

糖尿病对老年患者术后认知功能的影响

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[摘要] 术后认知功能障碍是老年患者术后的常见并发症。目前患有糖尿病的老年人日益增多, 接受手术治疗的老年患者也逐年增加。糖尿病患者发生认知功能损伤的概率较正常人群高, 可能与血糖控制不佳, 血糖波动较大, 胰岛素分泌异常及信号异常有关。本文就接受手术的老年糖尿病患者, 分析研究血糖异常对其术后认知水平的影响及其可能的作用机制进行综述。

[关键词] 糖尿病; 手术后并发症; 认知功能障碍; 老年人

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[Abstract] Postoperative cognitive dysfunction is a common complication in elderly patients. The number of elderly patients undergoing surgery is increasing yearly accompanying with more and more elderly patients with diabetes. The incidence of cognitive impairment in diabetic patients is higher than that of normal population, which might probably due to poor control of blood glucose, high fluctuation of blood glucose, abnormal insulin secretion and abnormal signal. In this paper, we will investigate the effects of blood glucose abnormalities on postoperative cognitive level of elderly patients and their possible mechanism of action.

[Keywords] Diabetes mellitus; Postoperative complications; Cognitive dysfunction; Aged

随着生活水平的提高, 平均寿命延长, 接受手术的老年患者日益增多, 因此老年患者的围手术期问题, 尤其是术后认知功能障碍 (POCD) 得到越来越多的关注。然而围手术期血糖水平与术后认知功能的关系并不十分清楚, 可能与术前血糖控制不佳有关, 也可能与术中血糖波动水平较大有关, 甚至可能与术前禁食水引起的低血糖有关。对于老年糖尿病患者, 研究围手术期血糖控制水平与术后认知功能损伤的关系具有一定的临床意义。

1 POCD 及发生机制

POCD 是指在接受手术和麻醉的数月里, 在神经心理领域出现功能减退, 包括记忆、执行能力和处理速度的下降等^[1]。全球多项研究表明, 不管在心脏手术或非心脏大手术中, 高龄都是 POCD 的高危因素^[2-4]。除此之外, POCD 的发生还与糖尿病、受教育程度、麻醉方式、手术应激等有关。关于 POCD 的发生机制, 目前认为可能与以下因素有关: (1) 神

经系统炎性反应: 手术和麻醉可使患者外周组织产生大量促炎因子, 并通过迷走神经的传入纤维和血脑屏障进入中枢神经系统, 引起有害的神经系统炎性反应, 尤其是海马区, 这些炎性因子损伤神经元和突触, 影响突触传递功能, 进而发生 POCD^[5-8]。(2) Tau 蛋白磷酸化: 有研究表明^[9], 脑脊液中总 Tau 蛋白和磷酸化 Tau 蛋白含量与神经损伤存在明显的相关性。动物研究也表明^[10], 在临床剂量的异氟醚麻醉状态下, 会加速 Tau 蛋白磷酸化过程, 导致 POCD。(3) A β 蛋白沉积: Shi 等^[11]对行髋关节置换术的老年患者术后认知进行研究, 发生 POCD 的老年患者血清 A β 蛋白含量明显增加。POCD 发生的潜在机制可能与 A β 蛋白和 tau 蛋白的升高有关。

2 糖尿病与认知功能障碍的研究进展

根据一项大型流行病学调查, 老年人的糖尿病患病率是青壮年的 3~4 倍, 且糖耐量减低 (IGT) 患病率也随年龄增长而增加^[12]。糖尿病引起的特异

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性血管病变与视网膜病变、高血压、冠状动脉粥样硬化、肾脏损伤、神经损伤等风险增加密切相关。近年来,糖尿病与认知功能障碍之间的关联得到越来越多的关注。与一般人群相比,患有严重认知功能缺损的老年人群中,2 型糖尿病患者是其他人群的 1.5~2 倍^[13-14]。越来越多的研究也支持这一观点:与普通人群相比,糖尿病患者患有认知功能障碍的风险更大^[15-17]。糖尿病引起认知改变从病理生理机制解释可能由于不受控制的蛋白质聚集,胰岛素信号受损,炎症反应,氧化应激,线粒体功能障碍,糖基终末产物大量形成等引起^[18]。有研究表明 2 型糖尿病患者常患有脑血管疾病,尤其是糖尿病合并高血压的患者,与血压正常的糖尿病患者相比,其认知改变的程度更大^[19]。此外,糖尿病合并血脂代谢异常、肥胖及其他疾病,对认知功能的改变也具有一定作用。

3 高血糖状态对术后认知功能的影响

围手术期由于麻醉和手术的应激会使患者的血糖出现不同程度的升高,尤其是糖尿病患者。根据具体的病理机制,将糖尿病分为 1 型糖尿病(不分泌胰岛素)和 2 型糖尿病(胰岛素受体抵抗)。在这两种情况下,患者的胰岛素功能受损均表现为血糖的异常升高^[20]。有研究提示^[21],过量的葡萄糖会损伤神经并影响正常的神经功能,从而导致糖尿病神经病变。持续高糖状态引起的代谢紊乱可能会导致神经系统缺血缺氧,加重机体酸中毒,蛋白激酶 C (PKC) 活性增加,糖基终末产物大量形成等,损伤大脑血管和神经元,影响中枢神经系统功能,最终导致轻度认知障碍^[22]。高血糖状态时脑细胞功能变化不仅局限于神经元,小胶质细胞同样也会受到影响。动物研究表明^[23],与非糖尿病大鼠相比,糖尿病大鼠对缺血引起的星形胶质细胞激活和脱髓鞘,其高糖状态会抑制星形胶质细胞的活化,加剧脱髓鞘并延迟髓鞘再生过程。体外行星形胶质细胞培养,葡萄糖水平增高会增加如肿瘤坏死因子(TNF)、白细胞介素-6(IL-6)、白细胞介素-1(IL-1)、白细胞介素-4(IL-4)和血管内皮生长因子(VEGF)等炎症因子的表达^[24]。高血糖会影响星形胶质细胞间沟通连接,并且对大脑的血管调节、能量代谢、胞间通路等重要功能产生损伤^[25]。围手术期的血糖升高,可能会通过改变血浆渗透压、增加线粒体自由基生成、增强氧化应激反应、活化神经元的凋亡过程等,改变老年糖尿病患者的术后认知水平。

4 低血糖状态对术后认知功能的影响

糖尿病患者往往由于血糖控制不佳,易出现低血糖。低血糖会影响大脑能量代谢,导致海马神经元变性萎缩甚至死亡。低血糖还可导致海马区谷胱甘肽含量明显减低,引起患者空间和背景记忆能力缺失。根据 Lee 等^[26]的研究,高龄、黑人种族、血糖控制不佳、降糖药的使用、肾功能损伤以及认知损伤均为严重低血糖的独立危险因素。一项荟萃分析提示^[27],低血糖和认知功能障碍相互作用,即低血糖会增加 MCI 的风险,相反认知功能降低也会增加低血糖的发生风险。在低血糖发作期间,由于肾上腺素分泌增加,致使血小板活化、白细胞动员,引起凝血功能和内皮细胞受损^[28]。Whitmer 等^[29]研究表明,急性低血糖会导致脑电图的改变,包括潜伏期延长和(或)感觉诱发电位幅度降低。低血糖引起认知功能障碍的病理生理机制可能包括低血糖后的神经损伤、炎症反应、凝血功能障碍和低血糖发作期间海马神经元的突触功能障碍^[30]。接受手术治疗的老年糖尿病患者,可能由于术前不当的禁饮禁食,在围手术期发生低血糖,对术后认知功能造成不良影响。

5 围术期血糖波动对术后认知功能的影响

术中血糖波动是指患者术中血糖在峰值和谷值之间不断变化震荡的过程^[31]。有研究表明,不管糖尿病或非糖尿病患者,术中血糖波动水平较大时,更易发生术后高血糖^[32-33],影响患者预后。Matsushima 等^[34]报道,术中血糖波动水平与患者远期预后具有显著相关性,且围手术期严重高血糖和低血糖均对术后远期生存率产生影响。有报道称^[35],持续高血糖或血糖波动较大时,会诱发机体释放大量炎症因子。外周炎症因子通过迷走神经传入纤维和血脑屏障进入中枢神经系统激活小胶质细胞,诱发有害的级联炎症反应,强烈而持久地作用于神经系统,影响突触传递功能,导致 POCD 的发生^[36]。动物实验也证实,急性血糖波动可能引起内皮细胞发生严重的氧化应激和炎症反应,促进单核细胞对内皮细胞的粘附,加速内皮细胞凋亡,对血管造成损伤,术后可能会引发心脑血管并发症,如 POCD 等^[37]。

6 胰岛素对术后认知功能的影响

胰岛素是一种调节葡萄糖代谢的肽类激素,此外也是一种中枢神经系统的传入信号和神经营养物质。近年来有研究提示胰岛素可以参与调节认知功能。而糖尿病患者常存在胰岛素抵抗或胰岛素缺

乏。胰岛素样生长因子(IGF-1)在促进细胞生长发育方面起着重要作用。动物研究表明,IGF-1 可以通过促进神经元的增殖、分化来促进中枢神经系统的神经再生。在大脑皮层和海马区普遍存在胰岛素受体,而中枢神经系统也广泛存在着 IGF-1 和 IGF-2^[38]。当胰岛素信号异常时,可能会引起大脑 A β 蛋白沉积,而 A β 聚合物可引起神经病理性变化,使突触功能丧失而导致记忆功能减退,继而引起认知水平的降低^[39-40]。

7 糖尿病并发症和合并症对术后认知功能的影响

大血管病变是糖尿病的主要并发症之一,当脑部血管硬化时,可能会影响脑血流动力学,使中枢神经系统长期处于慢性缺血缺氧状态,对认知水平产生影响;微血管病变是糖尿病另一主要并发症,其病理改变包括微循环障碍、微血管形成和基底膜增厚,手术和麻醉的应激可能会加重这一病理改变,继而加重认知损伤。

2 型糖尿病患者往往合并有高血压及血脂代谢异常等合并症,糖尿病合并高血压的患者,较血压正常的糖尿病患者,其认知功能的下降更加明显。而血脂代谢异常和高血糖共同作用于毛细血管,引起血管痉挛、管腔狭窄、血流缓慢等,引起大脑发生缺血改变,影响大脑氧灌注,使脑组织发生损伤,改变患者认知水平^[41]。

8 展望和讨论

对于老年糖尿病患者,由于自身存在代谢紊乱和慢性炎症,脑部血管和神经元已经存在基础性的病理改变和损伤,而手术和麻醉可能会加重脑灌注不足或脑栓塞,引起短暂性脑缺氧,导致 POCD 的发生。其病理生理学机制可能与下列因素有关:(1)大脑在缺血缺氧时,对循环中血糖升高更加敏感,刺激神经元对血糖的摄取增加。细胞内葡萄糖蓄积刺激乳酸产生,引起乳酸酸中毒,蛋白质糖基化和大量自由基产生,最终大脑缺血半暗带转化成梗死灶^[42]。(2)高血糖也会进一步增强围术期的炎症反应,使血浆 C 反应蛋白、炎症因子和皮质醇这类具有神经毒性的产物释放增加。(3)胰岛素抵抗也是引起围术期高血糖的一种内分泌机制,围术期的炎症反应和手术应激可以加剧胰岛素抵抗。炎症因子 TNF- α 可能会阻止胰岛素受体底物-1 酪氨酸磷酸化,降低胰岛素受体-1 酪氨酸激酶活性,同时使糖转运蛋白数量减少,这些都会加剧脂肪细胞胰岛素抵抗^[43]。在 IL-6 作用下,胰岛素受体的酪氨酸激酶

磷酸化及其 β 亚基的活性降低,葡萄糖转运体-4 的表达也随之减少,从而导致胰岛素介导的葡萄糖转运障碍^[44]。

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· 保健论坛 ·

老年综合评估门诊在老年人健康管理中的作用

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[摘要] 随着我国进入老龄化社会, 老年人口迅速增多, 老年人的健康已经成为全民健康的重要组成部分。增龄所致的器官功能变化, 老年人常见的共病、老年综合征、精神心理以及社会角色的变化, 使老年人的躯体功能也随之发生着改变, 逐渐造成衰弱、甚至失能。老年综合评估 (CGA) 多维度地评估老年人整体健康水平, 旨在及时尽早发现老年人存在的健康相关问题和风险, 给予合理干预, 减慢衰弱的发生, 延缓老年人的失能。老年综合评估门诊是老人进行 CGA 的场所之一, 是老年人健康管理的重要组成部分。本文就老年综合评估门诊在老年健康管理中的作用作一个综述。

[关键词] 老年医学; 健康促进; 疾病管理; 健康影响评估; 症状评估

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The importance of establishing GEM-clinics in elderly health management Lai Bei, Zhang Jie, Shi Hong (Geriatric Medicine Ward, Beijing Hospital, National Center of Gerontology, Beijing 100730, China)

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[Abstract] Our country has entered into an aged society, with the number of elderly people has increased rapidly and the health of the population has become one of the most important concerns within our national health system. Be-

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