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Analyzing serological screening of the functional state of gastric mucosa in clinical practice

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ABSTRACT

Aim. To analyze the results of the GastroPanel and GastroScreen-3 tests over a 15-year follow-up and determine the incidence of autoimmune gastritis (AIG) in clinical practice and in a random sample of Novosibirsk residents.

Materials and methods. Biomarkers were analyzed in two groups: 1,742 people, average age of 50.0 ± 13.53 years (GastroPanel test, Biohit Oy, Finland), and 170 people, average age of 53.8 ± 12.89 years (GastroScreen-3 test, Vector-Best, Russia), from 2007 to 2022. The AIG incidence was calculated in current clinical practice and in a random sample of Novosibirsk residents aged 45–69 years. The PGI level of 160 μg / l was taken as the upper limit of normal, PGI of 31–50 μg / l indicated moderate atrophy, PGI < 30 μg / l and the PGI / PGII ratio ≤ 3 indicated severe gastric fundus atrophy. AIG was considered at PGI ≤ 10.1 μg / l, the PGI / PGI ratio ≤ 1.3, and gastrin-17 ≥ 42.4 pmol / l (GastroPanel) and at PGI ≤ 16.8 μg / l and the PGI / PGII ratio ≤ 1.5 (GastroScreen-3). The *H. pylori* IgG level > 42 EIU was considered to be positive. Antibodies to CagA protein were determined using the Helico-Best Antibody test (Vector-Best, Novosibirsk).

Results. Serological signs of severe and moderate gastric fundus atrophy were detected in 10 and 9.4% (GastroPanel test) and in 13.3 and 7% (GastroScreen-3 test) of those examined, respectively. Signs of multifocal atrophy were found in 0.7% of cases. Antibodies to *H. pylori* were detected in 57.7%, CagA+ strain – in 56.1% of cases. Peptic ulcer disease (PGI ≥160 μg / l) was found in 15.3% (GastroPanel test) and 10% (GastroScreen-3 test) of the examined. According to the GastroPanel and GastroScreen-3 tests, the incidence of AIG was 1.6% in a random sample and 2.6 and 3.5% in current clinical practice, respectively.

Conclusion. Twenty percent of the examined persons were at risk of developing gastric cancer and 10–15% had peptic ulcer disease, which requires further examination. The incidence of AIG in different study groups based on serological screening was 1.6–3.5%.

Keywords: pepsinogens, GastroPanel, GastroScreen-3, *Helicobacter pylori*, fundus atrophy, autoimmune gastritis

Conflict of interest. The authors declare the absence of obvious or potential conflict of interest related to the publication of this article.

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Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the Bioethics Committee at Research Institute of Internal and Preventive Medicine, Branch of the Institute of Cytology and Genetics, SB RAS (Protocol No. 11 of 02.03.2021).

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Анализ серологической диагностики функционального состояния слизистой желудка в клинической практике

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РЕЗЮМЕ

Цель. Проанализировать результаты тест-систем «ГастроПанель» и «ГастроСкрин-3» за 15 лет наблюдения и определить частоту аутоиммунного гастрита (АИГ) в клинической практике и в случайной выборке жителей г. Новосибирска.

Материалы и методы. Показатели биомаркеров были проанализированы в двух группах: 1 742 человека, средний возраст 50,0 ± 13,53 лет (тест-система «ГастроПанель», компания «Биохит», Финляндия), и 170 человек, средний возраст 53,8 ± 12,89 лет (тест-система «ГастроСкрин-3», АО «Вектор-Бест», Россия), с 2007 по 2022 г. Расчет частоты АИГ проводился в текущей клинической практике и в случайной выборке жителей г. Новосибирска 45–69 лет. Верхней границей нормы считали показатель пепсиноген I (ПГI) – 160 мкг/л, умеренной атрофии соответствовал диапазон ПГI 31–50 мкг/л, а ПГI ≤ 30 мкг/л и соотношения ПГI/ПГII ≤ 3 – выраженной фундальной атрофии. Аутоиммунный гастрит рассматривали при показателях ПГI ≤ 10,1 мкг/л, ПГI/ПГI ≤ 1,3; гастрина-17 ≥ 42,4 пмоль/л («ГастроПанель») и ПГI ≤ 16,8 мкг/л, ПГI/ПГII ≤ 1,5 тест-система («ГастроСкрин-3», АО «Вектор-Бест», Россия). Положительным считали уровень иммуноглобулина класса (Ig) G *H. pylori* более 42 EIU. Антитела к CagA-белку определяли с помощью тест-системы «Хелико-Бест антитела» (АО «Вектор-Бест», г. Новосибирск).

Результаты. Серологические признаки выраженной и умеренной фундальной атрофии выявлены: 10 и 9,4% («ГастроПанель»), 13,3 и 7% («ГастроСкрин-3») соответственно. Признаки мультифокальной атрофии обнаружены в 0,7%. Иммуноглобулины класса G *H. pylori* определялись в 57,7%, CagA+ штамм – в 56,1% случаев. Язвенный фенотип гастрита был обнаружен у 15,3% («ГастроПанель») и у 10% («ГастроСкрин-3»). Частота АИГ по данным тест-систем «ГастроПанель» и «ГастроСкрин-3» в случайной выборке составила 1,6%, в текущей клинической практике – 2,6 и 3,5% соответственно.

Заключение. В группу риска развития рака желудка попали 20% обследованных, у 10–15% обнаружен язвенный фенотип, что требует дообследования. Частота АИГ в исследуемых группах на основании серологического скрининга составила 1,6–3,5%.

Ключевые слова: пепсиногены, «ГастроПанель», «ГастроСкрин-3», *Helicobacter pylori*, фундальная атрофия, аутоиммунный гастрит

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Работа выполнена по государственному заданию в рамках бюджетных тем «Изучение молекулярно-генетических и молекулярно-биологических механизмов развития распространенных терапевтических заболеваний в Сибири для совершенствования подходов к их ранней диагностике и профилактике», 2024–2028 гг. (FWNR-2024-0004); «Совершенствование методов диагностики, профилак-

тики и лечения больных распространенными заболеваниями гепатобилиарной системы и желудочно-кишечного тракта в Сибири», 2023–2025, FWNR-2023-0003.

Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено комитетом биомедицинской этики НИИТПМ – филиала ИЦиГ СО РАН (протокол № 11 от 2.03.2021).

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INTRODUCTION

The function of the stomach and its mucosal structure are closely associated with each other. Normal levels of such biomarkers as pepsinogen I, pepsinogen II and their ratio (PG I, PG II, PG I/PG II), gastrin-17, as well as the absence of IgG antibodies to *H. pylori* and CagA cytotoxic protein are surrogate markers of healthy gastric mucosa, with the exception of nonspecific inflammation or microerosions that do not affect their profile [1, 2]. Test panels include biomarkers that reflect the morphological changes and the function of the gastric mucosa. In non-atrophic gastritis associated with *H. pylori* infection, the levels of pepsinogens, especially those of PG II, increase [1, 2].

Changes in the levels of biomarkers can also show the localization of the process. PG I is an indicator of damage to gastric glands in the stomach body, PG II is synthesized in every part of the stomach, and PG I / PG II ratio is correlated with the progression of fundus atrophy in the mucosa [1, 3]. Gastrin-17 is the principal hormone that regulates the secretion of hydrochloric acid by parietal cells of the stomach. Its basal level is decreased in persons with hyperacidity (hypersecretion). The development of atrophy in the antral part also leads to decreased levels of gastrin-17, including its postprandial fraction [4, 5].

According to the last Maastricht Consensus, atrophy determinates the risk of non-hereditary gastric cancer and can be found with the use of invasive (biopsy) and non-invasive methods [6]. A decrease in PG I and / or PGI / PG II ratio with high levels of gastrin-17 indicates the presence of gastric fundus atrophy and is characteristic of autoimmune gastritis as well as high levels of anti-parietal cell antibodies (APCAs) and / or anti-intrinsic factor antibodies (AIFAs) [2, 4, 7]. Thus, all these parameters provide important information about the functional state of the gastric mucosa [6].

Test kits that include a panel of atrophy biomarkers have proven to be effective in non-invasive diagnosis both in individual patients and in population screening [1, 2, 4, 8]. GastroPanel test (Finland) is one of the most used kits that includes PG I, PG II, PG I / PG II ratio, gastrin-17, and IgG antibodies to *H.pylori*. Its sensitivity is 83%, and its specificity ranges from 95 to 98% [9]. The Russian test system GastroScreen-3 has been introduced into clinical practice recently. It includes PG I, PG II, PG I / PG II ratio, and antibodies to CagA protein.

The aim of the study was to analyze the results of serological screening of the functional state of gastric mucosa using two test systems (GastroPanel and Gastroscreen-3) and to determine the frequency of autoimmune gastritis (AIG) in clinical practice and in a random sample of Novosibirsk residents.

MATERIALS AND METHODS

Biomarker data obtained using the GastroPanel test (Biohit Oy, Finland) were analyzed in 1,742 people with an average age of 50.0 ± 13.53 years during a 15-year follow-up from 2007 to 2022. Women made up a larger proportion of individuals in the group (1,210 people, which is 69.5 %) than men (532 men – 30.5 %, $p < 0.001$). Using the GastroScreen-3 biomarker panel (Vector Best, Russia), the analysis was carried out in 170 people with an average age of 53.8 ± 12.89 years over a 4-year follow-up from 2018 to 2022. The proportion of women in this group was also larger than that of men (79.4 and 20.6%, respectively; $p < 0.001$). All patients went to the clinic at the Research Institute of Internal and Preventive Medicine, Branch of the Institute of Cytology and Genetics, independently or following a doctor referral.

A random sample of Novosibirsk residents was examined using the GastroPanel test to study the incidence of AIG. The group consisted of 246 people (117 men and 129 women) with an average age of 59.4 ± 7.0 years, selected by simple random sampling

from 9,360 people aged 45–69 years based on the data of the cross-sectional study which was part of the HAPIEE project conducted at the Research Institute of Internal and Preventive Medicine in 2003–2005.

Serum samples were tested using the GastroPanel (Biohit Oy, Finland) and GastroScreen-3 (Vector-Best, Russia) tests for enzyme-linked immunosorbent assay, according to the manufacturer's instructions [10]. The PGI value of 160 μg / l was considered the upper limit of normal, and the PGI level ≤ 30 μg / l and / or the PGI / PGII ratio of ≤ 3 indicated severe gastric fundus atrophy. The PGI range of 31–50 μg / l indicated moderate gastric fundus atrophy. Multifocal (pangastritis) atrophic gastritis was determined when the level of PGI decreased to ≤ 30 and gastrin-17 was less than 1 pmol / l [10]. The level of IgG antibodies to *H. pylori* was considered significant in terms of diagnosis when the level was more than 42 EIU. *H. pylori* CagA antibodies were assessed using the Helico-Best Antibody test system (Vector-Best, Russia).

In our previous study, we determined cutoff values for autoimmune atrophic gastritis in patients with verified AIG. For the GastroPanel test, the values were the following: PG I ≤ 10.1 μg / l, the PG I / PG II ratio ≤ 1.3, and gastrin-17 ≥ 42.4 pmol / l. For the GastroScreen-3 test, the values were as follows: PG I ≤ 16.8 μg / l and the PG I / PG II ratio ≤ 1.5 [11].

Statistical analysis of the obtained results was performed using the SPSS statistics (16.0 version). The distribution of quantitative variables was assessed using the Kolmogorov – Smirnov test. We calculated mean values ($M \pm \sigma$) for a normal distribution and the median (*Me*) and the interquartile range [Q_{25}; Q_{75}] for a non-normal distribution. The Student's *t*-test and the Mann – Whitney *U* test were used to determine the statistical significance of the differences. The Pearson's chi-squared test was used to compare proportions. The critical value of the null hypothesis was considered at $p \leq 0.05$.

The study was conducted in accordance with the Declaration of Helsinki and approved by Biomedical Ethics Committee at the Research Institute of Internal and Preventive Medicine – a Branch of the Institute of Cytology and Genetics (Protocol No. 11 of 02.03.2021). All patients signed an informed consent to participate in the study.

RESULTS AND DISCUSSION

The mean and median values of biomarkers measured in all participants using two test systems during the follow-up are shown in Tables 1 and 2. In men, the levels of PGI and the PGI / PGII ratio (GastroPanel) were higher, and the level of gastrin-17 was lower than in women (Table 1).

Table 1

Parameters of the GastroPanel test over a 15-year follow-up in men and women, *Me* [$Q_{25\%}$; $Q_{75\%}$]

Parameter	Men, *n* = 532	Women, *n* = 1,210	Total, *n* = 1,742	p_{m-f}
PG I, μg / l	97.4 [65.2; 139.7]	83.9 [54.4; 125.0]	87.7 [57.9; 128.7]	<0.0001
PG II, μg / l	10.6 [6.5; 19.7]	10.1 [6.1; 19.0]	10.2 [6.2; 19.4]	0.168
PG I / PG II	8.5 [5.6; 11.8]	7.9 [4.9; 11.7]	8.2 [5.1; 11.7]	0.036
Gastrin-17, pmol / l	4.3 [1.4; 11.6]	4.9 [1.9; 15.2]	4.7 [1.7; 14.0]	<0.0001
IgG to *H. pylori*, EIU	62.0 [17.7; 105.1]	56.3 [16.9; 108.2]	57.8 [17.3; 107.4]	0.996

Table 2

Parameters of the GastroScreen-3 test over a 4-year follow-up in men and women, *Me* [$Q_{25\%}$; $Q_{75\%}$]

Parameter	Men, *n* = 35	Women, *n* = 135	Total, *n* = 170	p_{m-f}
PG I, μg / l	98.6 [53.5; 139.5]	89.8 [59.4; 122.7]	91.5 [58.8; 129.9]	0.458
PG II, μg / l	10.6 [6.5; 19.7]	10.1 [6.1; 18.9]	9.1 [5.7; 16.7]	0.906
PG I / PG II	8.6 [6.3; 12.0]	8.7 [5.6; 13.2]	8.6 [5.7; 13.0]	0.882

H. pylori infection is recognized as the main cause of atrophic gastritis and a class one carcinogen [4, 12]. In this study, IgG to *H. pylori* was detected in 57.7 % of the participants (out of 1,742 people) with high prevalence of cytotoxic CagA+ strain (56.1%). In the GastroScreen-3 group, a more carcinogenic CagA+ strain of *H. pylori* [6, 13] was found in 42% of the participants (out of 170 people). It is possible that the percentage of those infected was higher because IgG to *H. pylori* can be negative due to elimination of bacteria in individuals with severe atrophy or after successful treatment. The literature describes cases of spontaneous disappearance of *H. pylori* in patients with severe atrophic gastritis, while the

probability of developing gastric cancer may increase [14, 15].

Serological signs of severe and moderate gastric mucosal atrophy were detected in 10 and 9.4% of 1,742 people examined using the GastroPanel test, respectively. Severe and moderate atrophy was detected in 10.6 and 7.1% of individuals in the GastroScreen-3 group (170 persons), respectively (Table 2). In total, over the follow-ups, serological signs of gastric fundus atrophy of varying severity were identified in 19.4% (GastroPanel) and 17.6% of cases (GastroScreen-3). According to several studies, the PGI / PGII ratio may be a more reliable marker of gastric fundus atrophy than PGI alone [7, 16]. The PGI / PG II ratio was found to be low in 11% of individuals in the GastroPanel group, and a combination of low PGI levels and low PG I / PG II ratio was detected in 7.3% of cases. The PG I / PG II ratio ≤ 3 was found in 8.2 % of the participants in the GastroScreen-3 group, while the combination of PG I ≤ 30 μg / l and the PG I / PG II ratio ≤ 3 was detected in 7.1% of patients in this group. Serological signs of multifocal atrophic gastritis with a high risk of developing gastric cancer were detected in 13 of 1,742 individuals (0.7%) (Table 2).

The detection of low biomarker values corresponding to the serological criteria of atrophy requires further endoscopic examination with multifocal biopsy and gastric atrophy grading according to the OLGA integrated system [17]. Thus, according to the latest consensus, both international and Russian, serological tests are useful for assessing individual risk of gastric cancer [6, 18, 19].

Peptic ulcer disease, elevated levels of hydrochloric acid, and PGI higher than 160 μg / l were found in 15.3 % of cases in the GastroPanel group and in 10% of cases in the GastroScreen-3 group (Table 3).

Table 3

Frequency of GastroPanel and GastroScreen-3 parameters with interpretation of possible risks, %, *Me* [$Q_{25\%}$; $Q_{75\%}$]

Parameter	GastroPanel, *n* = 1,742	GastroScreen-3, *n* = 170	Interpretation
PG I (51–160 μg / l)	64.5 [62.3; 66.7]	71.8 [65; 78.5]	No signs of atrophy
PG I (≤ 30 μg / l)	10 [8.6; 11.4]	10.6 [6.0; 15.2]	Severe gastric fundus atrophy. Risk of gastric cancer
PG I / PG II ≤ 3	11 [9.5; 12.5]	8.2 [4.1; 12.3]	
PG I ≤ 30 μg / l + PG I / PG II ≤ 3	7.3 [6.1; 8.5]	7.1 [3.2; 11.0]	
PG I (31–50 μg / l)	9.4 [8.0; 10.8]	7.1 [3.2; 11.0]	Signs of moderate gastric fundus atrophy. Risk of gastric cancer
PG I ≤ 10.1 μg / l + Gastrin-17 ≥ 42.4 pmol / l	2.6 [1.9; 3.3]	–	Autoimmune gastritis. High risk of iron deficiency, vitamin B12 deficiency, anemia, and gastric cancer
PG I ≤ 16.8 μg / l + PG I / PG II < 1.5	–	3.5 [0.7; 6.3]	
PG I (≥ 160 μg / l)	15.3 [13.6; 17.0]	10 [5.5; 14.5]	Hypersecretory state. High risk of erosive and ulcerative damage to gastric mucosa
PG I ≤ 30 μg / l + Gastrin-17 <1 pmol / l	0.7 [0.3; 1.1]	–	Pangastritis. Multifocal atrophy (body + antrum). High risk of developing gastric cancer

Thus, over 15-year (GastroPanel) and 4-year (GastroScreen-3) follow-up, 20% of the participants were included in the gastric cancer risk group, and 10–15% of the participants were included in the risk group for erosive and ulcerative damage to the gastric mucosa which requires a further detailed examination.

According to the literature, the levels of pepsinogens, especially those of PGII, increase in *H. pylori*-associated gastritis [3, 20]. In this study, average values of PGI and PGII were also significantly higher in the *H. pylori*-positive individuals compared to the *H. pylori*-negative persons (111.6 ± 63.4 vs. 83.6 ± 56.7 μg / l and 18.4 ± 13.9 vs. 9.9 ± 9.2 μg / l, $p < 0.0001$, respectively), and PGII was also higher in the CagA-positive individuals (14.9 ± 10.5 vs. 10.6 ± 7.8 μg / l, $p = 0.004$).

In addition to *H. pylori* infection, AIG can also be the cause of atrophic changes in the mucosa [21]. Based on previously obtained cut-offs for atrophy biomarkers, the incidence of AIG in current clinical practice was 2.6% (GastroPanel, 1,742 participants) and 3.5% (GastroScreen-3, 170 participants) (Table 2). In the random sample (45–69 years, 246 participants), the incidence of AIG was 1.6% (GastroPanel). These values do not contradict the literature data [22, 23]. In addition to the risk of developing hematologic disorders, AIG poses a risk of developing neuroendocrine tumors and adenocarcinomas. However, it should be noted that stage III–IV atrophic gastritis (according to OLGA) associated with *H. pylori* infection determines a greater risk of developing gastric cancer [6].

CONCLUSION

The conducted analysis of the results of serological screening in clinical practice in people from a wide range of age groups over a long follow-up period showed high frequency of gastric fundus atrophy of varying severity with coexisting *H. pylori* infection with high prevalence of cytotoxic CagA+ strain or AIG, which requires a more detailed examination. The frequency of AIG was 1.6–3.5% in different study groups based on serological tests.

Therefore, serological screening of gastritis types using diagnostic panels, such as GastroPanel or GastroScreen-3 tests, is an effective tool to determine the functional state of the gastric mucosa.

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Authors' contribution

Belkovets A.V., Ozhiganova N.V. – conception and design, analysis and interpretation of the data, justification of the manuscript. Kruchinina M.V. – critical revision of important intellectual content, final approval of the manuscript for publication. Polonskaya Ya.V. – analysis and interpretation of the data. Shcherbakova L.V. – statistical processing of the data.

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