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【临床研究】

食管癌患者抑郁状态与血清瘦素、胃促生长素水平相关性分析

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摘要: **目的** 探讨食管癌患者抑郁状态与血清瘦素、胃促生长素水平的关系。**方法** 选择河南省肿瘤医院放疗科2016年2月至2017年3月收治的45例成年男性食管癌患者为研究对象,根据是否合并抑郁症分为抑郁组($n=20$)和非抑郁组($n=25$);食管癌患者均接受放射治疗,合并抑郁患者同时进行抗抑郁治疗。另选择20例健康成年男性作为对照组。检测所有受试者血清瘦素、胃促生长素水平,治疗前后采用汉密尔顿抑郁量表(HAMD)评估食管癌患者精神状态。比较2组受试者体质量、体质量指数(BMI)及激素水平等,并分析食管癌患者抑郁状态与血清瘦素和胃促生长素水平的相关性。**结果** 非抑郁组和非抑郁组患者治疗前后体质量、BMI均显著低于对照组($P < 0.05$),抑郁组与非抑郁组患者治疗前体质量、BMI比较差异均无统计学意义($P > 0.05$)。抑郁组与非抑郁组患者治疗后体质量、BMI显著低于治疗前($P < 0.05$);治疗后,抑郁组患者的体质量、BMI显著低于非抑郁组($P < 0.05$)。非抑郁组患者治疗前血清瘦素水平与对照组比较差异无统计学意义($P > 0.05$),治疗后血清瘦素水平显著低于对照组($P < 0.05$);抑郁组患者治疗前和治疗后血清瘦素水平均显著低于对照组($P < 0.05$)。非抑郁组患者治疗后血清瘦素水平显著低于治疗前($P < 0.05$),抑郁组患者治疗后血清瘦素水平与治疗前比较差异无统计学意义($P > 0.05$)。治疗前,抑郁组与血清瘦素水平显著低于非抑郁组($P < 0.05$);治疗后,抑郁组与非抑郁组患者血清瘦素水平比较差异无统计学意义($P > 0.05$)。3组患者血清胃促生长素水平比较差异均无统计学意义($P > 0.05$)。食管癌患者精神状态与血清胃促生长素水平呈正相关($r = 0.360, P < 0.05$),与血清瘦素水平呈负相关($r = -0.412, P < 0.05$)。**结论** 食管癌患者的抑郁状态与血清瘦素水平呈负相关,与胃促生长素水平呈正相关。

关键词: 食管癌;放射治疗;抑郁;瘦素;胃促生长素

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Correlation between the depression and serum leptin, ghrelin levels in patients with esophageal cancer

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Abstract: **Objective** To study the correlation between the depression and serum leptin, ghrelin levels in patients with esophageal cancer (EC). **Methods** Forty-five male adult patients with EC in the Department of Radiation Oncology, Henan Cancer Hospital from February 2016 to March 2017 were chosen as study objects, the EC patients were divided into depression group ($n=20$) and non-depression group ($n=25$) according to whether they had depression or not. All EC patients received radiotherapy, while the patients with depression received antidepressant therapy. Twenty male healthy adult were recruited as control group. The levels of leptin, ghrelin in serum of all subjects were detected. Depression status was evaluated by hamilton depression scale (HAMD) before and after treatment. The body weight, body mass index (BMI) and hormone levels were compared between the two groups. The correlation between depression status and serum levels of leptin, gastrin were analyzed.

Results The body weight, BMI of patients in depression group and non-depression group were significantly lower than those in the control group before and after treatment ($P < 0.05$). There was no significant difference in the body weight, BMI of patients in depression group and non-depression group before treatment ($P > 0.05$). The weight, BMI of patients in depression group and non-depression group after treatment were significantly lower than those before treatment ($P < 0.05$). After treatment, the body weight, BMI of patients in depression group were significantly lower than those in non-depression group ($P < 0.05$).

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There was no significant difference in the serum level of leptin between non-depression group and control group before treatment ($P > 0.05$), but the serum level of leptin of patients in non-depressive group was significantly lower than that in the control group after treatment ($P < 0.05$). The serum level of leptin of patients in depression group was significantly lower than that in the control group before and after treatment ($P < 0.05$). The serum level of leptin of patients in non-depression group after treatment was significantly lower than that before treatment ($P < 0.05$); there was no significant difference in the serum level of leptin of patients in depression group between after treatment and before treatment ($P > 0.05$). Before treatment, the serum level of leptin of patients in depression group was significantly lower than that in non-depression group ($P < 0.05$); after treatment, there was no significant difference in the serum level of leptin between depression group and non-depression group ($P > 0.05$). There was no significant difference in the level of serum ghrelin among the three groups ($P > 0.05$). The mental status of EC patients was positively correlated with the serum level of ghrelin ($r = 0.360, P < 0.05$) and was negatively correlated with the serum level of leptin ($r = -0.412, P < 0.05$). **Conclusion** Depression can change the serum levels of leptin and ghrelin in patients with EC, and appropriate antipsychotic treatment may improve the prognosis of patients by changing their body mass.

Key words: esophageal carcinoma; radiotherapy; depression; leptin; ghrelin

食管癌是消化系统发病率较高的一种恶性肿瘤^[1-2]。恶性营养不良是导致肿瘤患者病死率高的主要原因。肿瘤恶病质和一些精神性疾病如抑郁焦虑症等与癌症相关恶性营养不良的发生密切相关^[3]。此外,食管癌患者确诊后及治疗期间抑郁症的发生率明显高于其他肿瘤患者^[5]。

米氮平是一种去甲肾上腺素能抗抑郁药物,可较好地控制癌症恶病质及放射和化学治疗引起的不良反应^[6]。使用米氮平进行抗抑郁治疗后,患者的体质量、体脂量及血清瘦素水平增加,而血清胃促生长素的水平降低^[7]。瘦素是脂肪细胞分泌的一种降低食欲的激素,可减少食物的摄入,增加能量的消耗。胃促生长素是一种由消化道分泌的促进食欲的激素,通过增加食物摄入,降低能量消耗而增加体质量^[3]。瘦素与体脂指数成负相关,而胃促生长素的水平则与体脂指数成正相关。研究表明,多种肿瘤患者血清胃促生长素水平升高,瘦素水平降低^[8],这些激素水平的改变主要与肿瘤造成的恶病质相关。与非恶病质肿瘤患者相比,发生恶病质的肿瘤患者血清促胃生长素水平升高,瘦素水平降低^[9-11]。因此,血清瘦素、胃促生长素被认为是治疗癌症恶病质以及放射治疗引起的神经厌食症的重要靶点^[12-13]。本研究旨在探讨食管癌患者抑郁状态与血清瘦素、胃促生长素水平的相关性。

1 资料与方法

1.1 一般资料 选择河南省肿瘤医院放疗科2016年2月至2017年3月收治的45例成年男性食管癌患者为研究对象,患者年龄49~67(58.93 ± 9.48)

岁,食管癌分级为Ⅲ~Ⅳ级(局部浸润),排除患有内分泌疾病、乙醇和药物成瘾及接受任何激素治疗的患者。食管癌患者根据是否合并抑郁症分为抑郁组($n = 20$)和非抑郁组($n = 25$)。另选择20例年龄与食管癌患者匹配的身心健康的成年男性作为对照组,受试者年龄48~66(57.65 ± 8.91)岁。本研究经郑州大学伦理委员会讨论批准,向所有受试者说明本研究的性质、目的、收益及风险,遵从自愿原则,与每位受试者签订相关《知情同意书》。由精神科医师通过临床问诊及心理测验评估食管癌患者治疗前后的精神状态。

1.2 治疗方法 患者均采用调强放射治疗(6 MV-X 直线加速器,Varian Truebeam)。放射治疗处方剂量达59.4~66.0 Gy,每次1.8~2.0 Gy,每周5次,共33次。危及器官限量:肺平均剂量 ≤ 13 Gy,两肺V20 $\leq 27\%$,V30 $\leq 20\%$;脊髓平均剂量9~21 Gy,最大量 ≤ 45 Gy;心脏V40 $\leq 40\% \sim 50\%$ 。合并抑郁症的食管癌患者在接受放射治疗的同时,给予米氮平(杭州默沙东制药有限公司,国药准字H20140031)抗抑郁治疗,每次15~30 mg,口服,每日1次。治疗期间,尽量避免使用其他可能影响体质量的药物。

1.3 观察指标 (1)分别于治疗前后测所有受试者的身高、体质量,并计算体质量指数(body mass index, BMI)。BMI = 体质量/(身高)²。(2)食管癌患者于治疗前后、对照组受试者于晨起时空腹采集静脉血,分离血清,于-70℃下储存备用。采用放射免疫法检测(试剂盒购自美国凤凰药物公司)检测血清瘦素和胃促生长素水平。(3)放射治疗前后

采用汉密尔顿抑郁量表(hamilton depression scale, HAMD)评估食管癌患者精神状态。

1.4 统计学处理 应用 SPSS 19.0 软件进行统计学分析,采用 Shapiro-Wilk 检验对变量分布进行正态性检验。符合正态分布的计量资料用均数 ± 标准差($\bar{x} \pm s$)表示,不符合正态分布计量资料用中位数和四分位数间距表示。受试者年龄、体质量及 BMI 比较采用独立样本 *t* 检验。食管癌患者治疗前后年龄、体质量及 BMI 比较采用配对 *t* 检验。不同组间激素水平的比较采用非参数 Mann-Whitney *U* 检验,治疗前后激素水平的比较采用 Wilcoxon 检验;采用 Spearman 相关进行相关性分析。为了排除年龄及 BMI 对瘦素和胃促生长素水平的影响,调整后激素水平值的计算如下:调整后激素值 = (测得激素值 × 年龄 × BMI) / (平均激素值 × 平均年龄 × 平均 BMI)。 *P* < 0.05 为差异有统计学意义。

2 结果

2.1 3 组受试者体质量、BMI 及激素水平比较

结果见表 1。非抑郁症组和抑郁症患者治疗前后体质量、BMI 均显著低于对照组 (*P* < 0.05)。抑郁症组与非抑郁症组患者治疗前体质量、BMI 比较差异均无统计学意义 (*P* > 0.05)。抑郁症组与非抑郁症组患者治疗后体质量、BMI 显著低于治疗前,差异有统计学意义 (*P* < 0.05)。治疗后,抑郁症组患者的体质量、BMI 显著低于非抑郁症组,差异有统计学意义 (*P* < 0.05)。非抑郁症组患者治疗前血清瘦素水平与对照组比较差异无统计学意义 (*P* > 0.05);治疗后,非抑郁症组患者血清瘦素水平显著低于对照组,差异有统计学意义 (*P* < 0.05)。抑郁症组患者治疗前和治疗后血清瘦素水平均显著低于对照组,差异有统计学意义 (*P* < 0.05)。非抑郁症组患者治疗后血清瘦素水平显著低于治疗前,差异有统计学意义 (*P* < 0.05);抑郁症组患者治疗后血清瘦素水平与治疗前比较差异无统计学意义 (*P* > 0.05)。治疗前,抑郁症组患者血清瘦素水平显著低于非抑郁症组,差异有统计学意义 (*P* < 0.05);治疗后,抑郁症组与非抑郁症组患者血清瘦素水平比较差异无统计学意义 (*P* > 0.05)。3 组患者血清胃促生长素水平比较差异均无统计学意义 (*P* > 0.05)。

表 1 3 组受试者体质量、BMI 及激素等水平比较

Tab.1 Comparison of body mass, BMI and hormone levels of subjects among the three groups

分组	<i>n</i>	体质量/kg	BMI/ (kg · m ⁻²)	瘦素/ (μg · L ⁻¹)	胃促生长素/ (μg · L ⁻¹)
对照组	20	87.2 ± 6.1	28.6 ± 3.3	3.7 (3.3)	299.8(382.4)
非抑郁症组	25				
治疗前		71.3 ± 6.3 ^a	25.3 ± 3.2 ^a	3.4 (3.8)	341.2(189.0)
治疗后		64.3 ± 8.3 ^{ab}	22.6 ± 4.3 ^{ab}	1.9 (2.2) ^{ab}	332.8(294.6)
抑郁症组	20				
治疗前		65.1 ± 9.3 ^a	23.7 ± 3.8 ^a	1.7 (2.1) ^{ad}	434.3(316.5)
治疗后		59.3 ± 8.3 ^{abc}	20.6 ± 5.0 ^{ab}	1.0 (1.7) ^a	362.7(273.7)

注:与对照组比较^a*P* < 0.05;与治疗前比较^b*P* < 0.05;与非抑郁症组治疗后比较^c*P* < 0.05;与非抑郁症组治疗前比较^d*P* < 0.05。

2.2 食管癌患者精神状态与血清瘦素及胃促生长素相关性 食管癌患者精神状态与血清胃促生长素水平呈正相关 (*r* = 0.360, *P* < 0.05);与血清瘦素水平呈负相关 (*r* = -0.412, *P* < 0.05)。

3 讨论

本研究结果表明,食管癌患者基础瘦素水平低于对照组,治疗后瘦素水平进一步降低,明显低于对照组及治疗前,与文献报道的结果一致^[8,11,14]。有研究发现,乳腺癌及甲状腺癌患者治疗前血清瘦素水平明显升高^[15-16],这可能是由于不同肿瘤激活的瘦素相关信号通路不同所致。目前关于食管癌患者放射治疗前后血清瘦素水平的研究较少。KOWALCZUK 等^[17]研究发现,放射和化学治疗不会改变非霍奇金淋巴瘤患者的瘦素水平。肿瘤本身或抗癌治疗会导致恶性营养不良及体质量减轻,例如,肿瘤放射治疗期间造成的口腔黏膜炎可造成营养不良,使患者体质量减轻^[18]。WALLACE 等^[19]研究也发现,消化道肿瘤患者瘦素水平与脂肪含量百分比成正相关。

此外,本研究还发现,抑郁症组患者血清瘦素水平明显低于非抑郁症组。抑郁症组患者的基础瘦素水平显著低于对照组,但非抑郁症组患者的基础瘦素水平与对照组比较差异无统计学意义。非抑郁症组患者治疗后瘦素水平明显降低,但抑郁症组患者治疗后瘦素水平较治疗前无明显改变。因此,瘦素水平可能与抑郁症相关,抗抑郁治疗可以部分调节激素水平的变化。尽管已有较多研究关注癌症患者瘦素水平的改变,但是对癌症患者精神状态与瘦素

水平相关性的研究较少。有研究认为,瘦素与抑郁症之间主要通过下丘脑-垂体-肾上腺轴、细胞因子及自主神经系统发挥相互作用^[20]。本研究中,抑郁症组患者瘦素水平降低,这一结果支持抑郁症患者瘦素功能受损的假设。抑郁症加剧食管癌患者体质减轻可能与其体内瘦素水平降低有关。

本研究中食管癌患者体质量、BMI均低于对照组,接受放射治疗后体质量、BMI进一步降低。米氮平抗抑郁治疗并未使抑郁症患者体质量增加或阻止其体质量减轻,可能的原因有:(1)抑郁症组患者样本量较少,使统计学结果出现偏倚;(2)本次研究对象包含门诊患者,不能确保所有受试者对米氮平治疗的依从性。在今后的研究中应进一步扩大样本量,同时严格控制受试者对抗抑郁药物的依从性。

总之,本研究提示食管癌合并精神疾病可能通过某些标志性激素(如瘦素)的作用影响癌患者的体质量。检测癌症患者合并的精神疾病并对其进行适当的抗精神病治疗可能会改善其预后。

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