

· 综述 ·

精神分裂症患者合并腹型肥胖对认知障碍影响的研究进展

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【摘要】 精神分裂症是一种严重的精神疾病,以认知障碍为核心症状之一。腹型肥胖等代谢并发症在精神分裂症患者中广泛存在,不仅增加了患者的心血管疾病风险,同时也与认知障碍,尤其是注意力、记忆力和执行功能的损害相关。精神分裂症合并腹型肥胖可能通过多种机制共同影响患者认知功能,如激发慢性炎症反应、胰岛素抵抗以及影响肠道菌群的构成,从而进一步加剧认知障碍。本文综述精神分裂症患者合并腹型肥胖的危险因素以及影响认知障碍的潜在机制和治疗策略,并展望未来研究方向,以期改善精神分裂症患者的腹型肥胖和认知障碍提供理论依据。

【关键词】 精神分裂症; 认知障碍; 腹型肥胖; 非典型抗精神病药物

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Research progress on the effect of schizophrenia complicated by abdominal obesity on cognitive impairment

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【Abstract】 Schizophrenia is a serious mental disorder characterized by cognitive impairment as one of its core symptoms. Metabolic complications such as abdominal obesity are widespread in patients with schizophrenia. This not only elevates the risk of cardiovascular disease in patients, but is also associated with

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cognitive deficits, particularly impairments in attention, memory, and executive function. Studies have shown that combined abdominal obesity in schizophrenia may affect cognitive function through multiple mechanisms, such as triggering chronic inflammatory responses, insulin resistance, and influencing the composition of the gut flora, which may further exacerbate cognitive impairment. This article describes the risk factors for combined abdominal obesity in schizophrenia, as well as the potential mechanisms and treatment strategies affecting cognitive impairment, and looks forward to future research directions, with a view to providing a theoretical basis for improving abdominal obesity and cognitive impairment in schizophrenia.

【 Key words 】 Schizophrenia; Cognition disorders; Abdominal obesity; Atypical antipsychotics

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精神分裂症是常见的慢性重型精神障碍之一,全球终生患病率约为1%^[1]。其病因及发病机制尚未完全阐明,症状表现复杂多样,主要包括阳性症状、阴性症状以及认知障碍3个方面^[2]。精神分裂症患者常并发躯体健康问题,尤其是代谢综合征,这一并发症增加了临床治疗的难度与复杂性^[3]。作为代谢综合征的核心表现,腹型肥胖与胰岛素抵抗、高脂血症以及高血压等代谢紊乱的风险升高均密切相关,更易引起心血管疾病等慢性疾病的发生,增加患者的死亡风险^[4]。

目前,肥胖对认知功能的影响日益受到关注,尤其腹型肥胖会明显增加认知障碍及痴呆的风险^[5]。认知障碍在精神分裂症首次发作和发病早期便已显现^[6]。对于精神分裂症患者,幻觉、妄想等精神病性症状短期可实现缓解,而认知功能的损害显著而持久^[7]。腹型肥胖可能进一步加剧患者的认知功能损害,严重影响其独立生活及就业能力^[8]。因此,本文就精神分裂症患者合并腹型肥胖影响认知功能的潜在机制和干预策略进行综述。

一、精神分裂症患者合并腹型肥胖的危险因素

肥胖是精神分裂症的常见共病之一,约39%的精神分裂症患者会出现腹型肥胖,其发病风险是普通人群的1.5~4倍,患者体重增加7%左右^[9-10]。与全身性肥胖不同,腹型肥胖是指脂肪组织在腹腔内脏器官及主动脉、肠系膜等部位的囤积^[11]。由于甘油三酯的异位积聚,患者内脏脂肪堆积明显高于皮下脂肪^[12]。精神分裂症患者合并腹型肥胖与遗传易感性、抗精神病药物的使用以及不良生活方式等因素有关^[13-15]。全基因组关联研究揭示了精神分裂症患者存在多个与肥胖有关的基因和遗传变异^[16]。然而,虽然观测到腹型肥胖与精神分裂症具有正向遗传相关性的趋势,但相关性并不显著^[17]。这提示遗传以外的因素起着更为重要的作用,特别是抗精神

病药物的使用。研究发现,以奥氮平和氯氮平为主的非典型抗精神病药物作用尤为显著,仅用药6个月内患者体重便可能出现明显增加^[18]。这些药物通过影响食欲调控、改变肠道菌群构成以及影响脂肪因子水平等多种机制增加内脏脂肪的沉积^[19-21]。此外,精神分裂症患者往往采取更为久坐的生活方式,且饮食习惯不良,进一步增加腹型肥胖的风险^[22]。

二、精神分裂症患者合并腹型肥胖与认知障碍的相关性及潜在机制

精神分裂症患者合并腹型肥胖与认知功能存在密切的潜在关联^[23],内脏脂肪的积聚不仅与认知功能受损相关,而且可能具有一定的因果关系^[24]。一项孟德尔随机化研究提供了证据支持,内脏脂肪每增加0.27 kg,认知功能下降的程度相当于生理年龄增长0.7岁^[25]。在精神分裂症患者中,几乎所有常见认知领域都出现了不同程度的损害,其中处理速度与语言学习领域受损最为严重^[26]。Zhuo等^[27]的研究指出,代谢综合征中的腰围参数是精神分裂症患者认知功能受损的显著相关因素,为精神障碍患者的管理和治疗提出了新型生物标志物参考和可能的干预点。精神分裂症患者合并腹型肥胖影响认知功能的潜在机制如下。

1. 慢性炎症的介导:精神分裂症和腹型肥胖均以全身炎症和神经炎症为共同特征^[22],通常伴随外周器官的慢性低度炎症以及下丘脑在内的中枢神经系统的促炎病理改变^[28]。精神分裂症患者的外周血中能检测到较高水平的细胞因子等炎性标志物,表明其潜在的全身慢性炎症状态。该炎性反应可能由遗传易感性、抗精神病药物不良反应或不良的生活方式因素所触发,确切机制尚未阐明^[29]。在腹型肥胖个体中,脂肪组织急剧扩张诱发细胞的缺氧和坏死可能促进IL-1 β 和TNF- α 等促炎细胞因子的释放,进而激活全身炎症反应^[30-31]。长期存在的慢

性炎症往往对中枢神经系统产生不利影响,其可能通过影响海马体等脑区中的细胞因子平衡进而损害认知功能。研究发现,IL-1 β 在海马体中的过量表达可破坏神经突触功能和突触可塑性,导致记忆受损^[32];而TNF- α 的升高与精神分裂症患者大脑处理速度和视觉功能的下降有关^[33]。Cannavale等^[34]的研究也揭示了肥胖引起的全身性炎症可能对注意力等认知领域存在负面效应。全身炎症通过激活促炎细胞因子和前列腺素的释放,并增加血-脑脊液屏障通透性,使外周细胞因子和免疫细胞进入脑内。这些变化可能诱发神经毒性,影响神经元再生和破坏大脑突触可塑性,最终损害中枢神经系统的认知功能^[35]。因此,精神分裂症与腹型肥胖可能共同通过促进炎症反应途径加重认知障碍^[36]。

2. 胰岛素抵抗的介导: 精神分裂症、腹型肥胖和胰岛素抵抗之间存在着复杂的作用网络。遗传研究表明,精神分裂症与胰岛素抵抗存在共同的遗传基础^[37],表明精神分裂症可能一定程度上直接影响胰岛素敏感性。精神分裂症与腹型肥胖伴随的慢性炎症状态也可能干扰胰岛素的信号途径^[38]。此外,腹型肥胖不仅直接与胰岛素抵抗和2型糖尿病紧密联系,还可通过分泌多种脂肪因子进一步扰乱胰岛素信号的传递^[39]。2型糖尿病不仅增加了认知障碍的发生风险,还会加速认知功能衰退,影响注意力、处理速度和语言学习等多个领域^[40]。Abi Saleh等^[41]的研究表明,受试者的腹围与认知障碍发生风险有关,糖尿病在这一过程中起到61%的介导效应。

胰岛素抵抗可能通过多种途径影响认知功能。首先,胰岛素抵抗可能加剧了淀粉样斑块的形成,从而影响认知功能。其次,胰岛素抵抗会影响大脑中多种神经递质的水平,包括血清素、多巴胺和乙酰胆碱等,这些递质与动机、警觉性和记忆等认知功能有关^[42]。最后,胰岛素抵抗可能加速大脑神经退行性过程,包括神经元的死亡和突触的受损,从而影响大脑功能^[43]。因此,针对伴有腹型肥胖精神分裂症患者,应当重视胰岛素抵抗对认知功能可能造成的影响。

3. 肠道菌群的失调: 精神分裂症患者的肠道菌群构成与多样性往往因服用抗精神病药物、饮食习惯改变或疾病本身导致的病理生理变化而受到破坏^[44]。Qian等^[45]通过纵向观察发现,随着服用奥氮平的大鼠肠道中厚壁菌与拟杆菌比例的上升,其体重及内脏脂肪显著增加,表明奥氮平可能通过影响肠道菌群及相关代谢途径引起内脏脂肪积累。肠道菌群

可通过肠脑轴与中枢神经系统沟通,进而影响大脑认知功能^[46]。Arnorriaga-Rodríguez等^[47]将肥胖受试者的肠道菌群移植到小鼠体内,发现其记忆功能明显下降;且厚壁菌水平与记忆评分呈正相关,拟杆菌水平与记忆评分呈负相关。研究表明,精神分裂症患者合并腹型肥胖会进一步引发肠道菌群失调,破坏IL-1、IL-6等促炎细胞因子正常传导,影响BDNF、GABA等神经递质水平以及饮食中营养物质的吸收,最终导致认知功能障碍^[48]。综上所述,精神分裂症患者肠道菌群失衡,特别是在合并腹型肥胖的情况下,可能是影响其认知功能的重要因素。

三、精神分裂症患者合并腹型肥胖相关认知障碍的治疗策略

1. 抗炎治疗: 传统抗炎药物如非甾体抗炎药和特定炎症因子抑制剂可改善精神分裂症患者的认知障碍^[49]。然而,长期使用这些药物可导致胃出血、肠道菌群失调等不良反应。而特异性促炎性消退介质(specialized pro-resolving mediators, SPMs)是机体在炎症反应过程中自然生成的化合物,具有促进炎症消退以及恢复组织功能的独特作用。研究发现,SPMs不仅能有效缓解神经炎症,还可改善肥胖,表明了其在治疗精神分裂症患者认知障碍方面的可能价值^[50]。与传统抗炎药物相比,补充SPMs似乎不会抑制免疫系统,因此其可能是一种更安全有效的治疗选择。此外,富含Omega-3脂肪酸和抗氧化剂的饮食也可帮助减轻慢性炎症,延缓精神分裂症患者认知功能的衰退^[51-52]。

2. 胰岛素敏感性的提高: 通过饮食管理和增加身体活动减轻腹型肥胖,并提高机体对胰岛素的敏感性可能有助于改善认知功能。对于精神分裂症患者而言,选择对胰岛素敏感性影响较小的抗精神病药物可能有助于减缓认知能力的下降,如阿立哌唑、齐拉西酮等^[53]。这种治疗方法不仅可以改善患者的代谢紊乱,也对其认知功能产生积极影响。胰高血糖素样肽-1(glucagon-like peptide 1, GLP-1)受体激动剂在控制血糖、减重以及改善血脂等方面疗效显著,已被批准用于糖尿病及肥胖的治疗。临床前研究也证实了GLP-1受体激动剂有改善认知缺陷的作用^[54]。GLP-1受体激动剂对代谢异常与认知障碍的双重改善极大地增加了其治疗优势。此外,鼻内胰岛素给药也可能有益于预防和改善认知水平的下降^[55]。

3. 肠道菌群的调节: 调整饮食、补充益生菌以及菌群移植等方式可调节肠道菌群的构成,这对认知

功能的改善尤为关键。一项动物研究发现,经15周摄入缺乏纤维的饮食后,小鼠肠道菌群受到破坏,表现为拟杆菌数量减少,变形菌数量增多,并伴有认知功能的下降^[56]。因此,增加高纤维食物的摄入可能有助于改善肠道菌群的构成,从而缓解认知功能损害。直接补充益生菌和益生元制剂也可促进有益菌群的增长,维持肠道菌群的多样性。Zheng等^[57]的研究表明丁酸梭菌能够正向调节肥胖小鼠的神经递质系统,改善认知功能。此外,将健康个体的肠道菌群移植给患者,可能有助于改善精神分裂症患者的肠道菌群失调和相关的认知功能障碍^[58]。但该方法还需要进一步的研究确认其安全性和有效性。

四、总结与展望

本文综述了精神分裂症患者合并腹型肥胖对认知功能的影响,其中慢性炎症作为一个共同的病理机制,在脑内外环境中均有显著影响。尽管目前对于这两者间关系的研究尚不充分,但现有证据已经足以支持炎症在精神分裂症认知障碍中的重要作用^[59]。此外,慢性炎症与腹型肥胖形成了相互强化的循环,进一步加剧了精神分裂症的认知损害。胰岛素抵抗不仅是精神分裂症合并腹型肥胖影响认知障碍的另一个潜在机制,也是一个重要的临床干预点。抗精神病药物的使用可能与腹型肥胖和胰岛素抵抗的发生密切相关。因此,临床中在药物选择和不良反应监测方面需更加谨慎。此外,个体化的饮食和运动干预以及新型药物治疗,如GLP-1受体激动剂,为改善代谢综合征和认知障碍提供了新的治疗方向^[60]。肠道菌群失调对认知功能的负面影响凸显了精神分裂症及腹型肥胖治疗中精准医学的潜力。随着微生物组研究的深入,针对特定菌群组成的调整可能成为未来治疗策略的一部分^[61]。

为解决精神分裂症患者合并腹型肥胖对认知障碍的影响,未来研究应集中于以下3个方面:(1)研究需要深入了解慢性炎症、胰岛素抵抗和肠道菌群失调等因素在认知障碍发病机制中的角色及相互关系。(2)需进一步研究并验证能够抑制炎症、增强胰岛素敏感性和调节肠道菌群平衡的干预措施;同时,通过临床试验确定这些干预对于认知功能改善的持久效果。(3)基于个体的治疗策略,如利用基因组学、蛋白质组学或肠道菌群分析实施定制化医疗,也越来越受到关注^[62-63]。

精神分裂症合并腹型肥胖引起的认知障碍具有多重复杂机制,因此在治疗中更需综合考虑患者的整体健康状况以及其生活环境因素。未来的临床实

践和科学研究都应重点关注跨学科和多维度的综合性治疗方案,以期全面提升患者的生活质量,并努力减轻其疾病负担。

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