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Expression and clinically significance of gastrin in the process os gastric mucosa carcinogenesis

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Abstract

Objective: To investigate serum gastrin expression and clinical significance in carcinogenesis of gastric mucosa. Methods: H. pylor was measured by the rapid urease enzyme test, Warthin-Starry silver stain and/or 14C-urea breath test. Serum gastrin in 412 cases of patients with carcinogenesis of gastrine mucosa was measured using radioimmunoassay analysis; Results: H. pylori-positive group, serum gastrin was higher than H. pylori-negative group (P<0.05); Serum gastrin in the process of gastric mucosa carcinogenesis was higher than that in gastric cancer groups (P<0.05). Conclusion: Serum gastrin is a better marker to identify the stomach of benign and malignant disease; therefore, detecting GAS serum levels of patients with intraepithelial neoplasia will be very valuable to diagnosis, for example, when GAS significantly declines, it is necessary to consider the possibility of disease progression.

[Key words] gastrin, H. pylor, atypical hyperplasic, gastric cancer

I. Introduction

Gastrin (GAS) has such physiological effects as promoting gastric acid secretion, speeding the growth of gastrointestinal mucosa and involving mucosal inflammation. This study was designed to explore the change characteristics of GAS level in upper gastrointestinal diseases, providing the basis for clinical diagnosis and treatment. In this paper, clinical data of 412 outpatient and inpatient cases from 2007 to 2011 in our hospital were retrospectively analyzed to investigate the variation rule and clinical significance of serum GAS levels in the process of gastric mucosa carcinogenesis, also to research the significance of monitoring serum GAS levels.

II. Subjects and Methods

2.1 Subjects: There were 412 cases (male: 192, female: 220) of outpatients and inpatients in Gastroenterology Department of our hospital from August 2007 to August 2011. Wherein there were 11 cases of normal gastric mucosa, 178 cases of superficial gastritis, 89 cases of atrophic gastritis, 55 cases of gastric ulcer, 51 cases of duodenal ulcer, 9 cases of intraepithelial neoplasia, and 19 cases of gastric cancer, all of which were confirmed by gastroscopy and pathological examination.

(1) Gastroscopy and biopsy: before the tests, the subjects fasted overnight for 12h. On the next morning, collect mucosa at gastric antrum (3-5 cm from the pylorus) with forceps, collect specimens at the place with certain or possible focuses separately, the specimens should be large enough to reach the mucosal muscle, and then conduct routine pathological examination, immunohistochemistry, gastric mucosal biopsy (Warthin-Starry stain) or a rapid urease test on the specimens collected from the gastric body and antrum.

(2) Pathological examination: in this paper, Consensus on Chronic Gastritis in China (2006) was adopted as the diagnosis criterion for atrophy grade of chronic gastritis. The atrophic gastritis is divided into three grades according to actual loss of glands (1/3): mild, moderate and severe. The intestinal metaplasia confined in the gastric pits is not regarded as atrophy, mucosa with lymphoid follicles is not atrophy either, which should be decided by the condition of the glands around. Tissue slices were interpreted by specially-assigned person with blind method.

(3) Hp infection determination: three methods were used to detect Hp: gastric mucosal biopsy (Warthin-Starry stain), rapid urease test and 14C urea breath test, wherein if two were positive, Hp infection was determined.

2.2 Radioimmunoassay of serum GAS levels: According to reference [1], 2mL of venous blood were collected respectively from subjects who were on an empty stomach in the morning. Centrifuge the blood sample (1000 r/min), after 15 min, transfer the supernatant and store it at -20 ℃ for later use. The testing should strictly accord with the steps of RIA Kit Manual. The kit was provided by Beijing Furui Biotech Co., Ltd. and the measuring device was II B6020 multiwell γ-counter.

2.3 Statistical analysis: all data were analyzed with SPSS 11.5 statistical software. The measurement data were expressed as X±s, t test was used to conduct the significance analysis between groups, P <0.05 was considered as statistically significant.

III. Results

3.1 The average age and sex ratio of patients in each group were not significantly different *(P*>0.05*)*, as shown in Table 1. Comparison of serum GAS level between groups with different atrophy grades: compared with the control group, subjects' serum GAS levels in each group were statistically significant *(P* <0.05). In addition, HP-positive subjects' serum GAS level was higher than the HP-negative subjects', there was a statistical difference *(P* <0.05); GAS of intraepithelial neoplasia group was significantly higher than that of gastric cancer group, the difference was statistically significant *(P* <0.05); in addition, GAS of atrophic gastritis groups with varying grades of atrophy also had a statistical difference *(P* <0.05), as shown in Table 2

3.2 Relevance between serum GAS and gastric mucosa carcinogenesis: in the HP-positive group and HP-negative group, the sequence of average serum GAS levels during the process of carcinogenesis was: intraepithelial neoplasia group> superficial gastritis group> duodenal ulcer group > gastric ulcer group> atrophic gastritis group> gastric cancer group, as shown in Table 3.

Tables

Table 1. Serum GAS levels in the process of gastric mucosa carcinogenesis.

Group	N (Male/Female)	Age	HP positive	N (Male/Female)	Age	HP negative
normal mucosa				11 (5/6)	29±5	36.98±13.29
surperficial gastritis	46 (22/24)	30±8	51.63±15.46*^	132 (63/69)	31±7	42.71±24.87*
atrophic gastritis	49 (21/28)	34±12	40.06±23.22*^	42 (20/22)	36±10	37.47±18.96
gastric ulcer	38 (18/20)	37±16	43.89±16.07*^	17 (7/10)	33±13	40.73±20.25*
duodenal ulcer	37 (19/18)	33±11	45.28±19.45*^	14 (7/7)	27±9	41.32±17.13*
intraepithelial neoplasia	5 (2/3)	35±3	69.43±31.25*^	4 (2/2)	39±5	48.97±16.34*
gastric cancer	13 (6/7)	57±13	39.63±15.32*^	6 (3/3)	60±11	38.45±12.64*

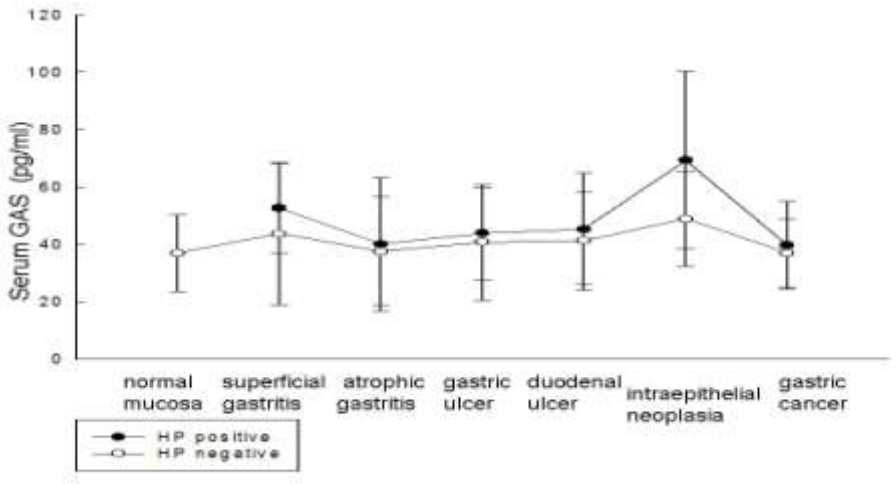
*P<0.05 vs normal mucosa, ^P<0.05 vs HP negative group.

Table 2. Serum GAS levels in varying degrees of atrophic gastritis.

Group	N	GAS levels (pg/ml)
mild atrophy group	31	40.85±15.63
moderate atrophy group	34	8.07±16.09*
severe atrophy group	24	35.34±13.28*

*P<0.05 vs mild atrophy group.

Table 3. Relevance between serum GAS and gastric mucosa carcinogenesis.



IV. Discussion

Gastrin (GAS) is an important gastrointestinal hormone. In 1905, it was first found in gastric antrum mucosa extracts by Jolm and Edkins, who considered it was related to the stimulation of gastric acid secretion. In 1964, Gognry and Tracy purified the substance and described its chemical structure, they confirmed it as a kind of gastrointestinal hormone[2]. Gastrin gene, located on Chromosome 17 at Area g, is 4.1kb and secreted by G cells through endocrine, paracrine and solinocrine. It has G-17 and G-34 two molecular forms, wherein G-17 accounts for 80% -90%, which is the main form of GAS at gastric antrum [3]. The main physiological functions of GAS include promoting the secretion of gastric parietal cells (bind with GAS receptor of enterochromaffin-like cell to promote its release of histamine, which stimulates gastric acid secretion of parietal cells; GAS can also bind with GAS receptors of parietal cells directly, thereby causing the gastric acid secretion), increasing gastric mucosal blood flow, promoting mucosal epithelial cell growth, accelerating repair of damaged mucosal tissue as well as involving mucosal inflammation by promoting the expression and release of cytokines and inflammatory mediators[4].

GAS is primarily secreted by G cells, which exist mostly at gastric antrum, followed by the fundus, duodenum and jejunum. The data of this paper showed that: serum GAS level of subjects in superficial gastritis group was higher than that in control group, which was due to the patients with chronic gastritis, especially severe inflammation in gastric antrum were often accompanied by gastric disorder, which resulted in food retention and caused the gastric antrum expansion, producing a mechanical stimulation to promote the release of GAS, so GAS secretion increased in a feedback way[5]. Theoretically, increase in GAS secretion and release can enhance gastric contraction, and reduce the retention of food in the gastric antrum to relieve indigestion symptoms. However, the clinical observation showed that many patients with chronic gastritis also suffered bile reflux, which caused G cells proliferation as the gastric antrum contacted with alkaline environment, secreting more GAS, leading to superficial gastritis[6]. When gastric mucosa had moderate or severe atrophy, due to inflammatory disease involved the middle or bottom 1/3 of glands, it would inevitably damage the G cells in addition to epithelial damage, leading to significant decline in the number of G cells; at this time, enhanced G-cell secretion could not compensate the reduction in their number, even if the Hp infection rate increased, it could not effectively stimulate G cells to release GAS[7]. Therefore, there was a significant reduction in serum GAS secretion, and then gastric acid secretion also reduced; the low-acid state would promote the Hp colonization in mucosa, which damaged gastric acid secretion and exacerbated gastric atrophy, a vicious cycle was formed[8], the research data of this study also confirmed the above results (Table 1).

Some studies have shown that GAS could affect the secretion of gastrointestinal hormones, affecting the balance between histamine and growth hormone. Therefore, the clinician has always believed that serum GAS level is the serological marker of gastrointestinal inflammation and ulcers[9]. GAS secretion is regulated by the vagus nerve, which can be stimulated by stress, anxiety, and fear to enhance gastric secretion and movement, leading to excessive secretion of GAS. It plays an important role in the incidence of duodenal ulcer. When feedback inhibition of parietal cells against G cells is weakened, secretion of G cells will increase, resulting in hypergastrinemia, which aggravates as mucus-mucosal barrier reduces[10]. The above mentioned outcome can be proved by the research data of this paper: the serum GAS level of gastric ulcer group was increased compared with the control group, and

there were a significant difference, showing that hypergastrinemia is closely related to the occurrence of gastric ulcers.

The research data also showed that serum GAS level of HP-positive group was significantly higher than that of HP-negative group. This result is consistent with other studies[11]; the increase in GAS serum level of HP infected group may be one of its carcinogenic mechanisms[12]. Currently, the possible mechanisms by which HP infection causes elevated level of serum GAS include: ① HP has urea enzymes which can be hydrolyzed to produce ammonia, neutralizing H+ of local mucous layer to change PH environment of antral mucosa, weakening the normal degenerative feedback mechanism of GAS release; ② locally produced ammonia diffuses through the lipid membrane, causing cell damage, leading to damaged gastric antrum mucus-mucosal barrier, anti-diffusion of H + increases, local pH increases, resulting in GAS secretion increases[13]; ③ vacuolating toxin produced by HP can cause direct damage to parietal cell, leading to reduced gastric acid secretion, which stimulates the G cells to increase secretion of GAS; ④ HP infection can stimulate gastric epithelial cells to produce a series of cytokines such as IL-1, IL-2 , IL-6, IL-8, which can stimulate gastric secretion of GAS in vitro[14], but the exact mechanism needs further study.

Gastrointestinal hormones play an important role in the incidence of gastrointestinal cancer. In recent years, the role of GAS during growth and development of gastric cancer has attached more and more attentions. Literature has reported that patients with intraepithelial neoplasia/gastric cancer had elevated serum GAS levels [15]. Serum GAS can nourish both normal gastric epithelial cells and gastric cancer cells, it can also regulate gastric cancer cells and other tumor cells. In this paper, patients with intraepithelial neoplasia/gastric cancer also suffered hypergastrinemia. Gastric mucosa carcinogenesis is a long pathological process with multiple steps and multiple stages[16]. Currently, many scholars have agreed that the development model of gastric cancer is: "normal gastric mucosa - superficial gastritis - atrophic gastritis - intraepithelial neoplasia - gastric cancer"[17]. It is worth noting that this study found diseases at different stages before gastric cancer had significantly increased serum GAS levels, especially in the intraepithelial neoplasia group; but the level was significantly reduced after gastric cancer was formed. Therefore, hypergastrinemia may be one of the symptoms of precancerous lesion. As the serum GAS levels varied largely in benign and malignant gastric diseases, it can be regarded as a good biological marker to identify benign and malignant diseases. However, the specific mechanism remains to be specified.

We found that positive rate of serum GAS was significantly high in the intraepithelial neoplasia group, it was relatively low in other steps of gastric mucosa carcinogenesis; therefore, detecting GAS serum levels of patients with intraepithelial neoplasia will be very valuable to diagnosis, for example, when GAS significantly declines, it is necessary to consider the possibility of disease progression. However, the quantity of samples in this study was limited, which was insufficient to make a more detailed grouping for the specificity of intraepithelial neoplasia and progression of gastric cancer, it is necessary to further expand the samples for analysis.

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