·综 述·

周围性听觉障碍与阿尔茨海默病的关系

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【摘 要】 周围性听觉障碍是好发于老年群体的感官障碍,阿尔茨海默病(AD)是患病率最高的神经系统变性疾病,研究发现周围性听觉障碍是AD发生的独立危险因素。目前两者相关的机制假说包括认知储备机制、社会隔离机制及共同病因机制。干预周围性听觉障碍可以延缓老年人认知功能减退,改善AD患者情绪及行为症状。

【关键词】 阿尔茨海默病;周围性听觉障碍;老化;助听器

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Association of peripheral hearing loss and Alzheimer's disease

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【**Abstract**】 Peripheral hearing loss is quite prevalent in senior population, while Alzheimer's disease (AD) is the most frequent neurodegenerative disease. Evidence showed that peripheral hearing loss is an independent risk factor of AD. The hypotheses regarding the mechanism of their relationship include cognitive reserve, social isolation and common etiology. Intervention of peripheral hearing loss attenuates the cognitive decline of senior population, and improves emotional and behavioral symptoms of AD patients.

【**Key words**】 Alzheimer's disease; peripheral hearing loss; aging; hearing aid

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阿尔茨海默病(Alzheimer's disease, AD)是最常见的神经退行性疾病,其病理特征包括神经炎性斑及神经原纤维缠结,临床主要表现为认知功能障碍、精神行为异常及日常生活能力受损。根据疾病进程,AD可分为临床前期、轻度认知障碍(mild cognitive impairment, MCI)期及痴呆期。AD患者病程越长,干预效果越差,因此,对AD高危人群进行早期诊断和干预尤为重要。近年研究发现,周围性听觉障碍与AD有着紧密联系。本文从听觉障碍的分类、周围性听觉障碍与AD的关系、周围性听觉障碍与AD发生的相关机制及干预周围性听觉障碍对AD的影响进行综述。

1 听觉障碍的分类

听觉障碍是老年群体患病率最高的感官功能障碍,其患病率随着年龄增长而升高。在年龄≥65岁的人群中,约40%~45%伴有听觉障碍,而在≥70岁的人群中,约83%患有听觉障碍[1]。听觉障碍根据

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病变部位可分为周围性听觉障碍和中枢性听觉障碍。前者为蜗神经核以下的听觉传导通路病变所致,主要由耳蜗病变引起,后者为蜗神经核及以上的听觉传导通路病变所致。周围性听觉障碍以听敏度下降和听阈升高为突出特点。中枢性听觉障碍不影响听敏度,主要表现为声音信号处理功能障碍,其最突出的特点是噪声中的言语感知功能障碍。本文主要讨论周围性听觉障碍与AD的关系。

2 周围性听觉障碍是AD发生的危险因素

Lin等[2]对347名认知正常、年龄≥55岁的中老年人进行听阈及多领域认知功能检测,结果提示听阈每升高25 db,认知功能下降程度相当于年龄增长6.8岁带来的影响,由此研究者认为,周围性听觉障碍可能加速认知功能下降。Taljaard等[3]的荟萃研究发现,外周听觉能力与多认知域的认知功能均呈显著正相关。多项大型队列研究发现,周围性听觉障碍越严重,认知功能下降越明显、痴呆发生率越高[4-7]。为探索周围性听觉障碍与AD的关系,Lin等[8]于2011年进行了队列研究,该研究纳入639名认知正常受试者,用纯音测听法检测其听阈,并进行了长达12年的随访,结果显示,试验终点受试者的AD发病率与听阈显著相关,听阈每升高10 db,AD发病率就升高1.2倍。由此可知,周围性听觉障碍不仅加速认知功能下降,更是AD发生的独立危险因素。

3 周围性听觉障碍与AD发生的相关机制

目前关于周围性听觉障碍与AD发生的相关机制有三种主流学说,即认知储备机制、社会隔离机制及共同病因机制。

3.1 认知储备机制

周围性听觉障碍患者由于输入的听觉信号较常人微弱,可能导致听觉信号传导通路及听觉相关脑区激活水平降低。同时在听觉信号处理方面需要非听觉相关的脑区进行功能代偿,消耗更多认知资源,使得用于其他方面的认知资源则明显减少,最终导致认知储备耗竭,脑功能乃至结构改变,从而促进AD发生发展[9]。

多项结构影像学研究发现,周围性听觉障碍患者中枢听觉传导通路白质纤维束完整性受损[10,11],颞叶、边缘系统、其他功能相关脑区乃至全脑皮层体积改变。Lin等[12]的队列研究结果提示,患有周围性听觉障碍的受试者与正常听力受试者相比,全脑及右侧颞叶(颞上回、颞中回、颞下回、海马旁回)的萎缩速度更快。Armstrong等[13]的队列研究结果提示,中年期周围性听觉障碍与右侧颞叶灰质、右侧海马及左侧内嗅皮层体积减小速度增快有关。此外还有多项研究发现,周围性听觉障碍与颞叶、边缘系统体积减小有关[14-18]。初级听觉皮层位于颞横回,对听觉传入信息进行初步处理。而颞叶的其他部分参与听觉传入信息的整合处理,颞中回和颞下回与语义记忆及语义整合有关,也参与AD源性轻度认知障碍的发生发展[12]。听觉信号减弱导致颞叶体积缩小,从而影响颞叶支配的大脑功能,导致患者出现颞叶功能缺损相关的语义理解障碍,长此以往也可能导致AD的发生发展[12,13]。边缘系统与颞叶功能位置临近、联系密切,听觉信号减弱也可能引起边缘系统体积缩小、功能障碍,促进AD的发生发展。此外,周围性听觉障碍也与颞叶以外的其他脑区及全脑体积改变有关[19,20]。周围性听觉障碍受试者与听觉正常受试者相比,右侧角回的灰质体积增加,而听敏度与右侧角回灰质体积有显著相关性。这是由于在颞叶功能减退的同时,其他认知相关脑区代偿性激活。角回与视觉、听觉传入信息的整合有关,听觉障碍患者由于听觉信号减弱,更加依赖唇语、面部表情等视觉语言信息,需要代偿性调动诸如认知控制网络、注意力网络等脑网络,对右侧角回的神经刺激增多,导致其体积增大[19]。

多项功能影像学研究发现,周围性听觉障碍受试者脑功能活动有广泛变化。Boyen等[21]发现听阈越高,声音刺激引起的皮质下听觉通路(内侧膝状体、下丘、蜗神经核)激活水平越低,Profant等[22]的研究也证实了这一结论。Wong等[23]对老年受试者进行言语刺激任务下的功能核磁评估,发现受试者听觉皮层激活水平减低与前额区激活水平异常增强有关。进一步研究发现,受试者左侧听觉皮层体积与前扣带回、额中回的激活水平呈负相关,与言语识别水平呈正相关[24]。Tyler等[25]发现在词语记忆测试中,年龄较大组的受试者左侧额颞叶灰质萎缩明显,且左侧额颞叶灰质萎缩水平与右侧额叶区域的异常激活有关,此异常激活帮助代偿脑萎缩所造成的认知功能障碍,使年龄较大组的受试者与年龄较小组的受试者表现出同等水平的词语记忆功能。综上,听觉皮层受损时,额叶区域代偿性激活,听觉皮层受损程度与额叶代偿性激活程度决定听觉障碍患者的行为功能。

3.2 社会隔离机制

长时间听力输入减少及其导致的交流障碍会降

低患者的社交质量,甚至引起社会隔离,产生孤独、抑郁和淡漠等情绪[26,27]。Husain 等[28]对受试者播放包含情绪的声音,应用功能核磁评估其脑代谢活动,发现周围性听觉障碍受试者杏仁核、海马旁回对上述声音反应降低、反应时间延长,这在神经影像学水平上反映了周围性听觉障碍与情绪反应的相关性。此外,多项临床研究发现,周围性听觉障碍严重程度与抑郁症状有显著相关性,周围性听觉障碍治疗后,抑郁情绪可得到显著改善[29-33]。以上研究提示周围性听觉障碍可以导致社会隔离及孤独、抑郁等异常情绪,而这些异常情绪是 AD 发生的危险因素[34,35],促进 AD 的发生发展。

3.3 共同病因机制

AD 与周围性听觉障碍都与人体老化相关,有共同的发病机制[36,37]。周围性听觉障碍和 AD 的发生发展可能与微血管因素和代谢紊乱有关,肥胖、糖尿病及高血压是其共同危险因素。Lindenberger 等[36]利用多元回归模型分析发现,≥90%的老年受试者认知功能减退与包括周围性听觉障碍在内的感觉功能减退有关。Anstey 等[37]发现,78.46%的老年受试者认知功能减退与包括周围性听觉障碍在内的感觉功能减退有关。由此研究者们推测,周围性听觉障碍和 AD 可能为老化相关神经系统退行性变的不同外在表现。然而 Lindenberger 等[38]的另一项近期研究发现,周围性听觉障碍和认知下降程度的相关性微弱,在校正年龄混杂因素后,两者间的相关性更加微弱,这提示周围性听觉障碍可能并非认知下降的独立危险因素。此试验与前述试验结果不同的原因可能在于前者为横断面研究,而后者为队列研究,且后者应用了更加先进的统计模型。

周围性听觉障碍与 AD 发生相关性的三种主流学说都有其合理性,但均未能完全解释周围性听觉障碍与 AD 发生两者间的关系,其机制有待于更多研究进一步探讨。

4 干预周围性听觉障碍对 AD 的影响

目前主要采用改善生活方式、佩戴助听器及植入人工耳蜗的方法对周围性听觉障碍进行干预。

4.1 对患有周围性听觉障碍的老年人进行听觉干预可延缓认知功能下降

Taljaard 等[3]的一项荟萃分析评估了周围性听觉障碍人群应用助听器或耳蜗植入对其认知功能的影响,结果提示接受听觉干预的人群比未接受听觉干预人群认知功能好。然而对于此研究结果的解读需谨慎,因为此项荟萃分析纳入的多数研究都没有随机化设计,且样本量较小。Deal 等[39]就听觉干预延缓周围性听觉障碍老年人认知功能下降的作用进行了随机对照研究,结果提示与对照组相比,听觉干预组在接受干预 6 个月时的听觉评分、记忆力均表现更佳。Maharani 等[40]长达 18 年的队列研究纳入 2 040 例患有周围性听觉障碍、认知正常的患者,每 2 年进行随访,结果提示,使用助听器显著改善记忆功能,降低认知功能减退速度。

4.2 对患有周围性听觉障碍的 AD 人群进行听觉干预对认知功能改善不明显

目前有关听觉干预对 AD 人群认知功能影响方面的研究较少。Nguyen 等[41]进行了一项多中心随机队列研究,该研究纳入 51 例患有周围性听觉障碍的 AD 患者,对于受试者使用助听器后的认知功能进行长达 12 个月的研究,干预组全程给予助听器辅助听觉(利用软件自动对受试者进行助听器适配),对照组后 6 个月给予助听器辅助听觉(适配方法同上),前 6 个月为对照期,期间不配戴助听器辅助听觉。结果提示,干预组与对照组 AD 患者的总体认知功能、行为症状及日常生活功能没有明显差别。研究者分析这可能与助听器未进行个性化适配导致声音放大作用不够强,以及干预组与对照组试验条件差别不够大有关,也可能与长期的听觉输入减少导致的脑改变短期内无法逆转及痴呆患者认知功能低下而导致助听器辅助的听觉信号输入无效有关。Hopper 等[42]对 31 例确诊痴呆且患有周围性听觉障碍的社区居民进行了横断面对照研究,结果提示使用助听器组与对照组认知测试评分没有明显差别。研究者认为阴性结果原因可能在于,测试时一对一的安静环境无法反映出受试者在实际生活中嘈杂情境下的听觉功能。此外,多项研究关注听觉干预对痴呆人群情绪及行为症状的作用,结果提示听觉干预对情绪、行为症状有改善[43-45]。

5 结 语

综上所述,周围性听觉障碍是 AD 发病的独立危险因素,但尚需更多大型临床队列研究进一步证实。周围性听觉障碍与 AD 发病之间有相关性,目前的三种主流假说均有合理性,但未能解释两者之间联系的具体机制,仍需深入研究探索。听觉干预有助于延缓老年人的认知功能减退,有助于 AD 人群的情绪、行为症状改善,但尚需高质量

的大型队列研究关注干预认知正常老年人的周围性听觉障碍对预防AD发病的作用及干预AD患者周围性听觉障碍对认知功能的改善效果。

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