

· 综述 ·

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原发性胆汁性胆管炎患者疲劳的发生机制及临床评估与干预

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摘要: 原发性胆汁性胆管炎(PBC)是一种以肝内胆汁淤积为特征的自身免疫性肝病,疲劳是其常见且显著影响生活质量的重要症状。PBC患者疲劳的发生机制复杂,可能与胆汁淤积引发的炎症反应、肠道菌群紊乱、脑结构和功能异常以及线粒体功能障碍等因素有关。当前,一线药物和肝移植对改善疲劳的效果有限,且缺乏统一的综合评估体系。新兴药物和生活方式调整等非药物干预手段,则表现出潜在的应用前景。本文系统综述了PBC患者疲劳的临床表现、发生机制、临床评估及干预措施的研究进展,旨在为优化治疗策略和推动新疗法研发提供参考。

关键词: 原发性胆汁性胆管炎; 疲劳; 治疗学

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Pathogenesis, clinical assessment, and intervention of fatigue in patients with primary biliary cholangitis

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Abstract: Primary biliary cholangitis (PBC) is an autoimmune liver disease characterized by intrahepatic cholestasis, while fatigue is a common symptom of PBC that significantly affects the quality of life of patients. The pathogenesis of fatigue is complex and may be associated with the factors such as cholestasis-induced inflammation, gut microbiota dysbiosis, brain structural and functional abnormalities, and mitochondrial dysfunction. At present, first-line therapies and liver transplantation have a limited effect in alleviating fatigue, and there is still a lack of standardized comprehensive assessment system. Emerging drugs and non-pharmaceutical interventions, including lifestyle modifications, have shown potential application prospects. This article systematically reviews the research advances in the clinical manifestations, pathogenesis, clinical assessment, and intervention of fatigue in PBC patients, in order to provide a reference for optimizing treatment strategies and promoting the research and development of new therapies.

Key words: Primary Biliary Cholangitis; Fatigue; Therapeutics

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原发性胆汁性胆管炎(primary biliary cholangitis, PBC)是一种以肝内胆汁淤积为主要病理特征的自身免疫性肝病,可进展为肝硬化及终末期肝病。其病因尚不明确,可能与遗传和环境因素引发的免疫失调有关^[1]。

PBC多见于中老年女性,男女比例约为1:10,常见症状为疲劳和皮肤瘙痒^[2]。其中,疲劳尤为突出,超过50%的患者受其困扰,约20%的患者疲劳严重,显著降低了其生活自理能力、工作效率和社会参与度,并可能导致睡眠障碍、焦虑及抑郁,严重影响患者的生活质量^[3]。值得注意的是,年轻PBC患者因疲劳导致的生活质量下降更为显著^[4]。PBC患者疲劳的发生机制复杂,可能涉及中枢神经功能障碍和外周肌肉代谢异常等。尽管目前熊去氧胆酸(ursodeoxycholic acid, UDCA)和奥贝胆酸(obeticholic acid, OCA)等药物已获批用于治疗PBC,但针对疲劳的干预方案尚不明确。本文系统综述了PBC患者疲劳的临床表现、发生机制及临床评估,探讨现有及潜在干预策略,旨在为优化治疗策略和新疗法研发提供参考。

1 PBC患者疲劳的临床表现

医学上,疲劳指个体出现难以承受的疲倦感、活力缺乏和精疲力竭的主观体验^[5]。对于PBC患者,疲劳的特征包括躯体耐力的降低以及维持日常活动所需的体力与精力水平下降,显著影响其生活质量。疲劳可分为中枢性疲劳与外周性疲劳两个类别:前者表现为自我激励不足,见于内心活动,属意图匮乏;后者表现为肌无力等,以肌肉等外周组织功能降低为特征,属生理能力不足^[6]。两类疲劳可单独或合并存在,导致患者躯体耐力下降,进而引发日常功能多维度受损^[3]。此外,PBC患者的疲劳还可继发认知及情感障碍,如记忆、睡眠障碍及抑郁等^[7-8]。因此,全面认识PBC患者疲劳的普遍性、差异性及各维度影响,对后续制订干预策略至关重要。

2 PBC患者疲劳的发生机制

2.1 中枢性疲劳发生机制

中枢性疲劳表现为动机减退及认知异常,患者常描述为“无法启动或维持需自我激励的注意力任务及体力活动”^[2]。其发生机制复杂,可能与胆汁淤积引发的炎症反应、肠道菌群紊乱、脑结构和功能异常、锰沉积及中枢神经递质通路改变等因素相关。

PBC的自身免疫特性会引发慢性炎症反应。胆汁淤积可导致毒性胆汁酸蓄积,并通过激活Toll样受体促进炎症因子释放。这些炎症反应会进一步激活脑内小胶质细胞并招募单核细胞,进而引起脑功能变化并引发疲劳^[2,9-11]。动物模型研究显示,此类脑功能变化导致的社交兴趣下降与PBC患者的中枢性疲劳表现一致;而

缺乏关键炎症介质的老鼠在胆汁淤积状态下未表现出中枢性疲劳症状,进一步凸显了炎症反应的重要作用^[10-11]。此外,PBC患者的肠道菌群紊乱可能通过炎症因子影响免疫反应和中枢神经系统,进一步参与疲劳的发生^[12]。

神经影像学研究为明确中枢疲劳机制提供了更多的证据。Mosher等^[13]通过静息态功能磁共振成像发现,无肝硬化的PBC患者深部灰质脑结构静息态功能连接(resting-state functional connectivity, rsFC)存在紊乱,其中壳核及运动皮质的rsFC减少与疲劳症状相关,而杏仁核等认知相关脑区的rsFC减少则与注意力不集中、言语工作记忆下降等相关。此外,早期PBC患者已出现脑白质病变,这可能与自主神经功能障碍及脑的自动调节功能受损有关,且肝移植后疲劳未见改善^[10,14]。双脉冲经颅磁刺激研究显示,PBC患者中枢激活功能受损,且这些异常在肝移植后仍持续存在,进一步提示脑部病变可能具有不可逆性^[2,10,15]。

脑磁化强度对比成像结合质子磁共振波谱分析显示,PBC所致肝硬化前期患者苍白球区域的磁化转移率显著低于健康人群,且与血锰水平相关。锰主要通过胆汁排泄,PBC患者的胆汁淤积可能导致锰在脑内沉积,进而成为疲劳的重要参与机制之一^[16-17]。此外,中枢神经传递通路,尤其是血清素与去甲肾上腺素通路的功能改变,也被认为是中枢疲劳的重要假说,但这一观点尚存在争议^[2-3]。现有小样本研究尚未证实血清素受体激动剂(如昂丹司琼)和选择性血清素再摄取抑制剂(如氟西汀)等对改善PBC相关疲劳具有明确疗效^[18-19]。综上所述,PBC相关的中枢性疲劳可能是多种因素相互作用导致脑功能受损的结果。由于现有研究多为小样本,未来亟需进行大样本多中心研究,以深入探讨相关机制及其相互作用,为靶向治疗提供更可靠的理论支持。

2.2 外周性疲劳发生机制

外周性疲劳主要表现为肌肉功能障碍,如活动能力下降和无法维持重复运动,患者常形容为“能量耗竭”或“电池耗尽”^[2]。其发生机制复杂,可能与线粒体功能障碍、能量代谢过度偏向无氧途径以及肌肉减少症等因素相关。

PBC的诊断多依赖抗线粒体抗体(anti-mitochondrial antibody, AMA),超95%的患者血清AMA呈阳性^[20]。研究表明,AMA靶向丙酮酸脱氢酶复合体(pyruvate dehydrogenase complex, PDC),可能与外周性疲劳相关^[10]。AMA主要针对PDC-E2亚单位的硫辛酰

结构域,此结构含有酶活性所需的 α -硫辛酸^[3]。PDC是线粒体基质中的多酶复合物,其活性缺失可导致丙酮酸代谢障碍,引发线粒体功能障碍,最终诱发疲劳^[20]。

外周性疲劳的另一机制可能是能量代谢向无氧途径过度偏向,导致肌肉内乳酸蓄积,加剧肌肉功能减退和延长恢复时间^[3]。小样本对照研究显示,与非PBC的慢性疲劳综合征患者、原发性硬化性胆管炎患者及健康人群相比,PBC患者运动后的乳酸中毒加剧,二磷酸腺苷和磷酸肌酸恢复延长,且pH恢复速度与疲劳程度相关^[21]。

肌肉减少症(简称肌少症),作为外周性疲劳的另一重要机制,其特征是肌肉质量、力量和功能进行性下降。非肝硬化PBC患者的肌少症发生率为23.1%~25.9%^[22-23],进展至肝硬化或终末期肝病时可升高至40%~70%^[22,24]。目前,PBC患者肌少症的发生机制尚未完全阐明,研究认为可能与“肝-肌轴”相关介质的异常密切相关,包括高氨血症、内毒素血症及白细胞介素6(interleukin 6, IL-6)、肿瘤坏死因子 α 等炎症因子水平升高。高氨血症可能抑制mTORC1信号通路,减少肌肉蛋白合成;内毒素血症因肠道微生物组改变和胃肠道黏膜屏障破坏而激活肌肉Toll样受体,增加蛋白水解;IL-6和肿瘤坏死因子 α 则可能导致蛋白质稳态失调,加速肌肉分解^[22]。肌少症会显著降低肌肉质量与力量,使患者在高强度日常活动时易接近最大力量极限,从而产生疲劳感^[25]。

综上所述,PBC患者的外周性疲劳可能是线粒体功能损伤、能量代谢失衡与肌少症共同作用的结果,其具体的调控通路及交互机制仍需深入研究。

2.3 PBC合并症加重疲劳的机制 研究显示,贫血、肝外自身免疫病、自主神经功能障碍、睡眠障碍及抑郁症等合并症,是加剧PBC患者疲劳的重要因素^[1]。这些合并症通常可通过多重机制的相互作用,显著加重患者疲劳程度。

贫血在PBC患者中相对少见,可能由自身免疫性溶血、胆汁淤积引起的红细胞膜损伤及脾功能亢进导致红细胞破坏等因素引起^[26-28]。贫血引起的组织缺氧会导致能量代谢障碍,加重疲劳。肝外自身免疫性疾病(如甲状腺功能减退症)也会加重疲劳,可能与免疫交叉攻击和肝脏代谢异常导致的甲状腺激素失衡有关。在PBC患者中,甲状腺激素水平的异常与自身免疫状态相互作用,形成复杂的病理网络^[29-30]。

此外,PBC患者普遍存在自主神经功能障碍,表现

为压力感受器反射敏感性降低等血压调节异常,干扰体内稳态并加重疲劳^[16]。睡眠障碍同样是常见的合并症,患者多表现为入睡困难和日间嗜睡等,睡眠质量差不仅会直接引起疲劳,还可能进一步导致认知功能减退^[16,31-32]。抑郁症在PBC患者中也较常见,合并抑郁症的患者疲劳症状更明显,这与心理及生理反应相关,可能通过改变神经生物学特征、影响激素水平及增强炎症反应等途径加重疲劳^[33-35]。上述合并症通常相互作用,共同加剧PBC患者的疲劳程度,并显著降低患者生活质量,其交互机制亟需深入研究以优化治疗方案。

3 PBC患者疲劳的临床评估

对PBC患者的疲劳评估需结合主观感受、客观指标及合并症筛查,综合判断疲劳的程度、类型及其影响因素,但目前尚缺乏统一的标准化评估体系。

3.1 主观评估工具 主观评估工具是量化PBC患者疲劳程度和辅助干预方案的重要手段,常用量表包括原发性胆汁性肝硬化生活质量量表(PBC-40)、疲劳影响量表(fatigue impact scale, FIS)和患者报告结局测量信息系统简表(patient-reported outcomes measurement information system, PROMIS)等。

PBC-40量表由Jacoby等^[36]于2005年开发,包含40个条目,涵盖疲劳、瘙痒等6个领域,采用5分制,分数越高表示生活质量越差。其疲劳分量表的内容效度已获得验证,是研究PBC相关疲劳的理想工具。FIS量表由Fisk等^[37]于1994年开发,最初用于评估多发性硬化症患者的疲劳程度,后续研究发现其在PBC患者中具有较高的可接受性和内部一致性。FIS量表同样包含40个条目,从心理社会功能、认知功能和身体活动3个方面评估过去1个月内疲劳造成的影响,采用0~4级评分,分值越高表示疲劳程度越严重。PROMIS疲劳简表由美国国立卫生研究院开发,包含7个条目,用于评估过去1周的疲劳体验及对日常活动的影响,采用5分制,分值越高表示疲劳程度越严重。尽管PROMIS疲劳简表尚未在PBC患者中专门进行内容效度验证,但因其评估高效和结果精准,可作为初步筛查或辅助评估工具^[38]。

3.2 客观评估方法 客观功能测试可量化PBC患者的身体功能,并辅助评估疲劳类型、严重程度和整体健康状况。尽管临床上可以采用脑成像、血清指标及身体机能等客观测量方法评估疲劳,但尚未形成针对PBC患者疲劳的统一评估标准^[6]。目前,区分PBC患者中枢性和外周性疲劳的方法如下:外周性疲劳可通过肌电图检测

肌肉兴奋性变化进行评估,血清乳酸和IL-6可作为生物标志物^[39-40];此外,声学肌动图等非侵入性方法也可用于评估外周性疲劳^[41]。对于中枢性疲劳,则可通过经皮神经刺激试验或经颅磁刺激评估,若肌肉力量显著提升,则提示可能存在中枢性疲劳^[42]。

3.3 PBC合并症的评估 PBC患者的合并症评估,应以详细病史、全面体格检查及辅助检查、实验室检验为基础。其中,贫血和肝外自身免疫性疾病的评估主要通过血清学检测。自主神经功能障碍的初步评估包括Valsalva动作测试、24 h血压和心电图心率变异性监测等。若体位性低血压等体征不明确,可考虑进一步行倾斜试验^[2]。对于睡眠障碍,可用Epworth嗜睡量表或PROMIS睡眠障碍和损害简表评估^[43];抑郁症状的筛查则推荐使用贝克抑郁量表、患者健康问卷-2、患者健康问卷-9及汉密尔顿抑郁量表等工具^[44]。

4 PBC患者疲劳的干预

4.1 药物治疗进展 目前,尚无获批用于改善PBC患者疲劳的药物,现有治疗手段效果有限。一线药物UDCA虽可延缓肝病进展并提高患者生存率,但研究表明其对疲劳症状无显著改善^[45-46];OCA同样未能缓解疲劳,且可能因剂量依赖性瘙痒加重睡眠障碍,进而间接加剧疲劳^[47]。在贝特类药物中,苯扎贝特Ⅲ期临床试验显示,15%的患者疲劳得到缓解(安慰剂组为9%),但其结局仅分为消失、间歇性或持续性,缺乏客观验证指标,结论有待进一步研究证实^[48]。现有研究表明,利妥昔单抗、莫达非尼,以及昂丹司琼、氟西汀等神经递质相关药物,连同维生素A、C、E及硒、蛋氨酸、泛醌等抗氧化疗法,均未对PBC患者的疲劳表现出明显的改善效果^[7]。

在具有潜在应用前景的药物中,选择性过氧化物酶体增殖激活受体 δ 激动剂司拉德帕(Seladelpar)在Ⅱ期研究中显示,55%~64%的患者PBC-40疲劳评分有所改善;然而,其Ⅲ期试验仅报告了PBC-40总分和瘙痒评分,疲劳数据未单独披露,其临床疗效有待进一步验证^[49-50]。此外,S-腺苷-L-蛋氨酸联合UDCA的小样本开放性试验显示,该方案对非肝硬化PBC患者的疲劳有显著改善作用^[51]。选择性NADPH氧化酶抑制剂Setanaxib(GKT137831)Ⅱ期研究显示其对疲劳可能有积极影响,目前Ⅲ期临床试验(NCT05014672)正在进行中,其结果值得关注^[52]。对于合并肌少症的PBC患者,通过营养支持方案(如补充支链氨基酸和维生素D),可改善肌肉合成与功能,间接缓解疲劳^[53]。

4.2 其他干预措施 PBC患者疲劳的非药物干预需以多维度综合干预为主,涵盖生活方式调整、合并症管理及心理支持等方面。在生活方式调整方面,“节奏策略”(最大化现有精力完成任务)与“时间策略”(在精力最充沛的早晨安排关键任务),可降低日常任务难度,减少疲劳诱因^[54]。另外,虽然针对中重度疲劳患者设计的12周家庭锻炼计划的研究结果尚未公布,但已有小样本研究表明,重复性锻炼可以改善PBC患者运动后的外周肌肉酸中毒和pH恢复延迟^[55-56]。此外,15 d的晨光治疗被证实可以提高主观睡眠质量,减少日间嗜睡,从而进一步缓解疲劳^[57]。合并症管理是疲劳干预的重要环节,临床需优先识别并治疗加剧疲劳的合并症,如抑郁症、睡眠障碍和自主神经功能障碍等,有效治疗可显著减轻患者的整体疲劳负担。心理支持和应对机制的建立同样重要,护理人员的共情理解以及认知行为疗法能增强患者对疾病的应对能力^[2]。中医针刺、艾灸、推拿疗法在改善患者疲劳症状方面具有独特优势,但有待更多研究验证^[58]。值得注意的是,虽然肝移植可以改善肝病结局,但术后仍有44%~47%的患者会感到疲劳,因此不应将其作为缓解疲劳的主要治疗手段^[59]。另外,小样本研究表明,血浆置换可能降低PBC-40的疲劳评分,其机制或与循环中PDC抗体的减少有关,为疲劳干预提供了新的思路^[60]。

5 小结与展望

PBC相关疲劳是影响患者生活质量的重要症状,超过50%的患者长期受其困扰,约20%表现为严重疲劳,年轻患者的生活质量下降尤为显著。疲劳分为中枢性疲劳与外周性疲劳,可单独或同时存在,导致患者身体耐力下降、日常功能减退,并常伴记忆障碍、睡眠问题及抑郁等。疲劳的发生机制复杂,可能与胆汁淤积引发的炎症反应、肠道菌群紊乱、脑结构和功能异常以及线粒体功能障碍等多种因素密切相关。在临床评估中,可结合PBC-40、FIS、PROMIS疲劳简表等主观量表与心电图、血清乳酸和IL-6等客观指标,以实现疲劳程度量化和分型,但目前尚缺乏统一的综合评估体系。在治疗方面,UDCA、OCA等现有药物对改善疲劳无效;苯扎贝特及新兴药物司拉德帕、Setanaxib等显示出潜在价值,但仍需进一步验证。此外,生活方式调整等非药物干预也展现出积极的应用前景(图1)。

未来研究应深入探索PBC患者疲劳的发生机制,明确炎症因子、肠道菌群及神经递质等关键靶点,为精准



图1 原发性胆汁性胆管炎患者疲劳的发生机制及临床评估与干预

Figure 1 The pathogenesis, clinical assessment and intervention of fatigue in PBC

干预奠定理论基础。同时,优化评估体系,构建主客观指标结合的标准化方案,实现疲劳的精准分型与量化。在治疗方面,应积极推进新药临床试验,规范非药物干预路径,并探索多维度联合治疗模式,以突破当前干预瓶颈,为患者提供个体化治疗方案,切实改善其生活质量与长期预后。

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