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慢性躯体疾病共病抑郁障碍及其生物心理影响因素的研究进展

任若佳 黄凡凡 赵天宇 刘不凡 王学义

050031 石家庄, 河北医科大学第一医院精神卫生中心 河北省精神卫生研究所 河北省精神心理疾病临床医学研究中心 河北省精神心理健康评估与干预技术创新中心

通信作者: 王学义, Email: 070@hebmh.edu.cn

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【摘要】 慢性躯体疾病共病抑郁障碍的患病率逐年上升。本综述从生物、心理及社会学的角度探讨慢性躯体疾病共病抑郁障碍的现状和影响因素, 如遗传、免疫、社会及家庭环境等。在数字技术高速发展的背景下, 结合药物、物理及心理治疗, 构建联络会诊的干预模式, 有望减少慢性躯体疾病患者的抑郁情绪, 提高其身心健康整体水平。

【关键词】 共病现象; 抑郁障碍; 慢性躯体疾病; 生物心理因素; 干预方法; 综述

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Biopsychological factors and current status of comorbidity between chronic medical disease and depressive disorder

Ren Ruojia, Huang Fanfan, Zhao Tianyu, Liu Bufan, Wang Xueyi

Mental Health Center, the First Hospital of Hebei Medical University & Hebei Institute of Mental Health & Hebei Clinical Research Center for Mental Disorders & Hebei Technology Innovation Center for Mental and Psychological Health Assessment and Intervention, Shijiazhuang 050031, China

Corresponding author: Wang Xueyi, Email: 070@hebmh.edu.cn

【Abstract】 The prevalence of chronic physical disease comorbid depression is increasing year by year. This paper discusses the current situation and influencing factors of chronic medical disease comorbid depression from the perspective of biology, psychology and sociology, involving genetics, immunity, social and family environment. Against the backdrop of rapid development of digital technology, combining medication, physical and psychological therapy to establish an intervention model of liaison consultation is expected to reduce depression in patients with chronic physical diseases and improve their overall level of physical and mental health.

【Key words】 Comorbidity; Depressive disorder; Chronic physical disease; Biopsychological factor; Intervention; Review

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抑郁障碍是一种反复发作的慢性精神障碍, 2019年我国抑郁障碍总患病人数近5 000万, 终生患病率约为3.4%^[1]。对于罹患慢性躯体疾病(如纤维肌痛、关节炎、哮喘、心血管疾病、糖尿病、高血压、癌症等)的患者, 共病抑郁障碍的风险较大。抑郁障碍和慢性躯体疾病对身心健康的损害有叠加效应^[2], 导致疾病治疗困难和预后欠佳。本文通过探讨慢性躯体疾病共病抑郁障碍的现状及其影响因素, 建立家庭、医院、社会联合的防治模式, 以期实现早期识别和管理, 减轻共病的痛苦和负担, 提高患者生活质量。

一、慢性躯体疾病共病抑郁障碍的现状

慢性躯体疾病与抑郁障碍之间的关联已在多项研究中得到证实。一项针对门诊患者抑郁障碍及抑郁症状发生率的荟萃分析显示, 在综合医院门诊就诊的41 344例患者中, 27%的患者存在抑郁症状或患有抑郁症, 其中耳鼻喉科门诊出现抑郁症状的患者比例为53%, 皮肤科为39%, 神经内科为35%^[3]。在癌症患者中, 研究显示治疗期间共病抑郁障碍的患病率为14%, 癌症治疗后第1年的共病抑郁障碍的患病率减少为9%^[4]。在心肌梗死患者中, 约28%

的患者共病抑郁障碍,其中前壁心肌梗死、共病高血压与疾病反复发作是共病抑郁障碍的危险因素^[5]。2023年一项前瞻性队列研究发现,抑郁障碍与心力衰竭疾病全因死亡率之间存在高度相关性($HR=1.44$, $95\%CI: 1.26 \sim 1.65$)^[6]。Khaledi等^[7]的研究发现,成人2型糖尿病(type 2 diabetes mellitus, T2DM)患者中共病抑郁障碍的患病率为23%,1型糖尿病(type 1 diabetes mellitus, T1DM)患者共病抑郁障碍的患病率为12%,且女性糖尿病患者共病抑郁障碍的患病率高于男性^[8]。除常见慢性躯体疾病外,罕见疾病发生抑郁障碍的年龄较早,通常会危及患者生命并伴随着生活质量大幅下降,如肺动脉高压和马凡综合征患者的抑郁严重程度明显增加^[9-10]。罕见疾病在诊断方面存在一定困难,反复诊疗可能导致患者本身的消极情绪,甚至引发家庭成员的焦虑和抑郁情绪,造成较高的精神负担和经济压力。

抑郁障碍与慢性躯体疾病之间存在年龄的相关性,尤其是高血压和癌症患者,年龄越小共病抑郁情绪的关联程度越强^[11],可能与青少年的心理发育、应对能力、适应性和复原能力差有关。目前青少年慢性躯体疾病的发病率逐步上升^[12],青少年发生抑郁障碍等精神疾病的概率是同龄健康人的近2倍^[13]。横断面研究显示,在癌症门诊就诊的儿童和青少年中,有26%的人符合重性抑郁障碍的诊断标准^[14]。2000—2020年的调查数据表明,T1DM和T2DM的儿童及青少年患者中,抑郁障碍的患病率分别为22.2%和22.7%^[15],提示疾病发展呈现年轻化趋势。

综上所述,慢性躯体疾病患者共病抑郁障碍的患病率较高,且与年龄、性别、疾病严重程度等因素有关。因此,对于慢性躯体疾病,应早期识别、诊断和积极治疗,以减轻患者的精神负担、恐惧心理以及减少共病抑郁障碍的发生。

二、慢性躯体疾病共病抑郁障碍的影响因素

慢性躯体疾病与抑郁障碍的发病机制涉及多种行为、认知和生理过程,共同影响身心健康发展。从生物、心理及社会层面全面了解慢性躯体疾病共病抑郁障碍的原因,有助于预防心身交互作用对患者的影响,实施针对性的早期心理和躯体干预。

1. 生物学因素:(1)遗传学因素。慢性躯体疾病与抑郁障碍之间的关联可能涉及部分遗传学机制。英国一项大型遗传学研究发现,抑郁障碍与多种躯体疾病存在遗传相关性,如缺血性心脏病($OR=1.30$, $95\%CI: 1.15 \sim 1.47$)、高胆固醇血症($OR=1.22$, $95\%CI: 1.12 \sim 1.34$)以及多种炎症性和胃

肠道疾病,如哮喘($OR=1.23$, $95\%CI: 1.06 \sim 1.44$)、食管炎($OR=1.32$, $95\%CI: 1.18 \sim 1.48$)和胃肠道出血($OR=1.26$, $95\%CI: 1.11 \sim 1.43$)^[16]。抑郁障碍、心血管疾病与代谢性疾病之间也存在显著的遗传相关性,促肾上腺皮质激素释放激素信号传导通路和G蛋白偶联受体信号传导通路可能是三者共有的基因传递通路^[17]。此外,在一项控制环境因素的双胞胎研究中同样发现慢性疼痛、心血管疾病和抑郁障碍的发病率同时增加^[18],也提示慢性躯体疾病与抑郁障碍可能存在共同遗传介导的生物学变化途径。然而,也有研究显示,抑郁障碍与常见的神经系统疾病(如多发性硬化症、PD、癫痫和AD)遗传因素的关联并不明显^[19]。Tylee等^[20]对多个全基因组疾病关联研究数据进行分析,结果显示抑郁障碍仅与甲状腺功能减退症存在基因重叠,与其他躯体疾病的基因关联不明显。因此,未来还需进行大量研究以探究遗传因素在抑郁障碍及慢性躯体疾病中的共同作用机制。(2)神经系统变化。下丘脑-垂体-肾上腺轴和交感神经系统等应激反应系统的激活被认为是抑郁障碍发生的生物标志物之一^[21],同时应激反应系统的过度激活与糖尿病、AD、冠心病和骨质疏松症等慢性躯体疾病的发生有关^[22]。Taylor等^[23]对血管疾病进行研究,发现局灶性血管损伤会导致脑白质高信号,可能会改变大脑认知和情感回路的活动,进而可能发展为抑郁障碍。抑郁障碍患者通常表现出心率增快或动态心率变异性不稳定,刺激迷走神经可改善其抑郁症状并降低心率,额叶-迷走神经脑网络通路可能是抑郁障碍和心血管异常的共同脑机制之一^[24]。因此,在抑郁障碍患者中观察神经回路和自主神经功能变化(如心率、血压和心率变异性)等对优化神经调控治疗慢性躯体疾病共病抑郁障碍的潜在靶点提供了方向。(3)代谢与免疫因素。代谢与免疫功能也是精神障碍和躯体疾病共同的病理生理机制之一。线粒体自噬与细胞代谢功能相关,充足的线粒体自噬对于ATP生成和减少氧化应激至关重要。线粒体自噬受损已被证实与抑郁障碍、心血管疾病以及神经退行性疾病有关^[25-27]。动物研究表明,线粒体融合和裂变过程的变化可能会导致心肌病、高血压、动脉粥样硬化和心力衰竭^[28]。与健康对照者相比,抑郁障碍患者表现出线粒体功能下降,ATP的生成减少^[29]。在免疫炎症方面,Patten等^[11]的研究发现,各类疾病与抑郁障碍的关联强度存在一定差异,其中与炎症相关的疾病与抑郁障碍关联性最强,如糖尿病、心脏病、肠易激综合征和关节炎等^[30]。炎性指标与乏力、精力缺乏、睡

眠不佳和食欲差等躯体化症状密切相关^[31]。例如,在T1DM患者中,外周血清IL-8水平升高,且与体重指数相关;而IL-6和TNF- α 的升高则发生在新发的患者中,表明慢性躯体疾病患者的炎症因子早期即被激活^[32]。长期的慢性压力(如童年创伤经历、被欺凌、经济贫困等)会导致慢性炎症状态^[30]。本课题组前期研究显示,经历童年创伤的抑郁障碍患者的抗炎因子IL-10水平降低^[33],表明细胞代谢与免疫炎症因素在抑郁障碍和慢性躯体疾病中发挥着一定作用。综上所述,遗传、神经系统、细胞代谢与免疫炎症等生物学因素可能是慢性躯体疾病与抑郁障碍共病的潜在机制,共同影响疾病的发生、发展。

2. 心理社会因素:(1)心理因素。慢性躯体疾病患者需要长期治疗甚至反复住院,导致社交活动减少及亲密关系疏远,这容易使其感到孤独无助,产生负性自我评价^[34]。负性评价使患者独立判断、情绪调整及自我身份认同的能力更差,加重抑郁症状^[35]。慢性躯体疾病患者的认知水平也会间接地影响其情绪状态,例如癫痫会影响认知和学习能力,使患者对自身学习能力出现负面信念,降低自信心,从而出现情绪低落^[36]。与健康青少年相比,患有慢性躯体疾病的青少年对身体形象和外貌的自我评价较低,这可能与疾病治疗对身体造成一定损害有关,例如手术造口、术后瘢痕以及药物造成的体重增加等^[37]。另一项研究显示,自我评价低会导致T1DM青少年对疾病过度担忧,生活满意度降低,进而使其自杀意念频率增加和抑郁情绪加重^[38]。此外,青春期激素的释放会引起大脑化学物质的变化,导致青少年对事物的敏感性和负性认知增加。在生长发育的过程中,由于缺乏生理心理学知识,青少年对手淫、性器官发育等现象认识不足,易引发自卑心理,导致负面情绪和歪曲认知的增多^[39]。Hoffman等^[40]在T2DM患者中发现,体重增加与抑郁情绪评分增加相关,而营养不良性疾病(如胃肠道疾病)导致的体重过低也会导致自卑感产生,促发和加重抑郁情绪^[41]。因此,早期评估负性认知和自我评价的影响因素对慢性躯体疾病共病抑郁障碍患者的治疗和预后具有现实意义。(2)行为因素。体力活动少、不良生活习惯和睡眠不佳是躯体疾病发生的关键驱动因素^[42-43]。抑郁障碍患者多存在动力不足及精力下降,睡眠、饮食不规律,吸烟、饮酒频率高等行为问题,导致慢性躯体疾病的发病率增高或症状恶化^[44]。睡眠不佳与免疫功能、注意力以及焦虑、抑郁程度密切相关^[45]。Szabo等^[46]的研究显示,患有炎症性肠病的青少年睡眠质量更差,且与

腹痛、抑郁和焦虑情绪程度显著相关。规律的饮食和睡眠、适当的户外运动可以使患者保持良好心态,有助于减少躯体疾病和不良情绪的发生。(3)家庭和社会因素。家庭和社会环境对慢性躯体疾病的心理发展也有一定影响,在T2DM青少年人群中发现,由于社会对疾病认识不足,与身心健康有关的社会歧视问题持续存在,有超过50%的患者存在病耻感,从而加重其抑郁情绪^[47]。Lucas等^[48]研究发现,患有慢性躯体疾病的青少年更容易受到欺凌及虐待,出现情绪不稳定、自残和自杀行为。本课题组前期研究发现,童年期虐待和忽视以及家庭暴力等童年期创伤与免疫功能失调、神经内分泌紊乱、脑结构和功能改变等因素有关,增加个体成年后罹患抑郁障碍或慢性躯体疾病的风险^[49]。经历童年期创伤和应激性生活事件的个体交感神经活性增加,血压控制不规律,促炎因子水平升高,使其成年后发生冠心病和脑血管疾病共病抑郁障碍的风险增加1.1~1.6倍^[50]。一项荟萃分析表明,家庭和谐有助于防止慢性躯体疾病患者合并抑郁焦虑情绪,并提高治疗的依从性^[51]。家庭的情感支持以及良好的经济水平可视为慢性躯体疾病的保护因素,对疾病的转归有促进作用,同时减少焦虑抑郁情绪的发生^[52]。

三、慢性躯体疾病共病抑郁障碍的处理

1. 药物治疗:慢性躯体疾病共病抑郁障碍的处理具有一定挑战性,药物间相互作用和药物不良反应是临床面临的常见问题。例如,在卒中后抑郁及癌症患者中,虽然证实抗抑郁药可以改善抑郁症状,但相较于无慢性躯体疾病的抑郁障碍患者,抗抑郁药的疗效及耐受性较低,可能与药物之间相互作用或药物代谢有关^[53-54],因此使用抗抑郁药应从小剂量开始,观察疗效与不良反应,有条件的机构可在服用药物5个半衰期后测量药物浓度,决定是否加减药物剂量以保证安全。所有抗抑郁剂在早期均可能引起不良反应,如食欲不振、恶心呕吐、焦虑失眠等,部分药物可能导致心电图QTc延长^[55],如西酞普兰、三环类抗抑郁剂和单胺氧化酶抑制剂。因此,在药物使用时应密切关注心血管不良反应问题,如高血压、心脏传导阻滞等。此外,SSRIs不仅可能增加骨质疏松和骨折的风险^[56],还会通过抑制血色素增加出血风险,与非甾体抗炎药和维生素K拮抗剂(如华法林)联用时出血风险更高^[57]。SSRIs类药物还可能引发钙拮抗剂和 β -受体阻滞剂的血浆药物浓度升高,联合服用这些药物时需要调整相关药物剂量^[58]。此外,SSRIs类药物对代谢和体重的作用相对影响较小,因此在T2DM共病抑郁障碍的患者

中优先考虑使用 SSRI 类药物,并注意密切监测患者血糖、血脂及体重指数变化^[59]。综上所述,在慢性躯体疾病共病抑郁障碍患者的药物治疗方面,应尽可能地完善药物基因检测和血药浓度检查,避免药物之间的相互影响,以便更精准地治疗。在选择药物和递增剂量时,需对患者的年龄、合并药物的种类、躯体疾病、抑郁焦虑的严重程度等进行综合评估,密切监测用药后各项生理指标及躯体症状的变化,提高药物治疗的安全性。

2. 非药物治疗: 心理治疗有助于改善慢性躯体疾病共病抑郁障碍患者对疾病的认知。Quittner 等^[60]的研究表明,认知行为疗法(cognitive behavioral therapy, CBT)通过提高自信、促进疾病认识等方式可显著提高镰状细胞病患者的抑郁症状、自我评价以及生活质量。CBT 对心血管疾病^[61]、糖尿病^[62]患者的抑郁情绪改善也有积极作用。随着互联网及数字化技术的快速发展,通过人工智能提供的远程心理健康教育及虚拟现实生物反馈技术等对于慢性躯体疾病合并心理障碍的患者是较好的选择^[63-64],特别适合行动不便的患者。物理治疗对部分慢性躯体疾病和抑郁障碍的患者也有较好的疗效,例如光照治疗不仅能改善抑郁情绪,还能改善 PD、AD 患者的运动及非运动症状(如认知损害)^[65];深部经颅磁刺激通过刺激不同脑区可以达到改善情绪和认知的效果,但合并癫痫的患者应慎用。多学科联络会诊从不同专业角度提供全面、个性化的治疗方案,对于冠心病、乳腺癌、糖尿病、高血压、脑卒中合并焦虑抑郁症状的患者效果良好^[66-68]。自我管理对于疾病的恢复也十分重要,如戒烟戒酒、健康的饮食、保证充足睡眠、坚持服药以及适当的运动等。运动疗法已被证实对冠心病、慢性心力衰竭及类风湿性关节炎患者的抑郁症状具有改善作用^[69]。总之,慢性躯体疾病共病抑郁障碍的治疗需采用多模式联合治疗,重建并提高患者的身心健康水平。

四、总结与展望

慢性躯体疾病共病抑郁障碍的患病率较高,两种疾病可能在遗传、神经、代谢与免疫及心理社会因素等方面存在共同的发病机制。因此,应结合个体的共病特点及发病机制,既考虑患者的躯体疾病也要关注患者的抑郁情绪及其变化,制订药物与非药物联合治疗方案,确保共病患者获得长期的情绪治疗与管理,促进疾病的转归和身心健康发展。

利益冲突 文章所有作者共同认可文章无相关利益冲突

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