·综述·

老年人群睡眠障碍与阿尔茨海默病相关性研究进展

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【摘 要】 睡眠模式随衰老而变化,老年人群易合并入睡困难、睡眠碎片化、白日嗜睡、早醒等睡眠障碍。阿尔茨海默病(AD)是衰老背景下的神经系统退行性疾病,也是老年人最常见的痴呆原因。目前,越来越多的研究发现,睡眠障碍与AD之间存在显著的相关性,尤其是睡眠觉醒障碍,可通过影响脑内淋巴循环代谢,导致β-淀粉样蛋白清除率降低,进而影响AD发生发展。尽管有一定的研究基础,但是睡眠障碍究竟是AD发生发展的因还是果仍未可知,睡眠障碍影响AD发生发展的潜在机制仍不明确,AD相关认知障碍患者的睡眠干预及调节策略仍缺乏统一的指导意见。因此,本文综述了衰老与睡眠生理变化、睡眠障碍与AD相关性及睡眠障碍干预与认知改善的最新研究证据,旨在提高人们对睡眠障碍及睡眠调节重要性的认识,以期达到疾病的早期预防。

【关键词】 老年人;睡眠障碍;阿尔茨海默病;昼夜节律
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Research progress in correlation between sleep disorders and Alzheimer's disease in the elderly

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【Abstract】 Sleep patterns change with aging, and the elderly are prone to sleep disorders including difficulty in falling asleep, sleep fragmentation, daytime sleepiness, and early awakening. Alzheimer's disease (AD) is an age-related neurodegenerative disease and the most common cause of dementia in the elderly. More and more studies have shown a remarkable correlation between AD and sleep disorders, especially sleep-wake disorders. They may affect the metabolism of the brain's lymphatic system, reduce the clearance of amyloid β protein, and play a key role in the onset and progression of AD. Despite the previous studies, the causality between sleep disorders and AD as well as the underlying mechanism remains uncertain. Moreover, consensus is yet to be reached for a guidance on sleep regulation for patients with AD-related cognitive impairment. In this article, we reviewed the latest research evidence on aging and physiological changes in sleep, the correlation between sleep disorders and AD, and management strategies for sleep disorders and cognitive improvement, aiming to raise the awareness of the importance of sleep regulation for early prevention.

【Key words】 aged; sleep disorders; Alzheimer's disease; circadian rhythm
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睡眠障碍在我国具有较高的发病率,中国社区老年人群睡眠障碍患病率高达41.2%,其中女性更为多见(45%)[1],严重影响患者及家属的日常生活质量。睡眠效率和睡眠时间随年龄增长显著下降,老年人群纵向研究发现,每10年睡眠效率下降3.1%,睡眠时间减少10 min[2]。阿尔茨海默病(Alzheimer's disease, AD)是衰老背景下,免疫介导的β-淀粉样蛋白(amyloid-beta, Aβ)和tau蛋白代谢、清除、降解等多环节退变复杂机制共同导致的常见老年神经系统疾病,严重影响老年人群的生活质量,加重社会和家庭的负担。近年来,越来越多的研究提示睡眠障碍与AD密切相关。睡眠障碍可激活炎症及应激反应,导致Aβ及tau蛋白沉积[3];进一步导致下丘脑视交叉上核等睡眠相关脑区神经元及突触损伤,从而加重睡眠障碍,形成恶性循环[4]。这些研究证据提示睡眠障碍与AD相互作用,为靶

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向睡眠调节防治AD提供了新的思路。然而,尽管有一定的研究基础,睡眠障碍与AD发生、发展的因果关系及两者之间的潜在影响机制尚未完全明确,认知障碍患者的睡眠调节策略仍缺乏统一的指导意见及标准化治疗方案。基于此,本文拟梳理和总结近年来睡眠障碍与AD相关性的最新研究进展,为疾病的早期预防和临床诊疗提供新的方向。

1 衰老与睡眠生理变化

睡眠质量和结构的变化是衰老的一部分,老年人群表现为夜间睡眠时间减少、睡眠效率降低、睡眠碎片化、白天小睡频率增加等宏观睡眠结构的变化,以及慢波睡眠期间纺锤波密度、K复合波密度及δ波下降等睡眠微观结构的改变。年龄增长与昼夜节律振幅降低及碎片化睡眠增加相关,老年人很难进入第2~3阶段的非快速动眼(non-rapid eye movement, NREM)睡眠阶段,因此大多睡眠偏浅,而Aβ病理会进一步加重碎片化睡眠[5]。

2 睡眠障碍与AD的相关性

2.1 睡眠障碍与认知损害程度相关

基于多导睡眠图的研究分析发现,与对照组相比,AD患者的总睡眠时间、睡眠效率、慢波睡眠和快速动眼(rapid eye movement, REM)睡眠比例显著降低,睡眠潜伏期、入睡时间、觉醒次数及REM潜伏期增加。此外,该研究还发现慢波睡眠和REM比例的降低与AD患者认知障碍严重程度显著相关[6]。Uleman团队通过构建系统动力学模型来计算散发性AD的多因果关系,发现睡眠质量和抑郁症状对认知功能下降影响最大,是模拟干预效果最强的AD可改变危险因素[7]。睡眠持续时间与认知障碍风险之间呈U型曲线关系,睡眠时间过长和过短均会加重认知障碍。另外,NREM睡眠、REM睡眠、睡眠效率、<1.0 Hz及1.0~4.5 Hz的NREM慢波活动等与认知功能之间也存在非线性关系[8]。而频繁且长时间的日间小睡也会加速认知功能下降,增加AD患病风险[9]。

2.2 睡眠障碍加重认知相关脑结构功能变化

研究发现睡眠障碍患者存在海马、额颞叶等多个认知相关脑区萎缩,平均体积显著减小[10]。慢性失眠患者的额叶、基底节区、半卵圆中心扩大的血管周围间隙数较对照组增多,且与简易智力状态检查量表(mini-mental state examination, MMSE)评分独立相关[11]。功能磁共振成像显示睡眠障碍患者丘脑与左侧壳核、海马旁回、杏仁核、苍白球和海马的连接减少[12]。在Aβ阳性的遗忘型轻度认知障碍人群中,睡眠潜伏期延长者脑干体积显著缩小,蓝斑与认知相关脑区的功能连接减少[13]。此外,横断面研究发现睡眠呼吸障碍老年人群在后扣带回、楔叶、楔前叶的Aβ负荷、灰质体积、脑灌注及葡萄糖代谢均较对照组高[14]。但也有研究发现此类患者表现为广泛脑血流灌注下降,尤其是在背外侧顶叶皮层和外侧前额叶皮层。这一表现与缺氧和碎片化睡眠显著相关,从而影响脑内功能网络连接,导致认知受损[15]。不同研究之间睡眠障碍患者脑结构及功能表现存在一定差异,可能与受试者年龄、睡眠障碍严重程度及病程长短等相关,因此呈现不同的脑活动调节。

2.3 睡眠障碍通过活化神经胶质细胞诱导神经炎症

进行睡眠碎片化干预的AD模型小鼠丘脑、杏仁核等多个区域小胶质细胞活化较对照组显著增多[16],提示存在神经炎症反应。而在社区老年人群中,碎片化睡眠与活化的星形胶质细胞特征基因高表达相关,后者与更重的认知障碍程度及更快的认知下降速度相关[17]。老年人群的纺锤波在慢波去极化阶段较早出现,通过影响星形胶质细胞及小胶质细胞活化介导的神经免疫炎症反应,直接干扰Aβ的降解及清除[18]。甚至在Aβ病理之前,前额叶快速频率(13~16 Hz)睡眠纺锤波减少也与神经胶质激活相关,从而对Tau磷酸化、突触退变等产生影响[19]。

2.4 睡眠障碍通过类淋巴系统影响AD病理蛋白的清除

Aβ沉积是AD淀粉样蛋白级联假说的核心特征。类淋巴系统是近期在啮齿动物大脑中发现的物质清除通路,通过动脉搏动驱动脑脊液沿血管周围间隙入脑,携带Aβ等有害代谢物质最终流入脑膜及颈部淋巴结等。而类淋巴的流入和清除表现出内源性的昼夜节律,且受到水通道蛋白-4(aquaporin-4, AQP4)的调节。尸检结果及动物模型研究均发现[20,21],AQP4表达水平随年龄增长而增加,额叶皮质血管周围AQP4定位减少,与Aβ增多及痴呆前期认知功能下降相关。而对野生型小鼠进行睡眠碎片化干预,可以观察到记忆学习损害及AQP4信号表达下降[16],两者之间可能存在因果联系。通过觉醒-睡眠周期的自我保护机制,机体达成致病物质清除和聚集之间的平衡。与睡眠期间相比,清醒时脑细胞间质液及脑脊液中的Aβ、Tau蛋白水平均较高,睡眠剥夺可使其进一步增加[22],一个晚上的睡眠剥夺可使脑脊液中的Aβ浓度增加约10%[23]。

3 睡眠障碍的干预与认知改善

当前证据表明睡眠节律或许是一种潜在的风险标志物,睡眠障碍的改善可能有助于 AD 的预防和延缓。目前虽然有一定的临床研究致力于探索睡眠调节对认知功能改善的作用,但研究结果尚不一致。

3.1 非药物干预

明亮光治疗(bright light therapy,BLT)通过增加白日强光照射刺激下丘脑视交叉上核,抑制褪黑素释放,增加个体白天的觉醒和活动,从而促进夜间睡眠,目前被越来越多的专家推荐为痴呆患者睡眠障碍的一线治疗方案。针对痴呆患者的随机对照研究发现[24],BLT 可显著降低夜间觉醒,提高睡眠质量及睡眠持续时间,减轻抑郁及易激惹等精神行为异常[25],对 AD 早期的认知功能下降具有改善作用。由于大部分研究样本量少,且可能合并治疗间相互作用,因此,BLT 在痴呆患者治疗中的有效性证据尚需大规模试验进一步明确。经颅光生物调节疗法(photobiomodulation therapy,PBM-T)利用单光源或多光源经颅定位直接照射脑组织,通过光生物调节达到治疗效果。研究发现,PBM-T 通过脑膜淋巴管刺激大脑 Aβ 的清除及增加脑组织血氧饱和度,可增加额叶、扣带回等皮层局部脑血流量,改善健康人群及主观认知下降者的认知功能[26-29]。远近红外光照射可促进细胞线粒体能量代谢,激活抗炎小胶质细胞吞噬作用,增强对 Aβ 的清除[30,31]。当前证据提示 PBM-T 可增加痴呆患者的总体获益,且无不良反应,可能是未来一项有潜力的非药物干预措施。

3.2 药物干预

褪黑素是一种与内源性睡眠节律调节相关的神经激素。AD 早期可有脑脊液褪黑素水平的降低,故外源性替代治疗或许能使 AD 患者获益。研究证明,褪黑素治疗组 MMSE 评分显著高于安慰剂组,且可降低轻度认知障碍患者脑脊液 tau 水平[32]。吡罗美拉汀是一类新型褪黑素 MT1/2/3 受体激动剂,在轻度 AD 患者中未发现治疗组与安慰剂组的认知改善存在差异[33],但对于未携带染色体 2q12 单核苷酸多态性位点的受试者,治疗组认知及睡眠评分上存在显著改善。对于常用的镇静催眠药,研究发现持续使用苯二氮䓬类药物对轻中度 AD 患者认知功能影响不大,但与谵妄、跌倒等风险的增加相关[34]。但非苯二氮䓬类药物治疗如艾司佐匹克隆,可使患者记忆、计算、日常生活能力等评分均有改善[35]。此外,食欲素水平升高与 AD 患者睡眠障碍及认知受损相关。莱博雷生(Lemborexant)是一种食欲素受体拮抗剂,用于成人失眠的治疗。一项 2 期临床试验结果提示 Lemborexant 可调节轻中度 AD 患者的昼夜节律[36],改善夜间睡眠情况,具有良好的耐受性及安全性,且不会加重患者认知障碍。

综上,睡眠障碍与 AD 相互作用,老年 AD 患者可呈现明显的睡眠障碍,而睡眠障碍亦可促进 AD 的发生发展。睡眠障碍影响 AD 发生发展的机制尚不十分清楚,可能与干扰脑功能活动调节、参与胶质细胞活化介导的神经免疫炎症反应、影响类淋巴系统的“清道夫”作用等密切相关。调节睡眠节律、改善睡眠障碍对于 AD 预防和管理具有重要意义。未来期待基础实验以明确睡眠障碍在 AD 病程中的潜在机制,开展临床试验以验证靶向睡眠节律等干预措施对于延缓 AD 发生、改善 AD 预后的重要价值。

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