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右向左分流相关隐源性脑卒中的临床特点及病因的探讨

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摘　要

目的：探讨右向左分流(right-to-left shunt, RLS)相关隐源性脑卒中(cryptogenic stroke, CS)患者的临床特点及引起卒中的可能机制。方法：收集2018年10月至2020年9月于我院神经内科住院并根据TOAST (Trial of Org 10172 in Acute Stroke Treatment)分型诊断为CS的患者。所有CS患者均行经颅多普勒发泡试验检查，根据有无RLS，分为RLS+组和RLS−组。比较两组人口学特征、脑血管病危险因素、血小板及凝血功能，心脏的结构与功能等方面的特点。结果：共纳入111例CS患者，RLS+组55例，RLS−组56例。血管病危险因素方面，RLS+组高血压、糖尿病及高血脂比例更少($P < 0.05$)，而合并偏头痛、卒中、短暂性脑缺血发作(transit ischemic attack, TIA)及下肢深静脉血栓比例更多($P < 0.05$)。血小板及凝血功能方面，RLS+组平均血小板体积(11.34 ± 1.34 vs 10.29 ± 0.82, $P < 0.001$)、D-二聚体含量(965.27 ± 1609.90 vs 320.54 ± 175.38, $P = 0.004$)均显著高于RLS−组。心脏结构与功能方面，RLS+组左房前后径(4.03 ± 0.40 vs 3.69 ± 0.34, $P < 0.001$)、肺动脉收缩压(30.82 ± 7.31 vs 28.48 ± 4.14, $P = 0.040$)均大于RLS−组。结论：伴RLS的CS患者血管病危险因素少见，但偏头痛、卒中、TIA、下肢深静脉血栓及肺动脉高压病史多见。伴RLS的CS发病可能与RLS患者存在血小板活化、血液高凝、左房扩大有关。

关键词

隐源性脑卒中，右向左分流，经颅多普勒发泡试验，临床特点，发病病因

Clinical Characteristics and Etiology of Cryptogenic Stroke with Right-to-Left Shunt

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Abstract

Objective: To explore the clinic characteristics and pathogenesis of cryptogenic stroke (CS) patients with right-to-left shunt (RLS). Methods: Patients admitted to the Department of Neurology of our hospital from October 2018 to September 2020 and diagnosed as CS according to TOAST classification were enrolled. All CS patients were examined by contrast-enhanced transcranial Doppler test, and were divided into RLS+ group and RLS− group according to the existence of RLS. Demographic characteristics, risk factors of vascular disease, platelet function, coagulation function, structure and function of heart were compared between two groups. Results: A total of 111 CS patients were enrolled, 55 patients in RLS+ group and 56 patients in RLS− group. In terms of risk factors of vascular disease, RLS+ group had less prevalence of hypertension, diabetes and hyperlipidemia ($P < 0.05$), but more prevalence of migraine, stroke, transit ischemic attack (TIA) and lower limb venous thrombosis ($P < 0.05$). In terms of platelet and coagulation function, the average platelet volume (11.34 ± 1.34 vs 10.29 ± 0.82, $P < 0.001$) and D-Dimer content (965.27 ± 1609.90 vs 320.54 ± 175.38, $P = 0.004$) were higher in the RLS+ group than the RLS− group. In terms of the structure and function of the heart, left atrial diameter (4.03 ± 0.40 vs 3.69 ± 0.34, $P < 0.001$) and pulmonary arterial systolic pressure (30.82 ± 7.31 vs 28.48 ± 4.14, $P = 0.040$) were higher in the RLS+ group than the RLS− group. Conclusions: Risk factors for vascular disease are rare in CS patients with RLS, but a history of migraine, stroke, TIA, deep venous thrombosis in the lower extremities, and pulmonary arterial hypertension is more common. The incidence of CS with RLS may be related to platelet activation, blood hypercoagul ability and left atrial enlargement in patients with RLS.

Keywords

Cryptogenic Stroke, Right-to-Left Shunt, Contrast-Enhanced Transcranial Doppler, Clinic Characteristics, Etiology

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1. 引言

隐源性卒中(cryptogenic stroke, CS)指经过标准评估后仍无法明确病因的一类缺血性卒中，约占全部缺血性卒中的 30%~40% [1]。近几年研究表明 CS 可能与卵圆孔未闭(patent foramen ovale, PFO)、隐匿性阵发性房颤、主动脉弓动脉粥样硬化等有关[2]。其中，高达 40%~56%的 CS 患者存在 PFO [3]。PFO 是房间隔发育异常的常见的先天性心脏病，在普通人群的发生率为 10%~27%，当右心腔压力增加(如屏气、Valsalva 动作等)，右心房压力大于左心房时，右房血液经过未闭合的卵圆孔形成心内的右向左分流(right-to-left shut, RLS) [4]。RLS 相关 CS 的发病可能与反常栓塞、PFO 通路内原位血栓形成、PFO 相关的房性心律失常有关[5]，但是具体发病机制仍不清楚。本研究通过比较伴 RLS 的 CS 与不伴 RLS 的 CS

患者的人口学特征、血管病危险因素、血小板功能、凝血功能及心脏的结构与功能等方面的特点，探讨RLS相关CS的可能病因。

2. 资料与方法

2.1. 研究对象

收集2018年10月至2020年9月于青岛大学附属医院神经内科住院的急性脑梗死患者，根据国际类肝素药物治疗急性缺血性卒中试验(the trial of org 10172 in acute stroke treatment, TOAST)分型[6]筛选出CS患者，所有患者均行(contrast-enhanced transcranial Doppler, c-TCD)检查。该研究通过医院伦理委员会审查。

纳入标准：① 年龄 < 55岁；② 急性脑梗死诊断符合1995年第四届全国脑血管病学术会议拟定的诊断标准，并经过头颅磁共振成像检查证实；③ 根据TOAST分型[6]标准筛选CS患者：无责任病灶相关的大动脉粥样硬化狭窄(>50%)或闭塞，不伴心房颤动、心房粘液瘤、严重心脏瓣膜病，小血管病，除外血管炎、动脉夹层、高凝状态及血液系统疾病等其他明确病因的。

排除标准：① 根据TOAST分型[6]标准诊断的其他类型卒中：大动脉粥样硬化型；心源性栓塞型、小血管闭塞型、其他明确病因型。② 合并心脏疾病者(心房颤动、心肌梗死、心房粘液瘤、扩张性心肌病、病态窦房结综合征、严重心脏瓣膜病等)；③ 合并严重感染、严重肝肾功能障碍、自身免疫系统疾病、恶性肿瘤、脑出血、癫痫及妊娠等。

2.2. 资料收集

患者入院后完善血生化、颅脑MRI及MRA、心电图、动态心电图、经胸超声心动图(transthoracic echocardiography, TTE)、下肢血管超声检查。回顾患者的电子病历，收集患者的年龄、性别、体质量指数、吸烟史、饮酒史、高血压、糖尿病、高血脂、偏头痛、卒中/短暂性脑缺血发作(transit ischemic attack, TIA)及下肢静脉血栓史。血小板及凝血功能指标：血小板数目、平均血小板体积(mean platelet volume, MPV)、C-反应蛋白、凝血酶原时间、活化部分凝血活酶时间、凝血酶时间、纤维蛋白原、D-二聚体。反应心脏结构与功能的TTE参数：左室舒张末期内径、左室收缩末期内径、室间隔厚度、左室后壁厚度、左心房前后径、左室射血分数、肺动脉收缩压。

2.3. c-TCD检查方法

采用中国德力凯公司EMS-9EB型经颅多普勒超声诊断仪。嘱患者取仰卧位，2.0MHZ探头于左侧颞窗探测大脑中动脉血流。指导患者练习标准Valsalva动作，使大脑中动脉收缩期峰值血流速度降低25%。于左侧肘正中静脉留置针穿刺建立静脉通路，连接三通管，并与两支20 ml注射器相连。一支注射器装有9 ml生理盐水和1 ml空气。另一支注射器回抽患者1滴肘静脉血，于两支注射器间反复推注20次混匀，制备成激活生理盐水，快速弹丸式注入肘静脉。此过程操作三次，第一次于平静呼吸时注入，第二、三次注入5 s后开始行Valsalva动作并持续10 s，每次至少间隔2 min，观察20 s内的微栓子信号数目并记录最多的一次。

2.4. RLS的诊断及分组标准[7]

根据有无RLS分为RLS−组与RLS+组。RLS−，无微栓子信号；I级，1~10个微栓子信号；II级11~25个微栓子信号；III级，>25个微栓子信号但未形成雨帘；IV级，形成雨帘。I~IV级为RLS+。检查结果由1名经验丰富的TCD医师和1名神经科医生判断。

2.5. 统计学方法

应用 SPSS25.0 软件进行统计分析，计量资料用均数±标准差($\bar{x} \pm s$)表示，两组间比较采用独立样本 t 检验。计数资料用频数(n)和百分比(%)表示，组间比较采用χ^2 检验或 Fisher 精确检验。$P < 0.05$ 为差异有统计学意义。

3. 结果

3.1. 临床特征

研究期间共收治急性缺血性脑梗死患者 783 例，筛选 123 例 CS 患者(年龄 ＜55 岁)。排除 12 例因颞窗通透不良、意识障碍或不能配合完成 Vasalva 动作而未行 c-TCD 检查者，最终 111 例患者纳入本研究。其中，RLS+组 55 例，RLS−组 56 例。两组患者临床特征比较发现，RLS+组脑血管病危险因素(高血压、糖尿病、高血脂)更少见($P < 0.05$)，而偏头痛、卒中、TIA、下肢深静脉血栓更多见($P < 0.05$) (表 1)。

Table 1. Clinical characteristics of RLS+ group and RLS− group
表 1. RLS+组和 RLS−组临床特征

特征	RLS+ (n = 55)	RLS− (n = 56)	t/χ^2 值	*P*
年龄(岁)	46.9 ± 6.9	45.2 ± 7.0	1.223	0.224
男性[例(%)]	41 (74.5)	48 (85.7)	2.178	0.140
BMI (kg/m^2)	25.12 ± 2.64	25.73 ± 2.61	−1.218	0.226
吸烟[例(%)]	13 (23.6)	15 (26.8)	0.146	0.702
饮酒[例(%)]	22 (40)	26 (46.4)	0.467	0.494
高血压[例(%)]	15 (27.3)	26 (46.4)	4.371	0.037
糖尿病[例(%)]	8 (14.5)	19 (33.9)	5.663	0.017
高血脂[例(%)]	13 (23.6)	24 (42.9)	4.613	0.032
偏头痛[例(%)]	19 (34.5)	7 (12.5)	7.518	0.006
卒中/TIA [例(%)]	17 (30.9)	8 (14.3)	4.394	0.036
DVT [例(%)]	5 (9.1)	0 (0)	5.331	0.027

注：BMI，体质量指数；TIA，短暂性脑缺血发作；DVT，下肢深静脉血栓。

3.2. 血小板及凝血功能检测

两组比较，RLS+组 MPV 更大(11.34 ± 1.34 vs 10.29 ± 0.82, $P < 0.001$)，D-二聚体含量更高(965.27 ± 1609.90 vs 320.54 ± 175.38, $P = 0.004$)。而血小板数目、C-反应蛋白、凝血酶原时间、活化部分凝血活酶时间、凝血酶时间、纤维蛋白原无统计学差异($P > 0.05$) (表 2)。

Table 2. Platelet and coagulation function between RLS+ group and RLS− group
表 2. RLS+组与 RLS−组血小板及凝血功能

指标	RLS+ (n = 55)	RLS− (n = 56)	t 值	*P* 值
PC (10^9/L)	210.04 ± 49.69	231.07 ± 71.43	−1.798	0.075
MPV (fl)	11.34 ± 1.34	10.29 ± 0.82	4.971	<0.001
C-RP (mg/L)	1.68 ± 4.49	2.08 ± 4.87	−0.448	0.655
PT (sec)	11.70 ± 2.43	11.50 ± 1.32	0.540	0.590

Continued

APTT (sec)	29.70 ± 4.59	29.55 ± 5.35	0.156	0.876
TT (sec)	17.97 ± 1.27	18.16 ± 1.38	−0.759	0.450
FIB (g/L)	2.80 ± 0.78	2.75 ± 0.90	0.311	0.756
D-D (ng/ml)	965.27 ± 1609.90	320.54 ± 175.38	2.979	0.004

注：PC，血小板数目；MPV，平均血小板体积；C-RP，C 反应蛋白；PT，凝血酶原时间；APTT，活化部分凝血活酶时间；TT，凝血酶时间；FIB，纤维蛋白原；D-D，D-二聚体。

3.3. 心脏结构与功能

两组比较，RLS+组左心房前后径更大(4.03 ± 0.40 vs 3.69 ± 0.34, $P < 0.001$)，肺动脉收缩压更高(30.82 ± 7.31 vs 28.48 ± 4.14, $P = 0.040$)。而左室舒张末期内径、左室收缩末期内径、室间隔厚度、左室后壁厚度、左室射血分数无统计学差异($P > 0.05$) (表 3)。

Table 3. Cardiac structure and function in the RLS+ group and RLS− group
表 3. RLS+组与 RLS−组心脏结构与功能

参数	RLS+ (n = 55)	RLS− (n = 56)	t 值	*P*
LVDd (cm)	4.68 ± 0.26	4.68 ± 0.42	0.020	0.984
LVDs (cm)	2.98 ± 0.24	3.05 ± 0.27	−1.442	0.152
IVS (cm)	1.09 ± 0.14	1.10 ± 0.24	−0.340	0.735
LVPW (cm)	1.02 ± 0.09	1.06 ± 0.22	−1.145	0.255
LAD (cm)	4.03 ± 0.40	3.69 ± 0.34	4.643	<0.001
LVEF (%)	63.84 ± 2.56	63.70 ± 2.77	0.276	0.783
PASP (mmHg)	30.82 ± 7.31	28.48 ± 4.14	2.076	0.040

注：LVDd，左室舒张末期内径；LVDs，左室收缩末期内径；IVS，室间隔厚度；LVPW，左室后壁厚度；LAD，左心房前后径；LVEF，左室射血分数；PASP，肺动脉收缩压。

4. 讨论

本研究共纳入 111 例 CS 患者，55 例(49.5%)患者发现存在 RLS，这与既往研究基本一致[8]。RLS+组脑血管病危险因素(高血压、糖尿病、高血脂)显著低于 RLS−组，而偏头痛、卒中、TIA 病史、下肢深静脉血栓的比例显著高于 RLS−组。既往研究显示伴 RLS 的 CS 患者年龄更小，合并脑血管病的危险因素(高血压、高胆固醇血症、吸烟)更少，而偏头痛更常见[9]。我们的另一项研究也显示 RLS 与偏头痛相关[10]。也有研究显示与无分流的患者相比，少量分流者更少患有高血压，大量分流者血液胆固醇水平更低[11]。反常性栓塞量表(risk of paradoxical embolism, RoPE)是评估 PFO 与缺血性卒中相关性的风险预测量表，患者年龄越低、血管危险因素(高血压、糖尿病、吸烟)越少、无卒中/TIA 病史、皮层梗死的影像学表现，就越提示缺血性卒中与 RLS 相关[12]。而且，本研究通过 TTE 检查还发现 RLS+组肺动脉压高于 RLS−组。肺动脉高压与 RLS 互为因果[13]。一方面，RLS 可以引起肺动脉高压，另一方面，肺动脉高压可以导致右心房压力增高，使左心房侧的原发隔被推开，引起卵圆孔继发开放，出现 RLS [14]。

本研究发现 RLS+组 MPV 显著高于 RLS−组。既往研究显示 PFO 封堵之后 MPV 下降[15]，少量 RLS 的患者比无 RLS 者 MPV 大[11]，MPV 是血小板活化的生物标志物[16]。因此，我们推测 RLS 引起 CS 的原因与血流经过未闭合卵圆孔时血流动力学改变形成的剪切力促进了血小板活化，血小板活化参与了

RLS 相关脑卒中的发病机制。本研究发现 RLS+组有 5 例患者存在下肢深静脉血栓，且 D-二聚体含量显著高于 RLS−组。D-二聚体是反映机体纤溶和高凝状态的分子标志物之一，D-二聚体含量显著增高提示血液存在高凝状态、深静脉血栓形成、纤溶系统亢进及凝血因子过度消耗。反常栓塞被认为是 RLS 引起脑卒中的主要机制[17] [18] [19]。一项荟萃分析显示凝血功能障碍是 PFO 相关缺血性卒中的决定因素[20]。因此，CS 患者要注意静脉系统及高凝状态检查，如：小腿静脉、骨盆静脉、蛋白 C、蛋白 S、抗凝血酶 III、同型半胱氨酸、抗心磷脂抗体及狼疮抗凝物等。对于伴有 RLS 但没有发现静脉血栓，尤其是青年卒中患者，需警惕遗传性和获得性血栓形成，如：凝血酶原 G2010A 和 V 因子的 Leiden 基因突变[21]。

左房的大小是心脏结构重塑的标志，与房颤、心血管疾病及栓塞性卒中的风险增加相关[22] [23]。左房的大小可通过评估左房前后径、面积、左房体积指数表示[24]。荟萃分析表明，左房直径每增加 1 cm，卒中风险增加 24% [25]。并且左房中－重度扩大，是卒中复发的独立预测因素[26]。本研究显示 RLS+组左房前后径显著高于 RLS−组。研究表明左房扩大会使左心耳血流速度降低，血流停滞，促进血栓形成[27]。Lee 等[28]发现 PFO 的患者，左房体积指数会增加，出现小的皮层梗死的机会较大。研究还显示当 PFO 封堵后，左房扩大会逆转，左房的大小与静息型 RLS、大量 RLS 及房间隔膨出瘤(Atrial septal aneurysm, ASA)有关[29]。此外，研究表明 TTE 检查左房扩大可以预测经食管超声心动图(transesophageal echocardiography, TEE)检查的 90%的左房血栓，证明了 TTE 检查左房扩大作为 TEE 检查左房血栓的筛查工具的实用性[30]。

PFO 通路内原位血栓形成是 RLS 相关卒中的另一机制。研究表明由于 PFO 存在，左右心房间形成通道样的结构，压力差减小，血液在通道内流速减慢甚至停滞进而形成血栓，当栓子清除能力减弱时可在 PFO 内形成原位血栓，导致脑栓塞[31]。RLS 相关 CS 还与房性心律失常有关[32]。Berthet 等[33]研究发现 PFO 或 ASA 患者中 58%的患者存在持续时间超过 60 秒、有效不应期和心房传导时间异常的诱导性房颤，而无 PFO 或 ASA 患者中这一比例为 25%。Mahfouz 等[8]研究认为，CS 伴 PFO 的患者左房的僵硬度和房性非同步化运动显著增加，发生心律失常的比例更高。Cotter 等[34]研究报道 CS 合并 PFO 患者房间隔阻滞和心房易损性增加，P 波持续时间延长，提出房间隔的牵张或压力是其发病机制。一些高危 PFO 的解剖结构也与 CS 有关，如：长隧道型的 PFO (>15 mm)、PFO 直径 ≥ 2 mm、静息型或大量右向左分流、合并 ASA (膨出房间隔至少 15 mm)、房间隔摆动幅度过大(≥10 mm)、过大的下腔静脉瓣(厚度 ≥ 1 mm 且在右心房突出 ≥ 10 mm)、希阿里氏网[35]。

综上所述，RLS 与 CS 的发病密切相关，临床工作中应该对 CS 进行 RLS 的筛选，明确 RLS 相关的卒中的临床特点，可以为卒中的预防提供有效的治疗靶点。但本研究为小样本的单中心研究，存在一定局限性，将来仍需增加样本量对 RLS 与 CS 之间的临床特点进行进一步研究。

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