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• 综述 •

吉兰-巴雷综合征的神经心理症状及治疗进展

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[摘要] 急性炎症性疾病伴随的神经心理症状逐渐引起临床医师的重视。吉兰-巴雷综合征(GBS)是一种获得性炎性多发神经根神经病,影响运动、感觉及自主神经系统,为引起急性瘫痪最常见的神经系统疾病之一。随着对该病认识的深入,GBS的神经心理症状逐渐引起关注,然而目前报道尚少,没有统一的诊断标准,也缺乏对治疗的研究。此外,神经心理症状对GBS患者康复及社会功能的影响不容忽视。本文归纳了GBS患者疲劳、焦虑、抑郁、认知障碍和睡眠障碍等神经心理症状的特点和诊治进展,以提高神经专科医师对GBS患者神经心理症状的认识,加强对GBS神经心理症状的评估与干预。

[关键词] 吉兰-巴雷综合征; 疲劳; 焦虑; 抑郁; 认知障碍; 睡眠障碍

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Neuropsychological symptoms and treatment of Guillain-Barré syndrome: recent progress

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[Abstract] Neuropsychological symptoms of acute inflammatory diseases have gradually attracted the attention of clinicians. Guillain-Barré syndrome (GBS) is a post-infectious autoimmune polyneuropathy which affects motor, sensory, and autonomic nerves. It is one of the most common neurological disorders resulting in acute paralysis. With the in-depth understanding of the disease, the neuropsychological symptoms of GBS have gradually attracted attention. However, researches on the neuropsychological symptoms of GBS are still scarce and there are still no diagnostic criteria and only few studies focusing on the treatment. In addition, the influence of neuropsychological symptoms on the rehabilitation and social function of GBS patients could not be ignored. This article summarized the characteristics, diagnosis and treatment progress of GBS patients with neuropsychological symptoms such as fatigue, anxiety, depression, cognitive disorders, and sleep disorders. Neurologists should improve the understanding of the neuropsychological symptoms of GBS patients and attach importance to the evaluation and intervention of neuropsychological symptoms of GBS.

[Key words] Guillain-Barré syndrome; fatigue; anxiety; depression; cognitive disorder; sleep disorder

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抑郁、焦虑、睡眠障碍和认知障碍等神经心理症状是慢性炎症性疾病常见的合并症^[1-2]。在多发硬化患者中,抑郁症的患病率>50%,是正常人群的2~3倍^[3]。视神经脊髓炎谱系疾病患者中有超过1/3的患者患有抑郁症^[4]。在慢性炎症脱髓鞘性多发性神经病(chronic inflammatory

demyelinating polyradiculopathy, CIDP)患者中,43%的患者有疲劳主诉,30%的患者合并抑郁^[5]。

急性炎症性疾病患者同样可能出现神经心理症状,但却常常被临床医师忽视。急性炎症性疾病神经心理症状不仅出现在疾病的急性期,也可出现在疾病的恢复期甚至长期存在。研究发现,新型冠状病毒

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毒感染早期患者可出现抑郁症状,且超过一半的患者在患病4个月后出现抑郁症状^[6]。急性炎症引起的长期神经心理症状可能与免疫记忆有关,Wendeln等^[7]研究发现外周炎症可以引起小胶质细胞介导的免疫记忆,而小胶质细胞介导的炎症反应与神经心理症状的发生关系密切。此外,其他因素也可导致急性炎性疾病患者出现神经心理症状。吉兰-巴雷综合征(Guillain-Barré syndrome, GBS)是一种外周神经炎性疾病,在急性期和疾病后期均可能出现焦虑、抑郁、睡眠障碍、认知障碍等神经心理症状。本文对GBS神经心理症状的发生情况、可能的机制及诊治方法进行综述。

1 GBS患者神经心理症状的发生概况

GBS是一种感染后自身免疫介导的急性炎性多发性神经根神经病,主要以急性进展性肌无力、腱反射消失和脑脊液蛋白细胞分离为特征^[8]。GBS全世界每年发病率为(1~2)/10万,男性发病率高于女性^[9-10],是急性神经肌肉麻痹最常见的原因。GBS有多种临床表型,包括急性炎性脱髓鞘性多发性神经病(acute inflammatory demyelinating polyneuropathy, AIDP)、急性运动轴突性神经病(acute motor axonal neuropathy, AMAN)、急性运动感觉轴突性神经病(acute motor-sensory axonal neuropathy, AMSAN)和米勒-费希尔综合征(Miller-Fisher syndrome, MFS)^[11]等。GBS的各亚型在不同地区发病率并不相同,欧美国家最常见的是AIDP,占90%以上;而我国和日本等亚洲国家最常见的是AMAN^[11-12]。

GBS临床症状多在2周左右达到高峰,多呈单相自限病程^[8],静脉注射免疫球蛋白(intravenous immunoglobulin, IVIg)和血浆置换等治疗手段可使大部分患者恢复正常,但约有20%的患者在发病后6个月仍不能独立行走,3%~10%的患者死亡^[13]。此外,许多患者合并疼痛、疲劳等残余症状,这些症状可能持续数月或数年^[14],患者常有生活质量下降的主诉^[15]。研究发现,除运动感觉障碍以外的其他症状如疲劳、焦虑、抑郁、认知障碍、睡眠障碍等神经心理症状也是影响患者生活质量的主要因素^[16-17]。Tzeng等^[18]研究发现,GBS患者神经心理症状的发生率为10.35%,以认知障碍、抑郁、睡眠障碍和精神错乱为主。尽管神经心理症状影响GBS患者及其家属的生活质量,但由

于对该类症状的认识不足,其对GBS患者的影响被大大低估。

GBS伴发的神经心理症状可以出现在疾病的不同时期。在疾病急性期,即发病后4周内,约30%的患者出现抑郁、焦虑、疲劳和睡眠障碍等神经心理症状,这些症状的出现可能与机械通气、自主神经功能障碍、沟通障碍、严重虚弱、恐惧和焦虑有关^[19-20]。在经历4周的急性期后,病情在随后的2~4周内保持稳定,这段时期也被称为平台期,随即进入长达数年的恢复期^[16,19,21]。在疾病恢复期,患者的运动和感觉功能恢复良好,但焦虑和抑郁症状改善不明显^[22]。Bernsen等^[23]研究发现,GBS患者发病1年后仍存在焦虑和抑郁症状。在发病后3年,尽管大多数患者运动功能和感觉障碍得到了改善,但仍有20%的患者合并疲劳、焦虑、抑郁、认知障碍和睡眠障碍等残余症状^[22,24]。这些症状的出现对患者的社会功能和生活质量产生了不良影响^[25]。虽然GBS患者出现神经心理症状的原因仍不甚清楚,但早期识别和处理这些症状可能会对患者的预后产生重要影响。

2 GBS患者常见的神经心理症状与相关机制

2.1 疲劳 在神经系统疾病相关研究中,疲劳的研究主要集中在中枢神经系统疾病,如脑血管疾病、多发性硬化和帕金森病,但随着研究的深入,人们逐渐认识到,疲劳也是外周神经系统疾病的一种重要症状^[26]。Chowdhury等^[27]研究发现,在GBS发病后1~13年,仍有13%的患者主诉疲劳。GBS患者的疲劳感可从发病之初持续到发病后数年,甚至一部分运动功能恢复良好的患者也存在疲劳感^[24,28]。与卒中后疲劳不同,GBS患者的疲劳感经过休息和睡眠后不能缓解^[29-30],疲劳是GBS致残率最高的残余症状^[31],严重影响患者的生活质量^[24,26]。Drory等^[28]对70例GBS患者进行随访,结果显示在3~5年的随访期内,27%的患者因疲劳而被迫改变生活方式。

在神经肌肉疾病中,疲劳的严重程度一般与疾病的严重程度相关^[17],但欧洲炎性神经病病因及治疗组研究发现,GBS患者的疲劳严重程度与运动、感觉障碍及症状持续时间无关^[32]。这可能是由于神经肌肉疾病通常是慢性进行性疾病,而GBS是一种急性单相病程的疾病^[26],同时也提示GBS的疲劳症状可能与疾病本身以外的其他因素

有关。

虽然疲劳是GBS患者常见的残余症状,但其发生机制目前仍不清楚。Drenthen等^[21]研究发现GBS患者的疲劳症状与轴突损伤的严重程度有关。GBS患者周围神经中轴索数量减少,使其所需要支配的肌肉纤维数量相对增多,周围神经无法完全激活肌肉^[33],导致患者在日常生活中必须要比健康人付出更多的努力,从而产生疲劳感。此外,已经有研究表明,炎症可以诱发疲劳,这可能与细胞因子参与情绪、认知和睡眠等生理功能的调节有关^[34]。细胞因子及其受体的失调可能会破坏细胞因子的正常生理稳态,并导致疲劳^[34]。

2.2 焦虑与抑郁 GBS患者可伴发焦虑、抑郁等形式的情绪障碍,且可能发生在疾病的任何时期。在GBS急性期,患者焦虑、抑郁的发生可能与运动和交流能力丧失等严重功能障碍有关^[14]。Weiss等^[20]对49例重症GBS患者进行了观察研究,结果显示82%的患者出现焦虑症状,67%的患者出现抑郁发作,且抑郁、焦虑的发生与四肢瘫、机械通气和颅神经受累相关。抑郁、焦虑症状与疾病进展速度无明显相关性^[35],但与脑脊液蛋白水平相关^[20],因此脑脊液蛋白水平或可作为GBS患者发生抑郁和焦虑的预测因子。

与疲劳症状相似,抑郁和焦虑也可出现在GBS的恢复期或作为残留症状出现^[36],对患者的康复和生活质量产生负面影响。在GBS恢复期,抑郁的发生多与疾病的预后相关,而与疾病的严重程度无关^[37]。GBS患者的心理健康在发病1年后仍有受损^[20]。Kogos等^[38]研究发现,虽然大多数GBS患者在发病1年后并不认为自己抑郁,但却有22%的受访者抑郁自评量表得分超过了临床抑郁临界值。约20%的GBS患者焦虑症状可持续至发病后6年^[39]。

GBS患者伴发抑郁和焦虑的机制目前尚不清楚,外周神经损伤引起的急性运动感觉障碍造成的心理应激可能是致病因素之一^[40]。免疫失调与情绪障碍的发生有关。许多抑郁症潜在发病机制研究表明,抑郁与免疫激活和细胞因子的产生有关^[41-42]。例如,炎症因子包括高敏CRP、IL-1 β 、IL-6、TNF- α 等引起的炎症级联反应会导致额叶皮质、边缘系统和基底核等部位的5-羟色胺耗竭,从而导致抑郁;外周炎症因子也可通过激活小胶质细胞引起神经炎症,进而导致白质炎性损

伤^[14,43]。在GBS患者中,T淋巴细胞和B淋巴细胞激活,IL-6、IL-12及TNF- α 等炎症介质表达增加^[44],这些炎症因子引起的炎症级联反应也可能是GBS患者发生抑郁和焦虑的原因之一。

2.3 认知障碍 GBS是多发性神经根病,不累及中枢神经系统,一般认为不存在认知损伤的疾病基础。但已经有研究发现,许多GBS患者存在认知问题。Tzeng等^[18]研究发现,GBS患者认知障碍的发生率为4.02%;与对照组相比,GBS患者发生认知障碍的风险增加了近4倍。即使在没有发生认知障碍的患者中,GBS导致的残疾症状也会影响患者的沟通、社会认知和社会功能^[45]。此外,重症GBS患者的认知障碍往往被忽视^[45]。

认知障碍可以出现在GBS的急性期和恢复期。在GBS急性期,由于患者可能伴有语言障碍,认知损伤会被忽视,往往需要特殊的检查方法才能发现。Ragazzoni等^[46]利用事件相关电位(event-related potential, ERP)监测大脑皮质活动,对2例完全瘫痪的急性GBS患者进行了为期6个月的认知功能评估,该2例患者的脑电图记录显示 α 节律正常,且血氧饱和度和脑CT/MRI检查正常,但是ERP成分中的N2峰值、P3峰值和关联性负变(contingent negative variation, CNV)样电位缺失;1例患者在运动功能逐渐恢复后,ERP中N2峰值、P3峰值和CNV样电位也逐渐恢复正常,且患者对在ICU前2周内发生的事不能完全回忆;另1例患者在治疗过程中死亡,其认知活动在病程中未见好转。在GBS恢复期,GBS导致的神经损害也会影响沟通、社会认知和社会功能,有时可能需要在专业康复服务机构接受治疗。有研究利用功能评估量表对GBS患者的康复情况进行评估,发现有一部分GBS患者确实存在认知障碍,且患者在入院到出院期间的认知功能改善并不明显^[45,47]。

GBS患者发生认知损伤的机制尚不清楚,可能是由多种因素导致的。在社会心理因素方面,Andrews和Middleton^[48]报道,GBS患者的认知能力随着疾病好转而部分改善,可能与社交范围增加有关,社交是影响认知功能的原因之一。在神经病理方面,Maier等^[49]通过尸体解剖研究发现,GBS患者的脊髓、延髓、脑桥和中脑存在小胶质细胞活化并伴有继发性髓鞘损伤,提示炎症可能是GBS患者认知损害的原因之一。这可能是由于外周的炎症反应激活了小胶质细胞,进而导致白质损伤^[14,43]。

此外,还有研究发现 GBS 患者脑脊液中载脂蛋白 E (apolipoprotein E, ApoE) 水平降低^[50],由于血脑屏障对载脂蛋白的通透性有限,因此这种变化可能源于脑组织局部 ApoE 合成和分泌减少。在中枢神经系统中, ApoE 主要由星形胶质细胞和小胶质细胞合成与分泌,有维持神经元稳定、修复和营养神经及调节免疫等功能^[51-52]。在认知正常者和轻度认知功能障碍患者中,脑脊液中 ApoE 水平低与纵向认知功能下降有关, ApoE 水平低的轻度认知功能障碍患者发展为痴呆的风险增加^[53]。因此, ApoE 水平降低也可能是 GBS 患者出现认知功能障碍的原因之一。

2.4 睡眠障碍 自身免疫病患者常伴有睡眠障碍。研究表明, GBS 患者存在睡眠结构异常及睡眠呼吸暂停等形式的睡眠障碍^[22]。虽然睡眠障碍在 GBS 患者中较常见,但却未引起足够的重视。

Karkare 等^[54]研究了 60 例 GBS 急性期患者的睡眠质量,发现超过 50% 的患者住院期间睡眠质量不佳,患者通常主诉睡眠质量差,出现失眠、夜间易醒、早醒及夜间睡眠时间减少等情况。这些睡眠障碍与焦虑、疼痛、感觉异常和运动障碍有关。通过多导睡眠监测研究发现,与健康人群相比,在 GBS 急性期,患者总的睡眠时间、睡眠效率和最低血氧饱和度降低,而觉醒次数、睡眠阶段转换指数和周期性腿动指数增多。随着运动和感觉障碍的恢复,这种睡眠异常并没有明显的改善,提示睡眠异常通常需要更长的时间恢复,早期关注和干预对于帮助患者恢复正常生活尤为重要。

GBS 患者发生睡眠障碍的机制尚不甚清楚,可能与多种因素有关。Gao 等^[55]研究发现,呼吸机的使用、肢体麻木、焦虑和严重的肢体活动障碍与睡眠障碍有关。下丘脑分泌素 1 参与了睡眠和觉醒周期的调节,而一些重症 GBS 患者脑脊液中下丘脑分泌素 1 水平下降^[56],提示下丘脑分泌素 1 水平降低可能是 GBS 患者出现睡眠障碍的原因之一。在我国,除了 IVIg 和血浆置换外,糖皮质激素也常用于 GBS 急性期的治疗。糖皮质激素可能对患者的睡眠结构产生影响^[57],因此糖皮质激素的应用可能也是导致 GBS 急性期患者发生睡眠障碍的原因之一。

3 GBS 患者神经心理症状的诊断和治疗

3.1 诊断 由于对 GBS 患者神经心理症状的认识

不足,绝大多数患者没有进行神经心理症状的筛查,目前尚未形成统一的针对 GBS 神经心理症状的诊断标准,最佳的筛查工具仍不确定。国内目前缺少对 GBS 神经心理症状的相关研究。临床中常用的筛查工具包括医院焦虑抑郁量表 (hospital anxiety and depression scale, HADS)、贝克焦虑量表 (Beck anxiety inventory, BAI)、贝克抑郁量表 (Beck depression scale, BDI)、汉密尔顿焦虑量表 (Hamilton anxiety scale, HAMA)、汉密尔顿抑郁量表 (Hamilton depression scale, HAMD)、简易精神状态检查 (mini-mental state examination, MMSE) 和蒙特利尔认知评估 (Montreal cognitive assessment, MoCA) 等^[58-60],但这些量表对神经免疫性疾病相关神经心理症状的有效性和可靠性仍不确定。疲劳严重度量表 (fatigue severity scale, FSS) 在免疫介导的多发性神经病中表现出良好的内部一致性、可靠性和有效性^[24]。在国外相关报道中, GBS 的焦虑和抑郁程度通常使用 HADS 进行评估^[17,36],睡眠质量通常用匹兹堡睡眠质量指数 (Pittsburgh sleep quality index, PSQI) 评估^[54-55],但目前仍缺乏 HADS 和 PSQI 对 GBS 相关情绪和睡眠障碍评估的有效性和可靠性研究。

在衡量任何形式的神经心理损害时,还要考虑症状对患者日常生活的影响。GBS 患者的神经心理症状通常会影响患者的生活质量,因此,对 GBS 患者生活质量的评估也十分重要。研究表明,健康状况调查问卷 (36-item short-form, SF-36) 对 GBS 患者的生活质量评估具有较好的有效性和内部一致性,可以作为评估 GBS 患者生活质量的工具^[61]。

3.2 治疗 GBS 患者的神经功能在血浆置换或 IVIg 治疗后恢复相对较好,但仍有部分 GBS 患者合并有严重的疲劳、焦虑、抑郁、认知障碍和睡眠障碍等神经心理症状,长期的神经心理症状可能会影响患者出院后的生活质量^[16]。

有氧训练可以减轻疲劳感,提高生活质量和身体素质。一项针对 GBS 和 CIDP 患者有氧训练的研究发现,在为期 12 周的自行车运动训练后,GBS 患者的疲劳分数下降了 20%,且身体功能及生活质量都得到了改善^[24]。有监督的个体化锻炼比无监督的家庭锻炼能更有效地减少 GBS 患者的疲劳感、提高其生活质量^[62]。有计划的锻炼可以改善 GBS 患者的身体机能、心肺功能并减少疲劳^[63]。

神经心理症状干预的非药物治疗有认知行为疗法 (cognitive behavioral therapy, CBT) 和职业康复等。这些方法可能会缓解 GBS 造成的社会后果 (如失业、履行家庭责任的能力降低和社会生活减少等) 所引起的抑郁和焦虑症状^[24]。心理教育和支持治疗可以通过提高 GBS 患者承担日常生活活动和参与社会生活的能力, 降低其神经心理症状的发生率, 提高其生活质量^[24]。

目前尚未见药物治疗及物理治疗应用于 GBS 患者神经心理症状治疗的相关临床研究。但在个案报道中, 伴发焦虑和抑郁的 GBS 患者使用选择性 5-羟色胺再摄取抑制剂后, 焦虑和抑郁症状得到明显改善^[64]。金刚烷胺可用于减轻多发性硬化患者的疲劳症状, 但 Garssen 等^[65]的研究结果表明金刚烷胺对 GBS 患者的疲劳症状并没有改善作用。

4 结 语

GBS 患者伴发神经心理症状的风险高于正常人群, 对 GBS 患者出院后的定期随访尤为重要。目前对 GBS 患者伴发的神经心理症状尚没有统一的诊断标准, 对其治疗的研究也相对缺乏。今后仍有必要深入探讨 GBS 患者躯体症状和神经心理症状之间的关系, 确定它们对患者的影响, 从而制定针对性的干预措施以改善预后、提高治疗效果。这是一项复杂的任务, 多学科团队在早期阶段的参与可能对改善 GBS 患者的预后至关重要。

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