

· 抑郁症专题 ·

抑郁障碍复发的危险因素

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【摘要】 抑郁障碍是一种可高度复发的疾病,对个人和公共健康造成重大影响。近年来随着人们对抑郁复发的深入研究,发现有多种危险因素影响抑郁障碍的复发,现就抑郁障碍复发的多种危险因素进行综述。

【关键词】 抑郁障碍; 复发; 危险因素; 综述

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【Abstract】 Depressive disorder is a highly recurring disease that has a major impact on personal and public health. In recent years, with the in-depth research on the recurrence of depression, it has been found that there are multiple risk factors affecting the recurrence of depression. This paper reviews the multiple risk factors depression recurrence.

【Key words】 Depression; Recurrence; Risk factors; Review

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抑郁障碍(depressive disorders)作为全球重大公共卫生问题,具有高患病率、高复发率及高自杀率的特点^[1]。抑郁障碍严重影响患者的身心健康和社会功能,给患者、家属乃至整个社会带来了沉重的负担^[2]。确定复发危险因素有助于为抑郁障碍患者制定更加个性化的干预策略,因此研究抑郁障碍复发的危险因素非常必要。

一、人口统计学危险因素

初次发病年龄较小被多数研究认为是抑郁障碍复发的危险因素。一项对老年样本(>60岁)随访5年的研究分析发现,发病年龄越早,复发风险越高^[3]。Mazzarini等^[4]发现在30岁之前出现抑郁症状的患者在未来复发风险增高。性别在复发风险的证据中更偏向于无明显影响, van Loo等^[5]发现,虽然女性抑郁障碍的发病率是男性的2倍,但在抑郁复发的危险因素中未发现明显的性别差异。一项对1269例抑郁障碍患者的研究发现,性别与发作次数、受教育年限、病史年限等其他复发危险因素无交互作用^[6]。妊娠是否会影响到抑郁障碍自然病程仍然缺乏证据,但患病妇女在怀孕期间停用抗抑郁药时,其复发率升高^[7]。复发患者在社会经济地位和婚姻方面的调

查结果有所差异, Tibubos等^[8]研究发现,较低的社会经济地位预示较高的抑郁障碍复发率,但与婚姻无显著相关性。

二、遗传学危险因素

有关家族史的研究中发现,具有情绪障碍家族史与抑郁复发明显相关。除了抑郁障碍或复发性抑郁障碍的家族史以外,一项大样本数据发现,有双相情感障碍家族史的抑郁患者复发率较高,双相障碍谱系与高复发性重度抑郁障碍也具有连续性^[9]。此外,一项对患有抑郁障碍的女性双胞胎($n=194$)的前瞻性研究发现,精神病家族史被证明是复发风险增加的相关因素^[10]。全基因组关联研究(Genome-Wide Association Studies, GWAS)未能报告全基因组范围的显著结果^[11],除了样本量的原因外,可能是因为涉及多个基因变异,且不同基因间常存在相互作用,同时基因表达还受到异位显性和表观遗传机制的影响,因此这一领域的研究依然任重道远^[12]。

三、神经影像学危险因素

1. 脑结构成像:在脑部区域结构改变的证据中,多个脑区参与了抑郁障碍的复发^[13]。一项对首发

未服药成年抑郁症患者的研究发现,边缘系统-皮质-纹状体-苍白球-丘脑环路相关的脑灰质体积均有所减小^[14]。

额叶皮层被认为是抑郁发作和维持的核心区域,既往的研究报道了首发未用药的抑郁患者存在额叶皮层体积减小^[13,15]。在一项历经4年的纵向研究中观察到,抑郁复发患者背外侧前额叶(dlPFC)的皮质厚度减小,这种体积变化与精神病药物治疗或抑郁的严重程度无关,而仅有一次抑郁发作的患者该区域无明显变化^[16]。

海马与重度抑郁障碍的起病和发展密切相关,海马体积可能是辨别重度抑郁障碍临床特征(复发次数、严重程度及治疗难易程度)的标志^[17]。某些抑郁复发的个体可能先天海马体积较小^[18]。此外,生活中遇到的压力性事件和长期高水平的皮质醇分泌也可以使海马体积减小,导致复发的可能性增加^[19]。

较薄的前扣带回皮层(anterior cingulate cortex, ACC)与处理抑郁情绪的难度更大相关,Foland-Ross等^[20]发现,与对照组比较,母亲是复发性抑郁患者的从未患过抑郁障碍的后代右ACC较薄。有研究根据对45例抑郁患者的5年随访发现,右ACC的体积更大是最能预测长期临床转归结果的变量,并认为右ACC可以作为长期临床转归的潜在生物学标志物^[21]。

2. 脑功能成像:抑郁障碍是涉及多个脑区、病变广泛的脑功能异常疾病。默认模式网络(default mode network, DMN)被认为与抑郁障碍的发展显著相关^[22]。DMN主要包括后扣带回皮质(posterior cingulate cortex, PCC)、内侧前额叶皮质(mPFC)和顶下皮质等,这些脑区在静息态活跃,在任务态被抑制^[22]。抑郁障碍患者达到临床治愈标准后,其DMN仍未完全恢复正常水平,提示DMN功能恢复迟滞于临床症状恢复,且与抑郁症的预后有关^[23]。Liu等^[24]研究发现,与首发抑郁障碍患者相比,复发性抑郁障碍患者存在DMN区域内部连通性加强,这种连通性改变参与了抑郁复发的病理过程。

有研究报道,首发未服药抑郁障碍患者和抑郁易感者静息态下额叶、颞叶、枕叶、顶叶、小脑及边缘系统等脑区神经元活动有异常改变,这些异常活动脑区可能既是抑郁症发病机制的核心脑区^[25]。崔健等^[26]发现,抑郁症患者在治疗前边缘皮质-纹状体-苍白球-丘脑这一神经环路的静息态功能交互低于健康对照组,经抗抑郁药物治疗后,右侧眶额叶皮质至右侧杏仁核的功能交互仍未恢复。

四、环境风险因素

抑郁障碍中最确定的环境风险因素是压力性生活事件。有充分的证据表明有童年虐待(定义为身体、性或情感虐待、家庭冲突或暴力或忽视)史的患者复发的概率更高^[27-28]。Torres-Berrio等^[29]发现,早期生活压力性事件可以通过表观遗传机制作用于大脑,增加抑郁易感性。在成年人中,Sheets和Craighead^[30]对119例经历过抑郁发作的患者随访了18个月后发现,人际压力(例如亲密关系、亲密的友情、社交生活、家庭关系等)可以预测抑郁症复发,而非人际压力(例如学业、工作、经济、个人健康以及家庭成员的健康)与抑郁症复发没有关联。

五、心理社会学危险因素

抑郁障碍患者的病情缓解并不表示重获正常的心理社会功能^[31]。De Jonge等^[32]评估了107例症状已缓解的复发性抑郁障碍患者,发现正性情感似乎在预测抑郁症的症状中起着独立的作用。外向、友善、尽职尽责和庞大的人际关系网络可减少抑郁障碍复发的风险^[3]。缺少社会支持是抑郁症状发生的风险因素,从工具支持和情感支持两个方面分析社会支持与抑郁症状发生风险的关联,结果表明情感支持相对于工具支持具有更强的保护作用^[33]。

六、临床特征危险因素

1. 既往史:相比人口统计学因素,临床特征更能预测抑郁障碍的复发^[34]。既往发作次数、严重程度、持续时间和残留症状等因素,均与复发风险有关^[35]。其中,既往发作次数被认定是预测复发的重要危险因素^[36]。抑郁复发的风险会随发作次数的增多而急剧上升,有3次或以上发作的抑郁障碍患者在10~15年内的复发率高达90%^[37]。抑郁持续时间与复发率呈正相关^[38]。

2. 认知损害:95%以上抑郁障碍患者经治疗后认知功能损害仍持续存在,而反复发作会造成进一步的认知功能损害,虽然在缓解期稍改善,但不会恢复至病前水平^[39],更严重的认知功能障碍又与之后更严重的抑郁发作相关^[40]。Figuroa等^[41]对处于缓解期的抑郁复发患者进行研究,发现反刍和认知灵活性降低的持续存在可能导致复发,并认为改善认知灵活性可以作为减少复发的干预措施。

3. 临床症状:自杀意念与更高的复发风险有关,即使是轻度的自杀意念也可能预示随后的复发^[35]。一项对老年样本(>60岁)随访5年的研究分析发现更大的复发风险与自杀意念有关^[3]。对国内357例抑郁发作患者进行1年随访,评估其复发情况,发

现抑郁发作时具有混合特征,混合特征个数更多的抑郁发作患者复发的风险更高^[36]。Mazzarini等^[4]发现伴有双相特质或混合特征的群体常为疾病的高复发群体。

4. 残留症状:有研究显示,在急性期治疗有效的抑郁症患者中仍有49.8%的患者有残留症状^[42]。以8个城市11家医院门诊就诊的抑郁症患者为研究对象,不同起病年龄抑郁症患者残留症状的特征不同,起病年龄越早,残留症状越多,其社会功能受损就越严重^[43],同时患者的生活质量和医疗的满意度也越低,病程越倾向于慢性化,自杀企图就会越高^[44]。残留症状很可能发展为下一次复发的前驱症状^[45]。

5. 共病:抑郁障碍与睡眠障碍、焦虑障碍的共病很常见,共病这两种疾病的抑郁障碍患者的复发率更高。一项纵向研究发现:睡眠时间短(<6h)的受试者发生抑郁障碍和复发性抑郁障碍的风险更高,而睡眠时间长(>9h)的受试者抑郁发作风险较低^[46]。老年人可能对睡眠时长更敏感,老年人经历了慢性睡眠剥夺,导致下丘脑-垂体-肾上腺轴功能失调,这与抑郁障碍的发生和复发密切相关^[47]。共病广泛性焦虑障碍(generalized anxiety disorder, GAD)、社交焦虑障碍和特殊恐惧障碍等预示着重度抑郁障碍发作年龄较早和发作次数较多^[48]。此外, Berwian等^[49]发现,共病有其他精神障碍的抑郁障碍患者,如果停用抗抑郁药,特别容易复发。

七、治疗的危险因素

服药依从性是抑郁发作患者复发的保护因素^[36]。英国国立健康与临床优化研究所(National Institute for Health and Clinical Excellence, NICE)指南推荐,对当前已经有过2次或2次以上复发的患者应使用抗抑郁药物进行至少2年的治疗作为预防复发的干预措施^[50]。对治疗的依从性降低以及不适当的治疗药物或剂量被认为是抑郁复发的预测指标^[51]。有研究发现,即使治疗反应良好,患者缓解期间药物不良反应的严重程度可能是复发的有价值预测指标,这提示随访中关注患者药物不良反应的临床意义^[35]。

八、小结

综上,抑郁障碍复发的危险因素涉及人口统计学、遗传学、神经影像学、外界环境、心理社会学、临床特征、治疗等方面。虽然抑郁障碍复发因素的相关研究已有进展,但因研究的异质性,仍需更多、更规范、同质化的研究。此外,即使已确定的抑郁障碍复发危险因素,各因素对复发的影响程度也各不相同。如何根据危险系数指导临床实践中对患者

开展个性化干预措施,是亟需解决的问题。随着科技的发展,学者们主张使用基于大数据的风险预测工具,即以多变量的形式组合帮助患者进行复发风险分层,致力于最大限度地减少或避免抑郁障碍的复发,针对高复发风险的患者给予预防复发的干预措施,精准施治。

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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