·专题综述·

主观认知下降临床研究进展

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【摘要】 主观认知下降是患者存在认知功能下降主诉但无客观临床证据的阿尔茨海默病临床前期阶段，被认为是早于轻度认知损害的更早阶段，进展为阿尔茨海默病的风险较高。目前国内对主观认知下降的认知有限，本文从主观认知下降概念、流行病学、研究框架、相关影响因素、与阿尔茨海默病关系，以及神经心理学测验、影像学研究进展进行综述，为临床早期诊断阿尔茨海默病提供可能。

【关键词】 认知障碍； 阿尔茨海默病； 痴呆； 综述

Clinical research progress on subjective cognitive decline

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【Abstract】 Subjective cognitive decline (SCD) refers to the preclinical stage of Alzheimer's disease (AD) in which patients have the chief complaint of cognitive decline but no objective manifestations. It is considered to be an earlier stage of mild cognitive impairment (MCI) than the preclinical stage of AD, and the risk of progression to AD is higher. At present, there is a limited understanding of SCD in China. This paper reviews the concept of SCD, the status quo of epidemiological research, research framework, related risk factors, its relationship with AD, as well as the progress of neuropsychological tests and imaging research, so as to provide the possibility for the early clinical diagnosis and treatment of AD.

【Key words】 Cognition disorders; Alzheimer disease; Dementia; Review

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痴呆是65岁及以上老年人病残的主要原因[1]。流行病学调查显示，我国65岁及以上痴呆患者约为1000万例[2]，其中阿尔茨海默病占63%～70%[3]。随着人口老龄化的加剧，阿尔茨海默病发病率逐年升高，截至2018年，我国60岁及以上阿尔茨海默病病例数高达983万例[4]，病死率约23.3/10万，略高于全球平均水平，成为严重危害国人健康的重大公共卫生问题，给社会经济带来沉重负担[5]。随着对阿尔茨海默病研究的深入，研究者将关注点聚焦于主观认知下降（SCD）阶段，即仅有认知功能下降主诉而无客观临床证据的临床前期阶段[6]。越来越多的研究表明，主观认知下降可能处于阿尔茨海默病临床前期阶段，并最终进展为阿尔茨海默病[7-8]。这一阶段尽管患者尚未表现出认知功能障碍或精神行为异常，但已发生脑结构改变，如灰质厚度变薄、白质纤维束完整性降低[9]，对预测临床转归、及时识别向阿尔茨海默病转化的高风险人群具有重要临床意义[10]。本文从主观认知下降的定义、流行病学、研究框架、相关影响因素、与阿尔茨海默病关系，以及神经心理学测验、影像学研究进展等方面进行综述，以为临床早期诊断阿尔茨海默病提供可能。

一、主观认知下降的定义

1982年，Reisberg等[6]首次提出“主观认知损害（subjective cognitive impairment）”概念，即个体有主观记忆力下降主诉，但客观神经心理学测验未见异常[11]。由于缺乏统一命名及诊断标准，随后20年间先后称为主观认知主诉（subjective cognitive complaints）、主观记忆主诉（subjective memory

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complaints）、主观记忆损害（subjective memory impairment）、主观记忆下降（subjective memory decline）等；直至2014年，主观认知下降国际工作组（SCD-I）将其统一命名为主观认知下降，定义为被他人观察到认知功能下降之前，患者自觉记忆力或认知功能减退，但客观认知功能评价正常或未达到轻度认知损害（MCI）诊断标准[7-8]。

二、主观认知下降的流行病学

主观认知下降病因复杂，与患有慢性疾病、低收入等因素密切相关[12]，且各个国家或地区对主观认知下降的诊断标准以及所采用的神经心理学测验量表并未统一[13]，使其患病率差异较大[14]。欧洲流行病学调查显示，约50%的德国成年人关注过自身记忆力[15]；瑞典主观认知下降患病率为8.96%～58.1%[16]；希腊一项研究纳入1456名65岁及以上认知功能正常的社区老年人，发现主观记忆下降发生率约为84.20%（1226/1456）[14]。美国疾病预防控制中心（CDC）对2015-2019年行为危险因素监测系统（BRFSS）中22个州的数据进行分析，发现约11%的45岁及以上人群存在主观认知下降主诉，且各州患病率略有不同（9.8%～17.3%），尤以45～64岁男性、在职、合并慢性疾病、非西班牙裔白种人的患病率更高[17]。亚洲主观认知下降相关研究较少，来自韩国的数据显示，50～64岁人群主观认知下降患病率为17.4%，65岁及以上人群升至29.4%[18]；我国北京市顺义区60～80岁人群主观认知下降患病率为14.4%～18.8%[19]。尽管上述研究显示亚洲国家主观认知下降患病率略低于部分欧美国家，但亚洲相关流行病学调查较少，尚不足以说明亚洲整体主观认知下降患病率较低。

三、主观认知下降的研究框架

2014年，主观认知下降国际工作组同时提出其研究框架，包括主观认知下降的定义、病程时限、发病年龄、自觉认知功能下降、排除其他引起认知功能障碍的疾病等内容。主观认知下降的评价及分类方法尚无统一共识，各项研究存在较大差异。部分研究基于问卷调查[14]、神经心理学测验[20]和主观陈述[17]，并分为主观认知下降和非主观认知下降两种研究类型[14]；亦有研究以认知域损害数目作为连续变量，采用频率、严重程度等描述主观认知下降患者的认知损害表现特征[21]。主观认知下降相关临床研究纳入对象、评价标准、结局指标，甚至文化和语言等差异均可影响其结果，因此有必要制定操作性较强的诊断标准，以减少主观判断，提高临床研究的可重复性及其间的可比性。研究框架强调患者主观感觉较之前正常状态有认知功能下降表现，且这种认知功能下降呈持续性，与其他可引起急性应激反应的病理状态或突发急性疾病无关，未达到轻度认知损害诊断标准，无法以精神障碍或除阿尔茨海默病外的其他神经系统疾病解释[7,21]。2017年，Molinuevo等[22]在此基础上增加了7项核心临床症状以判断主观认知下降作为阿尔茨海默病临床前期阶段，即主观认知下降叠加（SCD-plus）标准：认知功能障碍以记忆障碍为主；病程≤5年；发病年龄≥60岁；载脂蛋白E（*ApoE*）*ε4*等位基因变异；阿尔茨海默病生物学标志物阳性；自我感觉记忆力较同龄人差、症状呈持续性，且对这种认知功能下降感到忧虑而就诊；知情者证实存在认知功能下降，同时排除轻度认知损害、阿尔茨海默病及其他类型痴呆的诊断。作为基于生物学标志物的诊断标准，主观认知下降叠加标准提高了诊断的可靠性[8]，便于临床研究筛选主观认知下降患者制定统一标准，具有较强的实用性。目前认为，主观认知下降诊断是排除性诊断，对于不符合轻度认知损害标准但具备主观认知下降叠加标准的记忆力减退主诉和担心记忆力减退的患者，可认为是主观认知下降的高风险人群[22]。此外，主观认知下降国际工作组还建议，临床研究应尽可能尝试使用部分一致性问卷或一致性方法以确定主观认知下降与轻度认知损害之间的界限以及探索敏感性和特异性最高的主观认知下降生物学标志物[7]。

四、主观认知下降相关影响因素

1. 主观认知下降危险因素　研究显示，约84.2%的主观认知下降患者自述总体记忆力减退，76.6%存在记忆力相关损害，而命名障碍、定向力和计算力障碍等发生率相对较低，并据此将主观认知下降分为记忆型和非记忆型[14]。主观认知下降的记忆力下降与性别相关，女性总体记忆力减退发生率高于男性[14]。高龄、受教育程度较低、焦虑或抑郁情绪、脑血管病危险因素、酗酒、社交缺乏等生活方式均为主观认知下降的危险因素[19]。抑郁和焦虑等精神疾病[23-24]、除阿尔茨海默病外的其他神经系统疾病及其他系统疾病、药物不良反应[25]等因素中，部分因素可通过音乐及冥想[26]、认知训练[27]等非药物治疗得以改善。虽然主观认知下降提示认知功能减退，但并非所有主观认知下降均进展为痴

呆。因此，提高主观认知下降诊断准确性，识别可能向阿尔茨海默病转化的高风险人群，对阿尔茨海默病的早期预防与治疗具有重要作用。

2. 主观认知下降进展为轻度认知损害或痴呆的危险因素　Meta分析显示，约14.1%的主观认知下降患者随访4年后进展为轻度认知损害，14%的患者则进展为痴呆[28]。老年主观认知下降患者痴呆发生风险是正常老年人的2倍，且认知功能下降速度更快[28]。主观认知下降进展为轻度认知损害约为15年，再继续进展为阿尔茨海默病约7年[29]。Roh等[18]发现，女性、主观压力大、抑郁、酗酒是50～64岁主观认知下降患者进展为轻度认知损害的主要危险因素，而离异等不良婚姻状况则是65岁及以上老年患者进展为轻度认知损害的主要危险因素。国内一项研究显示，年龄、受教育程度＜6年、社交缺乏、酗酒是主观认知下降进展为轻度认知损害的危险因素[19]。焦虑较抑郁对主观认知下降转归的影响更显著[23]，持续性焦虑是主观认知下降进展为轻度认知损害的较强预测因素[28]，受教育程度低是主观认知下降进展为痴呆的较强预测因素[30]。脑组织β-淀粉样蛋白（Aβ）沉积或者脑脊液Aβ降低的主观认知下降患者进展为轻度认知损害的风险更高[31]，尤其是同时存在Aβ沉积以及磷酸化tau蛋白或总tau蛋白水平升高的患者[32]。Ribaldi等[33]的研究发现，不伴精神症状或躯体疾病的主观认知下降患者*ApoEε4*等位基因携带率更高，血浆$A\beta_{42}$水平更低，认知功能下降趋势更显著，提示伴阿尔茨海默病病理特征的主观认知下降患者认知损害更严重，进展为痴呆的风险更高。

五、主观认知下降与阿尔茨海默病

主观认知下降患者是进展为阿尔茨海默病的高危人群，同时存在阿尔茨海默病生物学标志物的患者进展为阿尔茨海默病的风险更高[20,32]，约27%患者脑脊液Aβ水平下降[34]，提示部分主观认知下降患者具有阿尔茨海默病病理改变。研究证实，主观认知下降与阿尔茨海默病之间具有Aβ级联假说参与，即脑组织Aβ沉积在主观认知下降阶段即已发挥作用，是导致神经元凋亡、丢失和痴呆发生的重要因素[35]，故推测主观认知下降可能是阿尔茨海默病连续疾病谱中的较早期表现。影像学和生物学检测技术的发展使阿尔茨海默病诊断从临床病理诊断向临床生物学诊断转变，为阿尔茨海默病早期诊断提供依据。主观认知下降患者Aβ主要沉积于颞叶、内侧前额叶、扣带回前部、后部皮质及楔前叶等脑区[36]，且黄斑区视网膜厚度变薄[37]，这些表现均与阿尔茨海默病相似。有研究显示，老年主观认知下降患者基底前脑后部静息态功能连接（FC）值下降与Aβ沉积呈正相关[38]；此外，主观认知下降患者脑组织Aβ沉积还与记忆力减退、执行功能障碍[11]、情感障碍[39]、焦虑[40]等显著相关，其脑组织Aβ异常沉积可能在出现客观认知损害表现前10余年即已出现[41]。伴血浆磷酸化tau蛋白（p-tau181和p-tau217）升高、$A\beta_{42}/A\beta_{40}$比值降低、神经丝轻链（NfL）蛋白增多、携带*ApoEε4*等位基因[42-43]等生物学特征，或伴内侧颞叶（海马）萎缩[44]等阿尔茨海默病典型MRI征象的主观认知下降患者进展为阿尔茨海默病的风险显著增加。携带至少1个*ApoEε4*等位基因和（或）有痴呆家族史的主观认知下降患者记忆力减退风险是其他认知域损害的1.7倍，且*ApoEε4*基因型与脑组织Aβ异常沉积密切相关[45]，提示以记忆力减退为主要表现的主观认知下降可能是阿尔茨海默病的临床前期阶段[8]。主观认知下降进展为阿尔茨海默病的危险因素主要包括携带*ApoEε4*等位基因、阿尔茨海默病生物学标志物阳性、海马神经元退行性变、内侧颞叶葡萄糖代谢降低[7,25]；此外，年龄≥65岁、存在阿尔茨海默病危险因素、应用抗胆碱药或镇静药的人群主观认知下降发生率显著增加[22]。

六、主观认知下降神经心理学测验研究进展

主观认知下降主要是患者主观感觉认知功能下降，而传统的神经心理学测验量表多针对轻度认知损害或痴呆进行设计，其敏感性较低且无法识别主观认知下降。Gifford等[46]研发的主观认知下降问卷-9（SCD-Q9）包括定性和发生频率两个维度，耗时3～5分钟，无论从受试者主观报告还是知情者报告，该问卷均可有效区分主观与客观认知功能下降患者。采用记忆主诉问卷（MAC-Q）调查发现，主观认知下降患者最常见的认知损害是情景记忆，其次是执行功能[47-48]。修订版疾病感知问卷（IPQ-R）记忆问卷部分包括症状、病因、结局（稳定或进展）、症状反复、病程、个人感知、治疗、症状持续时间和情绪共9项内容，其信度和效度均较高，适用于评价中老年主观认知下降患者的记忆功能[49]。日常认知量表（Ecog）也是临床评价主观认知下降的常用量表，包括日常记忆、语言功能、视空间能力、计划、组织和分散注意力共6项内容，其中日常记忆可用于

鉴别正常人与轻度认知损害患者[50]。西班牙版面孔-姓名关联记忆测试(S-FNAME)主要用于评估记忆力,其评分与脑脊液Aβ水平呈正相关[42]。由于国内对主观认知下降的认知不足,尚缺乏适合国人的主观认知下降诊断与鉴别诊断的神经心理学测验量表。首都医科大学宣武医院韩璎教授团队发现,部分轻度认知损害患者SCD-Q9问卷评分为零,提示该问卷可能未涵盖所有主观认知下降主诉,他们在SCD-Q9问卷基础上对其上位条目池SCD-Q21问卷进行汉化,以期探寻适用于我国的早期阿尔茨海默病筛查量表[43];他们还采用SCD-Q9问卷和听觉词语学习测验长延迟回忆(AVLT-LR)对2689名社区老年人进行认知功能评价,发现AVLT-LR评分降低者SCD-Q9问卷无异常[19],提示不同量表的效度和信度不同,需要根据不同人群选择不同量表,AVLT-LR可能是适合国人的主观认知下降记忆评价量表,未来尚待更多研究进一步证实。此外,尚未进展到痴呆的临床前期阿尔茨海默病患者对自身认知功能改变有主观体验,但进展至痴呆阶段时,患者自知力丧失,导致这种主观体验逐渐消失,提示对于主观感受自身认知功能持续下降但神经心理学测验无明显异常或仅呈轻度损害但未达到轻度认知损害的患者,可能是处于阿尔茨海默病临床前期的高风险人群,应尽早干预,将治疗时间窗提前,可以有效阻止或延缓其进展。

七、主观认知下降影像学研究进展

由于缺乏客观量化指标,主观认知下降的诊断主要依靠临床评估,极易误诊、误治。随着影像学技术的发展,MRI技术为主观认知下降的早期诊断、疾病严重程度评估和临床预后等提供了更多信息,其中,结构性磁共振成像(sMRI)由于可以测量脑容积及皮质厚度,量化脑结构改变,临床普及度较高,业已成为临床评估认知功能障碍性疾病的重要手段。主观认知下降的影像学征象主要包括基底前脑萎缩,海马体积缩小,前额叶、颞叶、岛叶皮质变薄,白质完整性破坏[51],且这些结构改变通常与其主诉相关[9]。以记忆力减退为主诉的患者多具有阿尔茨海默病易受累脑区(顶下区、颞下区、颞中区)特征性皮质萎缩模式[52-53],并最终进展为阿尔茨海默病。Fu等[54]对比分析主观认知下降患者、遗忘型轻度认知损害患者、阿尔茨海默病患者和健康志愿者的sMRI,发现3种疾病患者脑体积、表面积和形状均呈现出显著的双侧不对称性改变,且海马形态不对称性与听觉词语学习测验(AVLT)即刻回忆($r=-0.184$,$P=0.025$)、长延迟回忆($r=-0.170$,$P=0.035$)、延迟再认($r=-0.213$,$P=0.011$)评分和蒙特利尔认知评价量表(MoCA)评分($r=-0.212$,$P=0.012$)呈负相关,伏隔核形态不对称性与AVLT即刻回忆评分($r=-0.183$,$P=0.026$)和MoCA评分($r=0.197$,$P=0.018$)呈负相关。采用经颅磁刺激(TMS)刺激主观认知下降患者左侧背外侧前额皮质(DLPFC)可诱导再认记忆恢复,sMRI显示默认模式网络(DMN)中左侧颞叶及额叶皮质厚度与再认记忆改善程度呈正相关[55]。符合主观认知下降叠加诊断标准的患者sMRI显示出与阿尔茨海默病相似的认知功能和脑容量特征,提示此类患者更有可能进展为阿尔茨海默病[56]。此外,主观认知下降患者最先萎缩的脑区是内侧颞叶,且萎缩程度与认知功能障碍程度呈正相关,进展性主观认知下降患者脑萎缩范围可逐渐累积颞下区和颞中区,与阿尔茨海默病皮质萎缩模式相似;主观认知下降患者还可出现基底前脑胆碱能神经核团(Meynert基底核)与海马CA1区体积显著减少,这种与阿尔茨海默病相似的海马亚区体积变化征象进一步说明主观认知下降是阿尔茨海默病临床前期阶段[57-58]。

综上所述,主观认知下降作为早于轻度认知损害的阿尔茨海默病临床前期更早阶段,进展为阿尔茨海默病的风险较高。临床医师应提高对主观认知下降的关注度,密切跟踪随访,将阿尔茨海默病的诊断与治疗关口前移。未来研究可将主观认知下降的神经心理学测验与生物学标志物和多模态影像学联合,实现临床前期识别阿尔茨海默病,为临床超早期诊断阿尔茨海默病奠定基础。

利益冲突 无

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