

急性缺血性卒中经颅多普勒超声微栓子信号监测 临床研究

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【摘要】目的 探讨大脑中动脉微栓子信号与急性缺血性卒中的相关性,以及单联和双联抗血小板治疗效果。**方法** 采用经颅多普勒超声(TCD)监测129例急性缺血性卒中患者大脑中动脉微栓子信号,单因素和多因素前进法Logistic回归分析筛查微栓子信号阳性危险因素,阿司匹林单药或联合氯吡格雷双联抗血小板治疗,评价药物疗效和预后。**结果** 129例患者中42例(32.56%)微栓子信号阳性。Logistic回归分析显示,高脂血症是微栓子信号阳性的独立危险因素($OR = 0.335, 95\%CI: 0.147 \sim 0.764; P = 0.009$)。经抗血小板治疗后,双抗组患者微栓子信号消失率高于单抗组($\chi^2 = 16.701, P = 0.000$);与治疗前相比,两组患者治疗后NIHSS评分减少($P = 0.000$),与单抗组相比,双抗组患者治疗后NIHSS评分亦减少($P = 0.025$),表明抗血小板治疗有效且双联抗血小板治疗效果优于单抗治疗。**结论** 高脂血症是TCD监测微栓子信号阳性的独立危险因素,双联抗血小板治疗可以阻止微栓子信号形成并改善患者近期预后。

【关键词】 脑缺血; 超声检查,多普勒,经颅; 血小板聚集抑制剂

Clinical study on microembolic signals monitored by transcranial Doppler ultrasonography in acute ischemic stroke

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[Abstract] **Objective** To explore the correlation between microembolic signals (MES) in middle cerebral artery (MCA) and the occurrence of acute ischemic stroke and also evaluate the clinical effect of single and dual antiplatlet therapy. **Methods** A total of 129 cases with acute ischemic stroke were tested by transcranial Doppler (TCD) ultrasonography to detect MES. Univariate and multivariate Logistic regression analysis were adopted to analyze and screen the positive risk factors for MES. Medication effects and prognosis were evaluated by treatment of aspirin and combination therapy of aspirin and clopidogrel. **Results** Among 129 patients, 42 patients (32.56%) were detected MES positive. According to Logistic regression analysis, hyperlipidemia was the independent risk factor of patients with MES positive ($OR = 0.335, 95\%CI: 0.147 \sim 0.764; P = 0.009$). After antiplatelet treatment, the disappearance rate of MES was higher in the dual-therapy treatment group than that in the monotherapy group ($\chi^2 = 16.701, P = 0.000$). The NIHSS score decreased significantly after 14 d of treatment in both groups ($P = 0.000$). The decrease of NIHSS score in dual-therapy group was more than that in monotherapy group ($P = 0.025$). It proves the effectiveness of antiplatelet treatment and the advantage of dual antiplatelet is superior to single antiplatelet. **Conclusions** This study demonstrated that hyperlipidemia is the independent risk factor for MES positive detected by TCD and dual-therapy can inhibit the formation of MES and improve the recent prognosis.

[Key words] Brain ischemia; Ultrasonography, Doppler, transcranial; Platelet aggregation inhibitors

脑血管病发病率、病死率和病残率均较高,其

中缺血性脑血管病发病率逐年增加,脑循环微栓子信号(MES)与缺血性脑血管病之间的关系已引起国内外学者的关注。早在1955年Millikam即提出微栓子信号学说^[1],国内刘建辉^[2]认为,源于不稳定型动脉粥样硬化斑块或附壁血栓的碎片脱落堵塞小

动脉致脑组织缺血。本研究采用经颅多普勒超声(TCD)监测急性缺血性卒中患者大脑中动脉(MCA)微栓子数目,进一步探讨单联或双联抗血小板治疗是否可以抑制微栓子形成及其对患者预后的影响,为大动脉粥样硬化性缺血性卒中患者的个体化治疗和疗效评价提供依据。

对象与方法

一、研究对象

选择2012年10月~2014年8月在安徽省铜陵市立医院住院治疗的急性缺血性卒中患者共129例,均符合1995年第四届全国脑血管病学术会议制定的急性缺血性卒中诊断标准,并经头部CT和(或)MRI证实急性大脑中动脉供血区梗死、CTA和(或)MRA证实大脑中动脉中至重度狭窄;排除非大脑中动脉供血区梗死患者,心源性、血管源性原因引起的缺血性卒中患者,颤窗闭合或无法耐受而未行TCD检查和微栓子信号监测患者,合并活动性消化性溃疡、严重肝肾功能障碍、血小板减少或凝血功能异常、近期手术史患者。男性69例,女性60例;年龄47~86岁,平均(66.98 ± 9.13)岁;入院时美国国立卫生研究院卒中量表(NIHSS)评分1~15分,平均(7.86 ± 2.72)分;高血压64例、糖尿病46例、高脂血症77例。本研究经安徽省铜陵市立医院道德伦理委员会审核批准,所有患者或其家属均知情同意并签署知情同意书。

二、研究方法

1. 经颅多普勒超声检查 采用TCD国内通用标准^[3]诊断颅内动脉狭窄[同时经头部CTA和(或)MRA证实患侧大脑中动脉狭窄],所有患者均于发病24~72 h内行微栓子信号监测,采用美国VIASYS NeuroCare公司生产的SONARA TCD仪,SN12-2193/12-2222型2 MHz双深度脉冲探头。参照文献[3]方法,患者仰卧位,以患侧大脑中动脉为监测部位,双深度脉冲探头获取最佳信号,采用美国Care Fusion公司生产的Spencer头架固定探头,扫描参数为:能量54%,增益12~18 dB,取样容积10 mm,探测距离通道1为60 mm、通道2为52 mm;微栓子信号阈值5 dB,监测时间15~30 min。监测时操作者始终监视显示屏并观察患者异动情况,实时记录微栓子信号。微栓子信号特征符合1995年第九届国际脑血流动力学会议制定的标准^[4]。

2. 统计分析方法 采用SPSS 11.0统计软件进

表1 MES阳性组与MES阴性组患者一般资料的比较

Table 1. Comparison of general data between MES positive patients and MSE negative patients

Item	MES positive (N = 42)	MES negative (N = 87)	χ^2 or t value	P value
Sex [case (%)]			1.704	0.192
Male	19 (45.24)	50 (57.47)		
Female	23 (54.76)	37 (42.53)		
Age ($\bar{x} \pm s$, year)	66.33 ± 9.22	67.30 ± 9.12	-0.562	0.575
NIHSS ($\bar{x} \pm s$, score)	8.45 ± 2.51	7.57 ± 2.78	1.732	0.086
Hypertension [case (%)]	25 (59.52)	39 (44.83)	2.447	0.118
Diabetes [case (%)]	14 (33.33)	26 (29.89)	0.157	0.692
Hyperlipidemia [case (%)]	32 (76.19)	45 (51.72)	7.047	0.008

Two-sample t test for comparison of age and NIHSS, and χ^2 test of comparison of others. NIHSS, National Institutes of Health Stroke Scale,美国国立卫生研究院卒中量表

行数据处理与分析。计数资料以相对数构成比(%)或率(%)表示,采用 χ^2 检验;计量资料以均数±标准差($\bar{x} \pm s$)表示,采用两独立样本的t检验;单抗组与双抗组治疗前后NIHSS评分的比较采用前后测量资料的方差分析。微栓子信号阳性危险因素筛查采用单因素和多因素前进法Logistic回归分析。以 $P \leq 0.05$ 为差异具有统计学意义。

结 果

一、一般资料的比较

129例患者中42例检测到微栓子信号(MES阳性组)、87例未检测到微栓子信号(MES阴性组),两组患者性别、年龄、入院时NIHSS评分以及高血压和糖尿病比例差异均无统计学意义($P > 0.05$),MES阳性组患者高脂血症比例高于MES阴性组($P = 0.008$,表1)。

二、微栓子信号阳性危险因素筛查

以微栓子信号为因变量,性别(赋值为女性=1,男性=0)、年龄、NIHSS评分,以及高血压、糖尿病、高脂血症(赋值均为有=1,无=0)为自变量。单因素Logistic回归分析显示,高脂血症为微栓子信号阳性的危险因素($OR = 0.323$, 95%CI: 0.137~0.764, $P = 0.010$;表2)。将该项自变量进一步代入多因素Logistic回归方程,结果显示,高脂血症是微栓子信号阳性的独立危险因素($OR = 0.335$, 95%CI: 0.147~0.764, $P = 0.009$;表3)。

表2 微栓子信号阳性危险因素的单因素 Logistic 回归分析

Table 2. The univariate Logistic regression analysis of risk factors for MES positive

Variable	b	SE	Wald χ^2	P value	OR value	OR 95%CI
Sex	-0.405	0.404	1.009	0.315	0.667	0.302-1.471
Age	-0.014	0.023	0.372	0.542	0.986	0.943-1.031
NIHSS	0.149	0.079	3.528	0.060	1.160	0.994-1.355
Hypertension	-0.663	0.407	2.651	0.103	0.516	0.232-1.144
Diabetes	-0.438	0.419	1.089	0.297	0.646	0.284-1.469
Hyperlipidemia	-1.129	0.439	6.616	0.010	0.323	0.137-0.764

NIHSS, National Institutes of Health Stroke Scale, 美国国立卫生研究院卒中量表

表4 单抗组与双抗阻患者治疗前后神经功能的比较 ($\bar{x} \pm s$, 评分)

Table 4. Comparison of nerve functions before and after treatment between 2 groups ($\bar{x} \pm s$, score)

Group	N	Before treatment	After treatment
Single anti-platelet	21	7.86 ± 2.59	6.57 ± 3.60
Dual anti-platelet	21	9.05 ± 2.33	3.00 ± 1.34

表3 微栓子信号阳性危险因素的前进法多因素 Logistic 回归分析

Table 3. The forward multivariate Logistic regression analysis of risk factors for MES positive

Variable	b	SE	Wald χ^2	P value	OR value	OR 95%CI
Hyperlipidemia	-1.094	0.421	6.753	0.009	0.335	0.147-0.764
Constant	0.753	0.581	1.680	0.195		

表5 单抗组与双抗组患者治疗前后神经功能的重复测量设计的方差分析表

Table 5. ANOVA for repeated measurement of neurological functions in dual-therapy and monotherapy groups before and after treatment

Source of variation	SS	df	MS	F value	P value
Treatment	29.762	1	29.762	5.460	0.025
Time	282.333	1	282.333	35.224	0.000
Treatment × time	119.048	1	119.048	14.852	0.000
Error between groups	218.048	40	5.451		
Error within group	320.619	40	8.057		

三、单联和双联抗血小板治疗效果的比较

按照随机数字表法将MES阳性患者进一步分为单联抗血小板组(单抗组, 21例)和双联抗血小板组(双抗组, 21例)。在常规治疗基础上, 单抗组予阿司匹林100 mg/d; 双抗组予首次负荷剂量氯吡格雷300 mg和阿司匹林100 mg, 第2天予以氯吡格雷75 mg/d和阿司匹林100 mg/d, 联合治疗7 d后改为氯吡格雷75 mg/d, 共治疗14 d; 两组均予阿托伐他汀钙40 mg/d强化调脂治疗。治疗14 d后再次进行TCD微栓子信号监测和NIHSS评分。经抗血小板治疗后, 双抗组19例微栓子信号消失、单抗组6例微栓子信号消失, 双联抗血小板治疗效果优于单联抗血小板治疗($\chi^2 = 16.701$, $P = 0.000$)。与治疗前相比, 两组患者治疗后NIHSS评分减少($P = 0.000$); 与单抗组相比, 双抗组患者治疗后NIHSS评分亦减少($P = 0.025$; 表4, 5), 表明抗血小板治疗有效且双联抗血小板治疗效果优于单联抗血小板治疗。仅双抗组有1例患者在治疗7 d时出现双下肢少量瘀点, 复查血常规、凝血酶时间(TT)、凝血酶原时间(PT)、活化部分凝血活酶时间(APTT)、纤维蛋白原(FIB)及肝肾功能试验均未见异常, 予停用阿司匹林、继续应用氯吡格雷治疗, 4 d后患者双下肢瘀点消失; 其余患者均未见明显牙龈、皮肤黏膜和消化道出血

等不良反应。刘秀琴^[5]研究显示, 超溶栓时间窗的急性脑梗死患者, 降纤酶组血浆纤维蛋白原水平较治疗前下降且差异具有统计学意义($P < 0.01$), 2周后患者神经功能明显改善($\chi^2 = 6.071$, $P = 0.014$), 降纤酶组出血事件无增加, 提示降纤治疗可能成为急性缺血性卒中的有效手段之一。

讨 论

TCD是研究脑血流动力学的无创技术, 微栓子信号监测已广泛应用于神经科、心血管科等医学领域。Idicula等^[6]对40例平均年龄为70岁的急性缺血性卒中患者发病后1小时的双侧大脑中动脉微栓子信号进行监测, 结果显示, 急性缺血性卒中后微栓子信号中度频繁出现, 有助于急性缺血性卒中的分型诊断。Wong等^[7]也在急性缺血性卒中患者大脑中动脉区检测到微栓子信号。王遐等^[8]的研究显示, 61例急性缺血性脑血管病患者中13例(21.31%)微栓子信号阳性。Hao等^[9]对67例急性缺血性卒中患者进行微栓子信号监测, 其结果显示, 第1天微栓子信号阳性率约为50.75%(34/67)。本研究129例急性缺血性卒中患者中42例微栓子信号阳性, 阳性率约32.56%, 与上述文献报道有所不同, 可能与样本量较小、监测时间滞后, 以及患者性

别、年龄、治疗情况、颅骨厚度和检查者技术水平等有关。

申丽红等^[10]根据颈动脉超声,将73例患者分为有斑块组(44例)和无斑块组(29例),检测血清总胆固醇(TC)、甘油三酯(TG)、低密度脂蛋白胆固醇(LDL-C)水平,并进行脑血管微栓子信号监测,结果显示,有斑块组患者微栓子信号阳性率较无斑块组增加[43.18%(19/44)对6.90%(2/29), $P=0.001$],有斑块组患者高血压($P=0.019$)、高胆固醇血症($P=0.021$)、高低密度脂蛋白血症($P=0.011$)比例明显高于无斑块组。Wu等^[11]研究显示,微栓子信号频率与大脑中动脉狭窄程度和临床症状呈正相关。本研究单因素和多因素前进法Logistic回归分析显示,高脂血症是微栓子信号阳性的独立危险因素($OR=0.335$,95%CI:0.147~0.764; $P=0.009$),与文献报道相一致。

2005年,Markus等^[12]采用TCD微栓子信号监测技术对氯吡格雷联合阿司匹林抗血小板治疗症状性颈动脉狭窄和(或)大脑中动脉狭窄效果进行前瞻性多中心随机双盲临床研究——颈动脉内膜切除术或支架成形术进行血管重建(CaRESS)研究,结果显示,联合应用两种抗血小板药物与单用阿司匹林相比,7天内双联抗血小板治疗微栓子信号阳性率相对减少39.80%,脑卒中复发率也有所下降,提示双联抗血小板治疗在减少微栓子信号数目和临床缺血事件两方面均优于单抗治疗。Assiri等^[13]的研究也证实7天内双联抗血小板治疗可显著减少微栓子信号。苏跃康等^[14]采用双联抗血小板药物治疗观察组,单纯阿司匹林治疗对照组,治疗7天后,两组微栓子信号数目均下降且差异有统计学意义($P<0.05$),双抗组未见出血等不良反应增加。Wang等^[15]在一项多中心随机临床试验中发现,在颅内动脉粥样硬化性缺血性卒中中联合应用两种抗血小板药物(氯吡格雷联合阿司匹林)与单用阿司匹林比较,7天后微栓子信号减少比例明显减少。阿司匹林通过抑制环氧合酶(COX)进而抑制血栓素A2(TXA2)合成,从而抗血小板聚集。氯吡格雷是第2代ADP受体阻断剂,通过抑制ADP诱导的血小板第I和II相聚集发挥,并具有解聚作用,还可与红细胞膜相结合,影响红细胞的变性能力,且具有保护血管内皮及稳定易损斑块的作用^[16]。本研究单抗组和双抗组患者治疗14天后微栓子信号数目均减少,且双抗组微栓子信号消失率高于单抗

组($P=0.000$);与治疗前相比,两组患者治疗后NIHSS评分均减少($P=0.000$),与单抗组相比,双抗组患者治疗后NIHSS评分亦减少($P=0.025$),表明双联抗血小板治疗效果优于单抗治疗。随着神经影像学技术的发展,多模态MRI技术的临床应用可有效评估缺血半暗带,从而使部分患者从溶栓治疗中获益。薛蓉等^[17]在多模态MRI指导下对20例急性缺血性卒中患者进行重组组织型纤溶酶原激活物(rt-PA)溶栓治疗,90天后随访,改良Rankin量表(mRS)评分0~1分14例(70%),2~3分6例(30%),无一例死亡,但该项研究样本量较小,其有效性尚待进一步研究证实。

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中英文对照名词词汇(三)

- 光学相干断层扫描术 optical coherence tomography(OCT)
- 国际疾病分类法-10 International Classification of Disease-10(ICD-10)
- 国际临床化学与检验医学联合会 International Federation of Clinical Chemistry and Laboratory Medicine(IFCC)
- 国际运动障碍学会 Movement Disorder Society(MDS)
- 汉密尔顿抑郁量表 Hamilton Depression Rating Scale(HAMD)
- 核内包涵体 intranuclear inclusions(INIs)
- 核糖核蛋白 ribonucleoprotein(RNP)
- 红细胞沉降率 erythrocyte sedimentation rate(ESR)
- 后部皮质萎缩 posterior cortical atrophy(PCA)
- 后交通动脉 posterior communicating artery(PCoA)
- 琥珀酸脱氢酶 succinate dehydrogenase(SDH)
- 画钟测验 Clock Drawing Test(CDT)
- 还原型烟酰胺腺嘌呤二核苷酸 nicotinamide adenine dinucleotide-reduced(NADH)
- 回波平面成像 echo planar imaging(EPI)
- 回波时间 echo time(TE)
- Glasgow昏迷量表 Glasgow Coma Scale(GCS)
- 霍普金斯词语学习测验 Hopkins Verbal Learning Test(HVLT)
- 肌醇 myo-inositol(mI)
- 肌酸 creatine(Cr)
- 肌酸激酶 creatine kinase(CK)
- 肌酸激酶同工酶 creatine kinase isoenzyme MB(CK-MB)
- 基于体素的形态学分析 voxel-based morphometry(VBM)
- 激励次数 number of excitation(NEX)
- 激励回波探测 stimulated echo acquisition mode(STEAM)
- 急性冠脉综合征 acute coronary syndrome(ACS)
- 加利福尼亚词语学习测验 California Verbal Learning Test(CVLT)
- 加拿大蒙特利尔神经病学研究所 Montreal Neurological Institute(MNI)
- N-甲基-D-天冬氨酸 N-methyl-D-aspartate(NMDA)
- 间碘苄胍 metiodobenzylguanidine(MIBG)
- 简明国际神经精神访谈 Mini-International Neuropsychiatric Interview(MINI)
- 简易智能状态检查量表 Mini-Mental State Examination(MMSE)
- 交感皮肤反应 sympathetic skin response(SSR)
- 胶质纤维酸性蛋白 glial fibrillary acidic protein(GFAP)
- 结蛋白 desmin(Des)
- 进行性多灶性白质脑病 progressive multifocal leukoencephalopathy(PML)
- 进行性核上性麻痹 progressive supranuclear palsy(PSP)
- 经颅磁刺激 transcranial magnetic stimulation(TMS)
- 经颅多普勒超声 transcranial Doppler(TCD)
- 颈动脉内膜切除术或支架成形术进行血管重建研究 Carotid Revascularization using Endarterectomy or Stenting Systems (CaRESS) study