

· 临床论著 ·

神经内科重症监护室中重症急性缺血性脑卒中患者小腿肌间静脉血栓发生率与危险因素

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摘要: 目的 探讨神经内科重症监护室中重症急性缺血性脑卒中(AIS)患者小腿肌间静脉血栓(CMVT)发生率并分析其危险因素。方法 回顾性分析2018年4月至2021年12月于南京鼓楼医院神经内科重症监护室治疗的重症AIS患者,发病7 d内行下肢深静脉超声检查,根据是否存在新发CMVT,分为无CMVT组(non-CMVT组, n=144)和CMVT组(n=49)。分析重症AIS患者入院后CMVT的发生率及相关危险因素。结果 重症AIS患者CMVT发生率为24.38%(49/201)。CMVT组患者年龄高于non-CMVT组[(74.53±9.81)岁 vs (69.19±14.10)岁, t=2.455, P=0.015]。CMVT组心房颤动病史患者的比例更高(44.90% vs 29.17%, χ²=4.082, P=0.043)。CMVT组D-二聚体水平高于non-CMVT组[8.71 (1.58, 5.67) mg/L vs 3.09 (0.89, 3.89) mg/L, Z=2.132, P=0.038]。单因素logistic回归分析示,年龄(OR=0.175, 95%CI: 0.035~0.309, P=0.015)、心房颤动病史(OR=0.145, 95%CI: 0.004~0.281, P=0.044)、D-二聚体(OR=0.242, 95%CI: 0.104~0.370, P<0.01)是CMVT发生的影响因素。多因素logistic回归分析显示D-二聚体是重症AIS患者并发CMVT的独立影响因素(OR=1.053, 95%CI: 1.005~1.104, P=0.030)。结论 高龄、心房颤动病史、高D-二聚体促进重症AIS患者并发CMVT,且D-二聚体水平升高是独立危险因素。

关键词: 急性缺血性脑卒中; 小腿肌间静脉血栓形成; 重症监护室; D-二聚体; 心房颤动; 神经内科

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Incidence and risk factors of calf muscular venous thrombosis in patients with severe acute ischemic stroke in NICU

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Abstract: Objective To investigate the incidence of calf muscular venous thrombosis (CMVT) and analyze its risk factors among patients with severe acute ischemic stroke (AIS) in the Neurological Intensive Care Unit (NICU).

Methods A retrospective analysis was conducted on patients with severe AIS treated in the NICU of Nanjing Drum Tower Hospital from April 2018 to December 2021. Lower extremity deep vein ultrasound examination was conducted in patients within 7 days of onset. According to the presence or absence of new CMVT, the patients were divided into non-CMVT group ($n=144$) and CMVT group ($n=49$). The incidence of CMVT and its related risk factors among patients with severe AIS were analyzed. **Results** The incidence of CMVT among patients with severe AIS was 24.38% (49/201). The age of patients in the CMVT group were older than that in the non-CMVT group [(74.53±9.81) years vs (69.19±14.10) years, $t=2.455$, $P=0.015$]. Proportion of patients with atrial fibrillation history was higher in the CMVT group (44.90% vs 29.17%, $\chi^2=4.082$, $P=0.043$). D-dimer levels in the CMVT group were significantly higher

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than that in the non-CMVT group [8.71 (1.58, 5.67) mg/L vs 3.09 (0.89, 3.89) mg/L, $Z = 2.132$, $P = 0.038$]. Univariate logistic regression analysis showed that age ($OR = 0.175$, 95%CI: 0.035–0.309, $P = 0.015$), history of atrial fibrillation ($OR = 0.145$, 95%CI: 0.004–0.281, $P = 0.044$), and D-dimer ($OR = 0.242$, 95%CI: 0.104–0.370, $P < 0.01$) were correlated with the occurrence of CMVT. Multivariate logistic regression analysis showed that D-dimer was independently associated with CMVT in patients with severe AIS ($OR = 1.053$, 95%CI: 1.005–1.104, $P = 0.030$).

Conclusion Advanced age, history of atrial fibrillation, and high level of D-dimer promote the occurrence of CMVT among patients with severe AIS, and elevated D-dimer is an independent risk factor.

Keywords: Acute ischemic stroke; Calf muscular venous thrombosis; Intensive care unit; D-dimer; Atrial fibrillation; Department of Neurology

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重症急性缺血性脑卒中(acute ischemic stroke, AIS)是神经内科重症监护室(Neurological Intensive Care Unit, NICU)最常见的疾病之一。重症AIS常合并很多并发症,其中静脉血栓栓塞症(venous thromboembolism, VTE)是其最常见、潜在致命但可预防的并发症,包括深静脉血栓形成(deep venous thrombosis, DVT)和肺栓塞(pulmonary embolism, PE)^[1]。小腿肌间静脉血栓(calf muscular venous thrombosis, CMVT)是指在比目鱼肌和腓肠肌的静脉中形成的血栓。长期以来,普遍对VTE较为重视,神经重症的患者CMVT的筛查率和治疗率都很低。虽然CMVT临床表现较隐匿,多数患者无症状,但CMVT一旦进展可蔓延至其他深静脉,甚至进展为PE。有研究发现,CMVT是AIS患者下肢DVT的最常见类型,发生率高达27.53%^[2],6%的CMVT患者可进展为其他类型的DVT和PE^[3],同时严重影响患者早期床边康复的开展,是重症AIS患者预后不良的重要危险因素。目前,关于NICU中重症AIS患者CMVT的发生率及相关危险因素的研究较少。本研究旨在调查NICU中重症AIS患者CMVT的发生率及相关危险因素,为NICU中重症AIS患者CMVT的早期发现及危险因素的防治提供临床参考。

1 资料与方法

1.1 研究对象 采用回顾性研究方法,纳入2018年4月至2021年12月南京大学医学院附属鼓楼医院NICU收治的重症AIS患者。根据是否存在新发CMVT,将患者分为两组:CMVT组和non-CMVT组。本研究经过南京大学医学院附属鼓楼医院伦理委员会审查及批准(批号:2018-091)。

1.2 纳入和排除标准 纳入标准:(1)入住NICU的经颅脑计算机断层扫描(CT)或磁共振成像(MRI)扫描明确诊断为AIS;(2)重症AIS定义为美国国立卫生研究院卒中量表(NIHSS)≥15分;(3)AIS起病

时间为24 h;(4)CMVT定义为在比目鱼肌和腓肠肌的静脉中形成的血栓;(5)入院即时双下肢深静脉超声检查未见血栓形成。排除标准:(1)既往有下肢VTE病史;(2)入院前长期使用抗凝药物等致患者凝血障碍病史;(3)血液疾病病史;(4)严重肝肾疾病病史;(5)恶性肿瘤病史;(6)3个月内有骨折且导致长期卧床病史;(7)入院前有其他原因所致长期卧床病史。

1.3 下肢静脉血栓评估 本研究入组患者均常规行双下肢彩色超声(DUS)检查。(1)入院及时行首次下肢深静脉DUS检查,排除既往DVT;(2)入组患者于起病7 d内完善DUS检查,行下肢DVT评估。由经验丰富的同一位超声医生进行检查并诊断。

1.4 临床资料及实验室检查收集 年龄、性别、住院号、吸烟史、饮酒史、心房颤动(房颤)史、入院时血红蛋白、C-反应蛋白、D-二聚体、凝血指标、白蛋白、血脂指标、同型半胱氨酸(Hcy)、NIHSS评分等资料。

1.5 统计学方法 采用SPSS25.0统计软件对数据进行分析。计量资料符合正态分布者用 $\bar{x} \pm s$ 表示,使用成组t检验;不符合正态分布者以中位数(上下四分位数)[$M(P_{25}, P_{75})$]表示,组间比较使用秩和检验;计数资料以例(%)表示,使用 χ^2 检验或Fisher确切概率检验。相关及危险因素的分析,分别使用单因素和多因素logistic回归分析。 $P < 0.05$ 为差异有统计学意义。

2 结 果

2.1 入组患者的临床诊断 2018年4月至2021年12月,NICU共收治重症AIS患者217例,排除起病时有陈旧性静脉血栓患者14例、资料不完善2例,初步纳入201例。201例中,起病7 d内共检出DVT阳性患者57例,其中胫后静脉3例,股静脉1例,腘静脉4例,CMVT患者49例。最终,本研究共纳入193例患者,其中CMVT组49例,non-CMVT组144例。在重症AIS的患者中,起病7 d内,CMVT检出率为

24.38% (49/201)。

2.2 两组一般资料比较 CMVT 组的年龄大于 non-CMVT 组 ($P=0.015$)，CMVT 组有房颤病史者比例更高 (44.90% vs 29.17%， $P=0.043$)。见表 1。

2.3 两组相关实验室指标比较 CMVT 组 D-二聚体水平较 non-CMVT 组明显增高，差异有统计学意义 ($P=0.038$)。两组其余实验室指标比较，差异均无统计学意义 ($P>0.05$)。见表 2。

2.4 影响 CMVT 发生的单因素和多因素 logistic 回归分析 选取表 1、表 2 中组间比较 $P<0.2$ 的变量进行单因素回归分析，以年龄、房颤病史、D-二聚体、白蛋白、Hcy 作为自变量，是否发生 CMVT 作为因变量（赋值：CMVT=1，non-CMVT=0），结果发现年龄、

表 1 两组患者入院时一般资料比较 [例(%)]

Tab. 1 Comparison of general data between two groups of patients at admission [case (%)]

项目	CMVT 组 (n=49)	non-CMVT 组 (n=144)	χ^2/t 值	P 值
男	29(65.90)	85(59.23)	<0.001	0.985
年龄(岁, $\bar{x}\pm s$)	74.53±9.81	69.19±14.10	2.455	0.015
吸烟史	10(20.41)	41(28.47)	1.223	0.269
高血压史	36(73.47)	105(72.92)	0.006	0.940
糖尿病史	16(32.65)	37(25.69)	0.889	0.346
冠心病史	4(8.16)	15(10.41)	0.647 ^a	
房颤病史	22(44.90)	42(29.17)	4.082	0.043
GCS 评分($\bar{x}\pm s$)	10.49±3.20	10.76±3.36	0.486	0.627
NIHSS 评分($\bar{x}\pm s$)	23.00±8.88	22.62±8.83	0.261	0.794
mRS 评分($\bar{x}\pm s$)	4.43±0.50	4.44±0.50	0.108	0.914
瘫痪侧肢体肌力>3	1(2.04)	3(2.08)	1.000 ^a	

注：^aFisher 精确概率检验；GCS 为格拉斯哥昏迷评分；mRS 为改良 Rankin 量表评分。

表 2 两组实验室相关指标比较 ($\bar{x}\pm s$)

Tab. 2 Comparison of relevant laboratory indicators between two groups ($\bar{x}\pm s$)

变量	CMVT 组 (n=49)	non-CMVT 组 (n=144)	Z/t 值	P 值
D-二聚体(mg/L) ^a	8.71(1.58,5.67)	3.09(0.89,3.89)	2.132	0.038
白蛋白(g/L)	37.36±3.71	38.51±3.90	1.804	0.073
血小板($\times 10^9/L$)	197.61±62.45	189.63±66.89	0.733	0.464
白细胞($\times 10^9/L$)	9.26±2.12	9.75±3.16	1.227	0.222
血红蛋白(g/L)	127.0±22.18	130.7±21.50	1.032	0.303
PT(mmol/L)	12.19±1.89	11.83±1.95	1.146	0.255
ALT(U/L) ^a	18.95(10.50,23.50)	21.21(11.00,23.15)	0.944	0.347
AST(U/L)	26.40±17.61	23.19±14.50	1.150	0.254
Hcy(μmol/L)	15.19±5.92	17.76±10.20	1.664	0.098
三酰甘油(mmol/L)	1.14±1.52	1.18±0.72	0.410	0.683
总胆固醇(mmol/L)	4.12±1.11	4.12±1.07	0.029	0.977
HDL-C(mmol/L)	1.14±0.38	1.11±0.31	0.577	0.564
LDL-C(mmol/L)	2.40±0.90	2.43±0.89	0.159	0.873

注：^a 表示数据形式为 $M(P_{25}, P_{75})$ ；PT，凝血酶原时间；ALT，丙氨酸氨基转移酶；AST，门冬氨酸氨基转移酶；HDL-C，高密度脂蛋白胆固醇；LDL-C，低密度脂蛋白胆固醇。

房颤病史、D-二聚体是 CMVT 发生的影响因素 ($P<0.01$)。进一步行多因素 logistic 回归分析结果示，高 D-二聚体与重症 AIS 患者并发 CMVT 独立相关 ($P=0.030$)，而年龄 ($P=0.136$) 和房颤病史 ($P=0.289$) 并非 CMVT 发生的独立影响因素。见表 3。

表 3 CMVT 发生因素的 logistic 回归分析

Tab. 3 Logistic regression analysis of the occurrence factors of CMVT

因素	单因素		多因素	
	OR(95%CI)	P 值	OR(95%CI)	P 值
年龄	0.175(0.035~0.309)	0.015	1.023(0.993~1.053)	0.136
房颤病史	0.145(0.004~0.281)	0.044	0.669(0.319~1.405)	0.289
D-二聚体	0.242(0.104~0.370)	<0.001	1.053(1.005~1.104)	0.030
白蛋白	-0.129(-0.266~0.012)	0.073		
Hcy	-0.139(-0.277~0.005)	0.058		

3 讨 论

NICU 中 AIS 患者多伴有肢体瘫痪，常需长期卧床，因此，下肢 DVT 是其最常见的并发症，而 DVT 易引发 PE，危及生命。神经内科脑卒中患者中 DVT 的发生率：国外为 5% ~ 20%^[4-6]，国内为 12.4% ~ 22.7%^[7-8]。近期国内研究发现脑卒中致重度瘫痪患者下肢 DVT 检出率为 34.88%^[9]。但目前的研究主要集中于股静脉、腘静脉等非肌间静脉所致 DVT，对于 CMVT 的研究和发病率较少报道。

本研究通过对 201 例 NICU 中重症 AIS 患者完善下肢深静脉 DUS 检查，下肢 DVT 的检出率为 28.36% (57/201)，其中 CMVT 的发生率为 24.38% (49/201)，占下肢 DVT 的 85.96% (49/57)。因此，CMVT 是下肢 DVT 最常见的类型^[10-11]。多数 CMVT 临床表现较隐匿，且重症 AIS 患者多无法表达其不适，因此极易被忽略。文献报道，5% ~ 10% 的患者如未及时处理，可进展为 PE^[12-14]。近期国内文献报道 CMVT 合并 PE 的发生率高达 10.9%^[15]。此外，因 CMVT 的脱落风险，床边康复的开展受到限制，严重影响患者的康复治疗和神经功能恢复。综合以上两个方面，对于 NICU 中重症 AIS 患者 CMVT 的筛查具有重要的临床意义。

近期研究通过构建脑卒中康复期患者 CMVT 发生的预测模型发现，脑卒中患者 CMVT 的发病率随着年龄的增长而增加^[16-17]，这可能与随着年龄增加，下肢肌力减弱，比目鱼肌和腓肠肌的肌肉泵作用减弱明显有关^[18-20]。与上述研究相似，本研究表明，NICU 中重症 AIS 患者年龄越大越容易发生 CMVT；笔者观察发现，瘫痪侧肌力对 CMVT 的形成影响不大，可能与本研究中纳入的为 NICU 中重症 AIS 患

者,瘫痪侧肢体肌力均显著减弱有关。

近年来通过对重度瘫痪的脑卒中患者下肢 DVT 危险因素分析发现,房颤增加下肢 DVT 形成风险^[11],考虑是否与房颤所致 AIS 患者肌力下降有关,故进一步分析了两组瘫痪侧肢体肌力之间的区别,发现并无统计学差异,这可能与入组患者均为重症,肌力下降都十分显著有关。房颤作为最常见的心律失常,随着年龄的增长,其发生率也随之增加^[21]。因其所致的血流速度缓慢、血液高凝状态、心房附壁血栓等,极易引起 DVT^[5]。本研究发现,既往有房颤病史的 NICU 中重症 AIS 患者较易形成 CMVT。提示对有房颤病史的患者需更加关注。

D-二聚体是一种纤维蛋白溶解产物,是非特异性血栓形成指标,当有血栓存在时其会升高^[22]。有研究通过对康复期脑卒中患者分析发现,高 D-二聚体与 CMVT 形成相关^[17],D-二聚体是 CMVT 形成的独立危险因素^[23]。本研究也发现在重症 AIS 患者中 D-二聚体普遍升高,可能与急性期应激相关,但 CMVT 组升高更显著。通过多因素 logistic 回归分析发现,高水平 D-二聚体是 NICU 中重症 AIS 患者 CMVT 形成的独立危险因素。因此,入院时异常升高的 D-二聚体患者需仔细排查 CMVT 的形成。

本研究具有一定的局限性,因本研究为单中心回顾性研究,纳入病例数有限,缺少对预后的评估等,今后应考虑进行多中心、随机对照临床研究,以探索重症 AIS 患者合并 CMVT 的转归、疗效及并发症。

本研究通过对 193 例 NICU 中重症 AIS 患者完善下肢深静脉 DUS 和临床资料分析,发现高龄、房颤病史和高 D-二聚体与 CMVT 的形成相关,且高 D-二聚体是其独立危险因素。为 NICU 医生对早期发现 CMVT 提供了一定的临床参考,应对存在该类风险的患者早筛查、早发现,以减少 CMVT 及严重并发症的发生。

利益冲突 无

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