

· 前沿进展 ·

# 阿尔茨海默病患者认知功能与自主神经功能关系的研究进展

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**【摘要】** 阿尔茨海默病(AD)是一种起病隐匿并呈进行性发展的神经系统退行性疾病,好发于老年人,主要表现为记忆力下降、认知功能减退、人格改变等。近年来随着我国人口老龄化进程加剧,老年AD发病率呈现指数级增长,给患者家庭及社会带来沉重负担,已成为重要的公共卫生问题之一。目前,临床上仍缺乏治疗AD的有效方法,药物只能帮助部分AD患者延缓认知障碍,尚不能阻止病情进展。近年研究表明,AD患者认知功能损伤可能与自主神经功能紊乱有关,而迷走神经刺激可能改善AD患者认知功能。本研究通过检索国内外相关文献综述了AD患者认知功能与自主神经功能的关系,旨在为改善AD患者认知功能提供新的思路。

**【关键词】** 阿尔茨海默病; 认知功能; 自主神经功能; 综述

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## Progress on Relationship between Cognitive Function and Autonomic Nervous Function in Patients with Alzheimer's Disease GAO Rui<sup>1</sup>, YI Xiao-shu<sup>1</sup>, YAN Ning<sup>2</sup>

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**【Abstract】** Alzheimer's disease, as one of progressive nervous system degenerative diseases with insidious onset, usually occurs in the aged and performs as memory deterioration, cognitive decrease, personality disorder and so on. As population aging process intensifies in recent years, morbidity of Alzheimer's disease occurs exponential increasing trend in the aged in China, which brings heavy family and social burdens and becomes one of important public health problems for now. At present, clinical effective method of Alzheimer's disease is still short of, though medicines may delay the cognitive disorder in some patients, but can not prevent the progression of disease. Recent studies showed that, cognitive impairment might be related autonomic nervous dysfunction in patients with Alzheimer's disease, and vagus stimulation may improve the cognitive function to

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some extent. This paper reviewed related literatures about relationship between cognitive function and autonomic nervous function in patients with Alzheimer's disease at home and abroad, in order to provide a new idea for improving the cognitive function.

【Key words】 Alzheimer's disease; Cognitive function; Autonomic function; Review

阿尔茨海默病 (Alzheimer's disease, AD) 是老年人群常见的神经退行性疾病, 主要临床表现为记忆力下降、认知功能减退、人格改变等。近年来随着我国人口老龄化进程加剧, 老年 AD 发病率呈现指数级增长, 尤其是 >85 岁高龄人群<sup>[1-2]</sup>; 此外, 中晚期 AD 患者常生活不能自理, 需长期专业陪护, 给患者家庭及社会带来沉重负担, 已成为不可忽视的社会问题。目前研究表明, 药物只能帮助部分 AD 患者延缓认知障碍, 尚不能阻止病情进展<sup>[3]</sup>。因此, AD 早期诊断及非药物治疗越来越受临床关注。近年来有研究表明, AD 患者早期认知功能减退可能与心脏自主神经功能障碍有关<sup>[4]</sup>。笔者通过检索国内外相关文献综述了 AD 患者认知功能与自主神经功能的关系, 旨在为改善 AD 患者认知功能提供新的思路。

### 1 AD 患者认知功能

认知功能指人脑接受外界信息, 经过加工、处理、转化为内在心理活动, 从而获取、应用知识的过程, 包括记忆、视空间、执行、计算、理解、判断等方面, 上述一项或多项认知功能损伤可导致认知障碍。目前基于大脑功能分区的研究结果显示, 认知障碍与不同脑区损伤有关<sup>[4-7]</sup>。相关影像学研究证实, 不同区域脑萎缩<sup>[8-11]</sup>及功能破坏<sup>[12-13]</sup>与早期 AD 患者认知障碍有关, 如海马、颞叶、枕叶、丘脑、胼胝体、皮质。GIRALDO 等<sup>[14]</sup>、DAULATZAI 等<sup>[15]</sup>研究结果显示, 海马、杏仁核、丘脑、颞叶、脑干孤束核与 AD 疾病进展有关; 相关影像学研究发现, 顶叶皮质、运动皮质、海马、基底核区铁沉积可能影响 AD 疾病进展<sup>[16-17]</sup>。为进一步明确各脑区与认知功能的关系, LINDEMER 等<sup>[10]</sup>发现, 胼胝体、扣带回与执行能力有关; FARRELL 等<sup>[18]</sup>发现, 后皮质区淀粉样蛋白阳性患者中年时就已经出现淀粉样蛋白相关的情景记忆下降; REAS 等<sup>[19]</sup>发现, 白质微结构改变与认知功能正常的老年人记忆下降有关。但由于大脑各区域之间存在复杂纤维联系及不同大脑区域共同掌控某一认知功能, 故不同大脑区域损伤所致认知障碍类型还有待进一步探究。

### 2 AD 患者自主神经功能

人体自主神经系统中枢位于大脑及脊髓, 主要由交感神经和副交感神经组成, 二者共同调节机体内环境稳定。大脑自主神经系统的结构主要包括下丘脑、部分大脑皮质、杏仁核和部分网状结构、脑干等。心脏自主神经系统是窦性心律的主要调节器, 正常情况下, 静息心率由交感神经和副交感神经张力 (即神经冲动的基础发放率) 共同决定。因此, 大脑相应部位损伤会导致心脏自主神经功能紊乱。既往研究表明, AD 进展过程中大脑皮质、皮质下层 (如杏仁核、丘脑、下丘脑、脑干、小脑) 等结构退行性病变会导致自主神经功能障碍<sup>[20]</sup>; AD 相关神经退行性病变早期与额叶神经元效能低下引起的自主神经功能障碍有关<sup>[21]</sup>。另外, AD 患者自主神经功能障碍也表现在外周神经, 如 FOTIQU 等<sup>[22]</sup>通过测量

瞳孔评估 AD 患者胆碱能缺乏发现, AD 患者瞳孔变化功能异常; KALMAN 等<sup>[23]</sup>研究发现, AD 患者皮肤血管阻力增加及血流量减少, 心电图 R 波间隔时间缩短, 长握力试验中收缩压下降, 表明 AD 患者自主神经功能障碍影响患者交感神经及副交感神经。

### 3 AD 患者认知功能与自主神经功能的关系

AD 的主要病理改变为  $\beta$ -淀粉样多肽 ( $\beta$ -amyloid peptide, A $\beta$ ) 在大脑皮质和海马区神经元外累积沉淀形成  $\beta$  淀粉样斑, 脑神经元内 Tau 蛋白异常聚集形成神经原纤维缠结上述蛋白并在大脑相应区域沉积, 进而影响自主神经功能。心率变异性 (HRV) 是临床常用的定量评估心脏自主神经系统功能的无创性技术, 主要包括时域分析法和频域分析法, 其中频域分析法主要用于记录交感神经及迷走神经功能变化<sup>[24-25]</sup>。

TOLEDO 等<sup>[26]</sup>研究结果显示, 相邻 NN 间期差值 >50 ms 的心搏数所占比例 (pNN50%)、相邻 NN 间期差值均方根 (rMSSD)、低频功率的归化值 (LFnu) 与 AD 患者认知功能呈正相关, 提示 AD 患者认知功能与副交感神经调节有关; 仰卧位时, 低频功率 (LF)、LF/高频功率 (HF) 与 AD 患者认知功能呈负相关, 提示 AD 患者认知功能与交感神经调节有关。JENSEN-DAHM 等<sup>[27]</sup>研究结果显示, 无自主神经功能损伤症状的 AD 患者存在自主神经功能损伤的内在表现, 主要表现为 Valsalva 动作时血压反应损伤。NICOLINI 等<sup>[28]</sup>通过分析 80 名轻度认知障碍患者及健康对照者在仰卧位自由呼吸、仰卧位 12 次/min 呼吸及站立位活动时 LFnu、高频功率的归化值 (HFnu)、LF/HF 发现, 站立位活动时 LFnu、HFnu、LF/HF 均下降, 与交感神经紊乱一致。FREWEN 等<sup>[29]</sup>进行横断面研究发现, AD 早期患者 24 h 内正常 NN 间期标准差 (SDNN)、LF/HF、LF 均下降, 提示 AD 早期即存在心脏自主神经功能紊乱, 且认知功能损伤程度与 SDNN、LF/HF、LF 下降程度有关。NEGAMI 等<sup>[30]</sup>研究发现, AD 患者 LF/HF 下降。STRUHAL 等<sup>[31]</sup>采用 HRV 的连续小波证实, 痴呆 (包括 AD) 患者存在自主神经功能障碍。MELLINGSETER 等<sup>[32]</sup>研究结果显示, 轻度认知障碍或伴有轻度认知障碍的 AD 患者倾斜 70° 时 HRV 指标发生变化, 主要表现为 HF 升高, LF、LF/HF 降低, 提示轻度认知障碍或伴有轻度认知障碍的 AD 患者交感神经反应较差。此外, 有研究表明, 认知功能与交感神经调制 (LF/HF) 呈负相关; 记忆功能与副交感神经调制 (HF) 呈正相关, 与交感神经调制呈负相关<sup>[33]</sup>。上述研究均表明, AD 患者认知功能与自主神经功能有关, 未来可能通过改善自主神经功能而减轻 AD 患者认知功能损伤。

### 4 迷走神经刺激

迷走神经是副交感神经的一种, 发端于延髓, 主要负责将胸、腹腔脏器 (除降结肠、乙状结肠) 感觉传递至大

脑不同部位,如目前研究发现传统迷走神经刺激可通过孤束核(nucleus of tractus solitarius, NTS)传递至蓝斑(locus coeruleus, LC),引起LC释放去甲肾上腺素(norepinephrine, NE),间接导致中缝背核(dorsal raphe nucleus, DRN)释放5-羟色胺(5-hydroxytryptamine, 5-HT),进而调节焦虑或抑郁情绪及癫痫发作<sup>[34-35]</sup>。此外,目前有关自主神经保持均衡治疗心力衰竭的临床二期实验正在进行<sup>[36-37]</sup>。CLANCY等<sup>[38]</sup>研究发现,迷走神经刺激可增加健康人HRV、减弱交感神经活动。目前有关迷走神经刺激治疗AD的研究仅限于小样本量研究及病例报告,如MERRILL等<sup>[39]</sup>对17例AD患者进行为期6个月迷走神经刺激治疗,结果表明AD患者对长期迷走神经治疗耐受,且认知功能有一定改善,与SJÖGREN等<sup>[40]</sup>研究结果相符。VONCK等<sup>[41]</sup>研究表明,短期迷走神经刺激对AD患者言语、记忆及识别功能有影响,长期迷走神经刺激对AD患者认知功能具有积极影响。魏天祺等<sup>[42]</sup>研究发现,迷走神经刺激可提高记忆功能再现过程。ANTONINO等<sup>[43]</sup>研究表明,迷走神经刺激能增加心脏压力感受器的敏感性,轻微减慢心率,降低HRV中LF/HF。上述研究均表明,迷走神经刺激可能改善AD患者自主神经功能及认知功能。

## 5 小结

目前研究表明,包括AD在内的多种认知障碍均存在心脏自主神经功能障碍,且自主神经功能紊乱类型与合并疾病有关<sup>[21, 26-27, 44-45]</sup>。AD患者自主神经功能紊乱主要表现为交感神经亢进,而副交感神经受抑制。目前,药物治疗并不能缓解AD病情进展,非药物治疗AD越来越受到关注,且迷走神经刺激属于非药物治疗方法。AD患者自主神经功能与认知功能有关,且迷走神经刺激会影响其认知功能,故未来可能通过干预自主神经功能而改善AD患者认知功能。

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