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• 专题报道 •

急性缺血性脑卒中神经影像学特征的性别差异及其临床意义

邹晨^{1,2,3△}, 张小曦^{3△}, 吴越^{1,2,3}, 杨鹏飞^{1,3}, 刘建民^{1,3*}

1. 上海理工大学健康科学与工程学院, 上海 200093
2. 上海理工大学东方泛血管器械创新学院, 上海 200093
3. 海军军医大学(第二军医大学)第一附属医院脑血管病中心, 上海 200433

[摘要] 性别差异显著影响急性缺血性脑卒中(AIS)的发生风险、临床表现及预后结局。总体而言,男性具有更高的AIS年龄标化发病率,而女性在高龄阶段却有更重的长期神经功能障碍和致残负担。本文系统整合全球疾病负担研究、人群队列与生物样本库、随机对照试验及多中心机械取栓研究的证据,分析性别差异在AIS神经影像学中的表现及其对再灌注治疗的临床意义。现有研究表明,性别相关的脑结构和脑血管影像学特征在AIS发生前即已逐步形成,并在急性期表现为缺血核心范围、侧支循环状态和病灶空间分布的差异。尽管女性与男性在神经血管解剖和病理生理基础方面存在差异,但采用现代影像学标准进行AIS患者选择并对基线特征充分校正后,静脉溶栓和机械取栓的相对疗效在两性别间总体相当。上述证据提示,性别不应作为限制再灌注治疗的依据,但在影像学解读和预后评估中具有重要背景价值。将性别相关影像学特征纳入综合评估框架,有望优化AIS患者分层并制定更加精准和公平的卒中治疗策略。

[关键词] 急性缺血性脑卒中; 性别因素; 神经影像学; 再灌注治疗

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Sex and gender differences in neuroimaging characteristics of acute ischemic stroke and their clinical implications

ZOU Chen^{1,2,3△}, ZHANG Xiaoxi^{3△}, WU Yue^{1,2,3}, YANG Pengfei^{1,3}, LIU Jianmin^{1,3*}

1. School of Health Science and Engineering, University of Shanghai for Science and Technology, Shanghai 200093, China
2. Oriental Pan-Vascular Devices Innovation College, University of Shanghai for Science and Technology, Shanghai 200093, China
3. Neurovascular Center, The First Affiliated Hospital of Naval Medical University (Second Military Medical University), Shanghai 200433, China

[Abstract] Sex and gender differences significantly affect the risk, clinical manifestations, and prognosis of acute ischemic stroke (AIS). Overall, men exhibit higher age-standardized incidence rate of AIS, whereas women bear disproportionate burdens of long-term neurological dysfunction and disability in advanced age. This review synthesizes evidence from Global Burden of Disease Study, population-based cohorts and biobanks, randomized controlled trials, and multicenter mechanical thrombectomy studies, and focuses on sex- and gender-related neuroimaging phenotypes of AIS and their implications for reperfusion therapy. Accumulating data indicate that sex- and gender-related brain structure and cerebrovascular imaging characteristics develop gradually before AIS onset and manifest as differences in ischemic core extent, collateral circulation status, and lesion topography during the acute phase. Although there are sex- and gender-related differences in neurovascular anatomy and pathophysiology, the relative efficacy of intravenous thrombolysis and mechanical thrombectomy is generally comparable between men and women when AIS patients are selected using modern imaging criteria and after adequate adjustment for baseline characteristics. These findings suggest that sex and gender alone should not restrict access to reperfusion therapies; however, such differences remain important contextual considerations for imaging interpretation and prognostic assessment. Incorporating sex- and gender-related neuroimaging features into integrated evaluation frameworks may improve AIS patient stratification and facilitate more precise and equitable stroke care.

[Key words] acute ischemic stroke; sex factors; neuroimaging; reperfusion therapy

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[作者简介] 邹晨, 硕士生. E-mail: zouchen1113@126.com; 张小曦, 博士, 副教授, 副主任医师. E-mail: 18801765148@163.com

△共同第一作者(Co-first authors).

*通信作者(Corresponding author). E-mail: liu118@vip.163.com

尽管脑卒中预防与再灌注治疗不断进步,急性缺血性脑卒中(acute ischemic stroke, AIS)仍是全球主要的死亡和致残原因之一^[1-2]。过去20余年,静脉溶栓和机械取栓的应用显著改善了AIS患者的临床预后,使AIS治疗逐渐由单纯依赖“时间窗”转向以影像学评估为核心的精准决策^[3-4]。在这一背景下,越来越多的研究开始关注生物学性别与社会学性别在脑卒中发生、临床表现及治疗结局中的潜在影响。

流行病学研究表明,男性的缺血性脑卒中年龄标化发病率和死亡率总体更高,而女性多在较高年龄段首次发病,并在整个生命历程中承担更重的长期致残负担^[5-6]。在临床表现方面,女性患者常有较高的发病前神经功能障碍和较重的基线神经功能缺损风险,并可能出现非典型或非局灶性症状,从而延误卒中识别和院前分诊^[7]。尽管早期研究提示女性再灌注治疗率较低,但随着卒中救治流程的规范和对性别差异认识的提高,静脉溶栓和机械取栓应用中的性别差距正在逐渐缩小^[8]。

性别相关的生物学差异可能影响脑血管结构、血管功能及脑组织对缺血的耐受性。雌激素在调控氧化应激、内皮功能及炎症反应中发挥重要作用,女性绝经后激素水平下降可能加速血管老化过程。此外,两性在脑血管解剖结构、侧支循环模式和白质高信号等方面的差异也会影响脑血管储备能力和缺血耐受性^[9-10]。这些长期存在的神经血管基础差异,可能在AIS急性期通过神经影像学特征得以体现。

目前,神经影像学已成为AIS急性期再灌注治疗决策的重要依据。基于CT和MRI对缺血核心、半暗带及侧支循环的评估为静脉溶栓和机械取栓患者选择提供了关键信息,并在延长治疗时间窗及大梗死核心患者管理中发挥重要作用^[11]。然而,性别相关的神经血管基础在多大程度上表现为急性期可识别的影像学差异,以及这些差异如何影响再灌注治疗策略和临床结局,仍缺乏系统整合。本文以性别差异为切入点,系统梳理AIS相关的神经影像学研究进展,并讨论这些证据在再灌注治疗患者选择及预后评估中的潜在临床意义。

1 AIS 流行病学与病理生物学的性别差异

1.1 AIS 流行病学性别差异概述 大量人群队列

及卒中登记研究证实,AIS在发病年龄、基线临床特征及结局方面均存在明显的性别差异^[12-16]。AIS发病率呈现显著的年龄相关性性别差异:年轻成人(20~35岁)女性发病率略高于男性,中年至老年前期男性发病率更高,而在高龄人群中这种差异逐渐减小(图1)^[12,17-20]。除发病率外,两性卒中症状表现亦存在差异。一项纳入58万例患者的meta分析显示,女性常以头痛、意识混乱或眩晕等非典型症状起病,而男性常表现为偏瘫或失语等局灶性神经功能缺损,这可能导致女性院前识别延迟,进而影响急性期救治效率^[21]。

多国卒中登记研究表明,女性患者通常起病年龄更大、发病前神经功能状态较差,且基线神经功能缺损更严重。但在校正年龄及主要合并症后,女性接受静脉溶栓和机械取栓的比例与男性总体相当,在部分研究中甚至略高^[15-16,22-24]。随着卒中救治体系的完善和再灌注治疗策略的普及,两性在治疗可及性和早期临床结局方面的差距正在逐渐缩小^[8]。

综上所述,AIS的流行病学性别差异具有显著年龄依赖性,同时受生物学因素、危险因素暴露水平及医疗体系等多因素影响。

1.2 全球疾病负担研究(Global Burden of Disease Study, GBD)揭示的AIS流行病学性别差异

GBD为理解AIS性别差异提供了宏观流行病学证据。GBD 2013的性别分层分析显示,男性具有更高的AIS年龄标准化发病率和死亡率,而女性在高龄阶段承担更重的致残负担,这与女性存活至卒中高风险年龄段的比例更高、绝对发病人数更多有关^[25]。

覆盖1990—2019年的更新数据表明,尽管两性脑卒中年龄标化发病率整体呈下降趋势,但由于人口老龄化和人口增长,AIS的绝对发病人数和伤残调整寿命年仍持续增加^[26]。在风险构成方面,男性脑卒中更多与吸烟、饮酒及不合理饮食等行为因素相关,而女性的致残负担则多与长期代谢异常暴露(如BMI升高、低密度脂蛋白胆固醇升高)和体力活动不足等相关^[27]。

GBD显示出稳定的AIS分布模式:男性在多数年龄段表现出更高的年龄标化发病率,而女性在高龄阶段承担更大的致残负担。尽管全球脑卒中年龄标化发病率总体下降,但人口老龄化仍推动绝对发病人数持续增加^[28-29]。

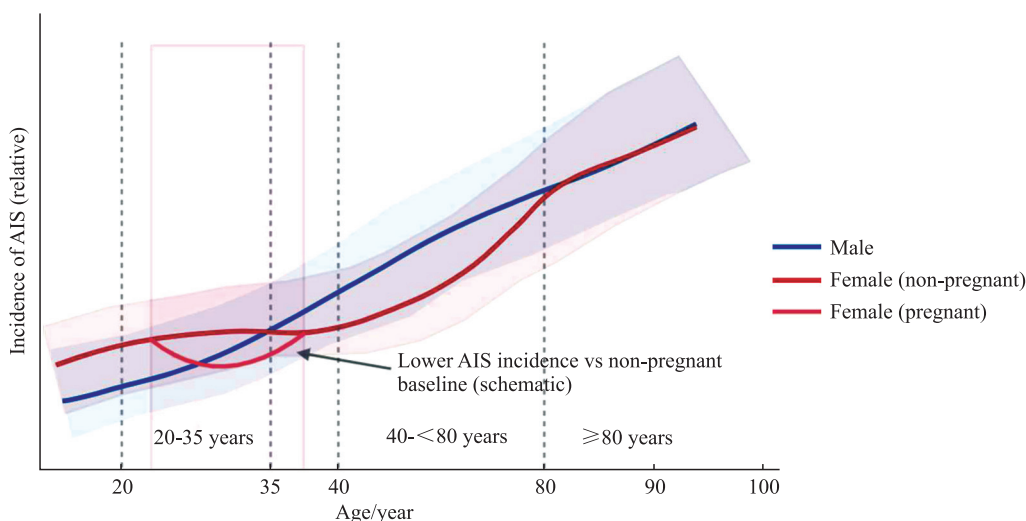


图1 不同性别人群 AIS 发病率的年龄依赖性变化示意图

Fig 1 Schematic illustration of age-specific changes in incidence of AIS by sex and gender

The incidence is slightly higher in females during early adulthood (20-35 years), whereas males show higher incidence during midlife and early older age (approximately 40-<80 years). At advanced ages (≥ 80 years), the sex and gender difference gradually diminishes. The shaded areas indicate the uncertainty of the trend (conceptual confidence interval). The pink shaded region indicates the pregnancy period, representing a transient female-specific life stage during which the incidence is depicted as slightly lower relative to the non-pregnant baseline. This element is included for conceptual illustration only and does not represent a quantitative estimate or imply causal inference. AIS: Acute ischemic stroke.

1.3 AIS 性别差异的病理生物学机制 AIS 的性别差异源于多层次病理生物学机制的共同作用, 这些机制从脑血管缺血易损性、血栓形成倾向及脑组织对缺血损伤的反应等多方面产生影响。

在全身调控层面, 性激素是介导性别差异的重要因素之一。研究表明, 雌激素可通过减轻氧化应激、维持内皮功能及调节炎症反应发挥血管和神经保护作用; 女性绝经后雌激素水平下降与血管老化及心血管代谢风险增加密切相关, 如腹型肥胖、血脂异常及胰岛素抵抗等^[30-31]。这些变化可加速女性动脉粥样硬化进展、增加缺血风险, 在一定程度上解释了男性中年 AIS 发病更为集中、女性高龄首发 AIS 更为多见的流行病学特征。

在中枢神经系统层面, 性激素可通过调节神经血管单元 (neurovascular unit) 及炎症反应影响缺血性脑损伤的发生与演变。研究表明, 雌激素不仅能够促进神经元存活, 还可调节免疫反应、减轻神经炎症, 从而降低继发性脑损伤程度^[32-33]。此外, 血流动力学研究显示, 在青年和中年阶段, 女性整体脑血流量及大脑中动脉血流速度通常高于男性, 这一优势随年龄增长逐渐减弱, 至高龄阶段趋于消失^[34]。

由此可见, 激素调控、脑血管结构与功能差异及炎症反应在多个层面共同作用, 塑造了具有性别特征的神经血管表型, 进而影响女性与男性 AIS 的发病模式与预后转归轨迹。

2 神经影像学视角下 AIS 的性别差异

2.1 脑老化进程与卒中易损性的性别差异 英国生物样本库 (UK Biobank, UKB) 为理解脑卒中性别差异提供了重要的人群神经影像学证据。与聚焦疾病负担的 GBD 不同, UKB 依托标准化多模态 MRI、深度表型信息及长期随访数据, 使性别相关脑结构和微血管表型能够在一般人群中得到系统评估, 为理解卒中易损性及恢复潜力提供了重要线索。

UKB 数据研究显示, 男性总体脑容量、白质体积及皮质表面积普遍高于女性; 校正体型因素后, 女性多数脑区有更高的皮质厚度^[35]。进一步研究发现, 女性绝经后皮质厚度和全脑体积下降加速, 同时伴随白质退行性改变, 这些改变被认为是脑小血管病的重要影像学标志^[36]。上述结果提示, 脑卒中相关性性别差异并非仅由急性期事件决定, 而是在脑老化进程、血管损伤累积及激素水平变化等长期因素作用下逐步形成。

2.2 急性期缺血核心、灌注模式与病灶拓扑结构的性别差异 临床随机对照试验 (randomized controlled trial, RCT) 及其内嵌影像学队列为揭示 AIS 的性别相关影像学差异提供了重要证据。在基于灌注成像的研究中,组织层面的性别差异明显。DEFUSE 3 研究发现,在影像学筛选阶段,女性缺血核心体积通常较小、灌注模式更优,提示在相类似大血管闭塞类型的前提下,女性可能具备更强的微血管灌注储备^[37]。MR CLEAN 试验及其登记研究的补充分析显示,男性更常出现不良的软脑膜侧支循环状态,而在校正年龄及血管危险因素后,女性侧支代偿情况更佳^[38]。

除缺血体积和灌注指标外,体素水平的病灶-症状映射研究还揭示了显著的性别相关病灶拓扑差异。女性梗死灶更易累及皮质功能关键区域或后循环区域,即使病灶体积较小也可能引发明显神经功能缺损;而男性更易出现范围较大的融合性前循环梗死,影像学严重程度与基线美国国立卫生研究院卒中量表 (National Institutes of Health stroke scale, NIHSS) 评分之间呈现更显著的线性关联^[39]。这些结果提示,病灶空间分布对解释性别相关临床表现差异具有重要价值。

此外,血管结构及血栓成分差异也可能参与塑造 AIS 急性期影像学表型。影像学和血管造影研究表明,女性 AIS 患者颅内动脉管径通常更细、走行更为迂曲,血栓成分在纤维蛋白及红细胞比例方面亦可能存在性别差异^[40-41]。

总体而言,急性期 AIS 神经影像学证据提示,性别可通过多个维度影响缺血核心范围、灌注模式、侧支循环状态及病灶空间分布,为理解性别相关临床表现与治疗反应差异提供了重要影像学基础。

3 神经影像学性别差异在 AIS 再灌注治疗中的转化意义

3.1 神经影像学性别差异与静脉溶栓和机械取栓总体疗效的关系 RCT 及大型汇总分析一致证实,在采用现代神经影像学标准筛选患者的前提下,性别并非影响静脉溶栓或机械取栓相对疗效的独立因素。早期合并 RCT 分析提示女性经重组组织型纤溶酶原激活剂溶栓治疗后获益可能大于男性,但这一结果来自非现代影像学筛选框架下的试验数据^[42]。在 MRI 引导的静脉溶栓研究中,WAKE-

UP 试验显示,尽管女性患者年龄更大、基线 NIHSS 评分更高,但关键影像学选择指标并无显著性别差异,且性别未对阿替普酶治疗 90 d 的功能结局 (改良 Rankin 量表评分) 产生显著交互作用^[43],提示不同性别患者在静脉溶栓组织学筛选标准上具有高度一致性。

在机械取栓领域,基于灌注成像筛选的 RCT 亦得到类似结论。DEFUSE 3 研究在影像学筛选阶段观察到女性通常具有较小的缺血核心体积和更有利的灌注特征,但这些组织层面的差异并未转化为性别相关的治疗效应差异^[37]。MR CLEAN 试验及其补充分析同样未发现性别与机械取栓疗效间存在交互作用^[38]。HERMES 个体数据 meta 分析进一步证实,不同性别患者在机械取栓中有相当的相对功能获益^[44]。即便在大体积梗死核心患者中,近期的 SELECT2 和 ANGEL-ASPECT 试验仍观察到两性获益相当^[45-46]。

与 RCT 结果一致,大型多中心观察性研究表明,未经校正时女性可能表现出较差的结局,但在调整年龄、合并症负担及发病前功能状态后,这一差异明显减弱甚至消失^[47-52]。总体而言,既往在静脉溶栓和机械取栓治疗率及早期结局方面存在的性别差异已明显缩小,目前残余差异主要由基线临床特征而非性别特异性再灌注生物学反应所致^[53]。性别相关 RCT 结果及大型登记研究证据见表 1。

3.2 神经影像学性别差异对机械取栓预后评估的影响 尽管 RCT 一致证实性别并不独立影响机械取栓的相对治疗效果,但观察性队列和影像学亚组分析提示,性别可能通过影响影像学指标的预后权重间接塑造患者的神经功能恢复轨迹。

在传统影像学指标方面,机械取栓队列研究显示,即便采用相同影像学阈值,缺血核心体积和侧支循环状态的预后价值仍存在性别差异。在前循环大血管闭塞患者中,尽管两性血管再通率总体相当,但缺血核心体积和净水分摄取量对男性神经功能结局的预测效能更为明显,而女性预后更易受基线神经功能缺损严重程度及关键神经通路受累情况影响^[54]。这一结果提示,病灶空间分布可能在解释性别相关功能恢复差异中发挥重要作用。

侧支循环状态是另一项具有重要预后意义且存在性别差异的影像学指标。既往研究显示,两性成功再灌注比例总体相当,虽然女性侧支代偿评分

较高,但在校正后90 d神经功能结局并未表现出相应优势^[55]。这一现象提示,侧支灌注的保护作用

可能受病灶拓扑结构、慢性微血管损伤负担及发病前神经功能状态等因素共同调控。

表1 AIS再灌注治疗中性别与治疗效果关系的证据总结

Tab 1 Summary of evidence on association between sex and treatment effects in AIS reperfusion therapies

Study	Treatment	Baseline and imaging characteristic differences	Sex-treatment interaction
WAKE-UP (MRI-guided IVT RCT) ^[43]	IVT	Women older, higher baseline NIHSS score	No sex differences in alteplase effect (90-d mRS score)
SITS-ISTR (large IVT registry) ^[49]	IVT	Women older, more severe deficits, longer onset-to-needle time	No independent sex modification after adjustment
AcT trial (posterior circulation analysis) ^[52]	IVT	Women older, greater baseline severity	No sex differences in functional or safety outcomes
Swiss Stroke Registry (registry-based cohort) ^[50]	IVT	Women older, greater pre-stroke disability, higher admission NIHSS score	No stable sex-related interaction with IVT-outcomes
Pooled analyses of IVT trials ^[42]	IVT	Women older, more hypertension, earlier treatment; similar baseline stroke severity	Significant sex-treatment interaction favoring women
US NIS (mild AIS cohort) ^[51]	IVT+/-MT	Women older, worse baseline clinical status	IVT benefit preserved across sexes
MR CLEAN ^[38]	MT	Women older, better collateral status; men more large-artery atherosclerosis	No sex-related modification of MT efficacy
DEFUSE 3 ^[37]	MT	Women smaller ischemic core, smaller perfusion lesions, favorable HIR	No sex difference in treatment effect
SELECT2 ^[45]	MT	Women smaller vessel diameter, often better collaterals	No sex-related treatment difference
HERMES collaboration (7 EVT RCTs) ^[44]	MT	Women older, better collaterals, smaller follow-up infarct volume	No interaction for functional independence, mortality, or sICH
ANGEL-ASPECT (RCT secondary analysis) ^[46]	MT	Women older, higher NIHSS score, more cardioembolic stroke	No sex differences in 90-d outcome, mortality, or sICH

AIS: Acute ischemic stroke; MRI: Magnetic resonance imaging; IVT: Intravenous thrombolysis; RCT: Randomized controlled trial; NIHSS: National Institutes of Health stroke scale; mRS: Modified Rankin scale; LVO: Large vessel occlusion; MT: Mechanical thrombectomy; HIR: Hyperintense region; EVT: Endovascular therapy; sICH: Symptomatic intracranial hemorrhage.

部分研究采用综合影像学框架对缺血组织特征进行整合分析,结果表明,女性在灌注特征相对有利的影像学表型中占比更高,但若功能关键通路最终发生梗死,其残疾程度可能更为严重^[56]。此外,在大脑中动脉M2段闭塞患者中,基于CT灌注错配而非单纯解剖学体积筛选的患者可在不增加出血风险的前提下拓宽机械取栓适应证,这一策略在病灶拓扑结构对神经功能影响更为显著的女性患者中尤具意义^[57]。

在方法学层面,自动化影像分析、影像组学及机器学习正逐渐应用于机械取栓预后评估。多模态影像学研究表明,整合多维影像特征的预测模型可显著提升90 d功能结局预测效能,并在两性中均保持良好校准^[58-59]。在此基础上,部分研究尝试将性别纳入多维风险谱而非单纯作为分层变量,构建更符合临床决策逻辑的预测模型,如GADIS (gender,

age, diabetes mellitus history, infarct volume, and current smoker)评分在取栓队列中表现出良好的区分能力^[60]。

上述研究结果共同揭示,尽管性别本身并不独立影响AIS再灌注治疗效果,但性别相关神经影像学表型差异可能会影响机械取栓术后影像学预后指标的解读。

4 总结和展望

AIS在流行病学特征、病理生物学基础及神经影像学表型方面均存在稳定的性别差异。男性总体发病率更高,女性多在较高年龄段首次发病且承担更重的长期致残负担,这与性激素变化、心血管代谢风险累积和血管老化等因素相关。

神经影像学为理解上述差异在AIS急性期的表现及其临床意义提供了重要视角。女性AIS患者更

常表现为缺血核心体积小、侧支循环状态好,但病灶易累及功能关键区,且常伴随较重的脑小血管病负担和发病前神经功能障碍风险;男性则更易出现大范围前循环梗死、侧支状态不良及以大动脉粥样硬化为主的血管病变背景。这些影像学特征可能影响卒中的基线严重程度、手术操作难度及部分影像学指标(如缺血核心体积和侧支循环状态)的预后权重。然而,多项RCT和大型汇总分析结果一致证实,在采用当代影像学标准筛选患者并校正基线差异后,性别本身不独立影响静脉溶栓或机械取栓的治疗获益。因此,性别更适合作为解读影像学临床指标的重要背景因素,而非限制再灌注治疗的依据。

未来研究应从单纯描述性别差异转向探索如何在卒中影像学和治疗决策中合理运用这些差异。首先,应在大型前瞻性卒中队列和机械取栓登记研究中系统纳入生物学性别及社会学性别因素,并推动多模态影像的标准化采集与分析。其次,需建立聚焦卒中性别差异的多中心协作网络,形成统一影像协议和标准化数据要素,提升研究结果的可比性和可重复性。此外,对于纳入性别因素后的影像学阈值、复合风险评分及人工智能决策支持工具,仍需通过前瞻性研究验证其对治疗决策、神经功能结局及医疗公平性的影响。总体而言,将生物学性别及社会学性别因素系统纳入卒中影像学解读和机械取栓决策,并通过高质量证据加以验证,有望在不降低治疗可及性的前提下进一步提升AIS再灌注治疗的精准性与公平性。

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