P > 0.05). There were no significant differences in the levels of TC and TG between FCC Group and PCC group (F = 0.37 ~ 0.97, all P = 1.000). The NHISS score and infarct volume in PCC group were significantly higher than those in FCC Group (t = 43.20 ~ 63.27, all P = 0.000). In FCC group and PCC group, serum levels of PDGF and SDF-1 were negatively correlated (r = −0.802, −0.826, P < 0.01). In PCC and FCC groups, PDGF levels were negatively correlated with NHISS scores and infarct volume at admission, while SDF-1 levels were positively correlated with NHISS scores and infarct volume at admission, respectively (r_{PDGF} = −0.839, −0.847, P < 0.01; r_{SDF-1} = 0.818, 0.837, P < 0.01). **Conclusion** Analysis of the correlation between the two markers(PDGF and SDF-1) and the establishment of cerebral collateral circulation in patients with acute cerebral infarction can predict the occurrence of collateral circulation and evaluate cerebral infarction. It also provides new clues for the diagnosis and treatment of cerebral infarction.

Keywords: acute cerebral infarction; cerebral collateral circulation; NIHSS score; infarct volume; PDGF; SDF-1;

急性脑梗死(actite cerebral infarction, ACI)在临床上有较高的发病率和致残率[1]。现阶段的研究发现脑侧支循环与脑梗死的发生、发展和预后关系密切[2]。研究表明,血小板源性生长因子(platelet-derived growth factor,PDGF)及基质细胞衍生因子-1(stromal-derived factor-1,SDF-1)在脑侧支循环开放过程中均起到重要的调节作用[3-4]。本研究通过检测急性脑梗死患者血清PDGF及SDF-1水平,旨在探讨两指标与脑梗死患者的侧支循环状态及预后的相关性。

1 材料与方法

1.1 研究对象 选择2017年3月~2019年3月在陕西省核工业二一五医院神经内科住院治疗的82例急性脑梗死患者作为研究对象。依据脑侧支循环评估分级分为侧支循环良好(fine collateral circulation, FCC)组和侧支循环不良(Poor collateral circulation, PCC)组。FCC组包括50例患者,男性27例,女性23例,年龄62.39 ± 11.43岁,其中有吸烟史者13例,高血压患者34例,糖尿病患者9例。PCC组包括32例患者,男性18例,女性14例,年龄63.17 ± 12.36岁,其中有吸烟史者7例,高血压患者22例,糖尿病患者8例。急性脑梗死的诊断标准依据《中国急性缺血性脑卒中诊治指南2014》[5]。所有患者在发病后24h内入院,均经头部核磁共振成像(magnetic resonance imaging,MRI)检查证实存在责任病灶。排除标准:既往曾发生过脑卒中患者,出血性脑卒中患者,并发颅内占位性疾病或感染者,行溶栓、机械取栓或介入治疗者,并发严重的心肝肾疾病、凝血功能障碍、自身免疫性疾病或肿瘤者。选择35例同期体检健康者作为对照组,男性20例,女性15例,年龄61.90 ± 12.25岁,其中有吸烟史者7例。各组研究对象的吸烟史、性别和年龄比较,差异均无统计学意义(P > 0.05)。本研究已获得陕西省核工业二一五医院医学伦理委员会批准,并得到所有研究对象的知情同意。

1.2 试剂和仪器 空腹血糖、胆固醇(total cholesterol,TC)及三酰甘油(triglyceride,TG)水平检测采用罗氏MODULARP800全自动生化分析仪。SDF-1和PDGF水平检测试剂盒分别由南京森贝伽生物科技有限公司和合肥莱尔生物科技有限公司提供。采用荷兰飞利浦公司生产的INTEGRIS C/V血管机进行数字减影全脑血管造影。采用3.0T Trio siemens磁共振扫描仪完成MRI检查。

1.3 方法

1.3.1 检测方法:收集患者的临床资料,包括性别和年龄以及吸烟史。PDGF和SDF-1水平检测采用酶联免疫吸附法,通过MRI检查结果得到患者的梗死体积。依据美国国立卫生研究院卒中量表(National Institutes of Health Stroke Scale Score,NIHSS)评价急性脑梗死患者入院时的神经功能状态(NIHSS评分)。

1.3.2 脑血管造影检查[6]:所有患者于入院第5天接受脑血管造影。按美国神经介入和治疗神经放射学会/介入放射学会的标准评估分级侧支循环,0级:缺血区无侧支循环形成;Ⅰ级:缺血区周边可见缓慢的侧支循环灌注,但仍可见充盈缺损区;Ⅱ级:缺血区周边可见快速的侧支循环充盈,缺血区内部分血流灌注;Ⅲ级:静脉晚期可见缺血区有缓慢但完全的侧支循环血液充盈;Ⅳ级:侧支循环快速而完全地充盈缺血区域。0~1级被定义为侧支循环不良;2~4被定义为侧支循环良好。

1.3.3 血样采集:脑梗死患者于发病后第5天禁食12h抽取静脉血5ml,对照组于体检时抽取空腹静脉血5ml。将血液样本以3 000 r/min离心,分离血清,用于检测PDGF,SDF-1,空腹血糖,TC及TG水平,所有试验均于2h内完成。

1.4 统计学分析 实验数据采用SPSS22.0统计软件进行分析,以均数±标准差($\bar{x} \pm s$)表示。PDGF,SDF-1,空腹血糖,TC,TG水平及研究对象年龄的组间比较采用单因素方差分析法和q检验分析法。NHISS评分及梗死体积的比较采用t检验分析法。吸烟史及患者性别的组间比较采用χ^2检验分析法。采用Pearson法进行相关分析。以$P<0.05$为差异有统计学意义。

2 结果

2.1 急性脑梗死患者的一般资料分析 见表1。FCC组和PCC组的收缩压和空腹血糖水平与对照组比较显著增加,差异有统计学意义($P<0.01$),而FCC组和PCC组间的收缩压和空腹血糖水平比较差异无统计学意义($P>0.05$)。对照组、FCC组和PCC组间的TC和TG水平比较,差异均无统计学意义(均$P>0.05$)。PCC组的NHISS评分及梗死体积显著高于FCC组,差异均有统计学意义($P<0.01$)。见表1。

2.2 急性脑梗死患者血清PDGF和SDF-1水平分析 见表1。FCC组和PCC组的SDF-1水平与对照组比较明显增加,其中PCC组增加更显著,差异均有统计学意义($P<0.01$)。FCC组和PCC组的PDGF水平与对照组比较明显降低,其中PCC组降低更显著,差异均有统计学意义($P<0.01$)。

表1 急性脑梗死患者一般资料及血清PDGF和SDF-1水平分析 ($\bar{x} \pm s$)

项目	对照组($n=35$)	FCC组($n=50$)	PCC组($n=32$)	F/t	P
收缩压(mmHg)	118.23±13.46	147.06±15.19	153.79±16.57	69.32	0.000
空腹血糖(mmol/ml)	4.92±0.97	6.33±1.10	6.51±1.23	29.26	0.000
TC(mmol/ml)	4.23±0.57	4.49±0.67	4.46±0.70	0.37	1.000
TG(mmol/ml)	1.29±0.37	1.33±0.36	1.42±0.41	0.97	1.000
NHISS评分(分)	——	11.49±5.27	26.75±9.37	63.27	0.000
梗死体积(cm^3)	——	6.39±5.03	11.07±7.96	43.20	0.000
PDGF(pg/ml)	163.20±33.19	127.21±27.32	62.37±13.56	65.23	0.000
SDF-1(pg/ml)	596.32±102.37	965.29±323.17	1 231.37±423.67	98.67	0.000

2.3 相关性分析 在PCC组和FCC组中,血清PDGF和SDF-1水平呈负相关性($r=-0.802,-0.826$,均$P<0.01$)。在PCC组和FCC组中,PDGF水平分别与NHISS评分和梗死体积呈负相关性,而SDF-1水平与NHISS评分和梗死体积呈正相关性($r_{PDGF}=-0.839,-0.847$,均$P<0.01$;$r_{SDF-1}=0.818,0.837$,均$P<0.01$)。

3 讨论

脑侧支循环通常分为一级、二级和三级。一级侧支循环指willis环的动脉段;二级侧支循环指眼动脉和软脑膜动脉,以及其他远端小口径动脉之间的吻合;三级侧支循环通过缺血区域周围的新生血管而形成微血管。研究发现,良好的侧支循环可以提高急性脑梗死患者缺血脑组织的血流灌注,降低相关出血转化的风险,减少组织梗死的数量和体积[7]。脑梗死患者缺血半暗带血流的改善以及神经功能的恢复与微血管新生的范围和程度直接相关,对预后有重要的预测作用[6]。本研究结果显示,FCC组的NIHSS评分较PCC组明显较轻,FCC组的梗死体积较PCC组明显

缩小。提示侧支循环的开放可以促进脑梗死后神经功能的恢复及受损脑组织的修复。

PDGF是一种由A,B肽链构成的具有多种生物学功能的多肽,现已证实PDGF水平的变化与新生血管的形成有关[8]。WANG等[9]的研究表明PDGF与急性脑梗死患者的脑修复有关。他们认为PDGF水平上调可以促进急性脑梗死患者新生神经元的成熟。本研究也印证了WANG等[9]的观点。近年来的实验数据显示PDGF表达减少会引起急性脑梗死患者侧支循环血管的直径减小和数量减少,反之,其高表达则有利于侧支循环血管形成[3]。本研究显示FCC组和PCC组的PDGF水平明显降低,其中PCC组较FCC组显著降低,显示PDGF与脑梗死患者侧支循环的开放程度有关。

既往的研究认为SDF-1及其受体CXCR4和血管内皮生长因子等外源性细胞因子能够诱导内皮祖细胞的募集和动员,从而促进血管新生及缺血脑组织的恢复[4]。WEI等[10]的动物实验表明在脑梗死后SDF-1与其受体CXCR4结合能促进成年鼠神经母细胞向缺血病变部位的迁移,他们进一步地研究显示SDF-1在大鼠梗死病变组织及其周围组织的表达明显上调。采用SDF-1治疗可促进血管内皮生长因子诱导的血管生成,进而增加梗死周围区域的神经及血管的数量。本研究的分析结果显示SDF-1水平分别与脑梗死患者的NHISS评分及梗死体积有显著相关性。进一步地研究结果显示FCC组SDF-1水平较PCC组明显降低,提示SDF-1与脑梗死后的组织修复和功能恢复有关。

综上所述,调节PDGF和SDF-1水平可促进急性脑梗死患者侧支循环的建立,减小梗死体积进而改善神经功能缺损。由于本研究样本量较少,下一步尚可通过动物实验扩大样本量进一步进行研究,旨在为临床治疗急性脑梗死提供更加可靠的证据。

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