

• 综 述 •

儿童超重肥胖与常见神经发育障碍的相关性研究进展

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摘要: 随着肥胖患病率的逐年增加,肥胖已成为影响儿童和青少年身心健康的重要公共卫生问题。越来越多的文献证据表明,超重、肥胖与注意缺陷多动障碍、孤独症谱系障碍等神经发育障碍具有较高的共患率。本文综述了儿童超重、肥胖与常见神经发育障碍相关性的文献,旨在提高临床医生对神经发育障碍患儿中超重或肥胖的识别,为常见神经发育障碍的综合管理提供依据。

关键词: 超重; 肥胖; 儿童; 神经发育障碍

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Correlation between overweight or obesity and common neurodevelopmental disorders in children

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Abstract: With the escalating prevalence of obesity, it has emerged as a significant public health concern affecting children and adolescents both physically and mentally. There is growing evidence indicating a substantial co-occurrence of overweight and obesity alongside neurodevelopmental disorders, notably attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). This paper reviews the literature exploring the correlation between childhood overweight, obesity, and prevalent neurodevelopmental disorders, with the aim of enhancing clinicians' recognition of overweight or obesity in children diagnosed with neurodevelopmental disorders, thereby furnishing a foundation for integrated management strategies for these common conditions.

Keywords: overweight; obesity; children; neurodevelopmental disorders

超重是指体内脂肪堆积过多,并可能对健康造成损害的前肥胖状态。肥胖是指因长期能量摄入超过消耗,引起体内脂肪蓄积过多、体重超过参考值范围的一种营养障碍性疾病^[1]。目前儿童肥胖已成为威胁全球儿童身心健康的重要公共卫生问题,2017年的一项权威研究显示,全球女童的肥胖率从1975年的0.8%增加至2016年的5.6%,男童的肥胖率从1975年的0.9%增加至2016年的7.8%^[2]。而在我国,2000—2018年7~17岁儿童和青少年的超重率从5.4%攀升至12.9%,肥胖率从2.5%增加至12.4%,我国已成为全球肥胖增长率最快的国家之一^[3]。神经发育障碍是指在发育时期,由多种遗传性或获得性病因影响大脑功能区(包括认知、运

动、社会适应能力、行为等)导致的一组慢性发育性脑功能障碍性疾病^[4]。由于超重或肥胖与神经发育障碍的高共患率,二者的关联已成为近几年的研究热点,然而目前尚缺乏系统的文献回顾。本文就儿童超重、肥胖与常见神经发育障碍性疾病的相关性进行了文献综述,为常见神经发育障碍的综合管理提供依据。

1 儿童超重肥胖与注意缺陷多动障碍

1.1 注意缺陷多动障碍流行病学特征 注意缺陷多动障碍(attention deficit hyperactivity disorder, ADHD)是一类起病于儿童早期的神经发育障碍,其核心症状为与发育年龄不相称的持续注意力不集中

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和多动、冲动症状^[4]。流行病学研究显示,超重或肥胖儿童中 ADHD 患病率为体重正常儿童的 2~4 倍,其中,肥胖女童的 ADHD 患病率为 10%~11%,肥胖男童 ADHD 患病率高达 17%~31%^[5]。在 ADHD 人群中,Li 等^[6]对 95 项研究的荟萃分析表明,6~12 岁 ADHD 儿童的超重、肥胖率分别为 18.8%和 13.5%,且这个数字会伴随年龄的增长而上升,在成年 ADHD 人群中,超重和肥胖率则分别达到了 31.2%和 19.3%。

1.2 ADHD 症状与超重肥胖的关系 ADHD 症状及其严重程度与超重、肥胖之间也存在关联性。Zhang 等^[7]在上海的 3 所小学和 4 所初中分层随机抽样了 546 名 3~11 年级的儿童,并进行了 ADHD 症状与饮食失调和体质量指数(body mass index, BMI)的纵向相关分析,结果表明,在饮食失调症状更重的高年级组中,更高的 BMI 水平与更严重的 ADHD 症状相关^[7]。来自挪威的 40 949 名 8 岁儿童的家庭内孟德尔随机化评估显示,BMI 的增高与 ADHD 症状的显著增加有关^[8]。在 ADHD 儿童群体中,BMI 与 ADHD 症状的不同维度亦存在关联。Turkoglu 等^[9]对 300 名 7~17 岁 ADHD 患儿的症状与 BMI 进行的结构方程模型分析显示,ADHD 患儿的注意力缺陷维度评分和对立违抗维度评分均与患儿的 BMI 百分位数呈显著正相关。Ben 等^[10]的病例对照研究显示,与正常体重的 ADHD 患儿相比,共患超重或肥胖的 ADHD 患儿冲动症状发生率更高。针对 ADHD 症状与 BMI 或体重的关系,现有研究多以横断面分析为主,提示需要更多的纵向研究证据以明确两者的关系。

1.3 两者之间潜在的关联机制 ADHD 与超重、肥胖的高共患率,可能与两者发病机制的同源性有关,包括基因、神经生物学、家庭社会心理因素等,可能是二者关联性的潜在原因^[11-12]。目前更多的研究显示 ADHD 症状先于肥胖的发生。多巴胺(dopamine, DA)稳态异常假说一直是 ADHD 发病机制中的研究重点,为了弥补 DA 不足导致的“满足感”与“欣快感”下降,ADHD 患儿更易出现饮食行为异常,如情绪性暴饮暴食、食物反应增加、接近食物等,以及饮食结构紊乱,如加工食品、油炸膨化类及含糖饮料摄入增多,而粗杂粮及蔬果类摄入减少,屏幕使用时间过长以及青春期身体活动缺乏等“奖励补偿”行为,从而导致体重增加^[13-15]。Seymour 等^[16]则指出,ADHD 与肥胖在奖励处理、反应抑制、情绪处理与调节的神经行为回路异常中有重叠。此外,ADHD 的核心内在特征是执行功能的损害,并会引

起注意力缺陷、多动与冲动等核心症状的发生^[17]。Graziano 等^[18]研究表明,ADHD 共患超重或肥胖的儿童更容易发生执行功能受损。执行功能的下降会反过来刺激患儿过度肥胖,恶性循环引起执行功能的下降加剧,并更容易导致个体减肥计划的失败^[19]。另外,来自 ADHD 患儿父母的批评、患儿的饮食限制、患儿的心理压力等也会导致 BMI 上升^[20]。

2 儿童超重肥胖与孤独症谱系障碍

2.1 孤独症谱系障碍的流行病学特征 孤独症谱系障碍(autism spectrum disorder, ASD)是以社会交往及交流障碍、狭隘兴趣、重复刻板行为和感知觉异常为主要特征的一类广泛性神经发育障碍^[4]。关于肥胖儿童群体中 ASD 患病率的相关研究较少,仅检索到 Wentz 等^[5]对 76 名儿童的研究显示肥胖儿童中 ASD 的患病率约为 13%,其中女性为 8.1%,男性为 17.9%,是一般人群中 ASD 患病率的 10 倍等^[5]。由于超重、肥胖是 ASD 的最常见共患病之一,大多的流行病学研究主要集中于 ASD 群体中的肥胖患病率^[21]。Sammels 等^[22]对 20 项主要集中于美国的研究进行荟萃分析,结果显示在 ASD 儿童和青少年中,肥胖患病率为 7.9%~31.8%。ASD 患儿的肥胖风险是普通人群的 1.4 倍^[23]。

2.2 ASD 症状与超重肥胖的关系 现有研究证据表明,ASD 症状更严重的儿童和青少年共患超重、肥胖的比例更高,且超重和肥胖往往在儿童生命早期即已出现:Levy 等^[24]对美国 668 名学龄前 ASD 儿童进行的队列研究显示,具有严重 ASD 症状的儿童患超重或肥胖的比例是有轻微 ASD 症状儿童的 2.7 倍。Healy 等^[25]对美国 875 963 名 10~17 岁 ASD 青少年的回顾性分析表明,具有较严重 ASD 症状青少年的肥胖率是具有轻微 ASD 症状青少年的 3.4 倍,提示肥胖与 ASD 症状的严重程度之间存在一定关联。然而荷兰的一项小样本研究表明学龄前 ASD 儿童的症状严重程度与 BMI 无显著关联^[26]。此外,亦有研究显示,共患超重或肥胖的 ASD 儿童具有更高的躯体合并症风险,如睡眠呼吸暂停、甲状腺功能减退、高血压等^[27]。

2.3 两者之间潜在的关联机制 多种因素可能在 ASD 儿童的肥胖发生中起作用,目前已知的主要包括遗传、肠道微生物群、激素水平、母体代谢、饮食行为、生活方式、睡眠模式、药物使用和继发性并发症等^[28-29]。此外,执行功能障碍可能是连接二者的潜在神经生理学机制。ASD 和超重、肥胖均与执行功

能障碍相关,该关联可能源于 ASD、超重、肥胖均与脑内参与调节社会认知和执行控制的两个神经网络连接异常有关,Kahathuduwa 等^[30]对 ABIDE 数据库中 81 名 ASD 儿童的静息功能磁共振成像数据进行分析,结果表明非超重肥胖的 ASD 患儿前后默认模式网络(default mode network,DMN)之间的连接性低下,而共患超重或肥胖的 ASD 儿童在前后 DMN 之间表现出超连接性。Kupis 等^[31]则对 129 名 6~18 岁儿童青少年的大脑共激活模式(co-activation patterns,CAPs)进行研究,结果表明 ASD 儿童的 CAP1 停留时间(dwell time,DT)较短,而 CAP1 DT 则与认知灵活性、抑制、社会功能和 BMI 呈负相关,提示认知灵活性可能在 ASD 儿童的 BMI 与大脑功能连接间具有调节作用。然而,当前这方面的研究尚少,且共患超重或肥胖的 ASD 儿童是否伴随更严重的执行功能损害,目前尚缺乏充分的研究证据,未来需要更多的纵向研究证据完善因果机制的推断。除个体因素外,家庭与社会心理学因素,譬如家庭、社会的支持及父母体育活动的参与,也与 ASD 儿童超重或肥胖的发生发展息息相关^[32]。

3 儿童超重肥胖与发育协调障碍

3.1 发育协调障碍的流行病学特征 发育协调障碍(developmental coordination disorder,DCD)是以粗大和/或精细动作协调能力明显受损为主要表现的一类神经发育障碍^[4]。Hendrix 等^[33]一项荟萃分析纳入了 21 项研究,结果表明在 4~14 岁儿童中,DCD 儿童具有更高的超重、肥胖风险,且该风险会随年龄的增长以及运动障碍严重程度的增加而上升。在肥胖儿童群体中,Wentz 等^[5]研究提示,肥胖儿童 DCD 患病率高达 25%,是一般人群的 5 倍。该风险可能存在性别差异,Zhu 等^[34]在我国台湾对 2 029 名 9~10 岁儿童进行了一项 DCD 与体重状况相关性的调查,结果显示,肥胖男童中 DCD 的患病率为 33.3%,而肥胖女童 DCD 患病率为 38.2%,提示肥胖女童 DCD 患病率高于肥胖男童。

3.2 DCD 症状与超重肥胖的关系 超重或肥胖与儿童的运动技能落后、运动协调性不佳相关。来自 33 项研究的荟萃分析表明,超重、肥胖与粗大运动技能水平落后、体力活动表现不足相关^[35]。相较于正常儿童,我国超重儿童的总运动协调能力、手部灵巧度与平衡能力更差^[36]。意大利一项纵向队列研究对 117 名 8~13 岁儿童进行了连续 4 年的评估,结果表明 BMI 与粗大运动协调分数呈显著负相关^[37]。然而,与正常体重的 DCD 儿童相比,共患超

重或肥胖是否与 DCD 儿童症状的严重程度相关,目前研究尚为空白。

3.3 两者之间潜在的关联机制 目前关于超重、肥胖与 DCD 之间的共患病机制以及因果关联研究有限,需要更多的研究证据以明确两者关系。执行功能的损害可能是超重或肥胖儿童共患 DCD 的潜在机制,Fernandes 等^[38]对 49 名学龄前儿童的横断面研究表明,超重儿童的执行功能任务得分与其粗大运动技能得分呈显著负相关,而在正常体重儿童中未观察到该关联,提示在超重人群的生命早期,其更差的运动技能可能源自于其更差的认知灵活性、工作记忆、计划和解决问题能力。此外,运动技能的落后也会导致儿童的活动意愿降低、身体活动的次数减少,这种恶性循环可能会导致体重进一步增加^[33]。Noordstar 等^[39]对 366 名 7~13 岁 DCD 儿童自我认知状况调查表明,与非超重 DCD 儿童和典型发育儿童相比,超重的 DCD 儿童自我运动能力认知损害更重、自我社会接受度更低,提示共病超重或肥胖的 DCD 儿童可能伴有自我认知受损,从而进一步降低其运动参与度^[39]。

4 儿童超重肥胖与智力障碍

4.1 智力障碍的流行病学特征 智力障碍(intellectual disability,ID)是以智力与适应功能障碍为主要特征的一类神经发育障碍疾病^[4]。目前,超重、肥胖已成为 ID 儿童的重要健康问题之一。Maiano 等^[40]对 16 项集中于西太平洋、欧洲、北美洲等研究行荟萃分析表明,ID 儿童中超重、肥胖的患病率分别为 15%、13%。Yuan 等^[41]对我国 35 所特殊学校的 1 873 名 ID 儿童的超重或肥胖患病率调查研究表明,ID 儿童和青少年的超重和肥胖患病率分别为 18.2%和 14.4%,其中男性、共患唐氏综合征或 ASD、城市地区生活者发生超重或肥胖的风险更高。来自英国 18 000 名儿童数据的纵向队列研究表明,在肥胖儿童群体内,ID 儿童占比达 5%~6%^[42]。

4.2 ID 症状与超重肥胖的关系 尽管 ID 与超重、肥胖具有较高的共患率,但目前的研究证据表明,超重或肥胖儿童与正常儿童的智力水平并无显著差异,肥胖本身并不能直接导致生命早期的智力下降^[43-44]。相反,儿童认知功能的损害与成年期的肥胖相关,尽管该结果可能会受到家庭背景混杂因素的影响^[45-46]。在超重、肥胖儿童中,体力活动、久坐时间、睡眠质量可能通过影响大脑皮质下结构的发育而与儿童的智力水平相关^[47-48]。然而,在 ID 儿童中,肥胖与其智力水平是否也具有同样的相关性,

目前研究尚为空白。而现有研究表明,共患肥胖更易使 ID 儿童出现躯体疾病,如支气管哮喘、高血压、高胆固醇血症、糖尿病和易于疲劳等^[27]。

4.3 两者之间潜在的关联机制 儿童 ID 与超重、肥胖的高共患率可能由多种因素决定,包括遗传、社会生活环境、临床因素等^[49]。Carvalho 等^[50]对 20 名综合征型肥胖患者的全外显子测序结果提示, *EHMT1* 和 *MYT1L* 基因变异已被确认与肥胖及 ID/发育迟缓的发生相关。此外,体育锻炼、饮食行为、药物使用等生活方式因素以及与 ID 有关的特定综合征(如唐氏综合征、Cohen 综合征、Bardet-Bied 综合征、Prader-Willi 综合征等)也可能导致这种关联^[51]。另外, ID 青少年由于更依赖于父母,其 BMI 亦被报道与父母的 BMI、经济收入和教育程度相关^[52]。

综上,儿童超重或肥胖与 ADHD、ASD、DCD 以及 ID 等常见神经发育障碍之间存在高共患率,同时在病因、发病机制以及症状严重程度之间也存在关联,执行功能障碍可能是超重、肥胖与神经发育障碍关联的潜在机制。在神经发育障碍性疾病的诊疗过程中,提高对共患超重或肥胖的识别,有助于神经发育障碍性疾病的综合管理。两者之间病因和发病机制的潜在关联,以及肥胖管理对神经发育障碍疾病症状学的影响,有待深入研究。

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