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· 综述 ·

灼口综合征多学科综合治疗进展

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【摘要】 灼口综合征(burning mouth syndrome, BMS)是一种以口腔黏膜烧灼样疼痛为特征的慢性口面部疼痛疾病, 发病因素与社会心理、神经病理、内分泌或免疫等多因素有关, 目前仍缺乏有效的治疗方案。随着BMS发病因素及治疗研究的不断进展, 多学科综合治疗逐渐被引入并成为了一种全新的诊疗趋势。由于BMS病因复杂, 在 multidisciplinary treatment 前, 必须经过充分且全面的诊断分析, 选择最佳的综合治疗方案, 以口腔科的诊断和治疗为基础和前提, 其他多学科联合治疗, 包括并发疾病治疗、心理干预、不良习惯纠正等; 联合激光治疗和心理干预是目前治疗手段中较为有效的治疗方式, 其舒适性高、患者接受程度好; 必要时可以辅以甲钴胺片, 氯硝西洋、 α -硫辛酸等药物营养神经与对症治疗。BMS的多学科综合治疗有望成为一种新的趋势, 为提升治疗效果提供新的策略。

【关键词】 灼口综合征; 烧灼样疼痛; 口腔健康相关生活质量; 多学科综合治疗; 心理干预; 药物治疗; 物理治疗; 中医治疗

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【Abstract】 Burning mouth syndrome (BMS) is a chronic oral and facial pain disorder characterized by burning pain in the oral mucosa, with multiple pathogenic factors including psychosocial, neuropathological, endocrine, and immune factors. There is still a lack of effective treatment options that have been demonstrated to work. With the development of research on the pathogenesis and treatment of BMS, multidisciplinary comprehensive treatment has gradually been introduced and become a new trend of diagnosis and treatment. Before multidisciplinary treatment, it is necessary to go through a full and comprehensive diagnosis and analysis, select the best comprehensive treatment plan, take the diagnosis and treatment of stomatology as the basis and premise, and apply other multidisciplinary combined treatment, including the treatment of concurrent diseases, psychological interventions, correction of bad habits, etc. A combination of laser therapy and psychological intervention is a more effective treatment method among the current treatment methods,

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with high comfort and good acceptance by patients. If necessary, mecobalamin tablets, clonazepam α -lipoic acid and other drugs can be used to nourish nerves and provide symptomatic treatment. The comprehensive multidisciplinary treatment of BMS is expected to become a new trend and provide a new strategy for improving the therapeutic effect.

【Key words】 burning mouth syndrome; burning pain; oral health-related quality of life; comprehensive multidisciplinary treatment; psychological intervention; drug therapy; physical therapy; traditional Chinese medicine treatment

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灼口综合征(burning mouth syndrome, BMS)是一种病因不明的慢性口面部疼痛疾病,不伴有明显的临床体征和病理损害,以口腔黏膜自发性、持续性或反复发作的烧灼样疼痛为特征,被认为是一种“神经病理性疼痛”^[1],可能与社会心理、神经病理、内分泌或免疫等多因素有关。随着多学科联合诊疗的发展,越来越多研究者倡导将BMS的疾病特点与多学科综合治疗紧密结合^[2],由患者和医师共同制定可量化的治疗方案,多视角、多方位、多途径融合,在缓解其口腔症状的同时,改善社会心理功能,以提高患者的口腔健康相关生活质量。本文将从BMS的分型、发病因素及多学科综合治疗进展展开综述,为后续开展临床实践及相关研究提供参考。

1 BMS分型

根据有无可识别的临床体征将BMS分为2型^[3]:

①原发性BMS:没有明确的系统或局部发病因素,可能与心理因素或某些未知因素有关;②继发性BMS:由明确的系统或局部发病因素所引起的口腔黏膜疼痛或烧灼感(除外口腔颌面部疼痛疾病及表现为口腔黏膜疼痛不适的口腔疾病)。根据24 h内疼痛严重程度波动将BMS分为3型^[4]:①I型BMS(约占35%):早晨醒来时没有明显疼痛,晚上疼痛达到峰值,呈进行性加重趋势,可能与糖尿病、营养缺乏等系统性疾病有关;②II型BMS(约占55%):疼痛可能持续一整天,影响睡眠,通常伴有焦虑等心理障碍;③III型BMS(约占10%):疼痛呈间歇性,白天没有明显疼痛,可能与接触过敏原有关。

2 BMS发病因素

2.1 社会心理因素

国内外学者逐渐重视BMS患者的一些社会心理及情绪障碍,主要关注点在焦虑和抑郁上,尤其是中老年女性BMS患者的舌部黏膜烧灼样疼痛被认为可能与社会心理因素有关^[5]。一方面,BMS患者有很高的神经质倾向,精神压力可通过调节 γ -氨基丁酸(γ -aminobutyric acid, GABA)A型受体,诱导下丘脑-垂体-性腺轴和下丘脑-垂体-肾上腺轴的下调,从而改变性激素水平^[6];另一方面,BMS患者多为焦虑和抑郁性格,各种社会生活应激事件及长期压力往往会引发或加重症状^[7]。

2.2 神经病理因素

2.2.1 外周神经纤维病变 研究报道,约20%的原发性BMS患者有三叉神经损害表现,主要累及舌神经、下颌神经或整个三叉神经,许多研究也证实了BMS患者中存在口腔黏膜局灶性的外周小神经纤维病变^[8-9],包括上皮神经纤维、乳头下神经纤维的缺失或密度减少,这可能解释了BMS患者口腔黏膜的温度觉、痛觉阈值较正常人迟钝的现象^[10]。研究发现,小躯体神经纤维的损害会使患者出现口腔黏膜烧灼感、疼痛感和麻木感,通常晚间症状最明显,而自主神经纤维的损害则会使患者出现口干、眼干等症状^[11],这似乎与BMS的疾病特征相符合。另外,BMS还可能与神经纤维中神经生长因子(neural growth factor, NGF)水平的增加和瞬时受体电位香草酸亚型1(transient receptor potential vanilloid 1, TRPV1)的表达及舌组织神经纤维中P2X3受体表达升高等相关^[12]。最近的研究发现,同时罹患BMS和糖尿病的患者,其血清神经元特异性烯醇化酶水平的升高,提示了BMS发病可能

的外周神经机制^[13]。综上所述,外周神经纤维病变参与了BMS发病的感觉异常和慢性疼痛机制。

2.2.2 中枢神经系统病变 研究认为,BMS的致病可能与躯体感觉神经系统的损伤和大脑神经网络的功能障碍有关^[14],包括疼痛控制的缺乏或多巴胺能神经传递的异常。BMS患者大脑中多巴胺(dopamine, DA)水平的降低,引起了多巴胺能系统活性的改变,若干病例应用左旋多巴或多巴胺受体激动剂成功治疗BMS,似乎验证了BMS患者存在多巴胺能神经传递的异常^[15-16]。另外,扣带回皮质似乎也特别参与了BMS患者的三叉神经疼痛处理和调节,其通过三叉神经传入纤维将伤害性信号传导到脑干,诱导左后扣带回旁区GABA的增加,引起N-乙酰天冬氨酸(n-acetylaspartate, NAA)的减少,而NAA是反应神经元受损的重要标志物,其浓度的下降说明BMS与神经元损伤有关^[17]。

2.3 内分泌因素

BMS常见于围绝经期和绝经后妇女,因此,性激素失调被认为可能是BMS另一个重要的致病因素。Tredal等^[18]采用局部麻醉的方式观察BMS患者对口腔疼痛的反应,发现患者雌激素水平下调和雌激素受体上调。可能的解释是,由于绝经后卵巢类固醇合成减少,引起肾上腺类固醇缺乏或功能障碍,致使类固醇对神经组织的神经保护作用消除;而类固醇中雌激素水平的降低还可引起机体物质代谢的紊乱,致多巴胺、去甲肾上腺素失调及阿片样物质活性降低,引起交感神经及副交感神经功能失常^[19]。以上研究表明,机体性激素水平的改变引起了与口腔躯体感觉有关的小神经纤维的退行性改变。

2.4 免疫因素

绝经后BMS患者小唾液腺功能的减退或唾液腺功能障碍患者,唾液流量过少容易导致口腔干燥和口腔黏膜的临床前炎症,研究发现BMS患者的唾液中促炎细胞因子水平升高,而抗炎细胞因子白细胞介素-10(interleukin-10, IL-10)水平反而降低^[20],另有超过250种蛋白质在BMS患者中上调,Krief等^[21]认为是神经营养因子信号通路通过增强p75神经营养因子受体(p75 neurotrophin receptor, p75NTR)活性参与BMS的病理生理过程,促进神经细胞凋亡,降低口腔黏膜乳头下神经纤维密度。另外,研究还发现BMS患者的CD8⁺细胞计数显著降低,而CD4⁺/CD8⁺比率显著升高,提示其免疫功能受到了特异性抑制^[22]。

3 BMS的多学科综合治疗

3.1 口腔临床治疗

口腔临床治疗以消除局部因素和改善全身因素为主,目的是缓解口腔黏膜局部症状,包括处理残根、残冠、不良修复体(银汞充填体、活动义齿)、纠正不良口腔习惯(伸舌自检)、排查既往病史(例如牙体牙周疾病、唾液腺疾病、糖尿病、甲状腺疾病、食物及药物过敏等)、纠正不良用药习惯(抗生素或其它药物的滥用),可考虑辅以局部消炎止痛、营养周围神经、调节免疫和保持口腔卫生方面的药物治疗,包括非甾体类抗炎药、甲钴胺片、复合维生素片、维生素B2、维生素E、谷维素、胸腺肽肠溶片、2%~4%碳酸氢钠含漱液等。对于长期、严重的口腔黏膜烧灼样疼痛且口腔临床治疗难以缓解者,可考虑行外周神经阻滞术:包括舌神经阻滞、下颌神经阻滞^[23]。

3.2 心理干预

认知行为疗法(cognitive behavioral therapy, CBT)^[24]及引导自助干预(guided self-help intervention, GSI)^[25]可有效缓解BMS患者的心理症状和减轻疼痛强度,CBT联合洋甘菊植物疗法或康复新液也显示出潜在的疗效。Le等^[26]的一项单中心回顾性研究通过观察心理干预对治疗BMS的有效性,发现只有36.8%患者仍需接受抗抑郁药物治疗,显著低于心理干预前比例(63.2%)。心理干预和心理支持对BMS的专病管理是重要的,有助于改善患者的社会心理功能,可考虑作为辅助策略。

3.3 药物治疗

对于顽固性疼痛,可考虑辅以疼痛科或神经内科药物治疗。研究发现,氯硝西洋局部或全身用药,可缓解与BMS患者的口腔黏膜烧灼感,但不能改善情绪、味觉障碍及口干,还可能引起嗜睡^[27]。 α -硫辛酸也可减弱BMS患者的口腔黏膜烧灼感,尤其在加巴喷丁或CBT同时使用时可显著改善疼痛强度。辣椒素的慢性刺激可使机体脱敏,逐渐减弱BMS患者的口腔黏膜烧灼感,但治疗前期局部应用后可能会立即增加烧灼感^[28]。

3.4 物理治疗

激光治疗具有缓解疼痛和改善生物刺激效应等作用,近年来被广泛应用于BMS的疼痛控制,包括低能量激光治疗(low-level laser therapy, LLLT)。研究证明LLLT在630~1064 nm波长^[29]和大于50 mW/cm²辐照度^[30]范围内对BMS的疼痛缓解较为有效。重复经颅磁刺激(repetitive transcranial

magnetic stimulation, rTMS)作为一种无创、安全的物理治疗方法,被广泛应用于神经康复及疼痛康复领域,其主要通过改变大脑皮质的兴奋性达到缓解疼痛的目的,近年来也被应用于BMS治疗的探索。Umezaki等^[31]评估前额叶高频rTMS治疗BMS患者的疗效,发现在2个月的干预后患者的疼痛强度减轻,4个月后随访疼痛强度仍然稳定,且味觉障碍也有所改善。

3.5 其它治疗

中医将BMS称为“舌痛”,由经脉气血运行不畅、不通引起。研究表明,针灸与耳穴贴敷相结合可以有效缓解患者的口腔黏膜烧灼样疼痛症状,改善口腔健康相关生活质量,这可能与口腔黏膜微循环的改善有关^[32-33]。另外,BMS患者口干症状的产生可能与空腹血糖水平高有关,甲状腺功能减退、性激素分泌失调也可能间接导致口腔黏膜烧灼感,口干症状和皮肤病之间也有联系^[34]。因此,如I型BMS患者还需要妇科、皮肤科、消化内科、内分泌科等多学科的配合,积极治疗系统性疾病或相关疾病,包括糖尿病、胃肠道疾病、甲状腺疾病、喉咽反流、干燥综合征、围绝经期综合征等。

4 小结

综上,BMS多学科综合治疗使灼口综合征的管理与治疗更加全面,可以最大限度地提升治疗效果,缓解口腔黏膜疼痛症状,促进患者社会心理功能康复,提高生活质量。灼口综合征的多学科综合治疗有望成为一种新的趋势,为提升治疗效果提供一种新的策略。

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