专家论坛

肌萎缩侧索硬化患者疼痛症状的研究进展*

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摘要 肌萎缩侧索硬化(ALS)是一种累及上、下运动神经元的致死性神经系统变性疾病,以进行性肌肉萎缩、无力的运动症状为主要表现。近年来,ALS 患者的认知、精神症状、疼痛等非运动症状也受到越来越多的关注,其中疼痛作为 ALS 常见的非运动症状,严重影响患者的生活质量。本文通过总结既往文献,系统阐述了 ALS 患者出现疼痛的流行病学、临床特征、可能的发病机制和管理方法,强调了早期识别并标准化评估 ALS 疼痛的重要性。

关键词 肌萎缩侧索硬化; 疼痛; 机制; 治疗
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Advance in research on pain in patients with amyotrophic lateral sclerosis *CHENG Yang-fan, SHANG Hui-fang*. Department of Neurology, West China Hospital, Sichuan University, Sichuan Chengdu 610041, China*
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Abstract Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease with fatal outcome, involving upper and lower motor neurons, mainly presenting progressive loss of limb strength and atrophy. Recently, more studies focused on the non-motor symptoms including cognitive impairment, psychiatric symptoms and pain in patients with ALS. Pain, as a common but largely neglected symptom of ALS, affects the quality of life of patients seriously. In this paper, we summarized previous studies and systematically described the epidemiology, clinical features, possible pathogenesis and management of pain in ALS patients, and emphasized the importance of early identification and standardized assessment of pain in ALS patients.

Key words Amyotrophic lateral sclerosis; Pain; Pathogenesis; Management

肌萎缩侧索硬化(amyotrophic lateral sclerosis, ALS)是一种罕见的神经系统变性疾病,其主要病变部位为大脑皮质、延髓和脊髓前角运动神经元,导致患者出现骨骼肌萎缩、肌无力、肌束颤动、延髓麻痹和锥体束征等临床表现[1]。多数患者常在起病后 3~5 年内因呼吸衰竭而离世,具有严重的致残性和致死性。近年来越来越多的研究者发现 ALS 除了典型的运动症状外,还有非常多的非运动症状,如神经精神症状、认知和行为改变、疼痛,睡眠障碍、疲劳和流涎等,严重影响了患者的生活质量[2~4]。其中,疼痛常常贯穿 ALS 疾病的所有阶段,甚至可能是运动症状出现前的首发症状[5,6]。既往研究也从临床[7]、病理[8,9]、影像[10~12]及 ALS 小鼠模型[13,14]多方面证明 ALS 发病过程中感觉系统也会受到损伤。因此,正确识别和标准化评估 ALS 患者疼痛的重要性是不容忽视的。本文根据最新研究阐述了目前对 ALS 患者疼痛的理解,描述了 ALS 患者出现疼痛的流行病学、疼痛的评估工具、疼痛的可能机制及疼痛出现的临床特征,最后对 ALS 患者疼痛的管理进行了总结,并呼吁需要更多针对 ALS 患者疼痛标准化评估以及治疗的研究。

ALS 患者疼痛的流行病学

既往研究报道有 15%~85%[6,15,16]的 ALS 患者会出现疼痛症状,荟萃分析显示 ALS 患者疼痛的患病率为 60%(95% 置信区间:50%~69%)[17],即约有 2/3 的 ALS 患者在整个病程中遭受疼痛的折磨。上述流行病学结果存在较大异质性的原因可能为各研究纳入患者的病程存在差异,缺乏统一的疼痛评价标准和疼痛症状评估工具,既往神经科医生和 ALS 患者对疼痛症状缺乏关注[18],ALS 患者的认知障碍对疼痛感知的影响等。目前对于 ALS 患者疼痛发生的系统性研究较少,纵向队列研究仅有 4 项[19,20],随访时间为 4 个月至 96 周不等。因此,对大样本 ALS 患者进行长期纵向随访研究以明确在病程中 ALS 患者疼痛的流行病学特点十分重要。

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疼痛发生的机制

进一步了解 ALS 患者疼痛发生的病理生理学机制可以帮助医生在临床实践中对患者进行个体化镇痛治疗和预防。根据发病机制不同,ALS 患者出现的疼痛可分为神经病理性疼痛、伤害感受性疼痛和中枢敏化。

神经病理性疼痛是由躯体感觉通路的损害所引起。诊断神经病理性疼痛的先决条件是存在影响躯体感觉通路的病变或疾病[23,24]。临床上可使用神经传导测试(nerve conduction studies, NCS)或皮肤活检来确诊;NCS 用于研究粗大的、传导本体感觉和触觉的有髓神经纤维,皮肤活检用于检查传递温度觉和伤害性刺激的无髓和薄髓神经纤维,并可量化表皮内神经纤维(intraepidermal nerve fibers, IENF)密度。*SOD1*^{G93A} ALS 小鼠模型发现了 IENF 变性的生物学基础,外周蛋白剪切变体(外周蛋白 56)特异性地积聚在小鼠背根神经节神经元中,增加 IENF 密度,从而改变神经丝的稳态[13]。既往对 18 例 ALS 患者进行 NCS 研究,发现有 12 例患者的远端神经(例如位于背侧腓肠和足底内侧的神经)存在 NCS 异常[25]。ALS 患者的皮肤活检研究显示小纤维周围神经的感觉神经纤维也存在功能障碍[26]。尽管基于 NCS 和皮肤活检结果表明躯体感觉通路受损,但电生理研究与疼痛缺乏关联性,并不支持大多数 ALS 患者的疼痛为神经病理性疼痛,因此还需要进一步的研究。

伤害感受性疼痛的定义为非神经组织的损伤而由外周伤害感受器响应机械或其他有害刺激所引起的疼痛[27,28]。既往研究表明,ALS 患者的疼痛通常与活动能力下降和局部皮肤受压有关,常分布于四肢、背部、肩部和头颈部,这种疼痛主要为伤害感受性疼痛,对非甾体类抗炎药(non-steroidal anti-inflammatory drug, NSAID)具有良好的反应性[29]。

此外,中枢敏化被认为在以慢性疼痛为主的各种临床病症中发挥关键作用,包括骨骼肌肉疾病。它可以使神经性疼痛和伤害性疼痛复杂化[30],是整个体感系统传递信号的时间、空间和阈值变化的结果。中枢敏化的定义为中枢神经系统(central nervous system, CNS)内的神经信号放大引起疼痛超敏反应或 CNS 神经元对引起无害感觉的正常或阈下传入输入的增强反应[31]。由于缺乏明确的诊断工具,目前没有研究通过中枢敏化机制来解决 ALS 患者的弥漫性疼痛的问题。ALS 患者的神经影像学研究表明病变超出了中央前回皮层和皮质脊髓束的范围,累及胼胝体、额叶、感觉和运动前皮层、丘脑和中脑[32],这些结构与慢性疼痛及感觉的认知情绪和情感处理中所涉及的前额叶皮层、前扣带皮层、岛叶、杏仁核、丘脑和中脑等大脑区域有所重叠[31],因此 ALS 患者的疼痛是否由于中枢敏化导致仍需要进一步研究。

30% ~75% 的疼痛可由遗传因素解释[33],因为基因突变会影响疼痛的发生和个体对镇痛剂的反应。有研究显示 C9orf72 突变的患者对疼痛刺激和温度的反应存在异常[34],采用 MRI 体素形态测量法分析表明,C9orf72 突变患者的躯体感觉症状与右后丘脑萎缩显著相关[35]。同时,病理学研究也证实丘脑受累可能与 C9orf72 突变患者出现无法解释的高频躯体和内脏疼痛有关[34]。

ALS 患者疼痛的特征

ALS 患者的疼痛类型和部位常常存在很大异质性,主要取决于疼痛发生的机制。疼痛的严重程度也会随病程有所变化。在一项病例对照研究中发现有 53% 的 ALS 患者报告存在一个以上部位的疼痛,其中 50% 的患者疼痛累及背部,47% 的患者疼痛累及四肢,42% 的患者疼痛累及关节[36]。患者会使用包括“触痛”、“隐痛”、“沉重”或“抽筋”来描述疼痛,因此在评估过程中应谨慎甄别。多篇研究都认为,延髓起病的 ALS 患者的疼痛少见,提示骨骼肌受累可能是一个重要的风险因素[15,20,37,38]。

ALS 患者的疼痛可以分为原发性疼痛和继发性疼痛。原发性疼痛一部分为神经病理性疼痛,表现为灼痛、刺痛、射击痛、异常性疼痛及痛觉过敏等,常分布于四肢末端,可以是局灶性的或弥漫性的。一项横断面研究表明,根据神经病理性疼痛诊断问卷,96 例出现疼痛的 ALS 患者中有 9 例(9%)具有神经病理性疼痛的特征[39]。另一部分原发性疼痛为伤害性疼痛,多表现为痛性痉挛(spasticity)[40]和抽筋(cramps)[20],是由于远端运动神经单元不稳定,与肌肉失神经支配有关。有研究显示,痛性痉挛常发生于 ALS 患者起病阶段,表现为夜间腓肠肌或四肢远端肌肉痉挛[41],也可由寒冷或活动诱发[36]。

继发性疼痛大多为伤害性疼痛,常由于肌肉无力萎缩,长期制动导致结缔组织、骨骼和关节发生退行性变化,导致关节挛缩,诱发骨骼肌肉疼痛。有研究报道 23% 的 ALS 患者由于肩周肌肉力量的丧失而出现肩部疼痛[42],这种疼痛通常呈慢性广泛分

布。此外,在患者疾病晚期,由于长期卧床而导致的褥疮溃疡[43]、无创通气装置对面部皮肤的压迫损伤、有创通气对喉管的压迫和牵拉,吸痰和医疗行为给患者带来的疼痛[44],往往被护理人员和医生忽视,给患者的生活质量带来负面的影响,值得更多的关注和研究。

还有一些因素也可能与疼痛发生相关。首先是情绪障碍,研究表明有抑郁的 ALS 患者出现疼痛更为常见[45,46],而有高达 86% 有慢性疼痛的 ALS 患者曾有抑郁症状[47,48]。其他情绪障碍如焦虑、冷漠和心境不稳定与 ALS 疼痛的关系尚未被研究。既往研究发现 ALS 患者疼痛常常伴随疲劳症状的出现[38],疼痛也可能是对躯体疲劳的一种描述。认知障碍可能会影响 ALS 患者对疼痛的敏感性[21,49],携带 C9orf72 突变的 ALS-FTD 患者对疼痛刺激的反应改变[35]。

临床工作中疼痛的评估工具

尽管疼痛在 ALS 病程中出现的频率很高,但有研究显示不到 20% 的医生会使用评分量表或问卷来评估 ALS 患者的疼痛[50],70% 的医生在评估时会使用开放式问句。对于 ALS 患者的疼痛症状通常没有使用标准化评估量表,因此充分识别和标准化评估 ALS 患者疼痛的重要性不容忽视。目前在国际上被广泛运用的评估工具包括简易疼痛量表(brief pain inventory questionnaire, BPI)[6,15,36,51],神经病理性疼痛问卷(neuropathic pain questionnaire, NPQ)[37,52] 简易 McGrill 疼痛问卷(the short-form McGill pain questionnaire)[19,53] 和法国神经病理性疼痛评估量表(douleur neuropathique-4, DN4)[16,39,54] 等。其中,BPI 因能便捷准确地用于患者自我评估:疼痛是否在当前或前一周对其社会功能和生活造成干扰,所以被广泛应用[55]。

疼痛的治疗

药物治疗 目前没有临床指南和专家共识证据指导 ALS 患者出现疼痛时的药物选择和使用,大多依靠临床医生的经验用药。对于神经病理性疼痛,2010 年国际神经病理性疼痛药物指南和 2013 年我国神经病理性疼痛诊疗专家共识认为,加巴喷丁(gabapentin)(900 ~ 3 600 mg/d)、普瑞巴林(pregabalin)(150 ~ 600 mg/d)和三环类抗抑郁药如阿米替林(nortriptyline)、氯丙咪嗪(clomipramine)(50 ~ 100 mg/d) 常常是有用的[56,57]。当患者出现抽筋时,推荐使用奎宁 (quinine)(250 ~ 500 mg/d)[58],美西律(mexiletine)(300 ~ 900 mg/d)可以降低抽筋发作的次数[59],EFNS 指南也推荐左乙拉西坦 (levetiracetam)(1 500 ~ 3 000 mg/d)作为一线治疗[56]。对于痛性痉挛,口服药物包括作用于中枢的药物,如巴氯芬(baclofen)、苯二氮卓类药物(benzodiazepines)和替扎尼定 (tizanidine),以及作用于外周的丹曲林(dantrolene)。巴氯芬和丹曲林是最常用的处方药,考虑到苯二氮卓类药物的呼吸抑制作用,因此将其作为二线药物。对于药物难以改善的痉挛,可以考虑放置鞘内巴氯芬泵(intrathecal baclofen)[60]。此外,注射肉毒杆菌毒素 A(botulinum toxin A)在一些 ALS 患者中也显示出良好的疗效[61]。关节肌肉等继发性疼痛可通过非甾体抗炎药(nonsteroidal anti-inflammatory drug)或对乙酰氨基酚/扑热息痛(paracetamol)来缓解[29],疼痛严重者可通过关节内注射利多卡因(lidocaine)或皮质类固醇(steroids)来减轻疼痛[62]。在疾病晚期,当患者出现弥漫性疼痛且其他药物控制不佳时,可使用阿片类药物(opioids)[63,64]。

非药物治疗 包括物理康复活动(拉伸与有氧活动)[65,66],针灸[67]、经皮神经电刺激、冷热敷以及辅助工具(如特殊的枕头和床垫、特制的轮椅或助行器)[65],可与药物疗法相结合,缓解患者继发性疼痛。此外,我国也开展多项使用中药来缓解 ALS 患者疼痛症状的临床试验[68]。

综上,由于 ALS 患者的疼痛症状并不少见,而且具有异质性,正确识别、明确疼痛的发生机制,有利于患者个体化的疼痛管理,进一步提高患者的生存质量。尽管目前对 ALS 患者的疼痛研究有了一定的进展,但 ALS 患者发生疼痛的个体易感因素及精准的发病机制尚有待于进一步明确。

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