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不同胃癌前病变中医证型 PG、G-17、CEA 和叶酸水平变化及相关性研究 *

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摘要 目的: 对不同胃癌前病变中医证型和血清胃蛋白酶原(pepsinogen, PG)、胃泌素-17(gastrin-17, G-17)、癌胚抗原(carcinoembryonic antigen, CEA)和叶酸水平变化的关系进行探讨, 为胃癌前病变的诊断提供一定的依据。**方法:** 以 80 例胃癌前病变(precancerous lesion of gastric cancer, PLGC)患者研究组, 80 例健康者为对照组, 对研究组患者进行中医临床辨证分型, 对两组研究对象的血清 PG、G-17、CEA 和叶酸进行测定比较。**结果:** 研究组 PLGC 患者中医证型分布不均匀, 差异显著($P<0.05$), 由多到少依次为湿热蕴胃并/兼脾胃虚寒证>胃络瘀阻并/兼气阴两虚证>痰湿中阻并/兼脾胃气虚证>肝胃气滞并/兼气阴两虚证>肝胃气滞并/兼脾胃虚寒证>湿热蕴胃并/兼胃阴不足证。PLGC 不同中医证型患者血清 PG I 和 PG II 水平差异显著($P<0.05$); 与对照组比较, 各证型 PG I 水平均显著降低, PG II 水平均显著升高($P<0.05$)。且湿热蕴胃并/兼脾胃虚寒证和胃络瘀阻并/兼气阴两虚证的 PG I 水平显著低于其他证候, 血清 PG II 水平显著高于其他($P<0.05$)。与对照组比较, 研究组不同证候的 G-17、CEA 水平显著升高, 叶酸水平显著降低($P<0.05$); 观察组中湿热蕴胃并/兼脾胃虚寒证和胃络瘀阻并/兼气阴两虚证 G-17、CEA 显著高于其他证候, 叶酸水平显著低于其他证候($P<0.05$)。**结论:** 胃癌前病变不同中医证型血清 PG、G-17、CEA 和叶酸存在明显差异。

关键词: 胃癌前病变; 中医证型; PG; G-17; CEA; 叶酸

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Study on the Changes and Correlation of the Levels of PG, G-17, CEA and Folic Acid in Different Types of Gastric Precancerous Lesions*

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ABSTRACT Objective: The relationship between TCM syndrome types of different gastric precancerous lesions and the changes of serum PG, G-17, CEA and folic acid levels was explored to provide a certain basis for the diagnosis of gastric precancerous lesions. **Methods:** Taking the study group of 80 patients with gastric precancerous lesions and 80 healthy persons as the control group, the patients in the study group were classified by TCM clinical syndrome differentiation, and the serum PG, G-17, CEA and folic acid of the two groups of subjects were measured and compared. **Results:** The PLGC patients in the study group had uneven distribution of TCM syndromes, and the difference was significant ($P<0.05$). From the most to the least, they were damp heat and stomach combined with spleen and stomach deficiency syndrome>Stomach stasis combined with both qi and yin deficiency syndrome>Phlegm Dampness and dampness combined with spleen and stomach qi deficiency syndrome>Liver and stomach stagnation combined with both qi and yin deficiency syndrome>Liver and stomach stagnation combined with spleen and stomach deficiency cold syndrome>Dampness and heat stagnation combined with qi deficiency syndrome. The levels of serum PG I and PG II in patients with different TCM syndrome types of PLGC were significantly different ($P<0.05$). Compared with the control group, the level of PG I in each syndrome type was significantly reduced, and the level of PG II was significantly increased ($P<0.05$). In addition, the PG I level of the damp heat syndrome combined with both spleen and stomach deficiency syndrome and gastric collateral stasis combined with both qi and yin deficiency syndrome was significantly lower than other syndromes, and the serum PG II level was significantly higher than other ($P<0.05$). Compared with the control group, the G-17 and CEA levels of the different syndromes in the study group were significantly increased, and the folic acid level was significantly reduced ($P<0.05$). The dampness and heat in the observation group were combined with spleen and stomach deficiency syndrome and gastric collateral stasis, G-17 and CEA with both Qi and Yin deficiency syndromes were significantly higher than other syndromes, and

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folic acid levels were significantly lower than other syndromes ($P<0.05$). **Conclusion:** There are obvious differences in serum PG, G-17, CEA and folic acid in different TCM syndrome types of gastric precancerous lesions.

Key words: Gastric precancerous lesions; TCM syndromes; PG; G-17; CEA; Folic acid

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前言

胃癌为一种高发恶性的恶性肿瘤,且诊断率较低,在胃癌之前有数十年的癌前病变过程^[1,2]。胃癌前病变(Precancerous lesions of gastric cancer, PLGC)是一种组织病理学的概念,发生于慢性萎缩性胃炎损伤的病理变化阶段,主要形式表现为肠上皮化生和异型增生^[3,4]。对早期胃癌进行内镜下根除术,患者的5年生存率可达90%,而进展期胃癌经治疗后的5年生存率仅为30%^[5]。对癌前病变进行及早的监控和干预,为胃癌的诊断、预防和治疗有重要的意义。胃癌诊断的金标准为内镜联合组织病理检查,但胃镜是一种侵入性检查,对仪器和医师要求较高,且对患者创伤较大,在治疗过程的定期随访复查中患者耐受性差,易产生活检组织定位不准、取材偏差等问题,从而影响检测结果的准确性^[6,8]。因此,选取适宜的检测指标对监测和控制胃癌前病变的进程至关重要。

多项研究表明,血清PG、G-17、CEA以及叶酸的联合检测在PLGC的诊断中有重要意义^[9-11]。PG和G-17可以反映胃粘膜的形态和功能,CEA和叶酸与肿瘤的发生发展有关^[12-14]。

PLGC在传统中医中没有明确的病名,根据胃脘隐痛、腹胀痞闷、纳呆嘈杂、泛酸、嗳气等症状表现,可归于“痞满病”“胃脘痛病”等范畴。本病以虚实错杂、本虚标实为特点。以脾胃气虚、脾胃阴虚为主,合并血瘀、痰凝、湿邪、热毒等实邪^[15]。目前胃癌前病变的中医分型尚无统一标准,不利于临床治疗。

因此本研究对不同胃癌前病变中医证型和血清PG、G-17、CEA和叶酸水平变化的关系进行探讨,为胃癌前病变的诊断提供一定的临床依据。

1 资料与方法

1.1 临床资料

以80例2017年3月-2020年3月于我院确诊的慢性萎缩性胃炎伴肠上皮化生和/或上皮内瘤变患者,作为研究组,另以80例同期于体检中心健康体检的健康者为对照组。其中研究组男性37例,女性43例,年龄范围28~74岁,平均年龄 55.3 ± 8.8 岁,对照组男性36例,女性44例,年龄范围30~71岁,平均年龄 53.1 ± 7.3 岁,两组患者基本信息经分析无统计学意义($P>0.05$),具有可比性。患者及家属均充分了解研究内容并签署知情同意书,本研究已获得医院伦理委员会的准许。

1.2 纳入与排除标准

纳入标准:(1)符合西医慢性萎缩性胃炎诊断标准:《中国慢性胃炎共识意见》《胃炎新分类悉尼系统》^[16];(2)符合中医证候诊断标准:《慢性胃炎中医诊疗专家共识意见》^[17];(3)经胃镜、病理组织学检查等确诊为慢性萎缩性胃炎伴肠上皮化生和/或上皮内瘤变者;(4)性别不限,年龄范围18~80岁;(5)能配

合完成中医辨证和血清检查者。

排除标准:(1)近期使用PPI、胃粘膜保护药等;(2)经检查已属癌变者,或合并其他系统肿瘤者;(3)妊娠或哺乳期妇女;(4)合并严重的其他系统疾病者;(5)精神病患者和智力、言语障碍者。

1.3 研究方法

采集研究组患者的中医四诊信息,对患者进行中医临床辨证分型^[18],包括湿热蕴胃并/兼胃阴不足、肝胃气滞并/兼气阴两虚、湿热蕴胃并/兼脾胃虚寒、痰湿中阻并/兼脾胃气虚、胃络瘀阻并/兼气阴两虚、肝胃气滞并/兼脾胃虚寒。诊断的标准,符合主症a、b、c、d,次症具备3项以上者可判断为该证候类型。

1.3.1 肝胃气滞并/兼气阴两虚证 主症为:a.胃脘痞胀痛,b.嘈杂,c.困倦乏力,气阴两虚证,d.口干。次症为:a.泛酸,b.胃脘灼热,c.痛窜两胁,d.舌红少津或淡,c.脉弦细。

1.3.2 胃络瘀阻并/兼气阴两虚证 主症为:a.胃脘疼痛,b.痛半年以上,痛处固定,c.胃灼热感,d.纳呆食少。次症为:a.胃脘据按,b.乏力,c.口干,d.嘈杂,e.舌紫暗或有瘀斑,f.脉沉细弱或涩。

1.3.3 湿热蕴胃并/兼脾胃虚寒证 主症为:a.胃脘痞胀,b.胃脘灼热,c.喜温按,d.泛吐清水。次症为:a.嘈杂,b.困倦乏力,c.小便黄,d.舌质淡,e.苔黄腻,f.脉沉迟或濡滑。

1.3.4 湿热蕴胃并/兼胃阴不足证 主症为:a.胃脘痞胀,b.胃脘灼热,c.口苦或臭,d.胃脘隐痛。次症为:a.嘈杂,b.似饥不欲食,c.便干,d.舌红少津,e.苔黄腻,f.脉沉细或滑。

1.3.5 痰湿中阻并/兼脾胃气虚证 主症为:a.恶心呕吐,b.纳呆食少,c.胃脘痞胀,d.困倦乏力。次症为:a.脘腹胀满,b.口淡不渴,c.大便溏薄,d.舌质淡,e.苔白腻,f.脉沉细弱。

1.3.6 肝胃气滞并/兼脾胃虚寒证 主症为:a.胃脘痞胀痛,b.嘈杂嗳气,c.喜温按,d.泛吐清水。次症为:a.痛窜两胁,b.困倦乏力,c.口淡不渴,d.舌质淡,e.脉弦或沉弱。

1.4 观察指标

对两组研究对象的血清PG、G-17、CEA和叶酸进行测定。研究对象应于血样采集前2w停止服用抑酸药,采集前空腹10h,于清晨采集5mL静脉血,置于促凝采血管中,于半小时内进行离心(3000 r/min, 10 min),取上清液于-80℃储存备用。

采用酶联免疫吸附法测定血清PG I、PG II和G-17,计算PG I/PG II比值,采用电化学发光免疫分析法测定血清CEA和叶酸水平。

1.5 数据处理

以SPSS 19.0对数据进行分析,计量资料以 $\bar{x} \pm s$ 表示,使用t检验,计数资料采用率(%)表示,计量资料使用 χ^2 检验, $P<0.05$ 为具有统计学意义。

2 结果

2.1 PLGC 中医证型分布

对研究组患者进行中医证型分类,结果见表 1 所示,PLGC 患者中医证型分布不均匀,差异显著($P<0.05$),由多到少依次

为湿热蕴胃并 / 兼脾胃虚寒证 > 胃络瘀阻并 / 兼气阴两虚证 > 痰湿中阻并 / 兼脾胃气虚证 > 肝胃气滞并 / 兼气阴两虚证 > 肝胃气滞并 / 兼脾胃虚寒证 > 湿热蕴胃并 / 兼胃阴不足证。

表 1 PLGC 中医证型分布
Table 1 PLGC TCM syndrome distribution

TCM syndrome type	Number of cases (cases)	Percentage
Dampness and heat to accumulate stomach and/or deficiency of spleen and stomach	28	35.00
Syndrome of Qi and Yin Deficiency	20	25.00
Sputum dampness obstruction and/or deficiency of spleen and stomach qi	12	15.00
Qi stagnation of liver and stomach and/or deficiency of qi and yin	9	11.25
Qi stagnation of liver and stomach and/or deficiency of spleen and stomach	6	7.50
Deficiency of dampness and heat in stomach and/or stomach yin	5	6.25
Total	80	100.00

2.2 不同中医证型与 PG 的关系

对各组成员的血清 PG I 和 PG II 进行检测,结果见表 2 所示。PLGC 不同中医证型患者血清 PG I 和 PG II 水平差异显著($P<0.05$);与对照组比较,各证型 PG I 水平均显著降低,PG II

水平均显著升高($P<0.05$)。且湿热蕴胃并 / 兼脾胃虚寒证和胃络瘀阻并 / 兼气阴两虚证的 PG I 水平显著低于其他证候,血清 PG II 水平显著高于其他($P<0.05$)。

表 2 不同中医证型与 PG 的关系
Table 2 Relationship between different TCM syndromes and PG

TCM syndrome type	PG I($\mu\text{g/L}$)	PG II($\mu\text{g/L}$)
Control group(n=80)	117.32 $\pm$ 27.92	6.57 $\pm$ 1.76
Dampness and heat to accumulate stomach and/or deficiency of spleen and stomach(n=28)	55.67 $\pm$ 9.12*	13.13 $\pm$ 1.81*
Syndrome of Qi and Yin Deficiency(n=20)	58.53 $\pm$ 6.25**	10.27 $\pm$ 1.63**
Sputum dampness obstruction and/or deficiency of spleen and stomach qi(n=12)	62.52 $\pm$ 12.76**	9.21 $\pm$ 2.42**
Qi stagnation of liver and stomach and/or deficiency of qi and yin(n=9)	68.56 $\pm$ 6.53**	8.68 $\pm$ 2.31**
Qi stagnation of liver and stomach and/or deficiency of spleen and stomach(n=6)	88.87 $\pm$ 14.11**	8.66 $\pm$ 1.53**
Deficiency of dampness and heat in stomach and/or stomach yin(n=5)	90.12 $\pm$ 10.34**	7.01 $\pm$ 1.42**

Note: * $P<0.05$ compared with the control group, ** $P<0.05$ compared with the dampness and heat to accumulate stomach and/or deficiency of spleen and stomach.

2.3 不同中医证型与 G-17、CEA 和叶酸的关系

对各组成员的血清 G-17、CEA 和叶酸水平进行测定,结果见表 3 所示。与对照组比较,研究组不同证候的 G-17、CEA 水平显著升高,叶酸水平显著降低($P<0.05$);观察组中湿热蕴胃并 / 兼脾胃虚寒证和胃络瘀阻并 / 兼气阴两虚证 G-17、CEA 显著高于其他证候,叶酸水平显著低于其他证候($P<0.05$)。

中医学认为 PLGC 病位主要在胃,与脾、肝密切相关,主要与饮食失常、外感邪气、情志因素、素体虚弱以及药物损伤等有关。脾胃位于中焦,互为表里,共同受纳、运化水谷,是机体内气机升降的枢纽。肝主疏泄,可调畅周身气机,使脾胃升降有序^[19]。如若中焦气机失调,则损伤脾胃,使体内运化失司,引起气血生化不足,脾胃虚弱,迁延不愈,久病致瘀,导致瘀血阻络,产生气滞、血瘀、痰浊、湿热等,进而导致胃失温养,使胃粘膜腺体萎缩、肠化及上皮内瘤变^[20]。现代医学认为,胃黏膜循环障碍、供

3 讨论

表 3 不同中医证型与 G-17、CEA 和叶酸的关系

Table 3 Relationship between different TCM syndromes and G-17, CEA and folic acid

	TCM syndrome type	G-17(pmol/L)	CEA(ng/L)	Folic acid(ng/L)
	Control group(n=80)	5.98± 1.36	1.13± 0.67	28.16± 9.14
Research group(n=80)	Dampness and heat to accumulate stomach and/or deficiency of spleen and stomach(n=28)	12.13± 2.87*	2.44± 1.01*	9.33± 2.34*
	Syndrome of Qi and Yin Deficiency(n=20)	7.87± 1.35* [#]	2.43± 0.46*	10.31± 2.21* [#]
	Sputum dampness obstruction and/or deficiency of spleen and stomach qi(n=12)	7.22± 1.51* [#]	2.36± 0.76* [#]	14.38± 2.26* [#]
	Qi stagnation of liver and stomach and/or deficiency of qi and yin(n=9)	6.83± 1.25* [#]	2.08± 0.58* [#]	14.82± 1.98* [#]
	Qi stagnation of liver and stomach and/or deficiency of spleen and stomach(n=6)	6.45± 1.17* [#]	1.97± 0.38* [#]	15.87± 6.13* [#]
	Deficiency of dampness and heat in stomach and/or stomach yin(n=5)	6.12± 1.87* [#]	1.89± 0.34* [#]	16.89± 5.67* [#]

血减少、氧气供应不足、防御功能下降,难以抵御攻击因子的侵入,炎症的反复发作会导致胃黏膜腺体萎缩、肠化、异型增生甚至癌变^[21-23]。萎缩性胃炎的病变之本,体虚、湿热、气滞、血瘀等为主要表现,因此对研究组患者进行中医证型分类,辨证为 5 种,PLGC 患者中医证型分布不均匀,差异显著,由多到少依次为湿热蕴胃并 / 兼脾胃虚寒证 > 胃络瘀阻并 / 兼气阴两虚证 > 痰湿中阻并 / 兼脾胃气虚证 > 肝胃气滞并 / 兼气阴两虚证 > 肝胃气滞并 / 兼脾胃虚寒证 > 湿热蕴胃并 / 兼胃阴不足证。本研究对各组成员的血清 PG I 和 PG II 进行检测,与对照组比较,各证型 PG I 水平均显著降低,PG II 水平均显著升高,且湿热蕴胃并 / 兼脾胃虚寒证和胃络瘀阻并 / 兼气阴两虚证的 PG I 水平显著低于其他证候,血清 PG II 水平显著高于其他。有学者研究胃癌前病变中医证型分布,探讨胃癌前病变中医证型与血清 PG、胃泌素 G-17、叶酸及 CEA 的相关性,结果显示胃癌前病变组血清 PG I、PGR(PG I/PG II)低于对照组,血清 PG II、水平高于对照组,血清 PG I 水平降低见于脾胃虚弱证、胃络瘀阻证、胃阴不足证;PG II 水平升高见于脾胃湿热证、脾胃虚弱证。但是该学者显示证型分布从高到低依次为:脾胃湿热证脾胃虚弱证肝胃不和证胃络瘀阻证胃阴不足证与本研究不同^[24],主要可能与样本量的特异性有关。重度萎缩性胃炎和血清 PG I 的水平显著低于正常人,而 PG II 的水平则显著升高,且随癌变程度的增加逐渐升高^[25,26]。胃泌素 G-17 与肿瘤的分化程度有关,随着肿瘤分化程度的增加,G-17 水平逐渐升高,患者预后越差,PG 和 G-17 可以反应胃粘膜情况,是动态监测胃癌前病变的重要诊断^[27,28]。CEA 为一种肿瘤相关抗原,正常情况下在体内含量极低,当机体细胞发生癌变时,CEA 水平明显增多,其水平的高低与肿瘤进展程度正相关^[29]。有研究显示单独的 CEA 检测对 PLGC 的灵敏度及特异性较低,且在胃癌前病变期 CEA 水平升高有限,易产生漏诊,需联合其它指标检测^[30]。体内的叶酸对机体有良好的保护作用,可以降低 DNA 异常甲基化的发生,叶酸可以参与胞内核酸的形成,当患有肿瘤时,肿瘤细胞的快速分裂和增值,使体内的叶酸水平下降,同时由于癌前病变患者消化系统功能减退,使叶酸的摄入量相对减少,进一步促进了叶酸水平下降^[31]。有研究表明,胃癌和癌前病变

患者体内血清水平显著低于正常人,而胃癌患者的叶酸水平更低^[32]。本研究对各组成员的血清 G-17、CEA 和叶酸水平进行测定,显示与对照组比较,研究组不同证候的 G-17、CEA 水平显著升高,叶酸水平显著降低,且观察组中湿热蕴胃并 / 兼脾胃虚寒证和胃络瘀阻并 / 兼气阴两虚证 G-17、CEA 水平显著高于其他证候,叶酸水平显著低于其他证候。有研究探究了胃癌前病变中医证型与血清 PG、胃泌素 G-17、叶酸及 CEA 的相关性,发现胃癌前病变组血叶酸水平低于对照组,胃泌素 G-17、CEA 水平高于对照组,同时该学者发现胃泌素 G-17 水平升高见于脾胃湿热证;叶酸水平降低见于脾胃虚弱证、胃阴不足证;CEA 水平升高见于胃络瘀阻证^[33]。分析其原因为观察组血清肿瘤标志物水平的高值峰出现在肝胃气滞并 / 兼脾胃虚寒证、胃络瘀阻并 / 兼气阴两虚证上。而在 6 种虚实关联证候 2 年演化中,5 个时段观察窗上 CEA 水平高值峰出现在湿热蕴胃并 / 兼脾胃虚寒证、胃络瘀阻并 / 兼气阴两虚证上,综合分析可以认为,癌变趋向程度最高的证候类型是:湿热蕴胃并 / 兼脾胃虚寒证,胃络瘀阻并 / 兼气阴两虚 2 种证型。而虚证中脾胃虚寒是最具癌变的危险虚证类型,它所兼的实证则具有不确定性,从证候层面揭示了最具癌变趋向的高危证型。

综上所述,胃癌前病变不同中医证型血清 PG、G-17、CEA 和叶酸存在明显差异,不同证型与各指标存在相关性。

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