·综 述·

血管危险因素与老年认知功能障碍的研究进展

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【摘 要】 血管危险因素与老年认知功能障碍的发生密切相关。由血管危险因素引起的老年认知功能障碍的发病率逐年上升,严重危害老年人的健康。高血压、糖尿病、高脂血症和慢性脑低灌注等是影响老年认知功能的重要的血管危险因素。研究血管危险因素与老年认知功能障碍的关系及作用机制,对于老年认知功能障碍的早期诊断和早期干预,具有重要的社会学和医学意义。

【关键词】 老年人;血管危险因素;认知功能障碍

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Vascular risk factors and cognitive impairment in the elderly: a review

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【Abstract】 Cognitive impairment in the elderly is closely associated with the vascular risk factors, and such impairment is increasing year by year, posing a serious threat to the health among the elderly. Hypertension, diabetes mellitus, hyperlipidemia and chronic cerebral hypoperfusion are important vascular risk factors for cognitive functions in the elderly. It is, therefore, of medical and social significance in the early diagnosis and intervention to investigate the relationship between vascular risk factors and cognitive impairment in the elderly and the underlying mechanism.

【Key words】 aged; vascular risk factor; cognitive impairment

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血管危险因素,如高血压、糖尿病和高脂血症等与老年认知功能障碍的发生密切相关[1]。老年认知功能障碍常见于阿尔茨海默病(Alzheimer disease,AD)和血管性痴呆(vascular dementia,VaD)等,>65岁的老年人认知功能障碍发病率高达5%[2]。由血管危险因素引起的认知功能障碍逐年上升,已成为严重危害老年人身心健康的公共卫生问题。研究血管危险因素与老年认知功能障碍的关系,对老年认知功能障碍的早期诊断和干预具有重要的意义。本文对常见的血管危险因素与老年认知功能障碍的关系及相关作用机制进行综述。

1 高血压

高血压是心脑血管系统最常见的疾病,可引起脑卒中、高血压性心脏病、慢性肾功能不全等靶器官损害,是老年心脑血管疾病死亡的主要危险因素。长期高血压可致脑动脉粥样硬化、脑低灌注和神经损伤等,从而导致高血压脑病的发生,严重影响认知功能[3]。高血压是影响老年认知功能障碍发生的重要血管危险因素。高血压患者由轻度认知功能障碍(mild cognitive impairment,MCI)进展为AD的风险比(hazard ratio,HR)为4.71[4]。不仅中年期高血压可以增加老年期认知功能障碍的风险,而且老年期血压水平也与认知功能障碍密切相关[5]。

高血压可引起不同程度、不同类型的大脑损害,包括脑血管和脑实质的损伤,涉及血管性细胞损伤、炎症反应和氧化应激等。高血压可导致脑血流自主调节能力下降,破坏血管内皮细胞功能,引起水通道

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蛋白(aquaporinaquaporin, AQP)过度表达,导致血脑屏障(blood brain barrier, BBB)通透性增加,造成大脑损伤[6]。过度表达的 AQP1 和 AQP4 还可引起严重的脑水肿,导致神经细胞变性和缺血性损伤[7]。长期高血压可使小胶质细胞和星形胶质细胞变性,导致肿瘤坏死因子-α、白介素-1β、环氧化酶-2 等表达增加,继发炎症反应,引起神经损伤[8]。另外,收缩压的增高程度与脑动脉粥样硬化程度密切相关,脑动脉粥样硬化导致大脑缺血缺氧,缺氧诱导因子 1-α、诱导型一氧化氮合酶、活性氧表达水平增加,造成突触丢失和认知功能障碍[9]。研究表明,脑白质损伤在 AD 和 VaD 中常见且严重。高血压可引起局部缺血、造成脑白质损伤,被认为是高血压导致认知功能减退的主要作用机制[4,10]。另外,高血压性脑出血造成显著的脑实质损伤,也是导致认知或运动功能障碍的重要因素。

2 糖尿病

糖尿病和老年痴呆的发病率随着年龄增长而增加,2 型糖尿病作为一种慢性代谢性疾病,随着疾病的发展,可导致全身血管系统及多器官损害,包括神经损伤和认知功能障碍。糖尿病的发生与认知功能障碍正相关,是最重要的血管危险因素之一[11]。研究表明,糖尿病是引起 AD 的一个重要的独立危险因素,60%~70%的糖尿病患者存在不同程度的学习与记忆能力下降,表现为简易精神状态检查量表(mini-mental state examination, MMSE)分值<24、蒙特利尔认知评估表(Montreal cognitive assessment, MoCA)分值<26 和 SAGE(self-administered gerocognitive examination, SAGE)分值<14[12]。

糖尿病导致老年认知功能障碍的作用机制复杂。高血糖引起的大脑萎缩、认知功能障碍,均与海马和杏仁核的萎缩密切相关[13]。另外,糖尿病引起的缺血性白质损伤也是造成认知功能障碍的主要因素之一。研究表明,高血糖可直接损害神经元功能,导致神经元代谢紊乱,影响神经递质和神经生长因子的表达,如突触蛋白和脑源性神经生长因子(brain-derived neurotrophic factor, BDNF)表达减少[14]。糖尿病患者易出现血糖控制不良,长期反复高血糖可损害脑血管内皮细胞,引起神经血管失耦联,细胞间信号传递异常[15]。高血糖还可引起细胞多种酶类异常,如醛糖还原酶活性增强,导致神经细胞高渗、细胞水肿和脱髓鞘等损伤[16]。近期研究表明,高血糖可引起神经突触变性和减少,影响突触功能,而且降低血糖可明显改善高血糖引起的认知功能障碍[17]。

3 高脂血症

血脂代谢紊乱是常见的老年慢性疾病,其中血清总胆固醇(total cholesterol, TC)、甘油三酯(triglycerides, TG)、高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)、低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)水平异常与老年认知功能障碍相关。VaD 患者存在显著的脂质代谢紊乱,TC、TG、LDL-C 均明显高于对照组,HDL-C 水平明显降低,高脂血症是老年 MCI 一个重要的独立危险因素,应用他汀类药物可明显改善患者的注意力、言语能力和长时记忆等功能[18]。

研究表明,长期高脂饮食可导致认知功能障碍,血脂升高一方面可导致脑动脉粥样硬化,直接破坏血管壁,导致管腔狭窄或闭塞,引起慢性脑缺血性损伤;另一方面,可通过影响神经细胞能量代谢,促进神经元变性或凋亡;其还可增加 BBB 通透性,促进微血管因子Ⅷ的表达,介导炎症反应,影响认知功能[19]。另外,血脂代谢异常可导致成纤维细胞生长因子-21(fibroblast growth factor-21, FGF-21)和碱性 FGF(basic FGF, bFGF)表达减少,减弱其修复内皮细胞的功能,损伤血管和神经,导致学习与记忆能力减退[20]。

4 慢性脑低灌注

慢性脑低灌注(chronic cerebral hypoperfusion, CCH)为长期脑血流降低所致的血流动力学性脑缺血,也是多种神经退行性疾病的基本病理状态,常见于颅内外血管狭窄或闭塞、脑动脉粥样硬化、AD 和 VaD 等[21]。CCH 可诱导血管损伤、BBB 功能失调、神经细胞变性和凋亡等,是导致老年认知功能障碍的重要原因[22]。

CCH 性认知功能障碍被认为是老年生命健康的“慢性杀手”,其发生机制可能与神经血管单元(neurovascular unit, NVU)损伤、神经细胞自噬及多种细胞信号通路异常等有关。NVU 由神经元、胶质细胞和血管构成,这一概念把神经与血管、细胞与细胞外基质视为整体[23]。在 CCH 情况下,NVU 细胞间信号传导和神经血管耦联异常,引起血管性损伤(通透性增加、血管内皮细胞代谢失调、微血管完整性破坏等)和胶质细胞活化,继发炎症反应、BBB 功能失调、神经元凋亡等,破坏 NVU 整体功能,导致认知功能障碍[24]。研究表明,自噬参与多种中枢神经系统疾病的病理过程,包括 AD、VaD 和衰老等[25]。

在CCH动物模型中,神经细胞自噬水平高低与神经损伤和认知功能障碍程度正相关,随着自噬水平的增加,神经损伤加重[26]。相反,在AD中,细胞自噬水平降低,导致细胞毒性物质蓄积,引起学习与记忆能力减退[27]。然而,适度增加自噬可抗衰老,改善认知功能,提示自噬在老年认知功能障碍中起重要的作用[28]。另外,CCH可抑制磷脂酰肌醇3激酶-蛋白激酶B细胞信号通路,减少BDNF的表达,激活c-Jun氨基末端激酶及细胞外调节蛋白激酶等细胞信号通路,促进细胞凋亡,引起认知功能障碍[29]。

5 脑卒中

血管危险因素可促使脑卒中的发生。新发脑卒中患者中老年人的比例高达70%~80%,且老年脑卒中的致残率、复发率和死亡率均都居于首位[30]。脑卒中引起的认知功能障碍主要包括AD和(或)VaD等[31]。据统计,老年脑卒中后出现认知功能障碍的患者高达64%[32]。

缺血性脑卒中和出血性脑卒中均与认知功能障碍的发生密切相关。研究表明,30%的缺血性脑卒中患者卒中后的学习与记忆能力下降,特别是在老年人中,高达30%的脑卒中患者1年内可进展为痴呆[33]。缺血性脑卒中引起认知功能障碍作用机制十分复杂,与急性或慢性脑缺血、脑水肿程度及炎症反应等相关。出血性脑卒中引起的认知功能障碍虽然与出血部位、是否破入脑室等疾病本身特点有关,但其发生率并不低,3年内痴呆发病率约为23%[34]。与<65岁脑卒中患者相比,老年脑卒中的恢复过程更长。在整个脑血管事件过程中,除病理作用机制外,老年人易发生的精神、心理等问题亦可导致认知功能障碍。

6 展望

血管危险因素可独立或相互作用损害血管和神经,影响认知功能。血管危险因素引起的老年认知功能障碍发病隐匿,难以预防和诊断,特别是在损害程度较轻的MCI阶段。因此,研究血管危险因素与老年认知功能障碍的关系及作用机制,对于早期预防控制及诊断治疗老年认知功能障碍,具有重要的社会学和医学意义。

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