

口腔癌患者情绪异常与下丘脑-垂体-肾上腺轴的调节障碍

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[摘要] 口腔癌是头颈部最常见的肿瘤,患者多伴有焦虑或抑郁情绪,而情绪异常又是癌症发生发展的“催化剂”和预后的预报器。口腔癌的情绪异常与下丘脑-垂体-肾上腺(HPA)轴调节紊乱应有一定关联性。本文提示以神经内分泌重要环节——HPA 轴调节紊乱为重要切入点,探讨口腔癌情绪异常的生物学机制,可为口腔癌的情绪异常及其干预措施的机制研究提供新思路,具有重要意义。

[关键词] 口腔癌; 情绪障碍; 下丘脑-垂体-肾上腺轴

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Relationship between the mood disorders of patients with oral cancers and disruptions in hypothalamic-pituitary-adrenal axis Jing Dian¹, Jia Yanfei², Liu Chuanxia³, Zhou Qizhi². (1. West China School of Stomatology, Sichuan University, Chengdu 610041, China; 2. Chronobiology Laboratory of State Administration of Traditional Chinese Medicine, Chengdu University of Traditional Chinese Medicine, Chengdu 610075, China; 3. Dept. of Oral Medicine, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, China)

[Abstract] Oral cancer is the most common neoplasm of the head and neck. Patients with oral cancer show elevated prevalence rates of mood disorder. Mood disorder is a kind of ‘catalyst’ in the development of cancer and the prognosis predictor. Mood disorder in oral cancer may be associated with circadian disruption in hypothalamic-pituitary-adrenal(HPA) axis. Based on this analysis, we recommend that alteration of circadian rhythm of the HPA axis may play a crucial role in biology mechanism of intervention on oral cancer with mood disorder.

[Key words] oral cancer; mood disorder; hypothalamic-pituitary-adrenal axis

研究^[1-2]表明,癌症属身心相关性疾病,不仅受各种心理因素的影响,而且也使患者产生各种心理症状,而下丘脑-垂体-肾上腺(hypothalamic-pituitary-adrenal, HPA)轴是神经内分泌系统的重要部分,参与控制心理应激的反应,并调节消化和免疫系统、昼夜节律以及情绪等生理和心理活动,是心理社会因素在癌症发生发展中的重要机制之一。本文以 HPA 轴为切入点,试探讨口腔癌的情绪异常的生物学机制。

1 口腔癌与情绪异常

有研究^[3-10]表明,口腔癌患者由于疾病本身、

手术以及放化疗等因素常可造成心理健康问题和情绪异常。Yang等^[5]连续调查舌癌术后1年患者的生活质量(quality of life, QOL)后发现,其QOL的整体水平均有不同程度的下降,说话、吞咽、咀嚼功能受到了很大影响,并且术前患者的疼痛、焦虑和抑郁水平明显偏高,手术后的情绪异常也较正常人群明显。Biazevic等^[6]对口腔和口咽癌患者手术后1年的随访研究也得到了其QOL下降的相似结果,并且发现患者焦虑情绪的平均积分从手术前36.0增高至手术后的70.7。Airoldi等^[7]运用心理-肿瘤学方法评价了口腔舌癌切除术和游离皮瓣重塑术加辅助放射疗法治疗口腔癌患者后发现,超过50%的病例出现中到重度的后期毒性反应,如唾液功能、吞咽困难以及味觉损害等,且患者严重的吞咽困难与抑郁、焦虑的高水平相关,吞咽和味觉损害与低水平的健康和QOL有关。Chen等^[8]研究结果表明,口腔鳞状细胞癌手

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术后1个月和放射治疗后1个月的患者均可出现中度的口面部疼痛,而且手术后1个月口面疼痛、口腔功能紊乱和心理障碍发生较放射治疗后严重,老年患者的口面部疼痛则表现为饮食、言语困难、抑郁以及情绪焦虑。Chen等^[9]另一项研究也显示,口腔癌患者在放射治疗或辅以化学治疗的3个月内,患者均显示出轻到重度的痛苦症状,如吞咽困难、食欲差、黏膜炎、疼痛和疲劳等,并伴有抑郁表现,症状严重程度和抑郁、焦虑水平在放射治疗或辅以化学治疗后约2个月最为严重。心理痛苦,特别是抑郁和焦虑情绪程度可作为口腔癌患者预后如何的预报器,这提示应给予癌症患者更多的心理监护。

癌症患者的焦虑、抑郁情绪普遍存在,心理社会支持和服务要求常得不到满足,且疾病病程的严重程度与焦虑、抑郁发生呈正相关关系^[10-11];一项系统评价结果^[12]证实,焦虑、抑郁与癌症患者心理痛苦疲劳症状密切相联。近年来,有专家明确把肿瘤称为“心身相关性疾病”,指出癌症的发生与社会心理因素密切相关,且情绪忧郁、精神压抑等强烈的心理应激可使病情加重、影响预后,焦虑、抑郁等负面情绪被喻为癌症的“催化剂”^[13]。可见,口腔癌和其他多数恶性肿瘤一样常伴情绪异常,情绪异常是口腔癌发生发展的“催化剂”及预后的预报器。癌症患者的心理健康问题已成为众多医学领域关注的热点问题之一。

2 肿瘤及其情绪异常与下丘脑-垂体-肾上腺轴

在2010年3月美国心身医学会明确提出了HPA轴在肿瘤生长中的直接作用。已有研究表明,HPA轴是神经内分泌系统的重要组成部分,当HPA轴兴奋时可大量释放中枢介质促肾上腺皮质激素释放激素和促肾上腺皮质激素(adrenocorticotrophic hormone, ACTH),进而促进肾上腺皮质激素分泌糖皮质激素,从而调节情绪等行为反应^[1]。神经内分泌和免疫系统紊乱,特别是HPA轴调节障碍是心理社会因素在癌症发生发展中的可能机制之一。心理、情绪异常能够引起肿瘤组织、瘤株动物以及癌症患者的严重节律紊乱:内分泌、代谢、免疫以及休息-活动周期等节律的异常变化。例如:与应激、情绪相关的昼夜节律紊乱可提示癌症预后不良;HPA轴可能与轮班工作制所引起乳腺癌的发生紧密相关,其患者体内的皮质醇等激素出现异常昼夜节律模式^[2]。另有研究^[14]表

明,HPA轴调节紊乱可以导致慢性生理或心理应激期间的再生功能抑制。目前已有研究^[15-16]显示,伴抑郁症状的癌症患者,其HPA轴的功能明显紊乱,如皮质醇(cortisol, GS)的昼夜变动幅度(relative diurnal variation, VAR)明显下降,且焦虑因子评分与抑郁症状评分呈正相关关系。Thornton等^[17]发现,伴有疼痛、抑郁和疲劳症状的晚期乳腺癌患者的HPA轴和自主神经系统协同变异的活性增高,进而导致了其血浆中GS、ACTH、肾上腺素和去甲肾上腺素水平的升高,并提示这4种应激激素可作为抑郁和焦虑的相关影响因素。

伴情绪异常的口腔癌患者可能也与HPA轴的调控紊乱相关。早有实验^[18]证实,可的松对仓鼠的肺癌、头颈部癌的转移有促进作用。另有研究^[19]表明,抗利尿激素及促肾上腺皮质激素是引起副肿瘤综合征的主要激素。最新研究^[20]提示,应激激素可以影响口腔癌细胞生物学行为:大多口腔癌患者存在严重的心理问题,其去甲肾上腺素和异丙肾上腺素增强了鳞状细胞癌(squamous cell carcinoma, SCC)细胞系中如SCC9及SCC25细胞中白细胞介素(interleukin, IL)-6的表达及口腔SCC细胞的增殖,低浓度皮质醇增强了SCC9细胞中IL-6的表达,并激活了应激条件。

肿瘤伴情绪障碍的发生不仅是单一系统的病变,而往往是全身系统性疾病,由此,不难推断口腔癌伴情绪异常同样与HPA轴的调节障碍密切相关,但其机制研究尚未见文献报道。基于此,从神经内分泌——HPA轴紊乱的角度出发,可为进一步探讨口腔癌情绪异常的干预机制提供研究新思路。

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(本文编辑 张玉楠)

(上接第 627 页)

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