·定性系统综述·

系统性红斑狼疮共病焦虑抑郁影响因素研究进展

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【摘要】 系统性红斑狼疮(SLE)是一种自身免疫介导的、全身多组织和器官受累的疾病,SLE与焦虑抑郁共病率高,严重影响患者的疾病转归,给临床诊治带来严重挑战。本文通过对SLE共病焦虑抑郁的影响因素进行综述,以期为优化SLE共病焦虑抑郁的治疗提供参考。本文共纳入25篇原始研究,系统分析了影响SLE共病焦虑抑郁的遗传因素、免疫因素、中枢神经系统因素以及社会心理因素。

【关键词】 系统性红斑狼疮;焦虑;抑郁;影响因素

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Research progress on the influencing factors of comorbid anxiety and depression in systemic lupus erythematosus

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【**Abstract**】 Systemic lupus erythematosus (SLE) is an autoimmune disease in which the immune system mistakenly attacks multiple tissues and organs of the body. The comorbid anxiety and depression are highly prevalent conditions among SLE, thereby worsening the prognosis of patients and posing a serious diagnostic challenge to the clinicians. The purpose of this article is to review the literature available for the influencing factors of comorbid anxiety and depression in SLE, and to provide references for optimizing treatment strategies for SLE patients with comorbid anxiety and depression. A total of 25 original research articles are included to provide a systematic and quantitative review, in which the genetic, immune, central nervous system and socio-psychological factors affecting the comorbid anxiety and depression in SLE are explored.

【**Keywords**】 Systemic lupus erythematosus; Anxiety; Depression; Influencing factors

系统性红斑狼疮(Systemic lupus erythematosus,SLE)是一种自身免疫介导的,以免疫性炎症为突出表现的弥漫性结缔组织病,通过产生致病性自身抗体和免疫复合物的沉积,导致心脏、皮肤、肺和肾脏等多器官损伤[1]。SLE患者常合并焦虑和抑郁等负性情绪[2]。既往研究显示,SLE患者发生焦虑和抑郁的风险是正常人群的2倍[3],SLE患者抑郁和焦虑的患病率分别为35.0%和25.8%[4]。SLE共病抑郁和焦虑往往会导致与疾病相关的心血管疾病、身体残疾、自杀甚至死亡[5-7]。目前,我国约有100万SLE患者,疾病负担较重,共病焦虑抑郁对SLE患者的治疗和预后存在负面影响,进一步加重疾病负担。因此,改善SLE患者的焦虑抑郁症状是提高其生活质量的关键。目前,关于SLE共病焦虑抑郁的病因和病理机制非常复杂,是生物、社会、心理等多方面因素共同作用的结果。研究表明,SLE疾病活动与焦虑和抑郁相关,活动性SLE与患者的抑郁和焦虑症状加重有关。然而,目前关于焦虑和抑郁与SLE疾病活动的相关性研究多为横断面研究,且未考虑混杂因素的影响[8-9]。全面探究SLE合并焦虑抑郁的病因和发病机制等,对SLE的预防和治疗至关重要。本文对SLE共病焦虑和抑郁的遗传因素、

免疫因素、中枢神经系统因素以及社会心理因素进行综述，以期为对SLE患者的负性情绪干预提供参考，进而提升患者的整体健康状况、提高生活质量。

1 资料与方法

1.1 资料来源与检索策略

1.1.1 资料来源

于2022年12月30日通过计算机检索中英文数据库，包括中国知网、维普、万方、PubMed和Web of Science，检索时限为建库至2022年12月30日。

1.1.2 检索策略

中文检索词：焦虑症、焦虑障碍、焦虑状态、焦虑、抑郁状态、抑郁症、抑郁障碍、抑郁、系统性红斑狼疮；英文检索词：anxiety disorder、anxiety、depressive disorder、depression、systemic lupus erythematosus、lupus、SLE。中文检索式：（“焦虑症”or“焦虑状态”or“焦虑障碍”or“焦虑”or“抑郁状态”or“抑郁症”or“抑郁”）and“系统性红斑狼疮”；英文检索式：（“anxiety” or “anxiety disorders” or “depressive disorder” or “depression”）and（“systemic lupus erythematosus” or “lupus” or “SLE”）。

1.2 文献纳入与排除标准

纳入标准：①研究对象为符合美国风湿病协会（American Rheumatism Association，ARA）系统性红斑狼疮诊断标准的患者；②研究内容涉及SLE共病焦虑和抑郁的影响因素；③中英文文献。排除标准：①重复发表、无法获取全文、无法提取数据的文献；②个案和综述；③质量较低的文献；④无法获取全文的文献。

1.3 文献筛选与质量评估

由2位作者按照文献纳入与排除标准独立进行文献筛选。将检索出的文献导入EndNoteX9，剔除重复文献及与本研究内容无关的文献，对于有争议的文献，由双方讨论决定，必要时由循证医学专家判定。对纳入的文献进行质量评价，对于不同研究设计类型的文献，采用不同的文献质量评价方法。采用动物实验研究报告指南（animals in Research：reporting in Vivoexperiments，ARRIV）评价动物实验，采用纽卡斯尔-渥太华量表（Newcastle-Ottawa Scale，NOS）评价病例对照研究和队列研究，采用美国医疗保健研究与质量机构（Agency for Healthcare Research and Quality，AHRQ）的评价标准评价横断面研究。

2 结 果

2.1 文献纳入情况

初步检索共获取中英文文献1 165篇，其中中文文献61篇，英文文献1 104篇。剔除重复文献，阅读文献标题、摘要及全文后，最终纳入文献25篇。文献筛选流程见图1。

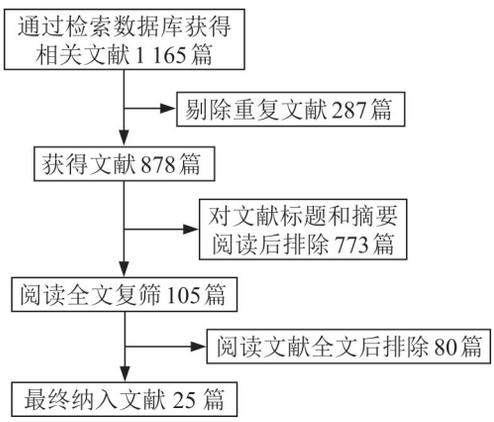

图1 文献筛选流程图

Figure 1 Flow chart of literature screening

2.2 纳入文献的基本特征和质量评价

在纳入的25篇文献中，SLE共病焦虑抑郁的影响因素遗传因素（5篇）、免疫因素（12篇）、中枢神经系统（3篇）、社会心理因素（5篇）。纳入文献质量评价结果显示，高质量文献4篇，中等质量文献12篇，低质量研究6篇，另有3篇文献缺乏质量评价工具。微信扫OSID二维码获取纳入文献基本特征信息和质量评价结果。

2.3 SLE共病焦虑抑郁的影响因素

2.3.1 遗传因素

SLE共病焦虑抑郁是遗传、免疫以及环境等多种因素共同作用的结果。全基因组关联性研究为开展复杂疾病的发病机制研究提供了方向。已有多项研究从基因多态性的角度揭示了SLE与焦虑抑郁在病因和治疗等方面的关联性。一项病例对照研究显示，RPEL1和miR-1307基因多态性（rs4917385和rs7911488）可能与中国人群SLE易感性以及SLE患者的抑郁、焦虑和生活质量有关[10]。FKBP4和FKBP5基因的遗传变异可能导致配体复合物的形成以及糖皮质激素受体（glucocorticoid receptor，GR）功能紊乱，从而导致下丘脑-垂体-肾

上腺(hypothalamic-pituitary-adrenal,HPA)轴功能紊乱,进而产生焦虑和抑郁情绪[11-12]。TWEAK 和 Fn14 通路可能通过促进炎性细胞因子的局部分泌而直接参与神经精神性狼疮(Neuropsychiatric lupus,NPSLE)的发病机制[13]。此外,最新的一项全基因组关联研究显示,免疫性疾病与精神疾病存在相关的基因位点,提示 SLE 和情绪障碍之间可能存在共同的遗传学基础[14]。

2.3.2 免疫因素

SLE 是一种复杂的免疫性疾病,涉及多细胞、多分子参与的免疫调节异常。在焦虑和抑郁障碍患者中,即使没有炎性疾病,其炎症指标水平仍偏高[15]。较高的血清肿瘤坏死因子 α(tumor necrosis factor-alpha,TNF-α)水平与 SLE 患者的焦虑抑郁情绪相关[16],且与更严重的抑郁症状独立相关[17]。对狼疮小鼠模型的研究结果表明[18],神经元 Nr4a1 信号传导对于吸引 C1q 突触沉积和随后小胶质细胞介导的突触消除至关重要,该研究揭示了神经元在协调小胶质细胞介导的突触丢失方面的积极作用,并强调了神经元 Nr4a1 和补体蛋白 C1q 是治疗 SLE 共病焦虑抑郁的关键成分[18]。既往研究表明,免疫系统的状态,特别是免疫细胞的比例,可以影响心理应激[19]。Gu 等[20]研究结果表明,与 SLE 密切相关的 T 细胞亚群($CD27^+CD28^+$Th/Treg、$CD27^-CD28^-$Th/Treg、$CD45RA^-CD27^-$Th、$CD45RA^+HLADR^+$Th)可能参与 SLE 患者焦虑症状的发生。肠道菌群失调相关的促炎反应不仅影响肠脑轴和认知功能,还影响免疫耐受的平衡,这也是 SLE 患者出现焦虑抑郁症状的重要原因[21]。SLE 患者共病情绪问题可能与较高的血清 S100A8/A9 浓度有关[22]。抑郁症患者 HPA 轴的过度激活和糖皮质激素水平的持续升高抑制了免疫反应,并导致血清 IL-6 和 IL-2 水平升高[23-24]。因此,使用激素治疗 SLE 可能增加患者焦虑抑郁的易感性。抗核糖体 P 蛋白抗体被认为是 SLE 的特异性抗体。多项研究表明,抗核糖体 P 蛋白抗体与焦虑症和抑郁症相关[25-26]。将抗核糖体 P 蛋白抗体直接注入小鼠脑室可诱导小鼠出现抑郁样行为,通过抗抑郁药物和阻断抗体可改善其抑郁样行为[27]。动物实验结果表明,脂质运载蛋白-2(Lipocalin-2,LCN-2)是 NPSLE 中有害神经免疫反应的主要调节因子,且脑脊液中 LCN-2 是 NPSLE 的新型生物标志物[28-29]。

2.3.3 中枢神经系统因素

Robinson 等[31]的研究结果显示,脑岛除了直接参与抑郁和焦虑外,还参与大脑对免疫的调节。当患者持续处于心理应激状态时,身体便长期处于全身性低度炎症激活状态,从而破坏信息处理的第一单元杏仁核,导致血脑屏障破坏,通透性增强[31]。SLE 患者的右侧岛叶血脑屏障通透性增加与 SLE 患者的抑郁焦虑情绪有关[32]。静息态功能磁共振研究显示,伴严重焦虑和抑郁症状的 SLE 患者大脑边缘和前额叶区域灌注动力学和功能连接性改变[33]。与健康对照组相比,NPSLE 组双侧背外侧前额叶皮层和腹内侧前额叶皮层的脑血流量和脑血容量降低,焦虑症状与额纹状体和右侧前扣带回灌注降低相关[34]。与不伴神经和精神症状的 SLE 患者相比,伴抑郁症状的 SLE 患者海马体和前额叶皮层血清脑源性神经营养因子(brain-derived neurotrophic factor,BDNF)表达较低,从而导致神经可塑性损伤。BDNF 调节 mRNA 的转录和转运,与神经精神疾病的发病有关。

上述研究提示,SLE 患者大脑结构和功能的改变可能既是复杂的自身免疫反应的结果,也是介导患者出现焦虑抑郁的重要原因。患者的情绪问题可能会激活或加重免疫炎症,影响中枢神经系统的结构和功能。因此,在对 SLE 的治疗中,除了关注 SLE 疾病本身的治疗,也需要对患者的情绪问题加以重视,采取积极的干预措施。

2.3.4 社会心理因素

年龄、超重、职业、收入、婚姻以及受教育程度等是 SLE 患者生活质量的影响因素[35-36]。SLE 患者可能面临自我认同感降低和身体形象改变,如面部皮疹、发病期间的体重波动等,同时,疼痛、疲劳、运动受限等躯体问题也会影响患者的社会功能[37]。这些均可能降低患者的自尊水平,产生病耻感,对外界排斥,不愿接受周围人的关怀和帮助[35,38]。此外,由于缺乏医学知识,对疾病的病因、治疗和预后等不了解,患者生病后仍保持着部分不良的生活方式,如饮酒、作息不规律等,且治疗依从性较差[39]。以上均可能增加 SLE 患者出现焦虑抑郁等情绪问题的风险,不利于疾病的恢复,影响患者的生活质量。因此,临床工作者可以通过为患者提供一定的社会支持,加强疾病健康教育,同时,可提高公众对 SLE 的认识和理解,减少社会歧视和污名化,帮助患者更好地应对疾病,改善患者的心理健康状态。

3 小 结

SLE患者焦虑和抑郁检出率较高，加重疾病负担，影响预后。遗传、免疫、中枢神经系统以及社会心理因素与SLE患者的焦虑抑郁情绪相关。但其他复杂因素如共病躯体疾病、接触有害物质、生活习惯等，是否也会导致SLE患者出现焦虑抑郁情绪，仍有待进一步研究。

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