

# 老年人群中睡眠障碍与阿尔茨海默病的关联性研究进展

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**【摘要】** 阿尔茨海默病是常见于老年人的一种以认知功能下降为主要改变的疾病, 对家庭及社会造成巨大的负担。睡眠障碍是阿尔茨海默病的重要临床表现之一, 与其发生、发展高度交织。睡眠障碍的发生会影响着生理及心理的各项功能, 从而引起一系列认知功能改变。现回顾近年睡眠及阿尔茨海默病的相关文献, 阐述睡眠障碍与阿尔茨海默病的关联和可能的机制。

**【关键词】** 睡眠障碍; 阿尔茨海默病; 干预; 综述

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## Research progress on the relationship between sleep disorders and Alzheimer disease in the elderly

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**【Abstract】** Alzheimer Disease(AD) is a common disease in the elderly with cognitive decline as the main change, causing huge burden to the family and society. Sleep disorder is one of the important clinical manifestations of AD, which is highly intertwined with its occurrence and development. The occurrence of sleep disorder will affect various physiological and psychological functions, thus causing a series of changes in cognitive functions. This paper reviews the related literature of sleep and AD, in the view of discovering the possible association mechanism between sleep disorder and AD.

**【Key words】** Sleep disorder; Alzheimer disease; Intervention; Review

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随着人口老龄化的加剧, 我国人均寿命逐年增加, 老年人的健康水平和生活质量逐渐成为一项需要重点关注的问题。老年人由于年龄的增长, 躯体机能逐渐衰退, 一些疾病也随之而来。其中, 阿尔茨海默病(Alzheimer disease, AD)作为一种常见于老年人群的神经退行性疾病, 会引起一系列的认知功能改变、生活能力的下降, 多有精神行为症状, 很大程度上影响了老年人的晚年生活质量, 也给照护人员带去了巨大压力和负担<sup>[1]</sup>。睡眠是人类正常生理活动之一, 影响着生理及心理等各项功能, 越来越多的研究发现, 随着年龄的增加, 睡眠会有相应的改变<sup>[2]</sup>, 而一旦睡眠出现问题, 会引起包括记忆力、注意力、执行功能在内的一系列认知功能改变, 并且会造成日常生活和学习能力的下降<sup>[3-4]</sup>。与此同时, 睡眠障碍也是AD的重要临床表现之一, 与其

发生、发展高度交织<sup>[5]</sup>。现回顾睡眠及AD的相关文献, 阐述睡眠障碍与AD的关联和可能的机制。

### 一、老年人睡眠障碍的特点

睡眠障碍是指睡眠量或质的异常, 或是睡眠时发生某些临床症状。老年人随着年龄的增长, 睡眠能力逐渐下降, 更易发生睡眠障碍<sup>[2]</sup>。一项国内荟萃分析的结果显示, 我国60岁以上老年人群睡眠障碍患病率约为47.2%<sup>[6]</sup>。随着年龄的增长, 睡眠结构发生一定改变, 尤其在中年步入老年的阶段, 睡眠总时长、睡眠效率、慢波睡眠比例均有一定程度下降, 而与之相反的是睡眠潜伏期、入睡后觉醒时间均有所增加<sup>[7]</sup>。在老年期, 由于生理因素(衰老、性别、内分泌改变、躯体疾病等)及社会心理因素(离退休、社会角色改变、生活习惯改变等)的共同影响, 老年人常常对自身睡眠质量呈负面态度, 经常抱怨

并放大夜间浅睡、频繁短暂的觉醒、白天易瞌睡等问题。相对年轻人而言,衰老会引起视交叉上核功能逐步下降<sup>[8]</sup>,造成睡眠时相前移、昼夜差异下降、适应时相改变的能力下降等变化<sup>[9]</sup>,因此老年人可能表现出更早的入睡及觉醒,以及难以适应轮班工作和倒时差带来的负面影响。

与此同时,正常衰老时睡眠改变与神经内分泌改变有关。研究表明,生长激素的分泌在青春期达到顶峰,在成年至中年期呈指数级下降,然后在中老年期缓慢下降<sup>[2]</sup>,这一现象与随年龄增长而下降的慢波睡眠改变相一致<sup>[10]</sup>。老年人睡眠结构的改变可能会放大与年龄相关的下丘脑-垂体-肾上腺轴功能下降,从而导致夜间皮质醇浓度升高,进而抑制慢波睡眠,并增加夜间觉醒次数<sup>[10]</sup>。老年人睡眠障碍特点在不同性别中存在一定差异。女性患者中失眠的发病率高于男性,可能是由于女性更容易受到压力的影响,也有可能和女性绝经后体内激素分泌改变有关<sup>[11]</sup>。但也有报道指出,虽然不同年龄段的女性均更易主诉存在睡眠问题,但多导睡眠监测结果与男性相比并无明显差异<sup>[12]</sup>。男性患者发生睡眠呼吸障碍的可能性比女性多出12%~15%<sup>[13-14]</sup>。随着年龄的增加,男性遭受睡眠问题的影响可能比女性更严重,有研究显示>70岁的男性比55岁男性的慢波睡眠减少了将近50%<sup>[15]</sup>。

此外,躯体疾病较多是老年人群的一大特点,而许多躯体疾病会直接或间接影响夜间睡眠,如慢性阻塞性肺疾病可引起夜间咳嗽,肾功能不全可引起夜尿增多,这些疾病导致的睡眠习惯及睡眠行为的改变,会导致老年人睡眠时间进一步碎片化。另外由于老年人夜眠较浅,伴侣的躯体问题所致的夜间活动也是影响自身睡眠的另一大困扰。

## 二、睡眠障碍与AD的发生发展高度交织

目前已有研究报道,在AD的临床前期,认知功能有明显临床改变的15~20年前,患者脑中 $\beta$ 淀粉样蛋白(amyloid  $\beta$ -protein, A $\beta$ )就已出现聚积<sup>[16]</sup>,而在此阶段,睡眠结构也发生一定的改变<sup>[17]</sup>。主观认知损害指主诉有记忆或日常能力下降,但无明显临床表现或量表评估的支持<sup>[18]</sup>,是AD预测指标之一<sup>[19]</sup>。一项2年随访的研究显示,睡眠问题在主观认知损害人群中很常见,而且此类人群的睡眠总时长较健康人群显著下降<sup>[20]</sup>。但需要注意的是,由于缺少客观证据,目前主观认知损害的诊断很大程度上取决于医师的临床经验和所供病史的详尽及可靠程度,因此存在一定的异质性。在已有认知能力下

降而未达到诊断标准的轻度认知损害(mild cognitive impairment, MCI)的人群中,睡眠障碍的发生率相较认知正常老年人更高,这很可能与大脑颞顶区神经网络变化以及影响夜间记忆整合的睡眠梭状波减少有关<sup>[21]</sup>。

睡眠障碍是AD的重要临床表现之一。AD是一种以认知功能下降为核心,患者日常生活能力、社会交往能力明显减退的神经退行性疾病<sup>[22]</sup>,约60%的AD患者至少患有一种睡眠障碍<sup>[23]</sup>。AD患者由于睡眠结构和睡眠昼夜节律的变化<sup>[24]</sup>,夜间睡眠时间减少、白天睡眠时间增多,呈现出碎片化的睡眠-觉醒模式,临床上常见的表现为日间嗜睡、失眠和“落日现象”等<sup>[25-28]</sup>。失眠通常指夜间难以入睡,入睡后难以维持睡眠,易早醒等,同时伴有与睡眠问题相关的日间症状<sup>[29]</sup>。日间嗜睡的患者通过白天不自觉的瞌睡行为来弥补当日的睡眠不足,这对患者的生活质量造成了极大的影响<sup>[25, 28]</sup>。随着疾病的进展,在部分AD的老年人身上可以看到“落日现象”<sup>[27]</sup>,即在傍晚之后出现的激越、易怒、徘徊等表现,这是痴呆伴发的重要精神行为症状之一。值得注意的是,由于AD患者伴发的睡眠以及夜间行为障碍会给护理人员带去巨大的心理和生活负担,睡眠障碍逐渐成为AD患者被送入院治疗的主要原因之一<sup>[30-31]</sup>。

睡眠障碍的发生会在一定程度上影响认知功能<sup>[32]</sup>。夜间睡眠结构的改变使实际睡眠和有效睡眠时间减少,影响白天记忆力和注意力的保持。一项Meta分析显示,急性睡眠剥夺会影响包括注意力和工作记忆在内的认知能力<sup>[33]</sup>。Honn等<sup>[34]</sup>的研究也证实了这一结论,睡眠不足会影响动态注意力的控制,从而影响了认知灵活性。慢性睡眠习惯的改变,在长期看来对记忆和日间警觉性有一定负面影响。一项研究睡眠与日常认知功能的Meta分析表明,与健康睡眠者相比,睡眠障碍患者在解决问题能力、工作记忆加工及保存方面存在明显损害<sup>[35]</sup>。Helfrich等<sup>[36]</sup>的研究表明,由于大脑老化,尤其是内侧额叶皮质的萎缩,影响慢波睡眠对睡眠梭状波的协调作用,而这一改变会损害夜间记忆整合,从而导致遗忘。Dai等<sup>[37]</sup>的研究揭示急性睡眠剥夺和慢性睡眠不足的患者脑灰质体积的改变上有重叠效应,提示灰质很有可能是在睡眠不足条件下,记忆和注意力改变的结构基础。另一项影像学研究表明,睡眠昼夜节律的改变,可以抑制海马神经元的生成,而进一步影响患者场景记忆能力<sup>[38]</sup>。此外,动物实验证据表明,睡眠障碍可能通过影响海马,进一步

影响空间记忆整合能力<sup>[39]</sup>。

睡眠障碍是AD发生的重要风险因素。中国台湾的一项研究发现,原发性失眠是AD的重要风险因素,其发生率是无原发性失眠患者的2.14倍,特别是40岁以下的患者,发生AD的风险要高于无原发性失眠的患者<sup>[40]</sup>。另一项关于失眠的研究中提到,在认知功能正常的失眠患者中,携带APOE- $\epsilon$ 4基因者,其日常执行功能更差,并且某些与AD相关的灰质区域,诸如左侧角回、双侧上额回、丘脑和右侧海马的体积更小<sup>[41]</sup>。有研究显示,阻塞性睡眠呼吸暂停综合征在轻度认知障碍患者中较健康人群更为常见,其主要表现为睡眠时气道的部分或完全关闭,从而导致夜间间歇性缺氧,致大脑氧储备不足<sup>[42]</sup>。与此同时,阻塞性睡眠呼吸暂停综合征的发生,多是由于肥胖、糖尿病等代谢疾病,缺氧和氧化应激,心血管疾病等原因<sup>[43]</sup>,而这些原因也是AD发生的重要风险因素,因此,阻塞性睡眠呼吸暂停综合征也被认为是AD发生的重要风险因素<sup>[44]</sup>。此外,睡眠障碍导致的行为模式和生活习惯的改变,也会提高认知下降的风险<sup>[45]</sup>。

### 三、睡眠障碍影响AD病理改变

A $\beta$ 沉积是目前AD的主流发病机制假说,有研究表明,在认知正常的老人中,更短的睡眠时长,睡眠效率以及更长的睡眠潜伏期与脑中A $\beta$ 的沉积有密切的联系<sup>[46]</sup>。睡眠活动能通过平衡脑间质液在脑中的流动,从而促进此类代谢产物的清除。但是当睡眠-觉醒周期被破坏时,促觉醒神经递质食欲素的水平升高和神经活动增强会相应增加,细胞代谢产物在中枢神经系统清除率就会降低<sup>[47]</sup>。通过正电子发射断层扫描(PET)技术检测可以发现,有睡眠问题的人在其脑部前额叶和岛叶的A $\beta$ 负担更多,而在无症状的中老年人中,睡眠质量欠佳的人A $\beta$ 负担更重,并且和衰老与AD相关的脑区体积更小<sup>[48]</sup>。

tau蛋白是另一种AD生物标记物,最新研究表明,在急性睡眠剥夺时,人脑脊液中tau蛋白含量增加约50%,而慢性睡眠剥夺增加了tau蛋白在神经网络中的扩散<sup>[49]</sup>。Benedict等<sup>[50]</sup>在一项关于健康年轻人的研究中发现,急性睡眠不足会导致总tau蛋白血液水平升高,证明即使在年轻人中,睡眠不足也会对脑部健康产生不利影响。此外,Lucey等<sup>[51]</sup>研究发现,在调整了年龄和性别等多个协变量之后,非快眼周期的慢波睡眠频率与tau蛋白呈负相关。

### 四、治疗

对于AD患者的睡眠情况进行干预,很大程度上

可以提高患者生活质量,减轻照护人员的负担。针对睡眠的认知行为治疗是目前治疗睡眠障碍的一线方案,推荐用于认知功能损害患者的睡眠管理<sup>[52]</sup>。通过保持良好的生活习惯和作息<sup>[53-55]</sup>,诸如保持适当躯体活动,减少午睡时间,避免摄入过多的咖啡等方式,达到睡眠限制以及刺激控制的目的,从而改善患者的睡眠。Cassidy-Eagle等<sup>[56]</sup>研究发现,对MCI患者进行认知行为治疗后,可提高患者睡眠质量,患者日间执行功能也能得到改善,但对言语记忆的帮助有限。光照疗法(bright light therapy, BLT)也可用于干预AD患者的睡眠,其主要通过刺激视交叉上核促进昼夜节律与环境明暗循环的同步,以改善睡眠节律紊乱。多项研究表明,BLT可以有效改善夜间睡眠质量,减少夜间觉醒次数,增加白天清醒时间,减少夜间激越行为,并改善认知能力,是一种对认知及睡眠均有作用的干预手段<sup>[57-58]</sup>。重复经颅磁刺激(repetitive transcranial magnetic stimulate, rTMS)<sup>[59]</sup>以固定频率和强度连续作用于某一脑区,能够增加慢波睡眠的波幅,加深睡眠深度,增强记忆,有助于机体恢复。其余如生物反馈疗法、音乐疗法等都有报道有益于改善睡眠,但需要更多研究支持<sup>[47]</sup>。

在药物治疗方面,中-短效苯二氮草受体激动剂(benzodiazepine receptor agonists, BzRAs)是治疗急性睡眠障碍的推荐用药,包括苯二氮草类药物和非苯二氮草类药物,但此类药物对于治疗AD的运用存在争议,有研究表明,苯二氮草类药物的使用会提高AD的风险( $OR=1.38$ ,  $95\%CI=1.07 \sim 1.77$ ),在使用时应避免长期服用并控制服用剂量<sup>[60]</sup>。此外,褪黑素受体激动剂和食欲素受体拮抗剂对于睡眠和认知功能均有一定效果。在一项为期6个月的随机、安慰剂对照、多中心的临床研究中发现,褪黑素治疗对合并睡眠障碍的AD患者的认知功能和睡眠的维持具有积极作用<sup>[61]</sup>。Kang等<sup>[62]</sup>研究发现,在急性睡眠剥夺和食欲素输注期间,脑间质液中A $\beta$ 的量会显著增加,但输注双重食欲素受体拮抗剂时则减少,这提示了食欲素受体拮抗剂能够通过调节睡眠节律,来减少A $\beta$ 的沉积从而延缓AD的进展。中医认为“痴呆”的病位在脑,但与肾、脾、心等部位功能失调也有关系<sup>[63]</sup>,宋代医家严用和在《济生方》中首次运用归脾汤治疗思虑过度,劳伤心脾,少寐、健忘等症,这为治疗认知及睡眠障碍打开了新的思路。

## 五、小结

睡眠障碍是老年人群中的常见病,其发生率高,形式多样,对老年人群生理和心理都有一定影响。AD随着老年人年龄的增长,其发生率也逐渐增加,一旦出现,对患者本人及家庭均带来重大的负担。在AD的发生发展过程中,睡眠问题贯穿全程,睡眠障碍既能从多方面影响认知功能,也是AD临床过程中的重要表现,甚至是多数患者被送至医院及养老院的重要原因。因此,探索睡眠障碍与AD的关联性,进一步研究其影响机制及可能的干预手段,能够为有认知能力下降和存在AD风险的人群提供潜在帮助。

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# 响度依赖性听觉诱发电位在情感障碍疾病中的应用进展

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**【摘要】** 中枢 5-羟色胺功能活性与情感障碍疾病密切相关, 而响度依赖性听觉诱发电位可反映中枢 5-羟色胺功能的活性, 为情感障碍疾病的诊断和疗效预测提供新的方法和依据。现将响度依赖性听觉诱发电位及其在抑郁症及双相情感障碍中的应用进行综述。

**【关键词】** 抑郁症; 双相情感障碍; 响度依赖性听觉诱发电位; 综述

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**Loudness dependence of auditory evoked potentials and its application in affective disorder** Gao Min, Xu Baoyan, Wang Qi, Sang Wenhua

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**【Abstract】** The functional activity of central serotonin is closely related to affective disorders, and the loudness dependence of auditory evoked potentials can reflect the functional activity of central serotonin, which provides a new method and basis for the diagnosis and prediction of treatment response of affective disorders. The loudness dependence of auditory evoked potentials and its application in depression and bipolar disorder are reviewed in this paper.

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