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新进展综述

带状疱疹后神经痛诊疗新进展

许冰, 陈启波(综述), 官学海(审校)

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作者单位: 530021 南宁,广西壮族自治区人民医院康复医学科(许冰,陈启波); 530021 南宁,广西医科大学第一附属医院麻醉科(官学海)

作者简介: 许冰(1983-),女,医学硕士,副主任医师,研究方向:神经康复、神经病理性疼痛的诊疗。E-mail:icexu05@aliyun.com

[摘要] 艾滋病患者、肿瘤患者、接受器官移植者及老年人是带状疱疹高危人群。带状疱疹后神经痛(postherpetic neuralgia, PHN)为带状疱疹的后遗症之一,严重影响患者的工作、学习、生活和娱乐等日常活动,导致患者焦虑、抑郁,甚至自杀。该文就 PHN 近年来的诊疗研究进展进行综述。

[关键词] 带状疱疹后神经痛; 预防; 诊断; 治疗

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New progress in diagnosis and treatment of postherpetic neuralgia XU Bing, CHEN Qi-bo, GUAN Xue-hai.
Department of Rehabilitation, the People's Hospital of Guangxi Zhuang Autonomous Region, Nanning 530021, China

[Abstract] Acquired immune deficiency syndrome(AIDS) patients, cancer patients, organ transplant recipients and the elderly are at high risk of herpes zoster. Postherpetic neuralgia(PHN) is one of the sequelae of herpes zoster and seriously affects the daily activities of the patients such as work, study, life and entertainment, leading to anxiety, depression, and even suicide. In this paper, we review summarizes the research progress of PHN diagnosis and treatment in recent years.

[Key words] Postherpetic neuralgia(PHN); Prevention; Diagnosis; Treatment

带状疱疹后神经痛(postherpetic neuralgia, PHN)为带状疱疹的后遗症之一,有 18.7% 的带状疱疹患者会出现 PHN,其疼痛源于感觉神经损伤,可表现为间歇痛、慢性痛或自发痛^[1]。有研究^[2]表明,PHN 患者脑灰质结构存在异常:扩散峰度成像研究表明 PHN 患者双侧岛叶、颞上回、左侧额中回及枕叶、右侧小脑前叶、右侧丘脑、尾状核及海马旁回出现参数的降低,双侧岛叶轴向峰度和右侧岛叶平均峰度的降低与患者的视觉模拟评分(Visual Analogue Scale, VAS)得分负相关。镜像同伦功能连接研究^[3]显示

PHN 患者前额叶皮质背外侧、楔前叶和扣带回后部半球间的功能整合降低,后两者降低的程度和患者的 VAS 得分相关。PHN 的诊治效果往往难以令人满意,现就近年来的研究进展综述如下。

1 PHN 的预防

预防 PHN 的最佳方法是避免感染带状疱疹病毒。带状疱疹病毒减毒活疫苗可降低带状疱疹及 PHN 的发病率,其安全性高、耐受性好、能提供长时程的保护^[4]。疫苗的最佳获益者是 70 岁左右的人群,女性获益高于男性。因其为活疫苗,有免疫缺陷的患者应禁用,正在使用免疫抑制剂的患者应慎用。有学者^[5]提出带状疱疹早期应用低能级的激光治疗可以降低 PHN 的发病率。神经阻滞疗法对预防 PHN 有一定的作用^[6]。重复的局部麻醉药联合皮质类固醇激素皮内注射可降低 PHN 的发病率^[7]。

2 PHN 的诊断

带状疱疹的病史及疼痛的性质对 PHN 的诊断至关重要,因此获取患者详细的病史,包括临床症状、感染史及详细的体格检查都非常重要。起过疱疹的皮肤可能有瘢痕,疼痛的部位可能出现皮疹、颜色改变及水肿。对感觉异常的区域,应仔细进行痛触觉、温度觉及振动觉的检查;可同时使用感觉定量评定量表。可通过随访或问卷调查的方式评估疼痛对日常生活的影响。

3 PHN 的治疗

一旦确诊为 PHN,治疗应当瞄准疼痛控制,并将治疗副作用降到最低。由于 PHN 主要影响老年人群,治疗的安全性和可耐受性是考虑的重要问题。目前没有统一的最佳单一治疗方案。在制定个体化的治疗方案前,医护人员应对患者的当前状况作认真评估。为了确保最优疗效,与患者沟通、监测治疗副作用、了解患者对治疗的满意度都非常重要。复诊时,应对疼痛程度、部位、性质重新评估,再制定下一步的个体化治疗方案。

3.1 药物治疗 目前一线治疗药物包括钙离子通道 $\alpha 2\text{-}\delta$ 配体(加巴喷丁、普瑞巴林)、三环类抗抑郁药(阿米替林、去甲替林、地昔帕明)、局部利多卡因贴剂;二线药物有阿片肽类、局部辣椒素贴剂/软膏。

3.1.1 钙离子通道 $\alpha 2\text{-}\delta$ 配体(加巴喷丁和普瑞巴林) 此类药物通过结合 $\alpha 2\text{-}\delta$ 蛋白,阻滞电压门控性钙通道,减少兴奋性神经递质的释放,抑制痛觉过敏和中枢敏化。加巴喷丁还可通过降低脊髓背角神经元的敏感性来减轻疼痛^[8]。中、重度 PHN 患者口服加巴喷丁(1 200 ~ 3 600 mg/d, 4 ~ 12 周)可减轻

至少 50% 的疼痛^[9]。鉴于加巴喷丁的非线性药代动力学特性及较短的半衰期,速释剂需要 3 次/d 服药,剂量 1 800 ~ 3 600 mg/d 均有效,但超过 1 800 mg/d 并无额外获益。治疗过程中,头晕和嗜睡的发生率较高^[10]。加巴喷丁缓释片是加巴喷丁药物前体,和速释剂相比有更加广泛的肠道吸收位点,药物暴露量和剂量成正比,用药 2 次/d,推荐用 4 d 达到 1 200 mg/d 的剂量。加巴喷丁胃滞留片服药 1 次/d,与餐同服,药物可以在胃内滞留 8 ~ 10 h,渐渐释放加巴喷丁至上段小肠的吸收位点,有效的治疗剂量为 1 800 mg/d^[11]。普瑞巴林在 2005 年被批准用于治疗 PHN。普瑞巴林可缓解 PHN、纤维肌痛症、糖尿病性周围神经病和脊髓损伤的相关神经病理理性疼痛^[12],无论发病时间长短均有明显效果^[13]。另外,普瑞巴林在改善 PHN 患者睡眠质量方面亦有显著疗效^[14]。普瑞巴林的治疗剂量是 150 ~ 600 mg/d,分 2 ~ 3 次服用,推荐通过 1 周时间加量以达到有效剂量。普瑞巴林缓释剂型,每天只需服药 1 次,副作用比速释剂型小,可持续治疗的时间长^[15]。新型药物咪唑巴林选择性结合钙离子通道的 $\alpha 2\delta\text{-1}$ 亚单位,具有长效且有力的镇痛效果,并且对中枢神经系统的安全性更高^[16]。此类药物的不良反应是相似的,多见头晕和嗜睡。剂量相关不良反应的发生率最高的是加巴喷丁速释剂,加巴喷丁缓释剂和普瑞巴林的发生率明显降低^[11]。使用此类药物的注意事项和风险与其他中枢神经系统药物相似,包括增加自杀想法或自杀行为^[17]。使用普瑞巴林治疗 6 周后可能出现体重增加,所以需要在治疗过程中监测体重^[18]。由于此类药物不通过细胞色素 P450 酶系统代谢,与其他药物发生相互作用的倾向较低,是老年患者的理想选择。需注意的是,由于此类药物经肾排泄,对肾功能不全的患者,需要调整药物剂量。

3.1.2 三环类抗抑郁药 三环类抗抑郁药阿米替林、去甲替林、丙米嗪和地昔帕明等可以增加 5-羟色胺、去甲肾上腺素水平,阻滞电压依赖性钠通道及 $\alpha\text{-}$ 肾上腺素受体,调节疼痛下行传导通路。此类药物起效相对缓慢,具有口干、便秘、尿潴留及镇静等副作用,并且与心肌梗死、心律失常等心血管事件有关联^[19]。

3.1.3 5% 利多卡因贴剂 利多卡因一方面阻滞电压门控性钠通道,减少由伤害性感受器损伤所引起的初级传入纤维的异位性冲动,进而减轻 PHN^[20];另一方面,可使 TRPA1 通道脱敏从而减少外周伤害性冲动的传入,降低初级及次级敏感化^[21]。5% 利

多卡因贴剂有以下优点:(1)有良好的可耐受性及安全性,可提高患者的依从性;(2)长期治疗后可获得持续镇痛作用;(3)可明显缩小疼痛区域。因此其在局部神经痛治疗指南中被推荐使用^[22]。有研究^[23]指出在 70 岁以上 PHN 患者中,无论治疗时间长短,5%利多卡因贴剂均可明显缓解自发痛及触摸痛。治疗中最常见的不良反应为轻到中度的局部反应,如短暂的瘙痒、红斑及皮炎。鉴于利多卡因贴剂良好的安全性及耐受性,在体虚及老年患者中有特别的价值。

3.1.4 阿片肽类镇痛药 在等待一线药物起效期间,低剂量的阿片肽类镇痛药可以用于减轻疼痛。在此期间阿片肽类镇痛药应被逐渐减量至停药。阿片肽类镇痛药也可慎重地用于对其他治疗疗效不佳的 PHN 患者。常用的药物有羟考酮、吗啡、美沙酮及曲马多等。有分析^[24,25]指出,并无充足的证据支持吗啡及芬太尼能使慢性神经痛获益。

3.1.5 辣椒素贴剂 辣椒素是 I 型辣椒素受体激动剂,通过对神经纤维的激活最终使其脱敏来起到镇痛效果。局部高浓度(5%及以上)的辣椒素较中低浓度更有效地缓解 PHN^[26]。有 Meta 分析指出,单独使用 8% 的辣椒素贴剂比 0.014% 的贴剂能取得更明显的止痛效果^[27]。但 8% 的辣椒素贴剂会出现明显的不良反应,包括皮肤红斑、瘙痒、丘疹及疼痛,并且在治疗期间常出现一过性的疼痛加重。

3.1.6 其他药物 皮内或皮下注射肉毒素在缓解 PHN 及改善睡眠方面均有明显效果^[28]。此疗法副作用少,在妊娠期 PHN 预防及治疗方面有不可替代的优势^[29],还可作为疗效欠佳患者的替代或补充性治疗^[30]。神经节苷脂在减轻 PHN 及缩短病程方面均有效,可作为一种新的辅助治疗手段(联合抗病毒、镇痛、神经营养因子等)^[31]。

3.1.7 合理的多药疗法 在 PHN 的治疗中,单药治疗,即便是最高剂量,可能还不能取得满意的疗效。可将不同作用机制的药物联合使用以达到最佳治疗效果。如一种口服药联合 5% 的利多卡因贴剂,或者加巴喷丁联合阿片肽类或三环类抗抑郁药。加巴喷丁速释剂($\leq 3\ 600\text{ mg/d}$)联合去甲替林($\leq 100\text{ mg/d}$)在缓解疼痛方面效果明显优于单药治疗,并且没有新的或更严重的副作用出现^[32]。

3.2 非药物治疗 微创介入治疗技术(神经介入技术和神经调控技术)被用于 PHN 的治疗,均有较满意疗效^[33,34]。中医治疗(针刺、周围针刺、针灸、电针、艾灸、火罐、中药等)也可使 PHN 缓解^[35~37]。

另有研究^[38]表明椎间孔臭氧注射可缓解神经病理性疼痛,并且增强加巴喷丁的镇痛作用。高压氧在 PHN 治疗上也取得一定疗效^[39]。

4 结语

PHN 严重影响患者的情绪、睡眠及生活质量。临床工作者可以通过早诊断、早治疗帮助患者减轻疼痛,应与患者建立良好的沟通,了解其期望值,在治疗的同时应密切观察疗效,严密监测治疗的副作用,为患者带来更好的疗效。

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