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Serological Criteria for Mild, Moderate and Severe Atrophy in Atrophic Gastritis

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Abstract

The study was carried out in a group of 360 dyspeptic Helicobacter pylori-infected patients. These patients were tested for markers of atrophy of the mucous membrane of the antrum section (gastrin-17) and corpus of stomach (pepsinogen-1). The markers were detected via the test panel for immune-enzyme analysis - "GastroPanel". All the 360 patients underwent the upper gastrointestinal endoscopy with subsequent biopsy of the antral and corpus mucosa. These markers were identified for a group of patients with severe atrophic gastritis and for a group of patients with mild and moderate atrophy. The level of the gastrin-17 was determined for the number of patients with mild, moderate and severe antral atrophic gastritis, which was identified with the use of upper gastrointestinal endoscopy followed by a biopsy of the antral mucosa. The level of the gastrin-17 in the serum was: mild antral atrophy - 7 ≤ pmol/L 0 10, moderate antral atrophy – 4 ≤ pmol/L <7, severe antral atrophy - 0 ≤ pmol/L < 4, no atrophy - 10 ≤ pmol/L. The level of the pepsinogen-1 was determined for the number of patients with mild, moderate and severe corpus atrophic gastritis, which was identified with the use of upper gastrointestinal endoscopy followed by a biopsy of the corpus mucosa. The bounds of the pepsinogen-1 level in the serum were: mild corpus atrophy - 15 ≤ µg/L <25, moderate corpus atrophy – 9 ≤ µg/L <15, severe corpus atrophy - 0 ≤ µg/L <9, no corpus atrophy - 25 ≤ µg/L. Rising of the effectiveness of serological screening considering the lines of serological markers severe atrophy and detected patients with high risk gastric cancer allows to avoid the upper gastrointestinal endoscopy.

Keywords: Screening; Atrophic gastritis; Risk gastric cancer; Gastrin-17; Pepsinogen-1

Introduction

Secretion of peptide hormones and pepsinogen into the circulation and muriatic acid into gastric lumen decreases at *H. pylori* – associated atrophic gastritis. The range of these pathophysiological changes depends on affected stomach zone. Atrophy antral mucosa is followed by decrease of gastrin-17 serum rates, especially after nutritive stimulation; gastric corpus atrophy is followed by decrease of pepsinogen-I level. So the comprehensive idea of patient`s gastritis nature can be received by definition of gastrin-17 serum rates, pepsinogen-I in a complex with anti- *H. pylori* IgG level. Results of using testing panel BIOHIT Gastro Panel research groups [1-4] show that contemporary definition of antibodies to *H. pylori*, gastrin-17 rates and pepsinogen-1 in serum can be used as biomarkers for gastritis and its localization. According to the quoted research`s data, it was pointed out that there is a connection between the decrease of gastrin-17 serum rates and pepsinogen-1 and increasing atrophy of mucous membrane, antrum zone и stomach corpus. The results of Sipponen`s research [2-4] coincided with the study, which was conducted previously by same scientists [5-7] and also by scientists from different countries [8-14].

Taking into account the known interrelations between the morphological status and functional activity of gastric corpus and antral mucosa and the secretion of, respectively, pepsinogen-1 and postprandial gastrin-17, we carried out a prospective study with the aim detect the optimal boundaries serological markers mild, moderate and severe atrophy of the gastric mucosa.

Materials and Methods

Ethics

This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This study was approved ethically by the Ethical committee of Medical Institute, North Caucasus State Academy of Humanities and Technology (Protocol No: 1/15. Date - 28.01.2015). All patients provided informed written consent.

Materials

The study was carried out in a group of 360 dyspeptic *Helicobacter pylori*-infected patients with age between 16 and 89 years, 236 female and 124 male, have been examined in the Republic of Karachay-Cherkessia, Russian Federation. Results of serological tests of 2 persons were lost. All the 360 patients underwent the upper gastrointestinal endoscopy. Subsequent biopsy of the antral and corpus mucosa was performed for 187 persons. The endoscopy was performed according to the requirements of the Sydney system: 2 biopsy from antrum, 1 biopsy from angulus ventriculi and 2 biopsy from corpus. Biopsy was interrupted in others 173 cases after getting probes from antrum. Markers of antrum atrophy (gastrin-17) and corpus atrophy (pepsinogen-1) are studied separately. Nobody have eradication of *H. pylori*. Nobody use PPI or H2 blocker.

Methods

Markers of mucosal atrophy of the corpus and antrum of the stomach were determined using a test panel for immunoassay - "GastroPanel". The set "Gastropanel" (produced by the Finnish company "Biohit") included: a marker of mucosal atrophy antrum –

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gastrin-17 (G-17), a marker of mucosal atrophy of the corpus of the stomach - Pepsinogen-1 (PG-1). HPAb IgG titrers were estimated as follows: < 32 enzyme immunoassay unit (EIU) – negative result, 32 – 44 EIU – doubtful result, > 44 EIU – positive result.

The pathology of the gastro duodenal area was detected on the basis of a complex of patients' complaints, specific evidence of anamnesis, results of objective and supplementary laboratory examination. In order to identify the content of pepsinogen-1 (PG-1) fasting blood sampling was carried out. The amount of gastrin-17 (G-17) after eating was identified in blood serum samples, which were taken 20 minutes after ingestion of protein dissolved in a beverage (one portion contains 10 g of protein). The samples were subject to centrifugation at 1500 × g for 10 minutes and were thereupon stored at the temperature -20°C until the conduction of analysis. We use video gastroscope KARL-STORZ with working channel 2, 8 mm and biopsy forceps 2,3 mm.

To increase the accuracy of endoscopic diagnosis, we carried out an additional chromoendoscopy with methylene blue staining allowing the detection of foci of intestinal metaplasia (IM) of gastric mucosa which were unrecognized by routine endoscopy. Biopsy specimens were stained with hematoxylin-eosin and PAS reaction in combination with blue at pH 2,5. The grade of stomach mucosal atrophy was estimated from 0 to 3 according to Houston visual analogous scale. Histological analysis was performed by an independent histologist using a blind method.

Analysis was performed as follows: serological analysis, at first; endoscopy and biopsy, 1 day later; chromo endoscopy 1-2 days later.

Statistical analysis was used to calculate the statistical significance of received data. Pearson's and Spearman′s correlation coefficient (r), sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) of diagnosis by Biohit GastroPanel®.

Results

Now used by us test system Biohit GastroPanel® allows to elicit atrophy of the mucous membrane of stomach, but it doesn`t show the level of elicited changes. Basing upon our own results, we have worked out functional markers of different levels atrophy of the mucous membrane of antrum and corpus sections of stomach. We have determined average values of serological concentrations of the studied metabolites (gastrin-17 and pepsinogen-1) depending on histological expression level of atrophy of the mucous membrane of stomach. Next, picking the lines of received 95% confidence intervals according to the final Sensitivity and specificity result, we traced marker`s lines of a certain level of atrophy of the mucous membrane of the corresponding part of the stomach (Tables 1 and 2). The results of ROC analyses are shown in Figures 1 and 2.

We have conducted a comparative analysis of statistic markers, which describe used methods of research, in order to establish an opportunity to use noninvasive immune ferment analysis method for atrophic and precancerous changes of the mucous membrane of stomach at *H. pylori*-infection diagnostics. The study demonstrates strong reverse correlation between histological markers of antrum atrophy and gastrin-17 (- 0.73), corpus atrophy and pepsinogen-1 (-0.63).

We have conducted a correlative analysis of the connections between gastrin-17 and pepsinogen-1 rates and other studied parameters (Tables 3 and 4).

According to Table 6, there is a strong inverse correlation between gastrin-17 amount in serum and histological level of antral atrophic gastritis expression (r - 0,85 и r_s - 0,7). Positively, it characterizes a functional link between these parameters. There is the moderate inverse correlation between gastrin-17 и pepsinogen-1 products. In other cases we can see presence or absence of mild correlation.

According to Table 7, there is a strong inverse correlation between pepsinogen-1 rate in serum и and histological level of corpus atrophic gastritis (r - 0,7; r_s - 0,7). Certainly, it characterizes a functional link between these parameters. Moderate direct correlation was elicited between pepsinogen-1 and active and chronic inflammation products (r 0,43 и 0,48; r_s 0,48 и 0,58). Similar link can point that it is incorrect to use pepsinogen-1 as a marker corpus atrophic gastritis at active and chronic gastritis, because the screening results will be distorted. So to say, active gastritis is a contraindication to serological screening. In other cases we can see presence or absence of mild correlation.

Further we have conducted a determination of sensitivity and specificity markers, negative and positive predictive value of immunoferment analysis method of "serological biopsy" and diagnostics of atrophic gastritis by determination of gastrin-17 and pepsinogen-1 in serum (Tables 5 and 6).

As shown in Tables 5 and 6, noninvasive detected atrophic gastritis methods, described in this article, have quite high sensitivity at detected non-atrophic and antral severe atrophic gastritis and corpus severe

Grade	Atrophy degree	Average value	95% confidence intervals	δ	Observation amount	Postprandial gastrin-17
1	No atrophy	18,07	3,88 - 32,26	7,09	19	10 ≤ pmol/l
2	Mild	8,78	3,83 - 13,72	2,47	45	7 ≤ pmol/l < 10
3	Moderate	6,03	2,45 - 9,61	1,79	100	4 ≤ pmol/l < 7
4	Severe	1,42	–1,72 - 4,55	1,57	194	0 ≤ pmol/l < 4

Table 1: Border marker of a certain degree of atrophy of the mucous membrane of stomach at antral atrophic gastritis.

Grade	Atrophy degree	Average value	95% confidence intervals	δ	Observation amount	pepsinogen-1
1	No atrophy	110,25	-10,48 - 230,98	60,37	105	25 ≤ µg/l
2	Mild	18,71	10,84 - 26,59	3,94	17	15 ≤ µg/l < 25
3	Moderate	12,67	1,70 - 23,64	5,48	37	9 ≤ µg/l < 15
4	Severe	6,92	2,35 - 11,49	2,28	26	0 ≤ µg/l < 9

Table 2: Border marker of a certain degree of atrophy of the mucous membrane of stomach at corpus atrophic gastritis.

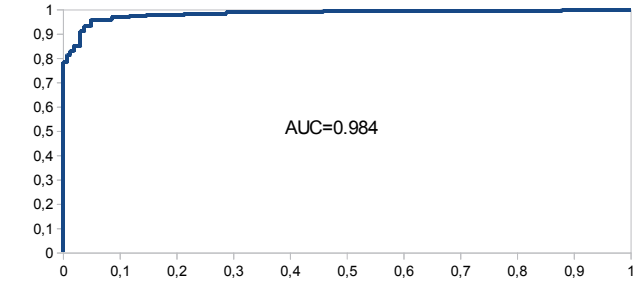

Figure 1: ROC-analyses of serological criteria (gastrin-17) for severe antral atrophy.

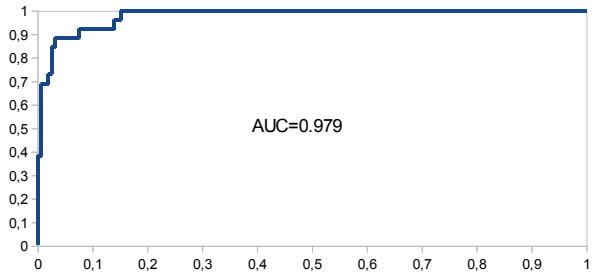

Figure 2: ROC-analyses of serological criteria (pepsinogen-1) for severe corpus atrophy.

Comparative parameters	R	r_s	n	t
gastrin-17 and antral atrophic gastritis	- 0,85	- 0,7	358	17,8
gastrin-17 and patient`s age	0,05	0,06	358	1,11
gastrin-17 end disease durability	0,04	0,04	358	0,77
gastrin-17 and palpation pain	0,06	0,27	358	5,23
gastrin-17 and H. pylori colonization of the gastric mucosa	0,09	0,2	178	2,73
gastrin-17 and activity of gastritis	- 0,27	- 0,26	185	3,63
gastrin-17 and mononuclear infiltration	- 0,2	- 0,13	185	1,81
gastrin-17 and intestinal metaplasia	- 0,1	- 0,06	358	1,21
gastrin-17 and anti-Hp IgG	0,01	0,08	358	1,55
gastrin-17 and dysplasia	- 0,1	- 0,06	358	1,19
gastrin-17 and pepsinogen-1	- 0,29	- 0,44	358	9,37

Table 3: Correlation gastrin -17 (pmol/l) to other parameters (Pearson's correlation coefficient, r, and Spearman correlation coefficient, r_s).

Comparative parameters	r	r_s	n	t
pepsinogen -1 and antral atrophic gastritis	- 0,7	- 0,7	185	13
pepsinogen -1 and patient`s age	- 0,12	- 0,13	358	2,55
pepsinogen -1 end disease durability	- 0,05	- 0,06	358	1,04
pepsinogen -1 and palpation pain	- 0,06	0,05	358	0,91
pepsinogen -1 and H. pylori colonization of the gastric mucosa	- 0,13	- 0,13	178	1,72
pepsinogen -1 and activity of gastritis	0,43	0,48	185	7,42
pepsinogen -1 and mononuclear infiltration	0,48	0,58	185	9,66
pepsinogen -1 and intestinal metaplasia	- 0,09	- 0,02	358	0,3
pepsinogen -1 and anti-Hp IgG	- 0,02	- 0,02	358	0,35
pepsinogen -1 and dysplasia	0,13	0,2	358	3,91

Table 4: Correlation pepsinogen-1(μg/1) to other parameters (Pearson's correlation coefficient, r and Spearman Correlation coefficient, rs).

atrophic gastritis, excepting mild antral atrophic gastritis and mild corpus atrophic gastritis cases. Discussed methods have quite high positive predictive value and negative predictive value.

Discussion

The conducted research has shown that serological markers of functional activity of stomach mucous membrane – pepsinogen-1 and gastrin-17 – can serve as the objects of reliable atrophy screening if *H. pylori* positives have any dispepsic symptoms. Further development of disregeneration and prolipherative processes in stomach mucous membrane in a view of foci intestinal metaplasia, according to our data, isn`t followed by statistical important changes of pepsinogen-1 and gastrin-17 at initial phases and is shifting. Thereby, noninvasive screening can`t be recommended for timely detection of intestinal metaplasia, in this case choosing method is a chromoendoscopy research of stomach mucous membrane, which can quite reliably detect foci intestinal metaplasia and make pinpoint biopsy for further histological research. So having received the results of serological screening, which significate that a patient has *H. pylori* associated atrophic gastritis, it is necessary to carry out chromoendoscopy with biopsy from corpus and antrum of stomach. Biopsy is needed to histological detection of precancerous changes of stomach mucous membrane. It should be considered that to determine the risk of stomach cancer development one has to know the rate of atrophy expression. Previously it was possible to determine only with the help of a histological research [15]. All the patients with severe antral atrophic gastritis and severe corpus atrophic gastritis have high risk of gastric cancer. But previously it was impossible to determine such patients by serological atrophy markers gastrin-17 and pepsinogen-1. Now we suggest to use the bounds of serological markers, which we have worked out, for severe antral atrophic gastritis and severe corpus atrophic gastritis to detect patients with high risk of gastric cancer. These patients should have the upper gastrointestinal endoscopy. It allows to detect early gastric cancer after previous effective serological

Antral atrophic gastritis (histological)	Se	Sp	PPV	NPV
No atrophy	89 %	97 %	61 %	99 %
Mild	64 %	91 %	51 %	95 %
Moderate	59 %	94 %	80 %	86 %
Severe	96 %	92 %	93 %	95 %

Table 5: Sensitivity (Se), Specificity (Sp), Negative Predictive Value (NPV), Positive Predictive Value (PPV) of the method of detected antral atrophic gastritis (Gastrin-17).

Corpus atrophic gastritis (histological)	Se	Sp	PPV	NPV
No atrophy	92 %	96 %	97 %	91 %
Mild	71 %	92 %	48 %	97 %
Moderate	70 %	96 %	81 %	93 %
Severe	88 %	97 %	82 %	98 %

Table 6: Sensitivity (Se), Specificity (Sp), Negative Predictive Value (NPV), Positive Predictive Value (PPV) of the method of detected Corpus atrophic gastritis (Pepsinogen-1).

Comparative parameters	r	r_s	n	t
pepsinogen -1 and antral atrophic gastritis	- 0,7	- 0,7	185	13
pepsinogen -1 and patient`s age	- 0,12	- 0,13	358	2,55
pepsinogen -1 end disease durability	- 0,05	- 0,06	358	1,04
pepsinogen -1 and palpation pain	- 0,06	0,05	358	0,91
pepsinogen -1 and H. pylori colonization of the gastric mucosa	- 0,13	- 0,13	178	1,72
pepsinogen -1 and activity of gastritis	0,43	0,48	185	7,42
pepsinogen -1 and mononuclear infiltration	0,48	0,58	185	9,66
pepsinogen -1 and intestinal metaplasia	- 0,09	- 0,02	358	0,3
pepsinogen -1 and anti-Hp IgG	- 0,02	- 0,02	358	0,35
pepsinogen -1 and dysplasia	0,13	0,2	358	3,91

Table 7: Correlation pepsinogen -1 (μg/l) to other parameters (Pearson's correlation coefficient, r, and Spearman correlation coefficient, r_s).

screening. Raising the effectiveness of serological screening, considering also bounds of serological markers of severe antral atrophic gastritis and severe corpus atrophic gastritis, and detecting patients with high risk of gastric cancer will allow to avoid the upper gastrointestinal endoscopy [16-18].

Author Contributions

S. Kotelevets performed the clinical research on serological screening of atrophic gastritis. S. Chekh performed the statistical analysis of this clinical research. S. Kotelevets and S. Chekh wrote the manuscript.

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