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标准与规范

新型冠状病毒肺炎后认知障碍诊治和管理共识

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新型冠状病毒肺炎(corona virus disease 2019, COVID-19)(简称“新冠肺炎”)在全世界的传播和蔓延给民众, 特别是老年人的身心健康带来了巨大影响, 约80%感染新冠肺炎的患者存在一个或多个长期的症状[1~3](Ⅰ级证据). 世界卫生组织(World Health Organization, WHO)将这种长期症状持续至少2个月以上的定义为长病程新冠肺炎(long COVID)[4]. 长病程新冠肺炎除肺部症状外, 往往还可出现注意力不集中、定向障碍或反应迟钝等多种认知障碍症状[5,6](Ⅰ级证据). 根据国内外关于新冠肺炎的相关文献, 结合我国实际情况, 就长病程新冠肺炎与认知障碍、相关危险因素及管理措施形成专家共识, 以期提高对这一疾病的认识, 减少新冠肺炎后认知障碍对人类日常功能的损害, 为新冠肺炎防控期间认知障碍患者的诊疗提供参考.

1 新冠肺炎后认知障碍的流行病学

目前全球新冠肺炎感染人数约5.3亿, 给全球造成极大影响[7]. 荟萃分析显示, 从2020年初至2021年底, 全球约1820万人死于新冠肺炎, 由此导致的超额死亡率(excess mortality)为120.3人/10万人, 21个国家的超额死亡率超过了300人/10万人[8](Ⅰ级证据). 新冠肺炎后认知障碍发病率有大量报道. 一项荟萃分析显示, 在新冠肺炎诊断3个月及以上的个体中, 22%出现认知障碍[5](Ⅰ级证据). 在另一项针对新冠肺炎后神经精神症状的荟萃分析中发现, 脑雾(brain fog)约占32%, 记忆障碍28%, 注意力障碍22%, 说明认知障碍在长病程新冠肺炎中广泛存在[9](Ⅰ级证据). 一项来自西班牙的多中心研究发现, 在1142名感染过新冠肺炎的患者中, 9.6%会出现脑雾, 19%出现记忆丧失等非呼吸道症状[10](Ⅱ级证据). 在国内, 有证据表明新冠肺炎可累及神经系统[11]. 一项针对武汉老年新冠肺炎患者(>60岁)的研究表明, 35.71%的重症患者有认知受损(包括痴呆和轻度认知损害), 出院6个月59.24%的重症患者认知减退[12](Ⅱ级证据). 在新冠肺炎后长期症状的荟萃分析和系统性综述中也报道记忆受损的患病率可达35%[13](Ⅰ级证据). 另外, 认知障碍患者的新冠肺炎感染风险显著高于认知正常人群. 一项观察性研究发现, 阿尔茨海默病(Alzheimer’s disease, AD)患者感染新冠

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肺炎的风险是正常人群的2.29倍，痴呆患者感染新冠肺炎的风险是正常人群的2.16倍[14](Ⅱ级证据).

推荐意见：应重视长病程新冠肺炎对认知功能造成的广泛损害，并开展对新冠肺炎后认知状况的评价(A级推荐).

2 临床表现和诊断

目前还没有国际公认的临床定义或明确的诊断标准，基于相关证据，将新冠肺炎后认知障碍(即新冠肺炎后3个月新发的认知障碍)分为以下两类.

一类仅表现为认知障碍，具有记忆、语言、定向、应用、注意力、知觉(视、听、感知)和执行功能障碍等症状[6,9,15](Ⅰ级证据)，提示新冠肺炎对大脑的结构和功能产生影响. 另一类为脑雾，是一种“大脑模糊状态”，是新冠肺炎后常见的神经系统症状. 脑雾是一系列症状的集合，表现为认知障碍(注意力不集中、失语、健忘等)，同时可能伴有疲劳、缺乏动力和睡眠障碍等. 脑雾并不一定伴有大脑的结构性损伤，部分患者可恢复正常[9,16,17](Ⅰ级证据).

临床上新冠肺炎后认知障碍可根据英国国家卫生和临床技术优化研究所(UK National Institute of Health and Clinical Excellence, NICE)提出的诊断标准进行临床诊断: 经实验室检查确认的新冠肺炎感染; 在新冠肺炎感染期间或之后出现认知功能减退(记忆力、语言、定向力、应用、注意力、知觉和执行能力等减退)，持续超过12周，不能用其他疾病解释[18].

此外，新冠肺炎前已存在认知障碍的这一部分人群症状更易加重[19~21](Ⅰ级证据)，具体是指在新冠肺炎感染前已经存在的各种变性病和非变性病引起的认知障碍. 变性病主要包括AD、路易体痴呆(dementia with Lewy body, DLB)、帕金森病痴呆(Parkinson disease with dementia, PDD)和额颞叶变性(frontotemporal lobar degeneration, FTLD)等. 非变性病主要包括血管性痴呆(vascular dementia, VaD)、正常压力性脑积水以及其他疾病，如颅脑损伤、感染、免疫、肿瘤、中毒和代谢性疾病等[22]. 痴呆患者在新冠肺炎感染最初阶段常有精神状态改变等不典型新冠肺炎症状(包括意识混乱、焦虑、迷失方向、拒绝照料和食欲不振等)，而发烧和咳嗽等典型症状往往滞后[23,24]，造成诊断和治疗的延误. 因此，对此类患者应该提高警惕.

推荐意见: 如果新冠肺炎后出现认知障碍症状，可以考虑诊断为新冠肺炎后认知障碍，可进一步完善头颅影像、认知评定、实验室检查等. 应在出院后6周或更长时间内随访疑似或确诊新冠肺炎人群的动态认知变化，必要时可咨询专业人员(专家共识).

推荐意见: 如果在新冠肺炎前就有认知障碍，发生新冠肺炎后加重，考虑为新冠肺炎前认知障碍，或混合加重，应对新冠肺炎期间认知障碍患者进行详细的病史询问，确定认知障碍加重因素，从而有针对性的处理(专家共识).

3 新冠肺炎后认知障碍的危险因素

新冠肺炎后认知障碍是一种复杂的多因素疾病，其发病的危险性是由自身和环境等多因素共同决定的. 目前已有初步证据表明自身因素(如年龄、性别、教育程度)、新冠病毒感染的严重程度、药物因素以及隔离、医疗支持缺乏等环境因素都与新冠肺炎后认知障碍的发生相关[5,25](Ⅰ级证据). 为了预防和干预新冠肺炎感染后认知障碍，明确其危险因素至关重要.

3.1 自身因素

国外已有报道显示女性新冠肺炎后认知障碍的发生率高于男性(56% vs. 36%)[5](Ⅰ级证据). 还有报道提出，女性新冠肺炎患者创伤后应激障碍(post-traumatic stress disorder, PTSD)、疲劳、抑郁、焦虑和强迫症状都更严重，增加了认知障碍的发生[26~29](Ⅰ级证据)，国内也有相似的报道[30](Ⅲ级证据). 年龄也与新冠肺炎后认知障碍的发生有关. 针对新冠肺炎患者认知功能的研究发现，高龄与新冠肺炎后认知能力下降相关[12,16](Ⅰ级证据). 我国一项针对新冠肺炎患者出院后认知障碍的研究，发现低教育水平是新冠肺炎患者认知能力下降的危险因素[12](Ⅲ级证据). 另外，遗传因素也与新冠肺炎后认知障碍的发生有关. 有研究发现*APOE ε4*会增加新冠肺炎感染的风险，同时也会增加新冠肺炎后认知障碍发生的可能[31](Ⅰ级证据).

3.2 新冠肺炎感染严重程度

认知障碍在不同程度的新冠肺炎感染后均有报道. 一项针对无症状新冠肺炎患者的研究发现，其在视觉、命名和流畅性等存在认知功能障碍[32](Ⅲ级证据).

另有针对轻-中度新冠肺炎感染者的研究发现, 78%患者持续存在轻度认知障碍[33](III级证据). 目前, 已有研究证实, 新冠肺炎感染的严重程度与新冠肺炎后认知障碍的发生相关[16,34~36](Ⅰ级证据). 一项纳入了1539名新冠肺炎患者认知功能的研究中, 重症新冠肺炎患者认知障碍的发生率高于非重症新冠肺炎患者(59.24% vs. 28.67%)[12](III级证据). 还有研究发现, 认知功能障碍与缺氧引起的神经元损伤相关[37](Ⅰ级证据), 而重症新冠肺炎患者即使在康复数月后仍然处于缺氧状态, 所以其认知障碍的程度也更为严重[38,39].

3.3　药物因素

为遏制新冠肺炎的感染与传播, 许多药物已经投入使用, 其中治疗新冠肺炎的抗逆转录病毒药物很可能具有神经毒性作用和认知损害作用[40,41](Ⅱ级证据). 皮质醇作为新冠肺炎用药, 也可能会导致认知障碍[42](III级证据). 另外, 一项纳入了16项随机试验的荟萃分析显示, 瑞德西韦与羟氯喹用于治疗新冠肺炎时与认知障碍有关[43](Ⅰ级证据). 少部分病人在使用托珠单抗后也可能出现认知损害的状况[44,45](Ⅰ级证据). 而新冠肺炎患者支持治疗时使用的苯二氮卓类药物[41,42](Ⅰ级证据)、阿片类药物[46](III级证据)、退热类药物[47]等也已被证明会增加认知障碍的风险. 因此, 针对新冠肺炎患者的用药可能会影响认知障碍的发病率. 同时, 在治疗新冠肺炎期间, 由于获取医疗支持的难度增大, 已有神经精神症状的患者可能会自行使用抗精神病性药物、安眠药及其他镇静药物[48](Ⅱ级证据), 医务工作者无法及时评估患者的药物用量及副作用, 这可能导致患者出现认知障碍[49,50](Ⅰ级证据).

3.4　环境因素

新冠肺炎期间, 隔离政策强有力地减少了患病率, 遏制了传染病扩散. 但也有研究证实, 隔离会带来更低的社会参与度(如独居、社会支持少、社交网络小、社交频率低)与更高的孤独感[49,51,52](Ⅰ级证据), 这将导致认知障碍的发生或恶化[53](Ⅰ级证据). 一项来自中国的随访研究证实, 在新冠肺炎隔离至少6个月后, 42%的轻度认知障碍患者、54.3%的AD患者以及72.7%的DLB患者的认知功能进一步受损[54](III级证据). 另外, 老年人, 尤其是养老院中的痴呆患者面临缺乏照料及医疗支持的情况. 来自澳大利亚的研究表明, 养老院中缺乏可靠的医疗指南与缺乏药物的报告率分别达到了19.9%与10.3%[55]. 另一项来自阿根廷的研究显示, 在新冠肺炎疫情期间, 60%的家庭暂停对养老院中痴呆患者的探望, 超过90%的痴呆患者家庭停止已经进行的认知及物理治疗[50,56,57](Ⅰ级证据), 大量养老院为减少感染与死亡实行了严格的探视制度, 但这也增加了护理人员的负担, 同时老年人的家属会面更为困难, 促进认知障碍发生的可能[58,59].

推荐意见: 要加强长病程新冠肺炎认知障碍危险因素的识别, 尽可能对危险因素进行有效控制(A级推荐).

4　新冠肺炎认知障碍的治疗与管理

4.1　药物治疗

首先应积极控制病原体, 疫苗接种是目前预防新冠肺炎经济、有效的措施, 已被全世界广泛应用. 除了疫苗接种作为预防措施外, 对于患者出现的相应症状应及时治疗. 目前为止, 改善认知障碍的药物包括促智药、胆碱酯酶抑制剂、离子型谷氨酸受体拮抗剂、麦角生物碱类制剂、钙离子拮抗剂、银杏叶提取物等. 其中治疗新冠肺炎后认知障碍的潜在药物已经开展3项临床试验(多奈哌齐、法莫替丁、沃替西汀)(https://trialsearch.who.int/Trial2.aspx). 但是截至目前, 还没有正式批准用于临床治疗的新冠肺炎认知障碍药物. 因此, 通过非药物治疗改善新冠肺炎认知障碍尤其重要.

推荐意见: 根据现有循证医学证据, 治疗新冠肺炎后认知障碍的药物疗效有待进一步证实. 建议加强非药物治疗新冠肺炎后认知障碍的临床研究(专家共识).

4.2　非药物治疗

(1) 日常体育活动干预. 老年人作为新冠肺炎的高危人群, 在新冠居家期间体育活动的急剧减少可能会通过加速衰老过程和与年龄相关的疾病而对老年人产生更严重的影响[60~62](Ⅰ级证据). 而体育活动在预防认知障碍中有重要作用[63~66](Ⅰ级证据). 因此, 对于老年人, 建议新冠肺炎疫情居家期间根据自身情况进行适度运动, 例如深蹲、俯卧撑、仰卧起坐、跳舞、爬楼梯以及在现场步行或跑步等[67~69](Ⅰ级证据). 此外, 可以考虑瑜伽或传统太极拳, 因为它们不需要任何设

备或大空间. 其中太极是一种中国传统的身心锻炼, 在新冠肺炎期间可以改善老年人的心理和情绪状态、认知和学习, 有助于维持大脑功能和建立认知储备[70~73](Ⅰ级证据).

推荐意见: 建议在隔离期间根据自身情况进行适度体育活动, 有助于疫情居家情况下预防认知障碍(A级推荐).

(2) 饮食干预. 新冠肺炎导致个人和全球的饮食习惯发生了变化. 一项大型意大利人口调查发现, 在新冠肺炎期间, 35.8%的研究对象食用较少的健康食品, 48.6%的人体重增加[74~76](Ⅰ级证据). 不健康饮食可能导致新冠肺炎预后不佳[77], 同时可能直接或间接参与认知障碍的发展[78,79](Ⅰ级证据). 因此在新冠肺炎期间采取健康、均衡的饮食习惯至关重要. 目前的证据鼓励食用新鲜和未加工的植物性食品, 如蔬菜、水果和全谷物产品, 补充适量维生素和矿物质(如锌、维生素C、D、A), 维持充足水分, 合理摄入脂肪, 避免过量糖和盐摄入等[80~83](Ⅰ级证据). 据研究发现地中海饮食可延缓衰老, 保护认知功能[84~86](Ⅰ级证据). 因此, 鼓励采用地中海饮食, 有可能减少新冠肺炎期间老年人认知障碍的发生.

推荐意见: 老年人群新冠肺炎期间提倡健康多样化饮食(如地中海饮食), 对预防认知障碍有益(A级推荐).

(3) 社交活动干预. 社会参与被定义为积极参与体育、文化、娱乐等各种活动[87,88]. 新冠肺炎期间社区隔离、限制探望亲友、社交距离增加等导致的社交活动减少可能会对认知功能产生负面影响[89,90](Ⅰ级证据). 为了预防因为社交活动限制导致的认知损害, 有专家提出, 可以利用电话、网络等方式与家人、朋友联系以获得心理支持; 丰富居家生活安排, 进行一些简单的家务或园艺活动等[91]. 也有国外专家建议医疗和社区服务组织提供电话支持热线, 或通过电子媒体提供自我帮助的指导(如放松或冥想练习的指导), 将健康教育与心理咨询相结合[92].

推荐意见: 建议加强社交活动, 医疗和社区服务组织为患者提供电话支持热线和自我帮助的指导(A级推荐).

(4) 认知刺激. 有多项研究指出, 认知刺激可以改善痴呆高危人群及痴呆患者的认知功能[93~95](Ⅰ级证据). 频繁的认知刺激, 如听广播、阅读报纸或杂志、读书、玩纸牌或拼图类的游戏等与AD风险降低有关[96]. 此外, 继续教育作为一种有效的认知训练, 以减轻与衰老相关的认知下降[97]. 因此, 在新冠肺炎期间, 认知刺激对于认知功能的保护有重要作用. 有专家提出, 在新冠肺炎期间, 可以使用电子设备(如手机、计算机等)、应用软件[91]、虚拟现实设备(virtual reality, VR)[98](Ⅰ级证据)等维持认知刺激. 有国内研究发现, 基于互联网、计算机的多认知域的适应性认知训练系统可以显著改善认知障碍患者整体认知功能[99,100](Ⅰ级证据)

推荐意见: 在长病程新冠肺炎中, 认知障碍高危老年人群提倡频繁的认知训练, 对预防认知障碍有益(A级推荐).

(5) 睡眠障碍管理. 睡眠障碍是新冠肺炎期间的主要神经心理症状之一[101](Ⅰ级证据), 国内外报告的新冠肺炎期间睡眠障碍的患病率分别为18.2%[102]和57.1%[103]. 充足的睡眠可减轻与新冠肺炎相关的认知障碍[104,105](Ⅰ级证据). Ransing等人[106]建议, 在新冠肺炎期间, 应维持规律的睡眠-觉醒周期. 同时, 认知行为疗法专家提出了几种易操作的行为干预措施, 以缓解新冠肺炎相关的睡眠质量恶化: 将对压力的思考限制在白天的特定时间(约15 min), 以减少对夜间睡眠的干扰; 使用社交媒体与家人和朋友分享压力和焦虑感, 同时分享积极信息, 但最好不将通讯设备带入卧室; 感到困倦时再上床睡觉, 并保持易于睡眠的昏暗光线; 睡前选择熟悉和放松的活动, 例如看书、瑜伽等[107].

推荐意见: 建议遵循规律的睡眠-觉醒周期, 并适当进行有利于睡眠的活动(A级推荐).

(6) 心理因素干预. 新冠肺炎疫情的发展趋势和长时间的人际关系疏远等因素给人们带来了心理影响. 一项荟萃分析发现, 新冠肺炎患者可能容易出现抑郁、焦虑等神经精神症状[101,108](Ⅰ级证据). 另一项小规模观察性研究发现, 焦虑与抑郁引起的皮质醇增高可能与新冠肺炎的不良预后有关[109]. 因此, 应注意新冠肺炎后抑郁、焦虑、疲劳、应激障碍和相关神经精神症状的发生. 需要提供新冠肺炎心理援助热线、心理咨询等社会人文支持. 同时可以通过电视、网络、媒体、公众号等渠道增加社会认知度, 增强民众社会安全感.

推荐意见: 建议关注新冠肺炎期间民众心理健康,

积极提供专业心理咨询(专家共识).

(7) 认知障碍人群新冠肺炎期间的护理. 按照国际痴呆专家和阿尔茨海默病国际组织的建议，需要为痴呆患者及其照顾者提供支持(https://www.alzint.org/resource/advice-and-support-during-covid-19-bame-communities-people-living-with-dementia-and-carers/). 例如，精神卫生专业人员、社会工作者、疗养院管理人员和志愿者应该协作为痴呆患者提供精神卫生支持. 这些可以通过电子媒体进行，比如可以通过电话或网络进行痴呆患者的一般管理工作，也可以为在家或养老院的护理员提供在线咨询[110].

推荐意见: 建议社会多方合作, 为痴呆患者及其照料者提供精神卫生支持(专家共识).

5　结论与展望

目前新冠肺炎后认知障碍的报道逐渐增多，严重地影响了新冠肺炎感染者的生活质量. 目前我国还没有新冠肺炎后发生认知障碍的专家共识，影响了临床医生和民众对这一综合征的认知度. 根据这一情况，我们组织了全国五十余名认知障碍专家，根据国内外大量文献报道, 结合我国国情, 提出了这一共识, 并经专家组讨论、反复修改, 最后形成了推荐意见. 本共识总结了新冠肺炎后认知障碍的较高发生率，提出了新冠肺炎后认知障碍的临床表现和危险因素，强调了非药物治疗和生活方式等诊治策略，有助于提升我国新冠肺炎后认知障碍的诊治和规范化管理水平. 新冠肺炎有可能在较短时间内得到控制，但是其对认知造成的后续影响应进一步进行临床研究，以减少其带来的负面影响, 提高我国新冠肺炎后认知障碍防治水平.

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Consensus on diagnosis, treatment and management of cognitive impairment after COVID-19

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