综述

癌因性疲乏发病机制及治疗的研究进展

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摘　要:癌因性疲乏是肿瘤患者常见症状之一,其发病率高达75%~100%。迄今有关癌因性疲乏发病机制尚不明确,可能与癌症治疗、肌肉代谢失调、免疫和炎症、中枢神经系统功能障碍等因素有关。目前临床治疗主张以非药物干预为主,辅之以药物治疗。中医辨证论治癌因性疲乏多以气虚、血虚为主,临床上常采用补益气血之法,以达到扶正抗癌的目的。全文总结近年来癌因性疲乏的研究进展,为其临床诊治提供一定的理论参考依据。
主题词:癌因性疲乏;发病机制;中西医治疗
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Research Progress on Pathogenesis and Treatment of Cancer-Related Fatigue

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Abstract: Cancer-related fatigue(CRF) is one of the most common symptoms of cancer patients, its incidence is as high as 75% to 100%. The pathogenesis of cancer-related fatigue is not clear, and may be related to cancer treatment, muscle metabolism disorders, immunity and inflammation, central nervous system dysfunction and others. The current clinical treatment is mainly non-drug intervention, supplemented by drug treatment. Traditional Chinese medicine considers that CRF is related to "Qi and Blood Deficiency", so the principle of "Nourishing Qi and Blood" is applied to treat CRF. This article summarizes the research progress of cancer-related fatigue in recent years, and provides a reference for its clinical diagnosis and treatment.
Subject words: cancer-related fatigue; pathogenesis; traditional Chinese and western medicine

癌因性疲乏(cancer-related fatigue,CRF)与癌症本身以及辅助治疗有关,并且可以持续很长时间,极大地影响了患者日常生活质量[1]。大多数患者在被诊断为癌症时即存在CRF,在积极抗癌的患者中的比例更是高达90%[2],且治疗结束后疲劳仍持续数年[3]。美国国家综合癌症网(NCCN)将CRF定义为[4]:与癌症或癌症治疗有关的令人沮丧的、持续的、主观的疲倦或疲惫感,与最近的活动不相称,并且会干扰正常生活。尽管在过去的二十年中已经提供了许多有关CRF证据和研究结果,但CRF病因、发病机制的研究尚无明确定论,且缺乏有效的干预手段。本文旨在分析CRF研究现状,以期获得更健康的指导和改善CRF治疗策略。

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1　癌因性疲乏发病机制

1.1　肿瘤本身治疗

手术带来的创伤、放化疗引起的毒副反应、肿瘤给患者造成的心理疾患都可能导致疲乏的发生。尽管没有任何癌症复发的迹象,但大多数癌症患者在完成癌症治疗后仍表现出严重的疲劳感,这表明化学疗法或放射疗法可促进CRF[5]。据报道,2177例接受了积极的门诊治疗患者中有983例(45%)患者出现中度或重度疲乏,515例完全缓解的乳腺癌、前列腺癌、结肠直肠癌或肺癌患者中有150例(29%)

出现中度或重度疲乏[6]。重度疲乏的病因包括肿瘤晚期,放疗、化疗、手术、激素疗法以及这些疗法的组合,重度疲乏的患病率在7%~52%之间,与仅接受紫杉醇的患者相比,接受环磷酰胺、氟尿嘧啶、阿霉素或多西他赛的患者疲劳更为严重[7-8]。但是,接受大剂量或标准剂量紫杉醇治疗患者的疲劳评分无统计学差异,表明疲劳程度随着化学疗法的不同类型和不同策略的组合而发生变化[9]。

1.2 骨骼肌和线粒体功能障碍

化疗是非特异性地针对骨骼肌,尤其是线粒体,一旦线粒体的结构和功能被破坏,细胞能量供应就会减少,从而导致各种令人不快的状况,例如疲劳、肌肉消瘦、运动能力下降、疼痛以及与抗癌相关的严重神经系统疾病等[10-11]。线粒体功能受多种因素调节,例如线粒体DNA(mtDNA)、核DNA(nDNA)、线粒体活性氧(mtROS)、线粒体活性氮物质(mtRNS)等[12]。当用化学疗法或放射疗法治疗时,线粒体的规则结构和功能通过不同信号传导途径被破坏,nDNA和mtDNA转录所涉及的过程被显著破坏,并且mtROS和mtRNS的水平上调[13]。mtROS产生增加使线粒体池活力降低,ATP合成受损,从而引起疲乏。骨骼肌是高度代谢的器官,需要足够的ATP代谢,已经证明,严重疲劳的根源在于线粒体功能障碍和ATP生成受损,但对线粒体功能障碍和CRF分子机制的更深入,更准确的描述尚不清楚[14]。

1.3 外周免疫激活和炎症反应

炎性细胞因子主要由免疫细胞产生,并通过免疫细胞之间的自分泌和旁分泌,或者中枢神经系统调节炎症反应。促炎症因子的释放可以导致抑郁、嗜睡和食欲不振等,这可能与CRF有关。越来越多的证据表明,CRF中存在持续的炎症反应,CRF患者血清促炎细胞因子标志物水平明显高于无疲劳的癌症患者或健康对照者[15]。一项关于299例乳腺癌患者的研究表明,与无疲劳患者相比,疲乏的乳腺癌患者表现出更高水平的C反应蛋白[16]。Schrepf等[17]发现,在治疗后1年中疲劳症状得到改善的卵巢癌患者血浆IL-6降低。有学者对37种炎症基因进行评估,发现IL-8、IL-10与肺癌患者疼痛和疲劳有显著性关联[18]。

1.4 下丘脑-垂体-肾上腺轴(HPA轴)破坏

近年来多项研究显示,癌症(或其治疗)会直接或间接破坏正常的HPA轴,引起内分泌紊乱,从而诱发CRF。正常生理情况下,HPA轴通常根据身体或心理压力调节应激激素皮质醇的释放,皮质醇具调节心血管系统平衡,维持免疫系统稳定和促进新陈代等重要生物学作用,此外皮质醇还能抑制细胞因子的产生。由于炎性应激,外周炎性细胞因子通过各种途径进入大脑,促炎性细胞因子(例如IL-1,IL-6,TNF-α)可能会破坏HPA轴,减少皮质醇合成和释放,从而引起疲劳[19]。两项研究调查了昼夜皮质醇水平与乳腺癌幸存者疲劳的关系,结果均显示乳腺癌幸存者CRF夜间皮质醇水平低于无疲劳者[20-21]。另有研究表明,激素治疗可以缓解疲乏症状[22]。癌症中HPA轴的变化可能继发于其他各种与疾病相关的因素,例如抗癌治疗,过量的促炎细胞因子或合并症(如睡眠障碍)。考虑到HPA轴对疲劳的影响,通过在治疗前,治疗中和治疗后更频繁地纵向测量皮质醇和糖皮质激素水平,可以更好地理解HPA轴在CRF中的作用。

1.5 睡眠障碍

研究发现,疲乏常与睡眠障碍、如焦虑、抑郁或疼痛有关[23]。焦虑、抑郁或是疼痛的发生,又导致失眠加重,因此产生恶性循环,从而产生重度疲乏。睡眠时间、睡眠质量不佳均会导致疲乏的发生。有学者提出,癌症患者会减少运动,花更多的时间在床上休息,白天睡眠增加和缺乏运动从而会干扰体内稳态的睡眠驱动力和昼夜节律,从而导致夜间睡眠减少,使疲乏发生增加[24]。Peoples等[25]对548例乳腺癌患者进行研究,发现睡眠质量差会导致疲劳加剧。

2 CRF筛选、评估和管理

有效的CRF管理对患者很重要,对临床医生也具有挑战性。已经开发出了许多用于筛选CRF评估量表,但是对于最佳可用评估量表尚未达成共识。

疲劳评估工具有两种类型[26]:一维工具和多维工具。这些工具中最简单的是一维工具,它是CRF的单项指标,例如视觉模拟量表(VAS)、短暂疲劳量表(BFS)、MD安德森症状量表。多维疲劳量表、癌症治疗疲劳(FACT-F)功能评估量表、Piper疲劳量表是多维工具,这些量表问卷更详细,主要用于临床研究。

根据NCCN指南,癌症疲劳的评估和治疗基于四个阶段:筛查、初步评估、干预和重新评估。通过定

量或半定量评估工具(例如 BFS,VAS 或 FACT-F)进行筛选，并进行记录。初步评估包括研究患者的病史和体格检查以及接受癌症治疗的评估，还包括 CRF 可治疗因素的评估[27],这些因素包括疼痛、睡眠障碍、贫血、甲状腺功能减退、药物副作用等。根据对疲劳评估和初步评估以及定期接受治疗的重新评估,计划为患者进行疲劳相关的治疗或干预。

3 CRF 治疗进展

目前临床上中度或重度疲劳者可以通过药物和非药物干预获益，而不干扰生活质量的轻度疲劳可以通过非药物干预治疗。

3.1 非药物治疗

一项包括 113 项研究和 11 525 例患者的荟萃分析显示,非药物干预,特别是运动干预和心理干预能改善癌因性疲乏，而药物干预并无显著性改善 CRF[28]。日常锻炼可以增强身体机能,促进新陈代谢，从而改善乏力症状,NCCN 指南将体育运动推为 1 类证据[4]。Oberoia 等[29]对 170 项研究进行分析,发现有氧运动、神经运动、抵抗运动和综合运动均可有效减轻疲劳，应该鼓励癌症患者在治疗期间和治疗后进行适度的体育运动。认知行为疗法是当前比较流行的一种治疗方法[26],包括小组治疗、放松训练、与疲劳有关的心理教育等，这些干预措施可以帮助个人进行自我管理,提升自信心,缓解焦虑、抑郁的情绪,以找到应对疾病的方法。一项有关乳腺癌的研究发现,认知行为疗法能减轻患者的疲乏[30]。睡眠障碍是癌因性疲乏患者的常见问题。任何提供良好睡眠和休息的方法都将帮助改善疲乏状况。睡眠的认知行为疗法有很多,最常用的包括刺激控制,睡眠限制和睡眠卫生。由于癌症和治疗会干扰饮食摄入,因此营养咨询可能有助于解决因厌食、腹泻、恶心和呕吐引起的营养缺乏，充足的水分和电解质平衡对于预防和治疗疲劳也至关重要。此外,研究发现瑜伽、太极和气功也有利于缓解患者疲乏症状。一项纳入 17 项研究,包括 2183 例患者荟萃分析显示,瑜伽可以改善乳腺癌患者的疲劳[31]。Wayne 等[32]发现太极和气功在改善患者疲乏及生活质量上有重要临床意义。

3.2 药物治疗

目前药物治疗以对因治疗为主，如促红细胞生成素治疗贫血,用抗抑郁药处理抑郁,用镇静催眠药治疗严重失眠等[33]。近年来研究发现莫达非尼并不能改善患者疲劳症状 [34],NCCN 指南已不推荐使用该药物。在接受癌症治疗的患者中,对精神兴奋药哌醋甲酯对 CRF 的疗效进行了评估,结果喜忧参半[35],在排除其他原因引起疲乏的情况下，接受积极抗癌治疗的患者可以考虑使用该药物。尽管有证据表明皮质类固醇可以改善与癌症有关的疲劳,但其安全性仍未得到证实,此类药物仅限于晚期癌症疲乏者[36]。此外,一些膳食补充剂,如西洋参、生姜提取物(6-姜辣素)或益生菌等也可以改善癌症患者的疲乏症状[37]。

3.3 中医药治疗

癌因性疲乏在中医属于“虚劳”范畴,一般以补益、扶正之法作为基本治则,以达到扶助正气而缓解疲乏的目的。中医药在改善肿瘤患者疲乏方面有其独特的优势。有学者[38]用温补脾肾法,黄芪建中汤和金匮肾气丸,大肠癌患者疲乏得到改善。参芪注射液也被证实有一定的作用[39]。此外有研究表明,针灸均能显著性改善癌症患者疲乏症状，尤其是乳腺癌患者,并且患者睡眠障碍、焦虑、抑郁等症状也得到了改善[40]。

近年来，随着人们对生活质量的追求以及对疾病认识的提高,癌因性疲乏逐渐引起了人们的重视。目前尚无有效的用于筛选的评估量表，研究者应该制定一套评估全面、可行性好、规范化的评估量表,对患者进行及时筛选和评估。虽然癌因性疲乏的机制目前仍未明确,但是一系列假说的提出,为癌因性疲乏研究提供了方向。越来越多的研究倾向将非药物干预作为首选治疗,这些方法疗效确切,同时无药物治疗所带来的副作用,将是今后研究的重点。

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