

衰弱合并脑血管病研究进展

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【摘要】 衰弱系多系统生理储备和功能下降导致的老年综合征,使老年人对内外环境的应激能力和维持稳态能力下降,并使不良事件风险增加。其中以脑卒中患者衰弱和衰弱前期发生率最高且明显高于非脑卒中患者,而衰弱人群脑血管病患病率亦显著增加且预后不良。本文拟对衰弱与脑血管病之间的潜在关联性进行综述。

【关键词】 蛋白质能量营养不良; 卒中; 老年人; 综述

Research progress of frailty complicated with cerebrovascular disease

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【Abstract】 Frailty is a geriatric syndrome caused by a decrease in multi-system physiological reserve and function, which reduces the elderly's ability to stress the internal and external environment and maintain homeostasis, and increases the risk of adverse health events. The incidence of frailty and pre-frailty in stroke patients is the highest and significantly higher than that in non-stroke patients, while the prevalence of cerebrovascular disease in frailty patients is also significantly increased and the prognosis is worse. This paper intends to review the potential association between frailty and cerebrovascular disease.

【Key words】 Protein-energy malnutrition; Stroke; Aged; Review

This study was supported by the National Key Research and Development Program (No. 2018YFC2000400, 2018YFC2002000) and the National Natural Science Foundation of China (No. 81971102).

Conflicts of interest: none declared

衰弱是一种老年综合征,在社区老年人群中十分普遍,以机体多系统生理储备和功能下降为特点,导致对常见或急性应激源反应能力降低,使跌倒、残疾、住院、全因死亡等不良事件的发生风险增

加^[1-3]。我国老年人群衰弱的患病率为13%~24%,80岁以上人群高达50%^[4]。衰弱使老年人罹患某些非传染性疾病的概率增加,反之慢性病也增加了老年人罹患衰弱的风险^[5-6]。脑血管病是老年人最常见的慢性病,系各种原因所致脑血管病变神经功能障碍的一类疾病总称。目前我国的老龄化趋势日益明显,衰弱和脑血管病患病率随着年龄的增长逐渐升高,因此,探讨衰弱与脑血管病之间的相互关联性对评估老年人脑血管病预后、降低病死率、提高生活质量、实现健康老龄化具有重要意义。

“衰弱”的概念可追溯到2001年Fried等^[7]提出的衰弱表型,此前数十年衰弱一直是老年病学的范畴,最早由O'Brien等^[8]于1968年描述,以社区老年人群对不良事件的反应为特征。目前,衰弱有两种

doi:10.3969/j.issn.1672-6731.2021.01.007

基金项目:国家重点研发计划项目(项目编号:2018YFC2000400);国家重点研发计划项目(项目编号:2018YFC2002000);国家自然科学基金资助项目(项目编号:81971102)

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应用较为广泛的定义方法,即 Rockwood 的“缺陷累积”模型^[9]和 Fried 的“衰弱表型”模型^[7]。Rockwood 的“缺陷累积”模型将衰弱定义为一种更高的不良健康风险状态,是与年龄相关的健康状态积累的结果^[9]。也有学者提出“衰弱前期综合征”或中度衰弱的概念,介于健康与完全衰弱综合征之间,如 Fried 的“衰弱表型”模型根据 5 项标准将衰弱定义为^[7]: (1)不明原因的体重下降。(2)疲乏。(3)躯体活动降低。(4)握力下降。(5)行走速度减慢。同时存在上述 5 项标准中的 3 项及以上者定义为衰弱,1~2 项者定义为衰弱前期,5 项均不存在则定义为健康。

衰弱和脑血管病的患病率均随年龄的增长而升高,二者亦可并存。大量临床研究业已证实,脑血管病患者衰弱患病率显著高于正常人群: Whitehall II 队列研究显示,包括 Framingham 脑卒中危险评分(FSRS)在内的 4 种心血管危险评分均可以预测衰弱的发病率,特别是 FSRS 评分每增加 1 个标准差、10 年后衰弱发病率即可增加 35%^[10]。Taylor-Rowan 等^[11]开展的前瞻性横断面研究根据衰弱指数(FI)标准^[12]评价脑卒中患者衰弱患病率,发现约有 80% 的急性脑卒中患者处于衰弱或衰弱前期状态,显著高于非脑卒中住院患者的 14% 和社区人群的 11%^[13-14]。衰弱前期对脑卒中的影响目前尚存争议,值得注意的是,超过 50% 的患者在脑卒中发病时即已处于衰弱前期状态,此类患者可在脑卒中后转变为衰弱,由此可见,脑卒中促进了衰弱前期向衰弱的转变。Meta 分析显示,脑卒中患者衰弱前期患病率为 49% (95%CI: 42.000 ~ 57.000, $P < 0.001$; $I^2 = 47.100\%$),衰弱患病率为 22% (95%CI: 16.000 ~ 27.000, $P < 0.001$; $I^2 = 50.800\%$)^[15]。衰弱患者的脑血管病患病率亦显著升高,研究显示衰弱前期和衰弱患者脑卒中患病率分别为 4% 和 10%^[15]。来自意大利的两项研究对心脑血管病与衰弱的相关性进行探讨,其中一项为社区研究,调查衰弱前期与心脑血管病(冠状动脉疾病、心力衰竭和脑血管病)之间的关系,共追踪随访 4.4 年,其结果显示,调整年龄因素后,基线无衰弱的人群心血管病发病率为 75/1000 人年,基线有一项衰弱标准的患者心血管病发生风险增加 30%,基线达两项衰弱标准者发生心血管病的风险增加 80%^[16];另一项研究显示,衰弱患者发病 8.7 年后发生心肌梗死、心力衰竭或脑卒中等心脑血管病的风险可增加 35%,这种关联性以女性病例更为显著^[17]。上述两项研究为衰

弱与脑血管病的关联性提供了重要信息,遗憾的是,这两项研究均未针对脑血管病得出单独结论。

研究显示,高血压^[18]、糖尿病^[19]、低体力活动等脑血管病危险因素均可促进衰弱的发生与发展。高血压是脑血管病的首要危险因素,高血压与衰弱之间为相互促进的关系:衰弱患者的高血压患病率为 72% (95%CI: 0.660 ~ 0.790, $P < 0.001$; $I^2 = 93.100\%$);高血压患者的衰弱患病率为 14% (95%CI: 0.120 ~ 0.170, $P < 0.001$; $I^2 = 96.200\%$)^[18],高于社区人群的 11%^[14]。糖尿病对血管内皮的损害可致动脉粥样硬化,是脑卒中的病理学基础^[20],由于胰岛素抵抗(IR)与肌肉含量呈负相关,因此糖尿病可通过胰岛素抵抗作用促进衰弱的发生^[19],而衰弱则是以肌肉减少为主且伴随人体机能减退的状态。躯体活动降低是 Fried“衰弱表型”模型 5 项标准之一^[7],适当的体力活动可以降低脑卒中发病率,而处于衰弱状态的老年人因体力活动减少而使脑卒中风险增加^[21]。此外,慢性炎症反应亦是衰弱与脑血管病共同的发病机制,慢性炎症反应是免疫衰老的一部分,也是衰弱的重要发病机制之一^[22]。研究显示,衰弱患者血清白细胞介素-6(IL-6)、肿瘤坏死因子- α (TNF- α)^[23]和 C 反应蛋白(CRP)^[24]等炎症因子表达水平显著高于非衰弱患者;缺血性卒中引起的大脑低灌注使 IL-6、TNF- α 和 CRP 等多种炎症因子在脑组织局部聚集,破坏血-脑屏障完整性,从而诱导神经细胞死亡、加重继发性脑损害^[25]。

衰弱与多种脑血管病的预后相关,是脑卒中后生存率的预测因子^[26]。改良衰弱指数(mFI)是评价衰弱的有效指标,与各种手术后不良事件发生率和病死率的上升呈正相关^[27-28]。就神经外科手术而言,mFI 每增加 1 个单位,术后不良事件发生率即增加 1.5 ~ 1.6 个单位、病死率增加 3 ~ 5 个单位,且这种关联性与年龄无关^[29-30]。衰弱对脑血管造影阴性的蛛网膜下腔出血患者预后、病死率和术后并发症发生率的影响表明,与非衰弱患者相比,衰弱患者病情更严重,Hunt-Hess 和 Fisher 分级更高、住院时间更长、入院时和出院时 Glasgow 昏迷量表(GCS)评分更低;且所有死亡病例均为衰弱患者;住院期间衰弱患者不仅各种并发症发生率如肺炎、下肢深静脉血栓等明显高于非衰弱患者,而且需行气管插管的概率亦高于非衰弱患者;此外,与非衰弱患者相比,衰弱患者出院回家的概率降低 6.2 倍^[31]。由此可见,随着衰弱程度的加重,脑血管病患者病死、术

后并发症和住院时间延长的风险也随之增加,同时手术治疗机会亦减少,最终预后不良。对脑血管病患者进行衰弱评价可以提供重要的临床预后信息,无论采用何种衰弱量表评价住院老年患者的衰弱程度,均是出院后预后不良如病死、生活质量下降、对社区需求增加和再住院率增加的预测因素^[32]。因此,早期针对老年患者的衰弱状况进行评价并将其作为脑卒中后的一项干预靶点,对于降低脑血管病发病率、改善患者预后、避免不良结局具有积极作用^[33]。

衰弱的某些症状如步态缓慢,可能与脑血管事件后的残疾直接相关,从这个角度看,探讨衰弱标准是否随疾病状态的改变而变化具有临床意义。值得注意的是,尽管衰弱的部分症状可能与脑血管病直接相关,但 Palmer 等^[15]认为,在有脑卒中病史的患者中有相当比例的患者并无 Fried 的“衰弱表型”模型标准中的任意一项。已有研究着眼于衰弱患者的脑血管病变,这可能是衰弱与脑血管病之间的重要纽带。来自中国台湾的一项社区研究显示,健康人群脑微出血发生率仅为 11.1%,而在衰弱前期和衰弱患者中这一比例则分别为 17.9% 和 34.4%,且发生于脑干的微出血使衰弱患病率增加了 13 倍^[34]。Avila-Funes 等^[33]的影像学研究显示,衰弱患者的脑白质高信号程度高于健康人群;Siejka 等^[35]的结论与之一致,即衰弱患者白质区域(包括胼胝体、内囊前肢、外囊和丘脑后放射)部分各向异性(FA)较低、扩散系数较高。由此可见,在脑血管事件发生之前,衰弱即已存在。

在研究衰弱与脑血管病之间关系时,还应考虑脑卒中后生存率对衰弱的影响。Palmer 等^[15]认为,对既往有脑血管病病史患者衰弱程度的评价应随研究对象所在地区脑血管事件后生存率的改变而改变,因为随着脑卒中后生存率的提高,罹患非致死性脑卒中的患者衰弱发病率亦随之增加^[15]。尽管根据现有研究证据尚无法确定脑卒中发病后出现衰弱的时间,但 42% 的脑卒中患者并无衰弱或衰弱前期表现的流行病学证据^[15],提示衰弱并非脑血管病的必然结果,脑卒中亦非一定与长期衰弱或衰弱前期有关。因此,探究衰弱与脑血管病的关系,还应对脑卒中与衰弱状态的时间关系及其随时间的变化进行更多研究。

尽管上述研究通过患病率的差异提示衰弱与脑血管病之间存在潜在的关联性,但仍有研究显

示,衰弱与脑血管病并非密切相关,脑卒中可能仅在衰弱前期向衰弱期的转变阶段发挥促进作用^[36]。而且衰弱与脑卒中的关系也可能存在性别差异, Lee 等^[37]认为,脑卒中与男性患者衰弱状态改善有关,但在女性患者中则与衰弱状态恶化相关。此外,几乎所有研究均基于衰弱与一系列慢性病的关系,而非针对脑血管病;现有研究涉及的脑血管病仅以脑卒中患者为观察对象,较少关注其他患病人群,且未区分缺血性卒中与出血性卒中所存在的差异。因此,未来需要更多针对衰弱与脑血管病的纵向研究,以明确衰弱是否影响脑血管病发作、脑血管病是否导致衰弱或促进衰弱前期向衰弱转变。

利益冲突 无

参 考 文 献

- [1] Arjunan A, Peel NM, Hubbard RE. Gait speed and frailty status in relation to adverse outcomes in geriatric rehabilitation [J]. Arch Phys Med Rehabil, 2019, 100:859-864.
- [2] Hertz K, Santy-Tomlinson J. Fragility Fracture Nursing: holistic care and management of the orthogeriatric patient [C]. Cham (CH): Springer, 2018: 15-26.
- [3] Kojima G, Iliffe S, Walters K. Frailty index as a predictor of mortality: a systematic review and meta-analysis [J]. Age Ageing, 2018, 47:193-200.
- [4] Liu CH, Hu S, Mao YJ, Xing A. Research progress of frailty [J]. Zhongguo Quan Ke Yi Xue, 2017, 20:2025-2033. [刘长虎, 胡松, 毛拥军, 邢昂. 老年人衰弱的研究进展 [J]. 中国全科医学, 2017, 20:2025-2033.]
- [5] Vetrano DL, Palmer K, Marengoni A, Marzetti E, Lattanzio F, Roller-Wirnsberger R, Lopez Samaniego L, Rodríguez-Mañas L, Bernabei R, Onder G; Joint Action ADVANTAGE WP4 Group. Frailty and multimorbidity: a systematic review and meta-analysis [J]. J Gerontol A Biol Sci Med Sci, 2019, 74:659-666.
- [6] Palmer K, Villani ER, Vetrano DL, Cherubini A, Cruz-Jentoft AJ, Curtin D, Denking M, Gutiérrez - Valencia M, Guðmundsson A, Knol W, Mak DV, O'Mahony D, Pagan F, Petrovic M, Rajkumar C, Topinkova E, Trevisan C, van der Cammen TJM, van Marum RJ, Wehling M, Ziere G, Bernabei R, Onder G; European Geriatric Medicine Society Pharmacology special interest group. Association of polypharmacy and hyperpolypharmacy with frailty states: a systematic review and meta-analysis [J]. Eur Geriatr Med, 2019, 10:9-36.
- [7] Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype [J]. J Gerontol A Biol Sci Med Sci, 2001, 56:M146-156.
- [8] O'Brien TD, Roberts J, Brackenridge GR, Lloyd WH. Some aspects of community care of the frail and elderly: the need for assessment [J]. Gerontol Clin (Basel), 1968, 10:215-227.
- [9] Rockwood K, Mitnitski AB, MacKnight C. Some mathematical models of frailty and their clinical implications [J]. Rev Clin Gerontol, 2002, 12:109-117.
- [10] Bouillon K, Batty GD, Hamer M, Sabia S, Shipley MJ, Britton A, Singh-Manoux A, Kivimäki M. Cardiovascular disease risk scores in identifying future frailty: the Whitehall II prospective

- cohort study[J]. *Heart*, 2013, 99:737-742.
- [11] Taylor-Rowan M, Cuthbertson G, Keir R, Shaw R, Drozdowska B, Elliott E, Stott D, Quinn TJ. The prevalence of frailty among acute stroke patients, and evaluation of method of assessment [J]. *Clin Rehabil*, 2019, 33:1688-1696.
- [12] Hébert R, Bravo G, Korner -Bitensky N, Voyer L. Predictive validity of a postal questionnaire for screening community -dwelling elderly individuals at risk of functional decline [J]. *Age Ageing*, 1996, 25:159-167.
- [13] Soong J, Poots AJ, Scott S, Donald K, Woodcock T, Lovett D, Bell D. Quantifying the prevalence of frailty in English hospitals [J]. *BMJ Open*, 2015, 5:e008456.
- [14] Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community -dwelling older persons: a systematic review[J]. *J Am Geriatr Soc*, 2012, 60:1487-1492.
- [15] Palmer K, Vetrano DL, Padua L, Romano V, Rivoiro C, Scelfo B, Marengoni A, Bernabei R, Onder G. Frailty syndromes in persons with cerebrovascular disease: a systematic review and Meta-analysis[J]. *Front Neurol*, 2019, 10:1255.
- [16] Sergi G, Veronese N, Fontana L, De Rui M, Bolzetta F, Zambon S, Corti MC, Baggio G, Toffanello ED, Crepaldi G, Perissinotto E, Manzato E. Pre-frailty and risk of cardiovascular disease in elderly men and women: the Pro. V. A. study [J]. *J Am Coll Cardiol*, 2015, 65:976-983.
- [17] Veronese N, Sigveirsdottir K, Eiriksdottir G, Marques E, Chalhoub D, Phillips CL, Launer LJ, Maggi S, Gudnason V, Harris TB. Frailty and risk of cardiovascular diseases in older persons: the age, gene/environment susceptibility - Reykjavik study[J]. *Rejuvenation Res*, 2017, 20:517-524.
- [18] Vetrano DL, Palmer KM, Galluzzo L, Giampaoli S, Marengoni A, Bernabei R, Onder G; Joint Action ADVANTAGE WP4 group. Hypertension and frailty: a systematic review and meta-analysis[J]. *BMJ Open*, 2018, 8:e024406.
- [19] Assar ME, Laosa O, Rodríguez Mañas L. Diabetes and frailty [J]. *Curr Opin Clin Nutr Metab Care*, 2019, 22:52-57.
- [20] Lau LH, Lew J, Borschmann K, Thijs V, Ekinici EI. Prevalence of diabetes and its effects on stroke outcomes: a meta-analysis and literature review[J]. *J Diabetes Investig*, 2019, 10:780-792.
- [21] Seixas AA, Henklewood DA, Williams SK, Jagannathan R, Ramos A, Zizi F, Jean -Louis G. Sleep duration and physical activity profiles associated with self - reported stroke in the United States: application of Bayesian belief network modeling techniques[J]. *Front Neurol*, 2018, 9:534.
- [22] Ferrucci L, Fabbri E. Inflammation: chronic inflammation in ageing, cardiovascular disease, and frailty[J]. *Nat Rev Cardiol*, 2018, 15:505-522.
- [23] Yarla NS, Polito A, Peluso I. Effects of olive oil on TNF- α and IL-6 in humans: implication in obesity and frailty[J]. *Endocr Metab Immune Disord Drug Targets*, 2018, 18:63-74.
- [24] Samson LD, Boots AMH, Verschuren WMM, Picavet HSJ, Engelfriet P, Buisman AM. Frailty is associated with elevated CRP trajectories and higher numbers of neutrophils and monocytes[J]. *Exp Gerontol*, 2019, 125:110674.
- [25] Shi K, Tian DC, Li ZG, Ducruet AF, Lawton MT, Shi FD. Global brain inflammation in stroke [J]. *Lancet Neurol*, 2019, 18:1058-1066.
- [26] Winovich DT, Longstreth WT Jr, Arnold AM, Varadhan R, Zeki Al Hazzouri A, Cushman M, Newman AB, Odden MC. Factors associated with ischemic stroke survival and recovery in older adults[J]. *Stroke*, 2017, 48:1818-1826.
- [27] Yagi M, Fujita N, Okada E, Tsuji O, Nagoshi N, Tsuji T, Asazuma T, Nakamura M, Matsumoto M, Watanabe K. Impact of frailty and comorbidities on surgical outcomes and complications in adult spinal disorders [J]. *Spine (Phila Pa 1976)*, 2018, 43:1259-1267.
- [28] Adams P, Ghanem T, Stachler R, Hall F, Velanovich V, Rubinfeld I. Frailty as a predictor of morbidity and mortality in inpatient head and neck surgery [J]. *JAMA Otolaryngol Head Neck Surg*, 2013, 139:783-789.
- [29] Seib CD, Rochefort H, Chomsky-Higgins K, Gosnell JE, Suh I, Shen WT, Duh QY, Finlayson E. Association of patient frailty with increased morbidity after common ambulatory general surgery operations[J]. *JAMA Surg*, 2018, 53:160-168.
- [30] Isobe N, Ikawa F, Tominaga A, Kuroki K, Sadatomo T, Mizoue T, Hamasaki O, Matsushige T, Abiko M, Mitsuhashi T, Kinoshita Y, Takeda M, Kurisu K. Factors related to frailty associated with clinical deterioration after meningioma surgery in the elderly[J]. *World Neurosurg*, 2018, 119:e167-173.
- [31] McIntyre M, Gandhi C, Dragonette J, Schmidt M, Cole C, Santarelli J, Lehrer R, Al-Mufti F, Bowers CA. Increasing frailty predicts worse outcomes and increased complications after angiogram - negative subarachnoid hemorrhages [J]. *World Neurosurg*, 2020, 134:e181.
- [32] Lewis ET, Dent E, Alkhouri H, Kellett J, Williamson M, Asha S, Holdgate A, Mackenzie J, Winoto L, Fajardo - Pulido D, Ticehurst M, Hillman K, McCarthy S, Elcombe E, Rogers K, Cardona M. Which frailty scale for patients admitted via Emergency Department: a cohort study [J]? *Arch Gerontol Geriatr*, 2019, 80:104-114.
- [33] Avila-Funes JA, Pelletier A, Meillon C, Catheline G, Periot O, Trevin O-Frenk I, Gonzalez-Colaço M, Dartigues JF, Pérès K, Allard M, Dilharreguy B, Amieva H. Vascular cerebral damage in frail older adults: the AMImage study[J]. *J Gerontol A Biol Sci Med Sci*, 2017, 72:971-977.
- [34] Chung CP, Chou KH, Chen WT, Liu LK, Lee WJ, Chen LK, Lin CP, Wang PN. Cerebral microbleeds are associated with physical frailty: a community-based study[J]. *Neurobiol Aging*, 2016, 44:143-150.
- [35] Siejka TP, Srikanth VK, Hubbard RE, Moran C, Beare R, Wood A, Phan T, Balogun S, Callisaya ML. Frailty and cerebral small vessel disease: a cross-sectional analysis of the Tasmanian study of cognition and gait (TASCOG)[J]. *J Gerontol A Biol Sci Med Sci*, 2018, 73:255-260.
- [36] Trevisan C, Veronese N, Maggi S, Baggio G, Toffanello ED, Zambon S, Sartori L, Musacchio E, Perissinotto E, Crepaldi G, Manzato E, Sergi G. Factors influencing transitions between frailty states in elderly adults: the progetto veneto anziani longitudinal study[J]. *J Am Geriatr Soc*, 2017, 65:179-184.
- [37] Lee JS, Auyeung TW, Leung J, Kwok T, Woo J. Transitions in frailty states among community - living older adults and their associated factors[J]. *J Am Med Dir Assoc*, 2014, 15:281-286.

(收稿日期:2021-01-05)

(本文编辑:彭一帆)