

鼻咽癌患者血清同型半胱氨酸水平 与临床病理特征的相关性分析*

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摘要:目的 研究鼻咽癌患者血清同型半胱氨酸(HCY)水平与临床病理特征的相关性,以及HCY在鼻咽癌疗效监测及预后判断中的作用。方法 选取郴州市第一人民医院南院2017年3月~2018年3月初次经病理确诊未经治疗的鼻咽癌患者作为观察组($n=72$),体检中心就诊的健康体检人群作为对照组($n=81$)。采集鼻咽癌患者治疗前、健康体检者当日空腹静脉血,离心分离血清,采用循环酶法检测血清HCY。比较两组人群的血清HCY水平,分析血清HCY水平与鼻咽癌患者临床病理特征的相关性。结果 鼻咽癌患者血清HCY为 $14.44 \pm 4.24 \mu\text{mol/L}$,健康体检人群血清HCY为 $10.96 \pm 2.06 \mu\text{mol/L}$ 。鼻咽癌患者、健康体检人群血清HCY异常率分别为93.05%(67/72)和58.02%(47/81)。鼻咽癌患者血清HCY水平、HCY异常率明显高于健康体检人群,差异有统计学意义($t=-6.331, P<0.05$; $t=24.629, P<0.05$)。血清HCY诊断鼻咽癌的敏感度为93.05%(67/72),特异度为41.98%(34/81)。血清HCY水平与鼻咽癌患者年龄、性别、肿瘤的分化程度以及临床分期相关($t=2.011, -2.673, -2.303, -2.409$, 均 $P<0.05$);与鼻咽癌浸润深度、淋巴结转移及远处转移无关($t=0.042, 0.537, 0.238$, 均 $P>0.05$)。结论 鼻咽癌患者血清HCY水平明显升高,且与年龄、性别、肿瘤分化程度以及临床分期相关。血清HCY有望成为鼻咽癌疗效监测及预后判断的肿瘤标志物。

关键词:鼻咽癌;同型半胱氨酸;临床病理特征

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Correlation Analysis between Serum Homocysteine Level of Nasopharyngeal Carcinoma Patients and Clinical Pathological Features

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Abstract: Objective To study the correlation between the levels of serum homocysteine and the clinical pathological features of nasopharyngeal carcinoma patients, and the role of homocysteine in therapeutic effect monitoring and prognosis judgement of nasopharyngeal carcinoma. **Methods** 72 patients with nasopharyngeal carcinoma who were diagnosed by pathology for the first time without treatment from March 2017 to March 2018 in the South Hospital of the First People's Hospital of Chenzhou City were selected as the observation group. The 81 healthy subjects in the physical examination center were treated as the control group. Fasting venous blood was collected from patients with nasopharyngeal carcinoma before treatment and those who underwent physical examination on the same day. Then the samples were centrifuged to separate serum for experiment. Serum homocysteine levels were measured by cycling enzymatic method. Serum homocysteine level of the two groups was compared by statistics. The correlation between the serum homocysteine levels and clinical pathological features of nasopharyngeal carcinoma patients was been studied. **Results** The serum homocysteine level of nasopharyngeal carcinoma patients and the health examination population was $14.44 \pm 4.24 \mu\text{mol/L}$ and $10.96 \pm 2.06 \mu\text{mol/L}$ respectively. The serum homocysteine abnormal rate was 93.05% (67/72) in nasopharyngeal carcinoma patients, and 58.02% (47/81) in the health check-up crowd. The serum homocysteine levels, homocysteine abnormal rate of nasopharyngeal carcinoma patients was significantly higher than that of healthy check-up crowd, and the distinction had statistical signification ($P<0.05$). The sensitivity of the serum homocysteine in the diagnosis of nasopharyngeal carcinoma was 93.05% (67/72), and the specificity was 41.98% (34/81). The serum homocysteine level was associated with the tumor differentiation and clinical stages of nasopharyngeal carcinoma ($t=2.011, -2.673, -2.303, -2.409$, all $P<0.05$), not associated with the infiltration depth, lymph node metastasis and distant metastasis ($t=0.042, 0.537, 0.238$, all $P>0.05$). **Conclusion** The serum homocysteine concentration of nasopharyngeal carcinoma patients was significantly elevated, and it was correlated with age, gender, degree of tumor differentiation and clinical stage. Serum homocysteine is expected to become tumor markers for curative effect and

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prognosis judgement of nasopharyngeal carcinoma.

Keywords: nasopharyngeal carcinoma; homocysteine; clinical pathological features

同型半胱氨酸(homocysteine, HCY)是蛋氨酸循环的中间产物,它被氧化为同型胱氨酸的同时产生超氧化自由基,对血管内皮细胞造成损伤,促进动脉粥样硬化、血栓形成等。近年来有研究发现 HCY 不仅是心脑血管疾病发病的重要风险因素^[1],还参与肾病代谢综合症、神经退行性疾病的发病。此外,它还被认为与肿瘤的发生发展相关^[2]。HCY 通过改变肿瘤患者的凝血、抗凝血和纤溶系统的状态,参与肿瘤患者的凝血和抗凝血活动,从而促进肿瘤细胞的生长和浸润^[3-4]。还有研究^[5-7]发现 HCY 在小细胞肺癌、肝癌、乳腺癌、胃肠癌等多种肿瘤中升高。鼻咽癌是常见的头颈部恶性肿瘤,早期症状无特异性易被忽视,且易发生转移,因而恶性程度高。目前,它主要靠病理活检确诊,缺乏早期诊断的肿瘤标志物。黄阶胜等^[8]研究发现鼻咽癌患者血清同型半胱氨酸也有不同程度升高。因此,本次研究拟通过检测鼻咽癌患者和健康体检人群血清 HCY,进一步明确鼻咽癌患者血清 HCY 水平,分析鼻咽癌患者血清 HCY 与临床病理特征的相关性,为鼻咽癌的早期诊断和预后判断等提供参考依据。

1 材料和方法

1.1 研究对象 选取郴州市第一人民医院南院 2017 年 3 月~2018 年 3 月肿瘤五区收治的 72 例初次经病理确诊未经治疗且分期明确的鼻咽癌患者作为观察组,男性 48 例,女性 24 例,年龄 29~73 岁,中位年龄 50 岁。排除冠心病、脑卒中、糖尿病以及吸烟、喝酒者。同时,选取同期该院体检中心的 81 例健康体检人群作为对照组,男性 52 例,女性 29 例,年龄 24~69 岁,中位年龄 47 岁,排除高血压、高血脂、糖尿病及肝肾功能严重异常者。两组人群年龄、性别均无显著性差异。

1.2 试剂和仪器 血清 HCY 检测试剂购自深圳奥萨医疗有限公司,检测仪器为西门子 ADVIA2400 全自动生化分析仪。

1.3 方法 采集鼻咽癌患者治疗前、健康体检者当日空腹静脉血,均于清晨空腹抽取 3.0 ml 静脉血置于分离胶试管中,室温静置 1 h,经 3 000 r/min 离心 10 min,分离血清后,采用循环酶法上机检测血清 HCY 水平。仪器日常维护良好,血清 HCY 每日室内质控均在控。严格按试剂说明书要求在西门子 ADVIA2400 全自动生化分析仪进行参数设置和操作。血清 HCY 正常参考范围:0~10 $\mu\text{mol/L}$,如 $>10 \mu\text{mol/L}$ 为升高。同时,收集所有研究对象的年龄、性别等基本信息;收集观察组

鼻咽癌患者的临床病例资料,包括肿瘤分化程度、浸润深度、淋巴结转移及远处转移情况、临床分期等。比较两组人群的血清 HCY 水平,分析血清 HCY 水平与鼻咽癌患者临床病理特征的相关性。

1.4 统计学分析 数据采用 SPSS20.0 进行统计分析。定量数据用均数 \pm 标准差($\bar{x}\pm s$)表示,鼻咽癌组和健康人群组的年龄构成采用非参数检验,其他数据分析均采用卡方检验。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组人群血清 HCY 水平及 HCY 异常率的比较 观察组 72 例鼻咽癌患者血清 HCY 水平为 $14.44\pm 4.24 \mu\text{mol/L}$,对照组 81 例健康体检人群血清 HCY 水平为 $10.96\pm 2.06 \mu\text{mol/L}$ 。72 例鼻咽癌患者中 HCY 升高者有 67 例,异常率 93.05%;81 例健康体检人群有 47 例,异常率 58.02%。鼻咽癌患者血清 HCY 水平及异常率明显高于健康体检人群,差异均有统计学意义($t=-6.331, P<0.05; t=24.629, P<0.05$)。血清 HCY 在诊断鼻咽癌的敏感度为 93.05%(67/72),特异度为 41.98%(34/81)。

2.2 血清 HCY 水平与鼻咽癌患者临床病理特征的相关性分析 血清 HCY 水平与鼻咽癌患者年龄、性别、肿瘤的分化程度以及临床分期相关($P<0.05$),而与鼻咽癌浸润深度、淋巴结转移及远处转移无关($P>0.05$),见表 1。

表 1 血清 HCY 水平与鼻咽癌患者临床病理特征的相关性分析

临床特征	n	HCY($\mu\text{mol/L}$)	t 值	P 值
年龄(岁)	≤ 45	17	12.14 ± 2.70	-2.673 0.009
	> 45	55	15.15 ± 4.39	
性别	男	48	15.18 ± 3.16	2.011 0.048
	女	24	13.13 ± 3.13	
分化程度	分化癌	19	13.66 ± 4.03	-2.303 0.023
	未分化癌	53	16.08 ± 4.27	
浸润深度	T1+T2	25	14.47 ± 3.18	0.042 0.966
	T3+T4	47	14.42 ± 4.74	
淋巴结转移	N0+N1	32	14.14 ± 3.58	0.537 0.593
	N2+N3	40	14.68 ± 4.73	
远处转移	M0	60	14.44 ± 4.43	0.238 0.984
	M1	12	14.42 ± 3.24	
临床分期	I+II	20	13.75 ± 2.46	-2.409 0.046
	III+IV	52	14.73 ± 4.49	

3 讨论 HCY 是人体内一种含硫的非必需氨基酸。它可与甲硫氨酸相互转化,在体内呈动态平

衡,维持恒定水平。HCY代谢与维生素B12和叶酸紧密相关^[9]。当维生素B12和叶酸含量不足时,HCY合成甲硫氨酸受阻,在血液循环中蓄积,造成高同型半胱氨酸血症^[10]。蓄积的HCY对细胞、神经及基因产生毒性,代谢过程中产生的氧化物和过氧化物损伤血管内皮,增强血小板聚集、黏附,影响调节基因的表达,导致上皮细胞出现增殖性改变;同时HCY生成的硫内酯也可使细胞内出现增殖性改变,从而促进肿瘤细胞的增殖^[11-12]。本次研究显示鼻咽癌患者血清HCY水平明显高于健康体检人群,表明鼻咽癌患者体内可能存在着甲硫氨酸循环障碍,鼻咽癌发生可能与HCY水平升高有关。我们推测HCY可能通过以下机制参与鼻咽癌的发生发展。一方面,HCY影响机体DNA甲基化进程,诱导高甲基化的发生,影响DNA合成与修复,促进鼻咽癌肿瘤发生^[13];另一方面,肿瘤细胞大量增殖,体内需要更多的叶酸和维生素B12参与核酸合成,从而造成叶酸和维生素B12相对缺乏,甲硫氨酸循环速度减慢,血清HCY在体内蓄积,进一步促进鼻咽癌肿瘤的发展。

国内有研究^[14]报道血清同型半胱氨酸联合其他检测指标对鼻咽癌诊断具有临床意义。本次研究表明血清HCY在鼻咽癌患者中升高,敏感度可达93.05%,HCY可作为鼻咽癌辅助诊断的肿瘤标志物;但其特异性差为41.98%,对鼻咽癌诊断的实际临床意义可能有限。

本次实验发现血清HCY与鼻咽癌患者年龄、性别相关,这可能是与人体血清HCY的基础水平相关,正常人群中HCY水平受年龄、性别等多种因素影响^[15]。在胃癌、结肠癌^[16-17]等其他肿瘤的研究中,发现HCY与肿瘤的临床分期相关,HCY可用于消化道肿瘤的诊断及预后判断^[18]。本实验也表明血清HCY水平与鼻咽癌肿瘤分化程度、临床分期相关。鼻咽癌患者肿瘤分化程度越低、临床分期越晚,血清HCY水平也相对越高,提示血清HCY水平可能与鼻咽癌的恶性程度以及肿瘤细胞的数量相关,可用于鼻咽癌疗效监测及预后判断。因此,血清HCY有望成为鼻咽癌肿瘤进展的一个标志物。

综上所述,血清HCY水平与鼻咽癌肿瘤的分化程度以及临床分期相关,提示HCY可作为鼻咽癌肿瘤进展的标志物,用于鼻咽癌的疗效监测和预后判断。同时,HCY参与鼻咽癌发病的具体机制暂不明确,进一步检测鼻咽癌患者体内甲硫氨酸的水平,可为其在鼻咽癌中的具体应用价值提供更有可靠的依据。

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