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老年患者髋部骨折术后谵妄的原因及可能机制

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摘　要

随着世界各地人口年龄和预期寿命的增加，预计发生髋部骨折的老年人数量将逐年增多。髋部骨折好发于老年患者，早期手术修复作为其关键治疗方式能最大限度地减少并发症、降低死亡率，老年患者髋部手术后谵妄的发生率在4%~53%之间，是老年患者最常见的手术并发症，与功能预后不良、住院时间延长及死亡率升高有关。术后谵妄的危险因素众多，有研究表明多达三分之一的高危患者可以预防谵妄的发生。针对其危险因素背后的机制探索可能帮助我们能更好地筛查和预防，更有针对性地制定围术期的医疗保健计划，从而在髋部骨折治疗后获得尽可能好的手术结果和更好的生活质量。

关键词

髋部骨折，术后谵妄，麻醉，手术，合并症

Causes and Possible Mechanisms of Postoperative Delirium in Elderly Patients with Hip Fracture

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Abstract

As the age and life expectancy of populations around the world increase, the number of older peo-

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ple suffering hip fractures is expected to increase year by year. Hip fracture tends to occur in elderly patients, and early surgical repair as a key treatment can minimize complications and reduce mortality. The incidence of postoperative delirium in elderly patients ranges from 4% to 53%, and it is the most common surgical complication in elderly patients, which is associated with poor functional prognosis, prolonged hospital stay and increased mortality. There are many risk factors for postoperative delirium. Studies have shown that up to a third of high-risk patients can prevent delirium. Exploring the mechanism behind the risk factors may help us to better screen and prevent them, and develop a more targeted perioperative health care plan, so as to obtain the best possible surgical outcome and better quality of life after hip fracture treatment.

Keywords

Hip Fracture, Postoperative Delirium, Anesthesia, Surgery, Comorbidities

1. 引言

髋部骨折是老年人的常见创伤之一，约有35%的髋部骨折幸存者无法恢复独立行走，骨折后1年死亡率为17%~28% [1] [2]，因其高致残率和高死亡率而被冠以“人生最后一次骨折”。随着人口老龄化的进展，髋部骨折患者的绝对数量不断增加，进一步加重了我国医疗保健系统和社会的经济负担[3]。

世界卫生组织在其发布的国际疾病分类第11版(ICD-11) [4]中，将谵妄定义为一种急性或亚急性起病的状态，主要表现为注意障碍(即难以指向、聚焦、维持和转移注意力)和意识障碍(即对环境的定向力减弱)。这种状态在一天内症状常会有波动，并且可能伴随其他认知障碍，如记忆、语言、视空间功能或感知觉方面的问题，同时可能影响睡眠觉醒周期。谵妄由多种潜在原因引发，包括急性躯体疾病、药物使用或戒断、创伤或手术；病程持续时间各不相同；症状表现多样；危险因素涉及多个系统；评估工具种类繁多且存在异质性，加之不同机构对谵妄培训的普遍缺乏，这些都造成了谵妄的诊断率相对不足[5]。

谵妄常见于医疗机构住院的老年患者[5]，包括老年病院、重症监护病房(ICU)、急诊科和疗养院，其患病率因患者群体和环境而异，一项包含33项住院患者研究的meta分析发现[6]，谵妄的总体患病率为23%。术后谵妄(postoperative delirium, POD)是指患者在经历外科手术后1周内出现的谵妄，其发生具有明显的时间特点，主要发生在术后24~72 h以内[7]，是老年髋部骨折患者常见的术后并发症之一[8]，POD与多种不良结局相关，如：延长患者平均住院时间，增加患者出院后死亡风险及痴呆风险[9] [10]，因此探究诱发POD的可能原因及机制具有重要的临床意义。

2. 麻醉

手术和麻醉对老年人有显著影响，这可能导致术后意识模糊和功能下降的风险增加。全身麻醉是一种通过多种药物实现的状态，研究表明许多药物会引发谵妄。大量临床研究对比了老年髋部骨折患者接受区域麻醉或全身麻醉对术后谵妄发生率的影响，结果显示：不同的麻醉方式对术后谵妄的影响无显著差异[11]-[14]。

小胶质细胞作为中枢神经系统中的主要免疫细胞[15]，能被麻醉药物激活，进而释放细胞毒性介质，如促炎因子IL-1β，TNF-α和IL-6，进而对邻近神经元产生毒性，因此小胶质细胞在认知功能障碍的发展

中发挥主要作用。

淀粉样蛋白β(Aβ)是一种天然存在于中枢神经系统中的肽，在老年人的大脑中水平较高[16]，某些全身麻醉剂可能会加重淀粉样蛋白β的寡聚化和沉积，从而增加术后认知功能障碍的风险。有实验室研究表明，2%异氟醚可通过诱导胱天蛋白酶3 (caspase-3)活化增加神经胶质瘤细胞中β淀粉样蛋白的产生，聚集的淀粉样蛋白β可以导致细胞凋亡[17]。

在无手术刺激的情况下，将大鼠暴露于1.4%异氟醚4h后，与记忆缺陷和脑损伤过程相关的细胞因子在血清和大脑中显著升高，提示异氟醚可能会引起炎症变化和认知缺陷[18]。七氟醚和异氟醚麻醉剂导致突触受体的表达改变、突触结构和功能以及钙稳态的改变，增加术后认知功能障碍的风险。

海马齿状回不断产生新的神经元，为海马体提供了特殊的结构可塑性。在动物研究中，长期镇静会导致认知障碍，可持续数天至数周，一种可能的机制是海马神经发生的减少，海马齿状回(DG)中颗粒神经元的生成减少与学习和记忆受损相关，抑制成体神经发生会产生一些行为障碍[19]，右美托咪定和咪达唑仑作用于不同的受体，通过涉及γ-氨基丁酸(GABA)能信号传导的共同途径减少神经元前体增殖，从而减少成年大鼠齿状回中的细胞增殖。(BDNF)是一种对神经元存活很重要的神经营养因子，丙泊酚暴露破坏了脑源性神经营养因子的信号通路，可能导致认知或情绪障碍[20]。

静脉麻醉药物和吸入性麻醉药物作用于中枢神经系统内的多个受体位点，它们的主要作用是降低神经元的活性。这一过程主要是通过激活一种叫做γ-氨基丁酸(GABA)A型受体来实现的。此外，烟碱型乙酰胆碱受体在认知功能中扮演着重要角色。简而言之，这些药物通过多种方式影响大脑，以达到麻醉的效果，并涉及到与认知和神经元活性相关的特定受体。一项纳入了28项随机对照试验的meta分析比较了使用丙泊酚的全静脉麻醉(total intravenous anaesthesia, TIVA)维持与吸入麻醉维持，术后谵妄的发生率几乎没有差异，没有证据表明术后谵妄因使用的麻醉剂类型而异[21]。

3. 手术

手术创伤可导致免疫系统激活和下丘脑－垂体－肾上腺轴过度活跃，引发中枢神经系统(CNS)中乙酰胆碱、去甲肾上腺素、5-羟色胺和其他神经递质的紊乱，最终可能导致手术后脑功能障碍[22]。手术应激导致交感神经张力上调和副交感神经张力下调、胆碱能功能受损、脑氧化代谢可逆性损害、多种神经递质通路异常受累和神经炎症[23]。Terrando等人发现[24]，小鼠外周手术激活了肿瘤坏死因子α (TNFα)/NF-κB信号通路，促进巨噬细胞迁移到脑实质，破坏血脑屏障(BBB)，引起手术后认知能力下降。

麻醉或手术后以sirtuin蛋白3依赖性方式调节小胶质细胞活化和神经炎细胞因子水平，SIRT3在CA1区域的过表达减弱了麻醉或手术诱导的学习和记忆功能障碍以及突触可塑性功能障碍和氧化应激反应，减轻小鼠认知功能下降[25]。

4. 高龄

高龄是髋部骨折的独立危险因素之一[26]，也是被普遍接受的髋部骨折术后谵妄的危险因素[27]-[29]。衰老与大脑的特征性结构和生理变化有关，功能性磁共振成像扫描显示皮层激活的模式发生了变化，大脑系统的效率降低，影响突触功能、轴突完整性和髓鞘形成的基因表达变化，衰老的大脑皮层中抑制性神经元的蛋白质标志物减少，包括：钙结合蛋白1 (CALB1)、生长抑素蛋白和GABA生物合成酶谷氨酸脱羧酶1，介导抑制性神经传递的GABA系统在衰老的人类前额叶皮层中降低，抑制性回路活动的减少可能会增加皮质激活，诱发兴奋性毒性，可能会改变神经网络并导致与年龄相关的认知变化[30]。

大脑老化引起线粒体功能下降，使神经元容易受到年龄依赖性病理的影响，自噬和蛋白质稳态的调节可能引起神经退行性疾病中的毒性蛋白质聚集，泛素化蛋白聚集体的积累通过氧化应激或氧化蛋白和淀粉样蛋白-β (Aβ)介导，引起tau样蛋白增多，可能与认知能力下降相关[31]。

虚弱在老年人中非常普遍，随着生理系统功能的加速衰退，机体的生理储备能力和对压力的抵抗能力下降，导致不良健康结局的风险增加[32]，如：跌倒、残疾、住院和死亡[33]。一项前瞻性队列研究发现，虚弱与发生谵妄的风险增加和随后的生存期降低相关，谵妄和虚弱结合增加老年人的不良结局风险[34]。合并虚弱的老年髋部骨折患者平均住院时长和术后并发症增加，谵妄是其中最常发生的并发症[35]。谵妄是弥漫性皮质功能障碍的行为表现，与多种神经递质系统的紊乱有关，抗胆碱能药物的毒性与谵妄的脑电图和行为表现相似[36]，值得注意的是，年龄的增长与胆碱能功能下降有关[37]。

5. 营养不良

营养不良在老年髋部骨折患者中非常普遍，老年髋部骨折患者的卡路里和蛋白质摄入量显著降低，骨折后摄入减少、失血和炎症的过度分解代谢状态，导致血浆蛋白减少，对骨折后的功能恢复产生负面影响[38]，一项研究显示[39]：经迷你营养评估简表(MNA-SF)确定的存在明显营养不良和有营养不良风险的髋部骨折患者与术后谵妄独立相关，且营养不良程度与术后谵妄之间存在剂量效应关系，存在明显营养不良的人发生术后谵妄的可能性是营养状况正常的人的 3.0 倍，而有营养不良风险的人发生术后谵妄的可能性是其 2.5 倍。营养不良是老年髋部骨折患者术后谵妄的有力预测因素[27]，补充营养可以减少氧化应激衍生产物的产生，降低谵妄的患病率和严重程度[40]。

6. 睡眠障碍

阿尔茨海默病患者脑脊液和脑组织中的褪黑激素水平较低，一项针对髋部骨折老年患者的研究中，在针对认知障碍或年龄分层的分析显示，有和没有谵妄的患者在平均褪黑激素水平方面没有发现差异[41]。

7. 合并症

研究表明，血糖控制不佳的老年患者与认知功能受损之间存在联系[27]，高糖浓度的毒性作用是通过多元醇和己糖胺途径、氧化应激和晚期糖基化终末产物的生成介导的。动物试验显示：暴露于吸入性麻醉剂的糖尿病大鼠与正常大鼠相比，海马匀浆中的半胱天冬酶 3 表达下降，IL-6、TNF-α、IL-8 和 IL-10 等炎症细胞因子增加，在认知功能下降中起作用[42]。一项 meta 分析显示：老年患者的认知障碍与低血糖之间存在双向关系[43]。与葡萄糖水平相关的认知功能障碍可能由以下原因之一引起：胰岛素抵抗、葡萄糖代谢改变、血管病变和/或 β 淀粉样蛋白和 tau 代谢[44]。胰岛素受体在大脑结构中扮演着至关重要的角色，尤其是在内侧颞叶皮层和海马区域，它们对于认知和记忆功能至关重要。然而，当发生胰岛素抵抗时，一种特定模式便会出现：慢性外周高胰岛素血症与大脑中胰岛素浓度的降低密切相关。这种变化进而可能导致清除 β 淀粉样蛋白的酶活性表达降低，对大脑健康构成威胁。更为严重的是，大脑中胰岛素浓度的降低还可能促使 tau 蛋白的磷酸化程度增加，这一变化会直接引发认知功能的下降。简而言之，胰岛素受体在大脑中的正常运作对于维持我们的认知和记忆能力至关重要，而其功能受损则可能通过一系列复杂的机制影响到我们的认知健康。

高血压可损害老年人的脑血管反应性，脑血管反应性会影响大脑的血液供应，高血压会降低脑血管自我调节能力，高血压引起的血管僵硬变化会进一步加剧脑血流量的减少。高血压和不规律使用降压药物与术后谵妄密切相关，可能与术中脑缺血引起的术后反应延迟有关，谵妄期间额叶、颞叶和枕叶皮层的区域脑血流量测量值低于正常状态，如果脑血管弹性和调节能力较差，则更容易发生术后谵妄[45]。

随着人口老龄化及麻醉和手术技术的改善，接受手术的老年患者人数将逐渐增多，因此，术后谵妄很可能会成为一个越来越普遍的问题，作为一种成熟的诊断实体，需要进一步研究以了解其病因以制定有效的预防和治疗策略。

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