DOI: 10.20514/2226-6704-2022-12-6-450-458
EDN: RFKOXS
УДК 616.327-002-009.8-07-085

А.А. Калугин*, А.А. Степченко, М.А. Степченко

Федеральное государственное бюджетное образовательное учреждение высшего образования «Курский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Курск, Россия

ВЗАИМОСВЯЗЬ ФЕНОТИПА ОКИСЛИТЕЛЬНОГО МЕТАБОЛИЗМА И АКЦЕНТУАЦИИ СВОЙСТВ ТЕМПЕРАМЕНТА С ПРИВЕРЖЕННОСТЬЮ К ТЕРАПИИ У ПАЦИЕНТОВ С ГАСТРОЭЗОФАГЕАЛЬНОЙ РЕФЛЮКСНОЙ БОЛЕЗНЬЮ

A.A. Kalugin*, A.A. Stepchenko, M.A. Stepchenko

Federal State Budgetary Educational Institution of Higher Education Kursk State Medical University of Ministry of Healthcare of the Russian Federation, Kursk, Russia

Relationship of Clinical Picture, Phenotype of Oxidative Metabolism, Accentuation of Temperament Properties and Compliance in Patients with Gastroesophageal Reflux Disease

Резюме

Цель исследования. Установить взаимосвязь акцентуации свойств темперамента, клинической картины заболевания и приверженности к терапии у пациентов с гастроэзофагеальной рефлюксной болезнью с различным фенотипом окислительного метаболизма. **Материалы и методы.** Для реализации поставленной цели было проведено исследование в дизайне «случай-контроль» 156 пациентов обоих полов в возрасте от 21 до 55 лет (101 мужчина и 55 женщин, средний возраст 38 лет (IQR 29-46)) с верифицированной гастроэзофагеальной рефлюксной болезнью с оценкой клинической картины, сопутствующей патологией, выраженности симптомов с помощью визуально-аналоговой шкалы, приверженности к терапии, фенотипа окислительного метаболизма с помощью препарата-маркера эуфиллина, определением личностных психофизиологических особенности с использованием теста акцентуации свойств темперамента. Статистический анализ проводился согласно целям исследования и особенностям совокупности данных. **Результаты.** У пациентов с гастроэзофагеальной рефлюксной болезнью были выделены три основных типа личности: гипертимный (29;19 %), смешанный (61;39 %) и эмоционально-нестабильный тип (66;42 %). По фенотипу окислительного метаболизма 156 пациентов подразделялись на быстрые (51; 33 %), промежуточные (82; 52 %) и медленные метаболизаторы (23; 15 %). Мультиномиальный логистический регрессионный анализ показал, что у пациентов с быстрым метаболизмом, в отличие от промежуточных и медленных метаболизаторов, следует ожидать низкую интенсивность болевого синдрома (p=0,014). Влияния на клиническую картину свойств темперамента не выявлено (p=0,063). При изучении с помощью мультиномиальной логистической регрессии зависимости приверженности к терапии от свойств темперамента и уровня метаболизма пациента, у пациентов с гипертимным типом акцентуации свойств темперамента вероятность высокой приверженности к терапии составила более 65 % у быстрых и промежуточных ме-

*Контакты: Андрей Александрович Калугин, e-mail: dr.kalugin2010@yandex.ru
*Contacts: Andrei A. Kalugin, e-mail: dr.kalugin2010@yandex.ru
ORCID ID: https://orcid.org/0000-0002-8339-3369

таболизаторов и 100 % у медленных метаболизаторов (p=0,006), у пациентов со смешанными типами вероятность высокой приверженности к терапии наблюдается только у медленных метаболизаторов (p=0,006), у пациентов с эмоционально-нестабильным типом высока вероятность низкой приверженности к терапии вне зависимости от уровня метаболизма (p=0,006). **Заключение.** Для прогнозирования приверженности к терапии пациентов с гастроэзофагеальной рефлюксной болезнью целесообразно определять уровень окислительного метаболизма и тип акцентуации свойств темперамента.

Ключевые слова: *гастроэзофагеальная рефлюксная болезнь, фенотип окислительного метаболизма, свойства темперамента, приверженность к терапии*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 13.05.2021 г.
Принята к публикации 25.07.2022 г.

Для цитирования: Калугин А.А., Степченко А.А., Степченко М.А. ВЗАИМОСВЯЗЬ ФЕНОТИПА ОКИСЛИТЕЛЬНОГО МЕТАБОЛИЗМА И АКЦЕНТУАЦИИ СВОЙСТВ ТЕМПЕРАМЕНТА С ПРИВЕРЖЕННОСТЬЮ К ТЕРАПИИ У ПАЦИЕНТОВ С ГАСТРОЭЗОФАГЕАЛЬНОЙ РЕФЛЮКСНОЙ БОЛЕЗНЬЮ. Архивъ внутренней медицины. 2022; 12(6): 450-458. DOI: 10.20514/2226-6704-2022-12-6-450-458. EDN: RFKOXS

Abstract

The purpose of the study is to establish the relationship between the accentuation of temperament properties, clinical picture of disease, and adherence to therapy in patients with gastroesophageal reflux disease with different phenotype of oxidative metabolism. **Materials and methods.** To achieve this goal, a case-control study was conducted in 156 patients aged 21 to 55 years (101 men and 55 women, mean age 38 years (IQR 29-46))with verified gastroesophageal reflux disease with assessment of the clinical picture, assessment of the severity of symptoms using a visual analogue scale, concomitant pathology, adherence to therapy, phenotype of oxidative metabolism with the eufillin marker drug, determination of personal psychophysiological features using a temperament accentuation test. Statistical analyses were performed according to study objectives and data set features. **Results.** In patients with gastroesophageal reflux disease, 3 main personality types were identified: hyperthymic (n = 29; 19 %), mixed (n = 61; 39 %) and emotionally unstable type (n = 66; 42 %). By oxidative metabolism phenotype, 156 patients were divided into rapid (n = 51; 33 %), intermediate (n = 82; 52 %) and slow metabolizers (n = 23; 15 %). Analysis of multinomial logistic regression showed that in patients with rapid metabolism, in contrast to intermediate and slow metabolizers, low pain syndrome intensity should be expected (p = 0.014). There was no effect on the clinical presentation of temperament properties (p = 0.063). When studying the dependence of adherence to therapy on the properties of temperament and the patient`s metabolic level by multinomial logistic regression in patients with a hyperthymic type of accentuation of temperament properties, the probability of high adherence to therapy was more than 65 % in fast and intermediate metabolizers and 100 % in slow metabolizers (p = 0.006), in patients with mixed types the probability of high adherence to therapy is observed only in slow metabolizers (p = 0.006), patients with emotionally unstable type have a high probability of low adherence to therapy regardless of metabolic level (p = 0.006).**Conclusion.** To predict adherence of patients with gastroesophageal reflux disease to therapy, it is advisable to determine the level of oxidative metabolism and the type of accentuation of temperament properties.

Key words: *gastroesophageal reflux disease, phenotype of oxidative metabolism, temperament properties, compliance*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 13.05.2021
Accepted for publication on 25.07.2022

For citation: Kalugin A.A., Stepchenko A.A., Stepchenko M.A. Relationship of Clinical Picture, Phenotype of Oxidative Metabolism, Accentuation of Temperament Properties and Compliance in Patients with Gastroesophageal Reflux Disease. The Russian Archives of Internal Medicine. 2022; 12(6): 450-458. DOI: 10.20514/2226-6704-2022-12-6-450-458. EDN: RFKOXS

ARDs — acute respiratory diseases, APTT — accentuation of personality traits test, CVHC — chronic viral hepatitis C, GERD — gastroesophageal reflux disease, GERD-Q — gastroesophageal reflux disease questionnaire, GIT — gastrointestinal tract, GSRS — Gastrointestinal Symptom Rating Scale, HetEM — heterozygous extensive metabolizers (intermediate oxidative metabolism genotype), HomEM — homozygous extensive metabolizers (fast oxidative metabolism genotype), NSAIDs — non-steroidal anti-inflammatory drugs, PM — poor metabolizers (slow oxidative metabolism genotype), QAA-25 — quantitative assessment of adherence, VAS — visual analogue scale, WHO — World Health Organization

Rationale

The prevalence of gastroesophageal reflux disease (GERD) varies across countries and regions and remains quite high. The prevalence of GERD in the United States is approximately 20 %, while the prevalence of this disease in the Russian Federation is from 11 to 15 % [1].

Quite detailed approaches to the management of patients with GERD are described in the guidelines [2].

Based on the publications in PubMed from 1985 to 2015, Patti M.D. et al. (2015) demonstrated that lifestyle modification, proton pump inhibitors, and laparoscopic fundoplication are reliable methods of GERD treatment. Based on this review, the authors conclude that GERD is a very common disease, and the best results after its diagnosis can be achieved by a multidisciplinary team providing personalized treatment [3].

However, there are factors that reduce the effectiveness of drug therapy, for example, the difference in the metabolic rate between patients; currently, there are single scientific papers on the study of the metabolic rate in GERD patients. Mayev I. V. et al. (2011) found that among 267 examined patients with GERD, significantly predominating are the patients with fast oxidative metabolism genotype (HomEM) — 84 %, whereas the share of patients with intermediate metabolism (HetEM) was significantly lower — only 14 % of patients, and only four patients had slow metabolism (PM) [4]. Personalization of therapy often requires the knowledge of oxidative metabolism phenotype rather than its genotype, since the correlation between genotype and phenotype is not indicative: 50 % of erroneous predictions are reported [5]. One of solutions to this issue would be to determine individual differences in drug product metabolism using xenobiotics as markers [6].

Various questionnaires and scales are used to assess the effectiveness of GERD management; they allow to objectify the effect of treatment, both on the clinical presentation and on the life quality (assessment of the severity of gastroenterological symptoms using Gastrointestinal Symptom Rating Scale (GSRS), SF-36) [7, 8]. It should be noted that it is quite convenient to use in clinical settings a simpler method for assessing the clinical presentation with the help of a ten-point visual analog scale (VAS).

Another factor affecting the effectiveness of treatment is the adherence to therapy, i.e. the voluntary compliance of a patient with the prescribed treatment regimen. Zimmerman Ya.S. et al. in their paper (2015) on acid-related diseases mentioned the importance of following the prescribed recommendations in order to improve the effectiveness of treatment, including lifestyle modification, abandoning bad habits, adopting dietary restrictions, avoiding stressful situations, as well as adherence to prescribed doses of drugs, regimens, and treatment duration. Besides, the authors highlight the importance of cooperation between the physician and the patient in the management of acid-related diseases (gastroesophageal reflux disease, peptic ulcer, etc.) and the ways to improve it [9].

One of the reasons for the decreased adherence to the therapy and, consequently, its ineffectiveness, may be personality traits of the patient. To study personality traits, temperament models were developed and several methods were proposed (by V.M. Rusalov, H. Eysenck, A. Thomas and S. Chess, J. Strelau, etc.) [10]. A common technique for studying personal psychophysiological characteristics in routine clinical practice in patients with somatic disorders is the accentuation of personality traits test (APTT) (D.V. Plotnikov et al., 2001) [11]. It should be noted that in available literature sources there are almost no studies of the impact of personality traits on the adherence to therapy in patients with GERD.

In view of this, it is of interest to identify the correlation between individual differences in the rate of oxidative metabolism that determine the antisecretory effect of drugs and the accentuation of personality traits and their effect on adherence to therapy in patients with GERD.

The objective of this study was the establishment of the correlation between the accentuation of personality traits, the clinical presentation of the disease, and adherence to therapy in patients with gastroesophageal reflux disease with different phenotypes of oxidative metabolism.

Materials and methods

Study design to achieve the objective, a case–control study was performed; the analysis included results of clinical examination of 156 patients of the Gastroenterological Department of the Kursk Regional Clinical Hospital; the study included the patients with gastroesophageal reflux disease, at the age between 21 and 55 years (mean age of 38 (IQR 29–46)) (Table 1). There were 101 male and 55 female patients (male to female ratio 2:1). The inclusion criteria were: the presence of gastroesophageal reflux disease with or without esophagitis, the diagnosis of GERD was confirmed by GERD-Q questionnaire [12], alginate test, and/or fibroesophagogastroduodenoscopy (Table 1). The exclusion criteria were: Barrett's esophagus, gastric and/or duodenal ulcerative process, including this associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs), refusal of the patient to participate at any stage of the study, chronic diseases in the acute or decompensation

Table 1. *Distribution of GERD patients by sex and esophagogastroduodenoscopy findings*

Nosology	Total amount	Sex	
		Men, amount	Women, amount
Gastroesophageal reflux disease without esophagitis	129 (83 %)	88 (57 %)	41 (26 %)
Gastroesophageal reflux disease with esophagitis	27 (17 %)	13 (8 %)	14 (9 %)
Total	156 (100 %)	101 (65 %)	55 (35 %)

stage. The patients with suspected acute respiratory disease (ARD) were included in this study, since the signs of laryngitis can be caused by GERD.

Before enrollment, all patients filled out a voluntary informed consent form with the information about the goals, objectives and description of the study. The abstract for this study with the protocol and the content of the informed consent form was approved by the Regional Ethics Committee of Kursk State Medical University.

The review of comorbidities in the examined population revealed the following patterns (Fig. 1). The most common comorbidities in patients were the symptoms of rhinitis and cough without fever (acute respiratory diseases) — in 28 patients (18 %), coronary heart disease — in 27 patients (17 %), and hypertension — in 22 patients (14 %). Among the GI comorbidities observed in 20 patients (13 %) were: functional dyspepsia, irritable bowel syndrome, fatty liver, and biliary dyskinesia.

The patients underwent clinical examination in accordance with the guidelines for GERD diagnosis and management. GERD was diagnosed in accordance with the WHO classification and recommendations of the Russian Gastroenterological Association [2].

Evaluation of the clinical presentation (severity of heartburn and pain syndrome) in patients with GERD was carried out using a ten-point visual analog scale (VAS). 1 point corresponded to the minimal manifestations of symptoms, 10 points — to their maximal manifestations. The results below 4 points were defined as mild heartburn or pain, 4–7 points — as moderate heartburn or pain, 8+ points — as severe heartburn or pain. The results of the clinical presentations evaluation were compared in patients with GERD with different metabolism and type of personality traits accentuation.

To study the adherence to therapy, the authors used a questionnaire proposed by Kolesnikova I.Yu. et al. (2005) [13] that included 5 items: taking medicines prescribed by a physician; satisfaction with treatment; dieting; smoking. Scores of the questionnaire range from 1 point (negative) to 3 (positive, no bad habits). The total score was also calculated; the sum from 5 to 10 was considered as low adherence, from 11 to 15 points — as high adherence [13]. This questionnaire was originally composed in the Russian language and validated for patients with acid-related diseases. No other questionnaires were used due to the large number of questions (QAA-25) as well as due to the fact that the questionnaires were validated mainly for patients with hypertension, coronary heart disease, type II diabetes mellitus, and not for patients with acid-related diseases. The difference between the amount of preparation handed out to the patient and the amount returned by the patient was not calculated. Additionally, information about the drugs taken was registered in the patient's protocol, and their average price in the pharmacies of Kursk was calculated; the frequency of administration per day, daily rate and duration of drug action were also recorded.

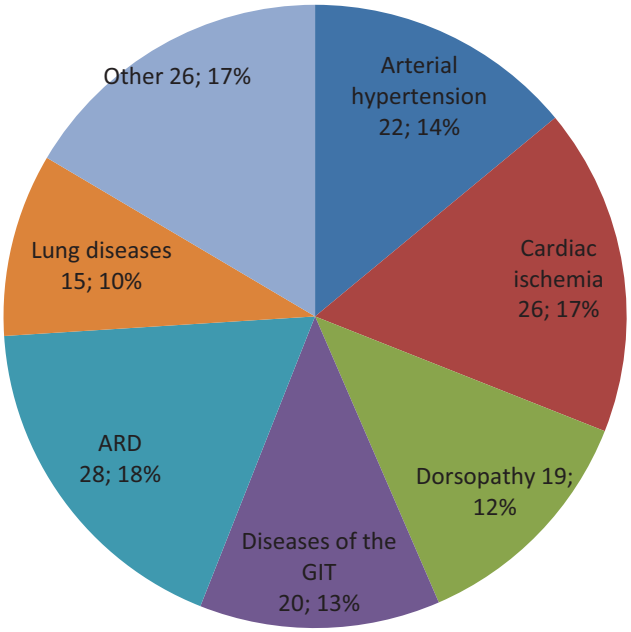

Figure 1. *Comorbidities in GERD patients*
Note: GERD — gastroesophageal reflux disease, ARD — acute respiratory diseases, GIT — gastrointestinal tract

The phenotype of oxidative metabolism in the examined population was studied according to the technique developed by the Pharmacokinetic Laboratory of Kursk State Medical University [6]. In particular, patients received oral aminophylline at a dose of 150 mg; its concentration during 24h in saliva was determined by the method of high-performance liquid chromatography. According to the method, patients were divided into the groups of fast metabolizers (half-life of aminophylline T½ < 9 hours), intermediate metabolizers (T½ = 9–15 hours) and slow metabolizers (T ½ > 15 hours).

The psychophysiological personality traits of patients with GERD were analyzed using the APTT questionnaire that includes 125 questions that should be answered "yes" or "no". The type of the accentuation of personality traits was established based on the previous factorial analysis of APTT scales as follows. Initially, APPT scales of accentuation were identified in the individual profile of each subject. Scale increase up to 8 STENs was regarded as a moderate accentuation of the trait, and three STENs were considered as a moderate deficiency of the measured trait. 9 and 2 STENs indicated a pronounced accentuation or deficiency of the measured trait. Maximum accentuation or deficiency of a trait was characterized by 10 and 1 STENs. It should be noted that the same patient may have accentuation on different scales. Then it was found out which of the generalized personal trait group includes accentuated scales. In accordance with this, the following types of accentuation were defined: hyperthymic, dysthymic, emotionally labile, inert, hyperthymic-labile, dysthymic-labile, inert mixed [11].

It was analyzed which of the generalized personal trait group includes accentuated scales, according to these, the type of accentuation was defined: hyperthymic, dysthymic, emotionally labile, inert, hyperthymic-labile, dysthymic-labile, inert mixed. The study was conducted once at the start of treatment course [11].

Statistical data analysis was carried out using the IBM SPSS Statistics Standard Edition 17.0 software package. Quantitative and qualitative ordinal characteristics (with more than 5 ranks) were represented by medians (Me) and quartiles (lower, Q1, and upper, Q3); qualitative characteristics — in the form of the absolute number of observations (n) and the percentage (%) of the total number of patients in the group. As a result of a preliminary data evaluation using the Kolmogorov–Smirnov test, it was revealed that the distribution of datasets differed from the normal one, therefore, in order to analyze the effect on the severity of the clinical presentation of metabolic rate and personality traits, as well as to assess the effect of the metabolic rate, treatment costs, frequency of drug administration, rate and duration of drug action on adherence to therapy, multinomial logistic regression was used [14].

Results

Accentuation of personality traits test in 156 patients with GERD revealed that 11 patients (71 %) has an accentuation in "neuroticism", "emotional inertia" and "emotional lability" scales (56; 36 % and 45; 29 %, respectively); the scales with the lowest representation were "aggressiveness" (39; 25 %), "vigorousness" (33; 21 %), "social activity" (36; 23 %), "sensitivity" (33; 21 %), "timidity" (28; 18 %).

Analysis of the results of the APTT questionnaire confirmed the heterogeneity of personality traits of the surveyed contingent: Hyperthymia with social and objective activity occurred (up to 8–10 STENs) in 29 patients (18.6 %). Emotional lability was expressed by increased score in APTT scales "neuroticism", "sensitivity", "timidity", "aggressiveness", "emotional lability" in 66 patients (42.3 %). Hyperthymic-labile, dysthymic-labile, inert mixed and emotional inert types were observed in 8 (5.1 %), 20 (12.8 %), 26 (16.7 %) and 1 (0.7 %) patients, respectively. Dysthymia, as opposed to hyperthymia (1, 2, 3 STENs), was observed in 6 (3.8 %) patients. No other combinations of APTT scales were found. It should be noted that the prevalence of emotional lability was revealed in patients with GERD.

Thus, according to the frequency of incidence, 3 main personality types were identified in patients with GERD: 1) hyperthymic type that is characterized by accentuation of scales indicating social and subject activity (29, 19 %); 2) mixed types combining the strengthening in scales indicating emotional lability, and scales indicating both social and objective activity and passivity; all other patients with GERD were assigned there (61, 39 %) 3) emotionally labile type with the accentuation in scales of asthenic emotions (66, 42 %).

At the next stage, the analysis of changes in the daily concentration of oral marker aminophylline in saliva in 156 patients with GERD revealed the following results: 51 patients (33 %) had fast oxidative metabolism phenotype, 82 patients (52 %) had an intermediate phenotype, and 23 patients (15 %) had slow oxidative metabolism phenotype.

Among the examined population, all 156 patients complained of heartburn, and only 119 patients (76 %) experienced pain in the lower third of sternum area. The severity of symptoms was checked using the VAS scale (Table 2).

To check the hypothesis about the correlation between the severity of clinical manifestations, the phenotype of oxidative metabolism and personality traits in patients with GERD, data were analyzed using multinomial logistic regression. Dependent variables included the results of the perception of heartburn and pain according to the VAS scale in points, the type of the accentuation of personality traits, and metabolism rate in each patient; they were determined as factors and denoted by nominal numbers.

As a result, the effect of metabolic rate ($p = 0.662$) and the type of the accentuation of personality traits ($p = 0.069$) on the severity of heartburn according to the VAS scale in patients with GERD was not confirmed (significance of the entire model $p = 0.163$). However, the results of multinomial logistic regression analysis performed for confirming the hypothesis of the effect of metabolism rate and personality traits on the clinical presentation, confirmed the difference in the assessment of pain syndrome in patients with different phenotypes of oxidative metabolism (chi-square = 25.093, p=0.014), however, no significant difference was found in the perception of pain in the patients with different types of personality traits accentuation (p=0.263).

It should be noted that the multinomial regression analysis when calculating the observed and predicted

Table 2. *The severity of clinical symptoms in patients with gastroesophageal reflux disease*

Name of indicator (n; MQR)	Number of patients with different intensity of heartburn and pain syndrome (n (%))		
	Low intensity ≤4 points	Middle intensity 4-7 points	Highintensity ≥8 points
The severity of heartburn according to the VAS (n=156, MQR 6-8 points)	3 (1,9 %)	81 (51,9 %)	72 (46,2 %)
Pain severity according to the VAS (n=119, MQR 3-6 points)	51 (42,9 %)	62 (52,1 %)	6 (5 %)

frequencies (cell probabilities) (Table 3) showed that the probability of detecting pain in fast metabolizers with weak intensity (below 4 points) was 41.4 %, and the probability of the incidence of pain intensity of 4–7 points according to VAS was 58.6 % (p = 0.014). At the same time, the probability of detecting low-intense pain syndrome in patients with GERD with intermediate and fast metabolism is 16.2 % and 18.7 %, respectively; the probability of detecting pain of moderate intensity (4–7 points according to VAS) was 74.2 % and 81.2 %, respectively (p = 0.014); and pain syndrome with the intensity over 7 points can develop only in the group of intermediate metabolizers, in 9.7 % of cases (p = 0.014).

For a deeper understanding of the effect of the analyzed factors (type of the accentuation of personality traits, metabolic rate) and conventional parameters (frequency of drug administration per day, rate and duration of action, as well as drug costs per treatment day) on the adherence to therapy, an analysis was carried out by the method of a multinomial logistic regression. The dependent variable "adherence to therapy" was determined in points by the total value (low adherence — the sum of points from 5 to 10, high adherence — from 11 to 15).

Results of this analysis showed that the costs of drugs (p = 0.094), frequency of administration per day (p = 0.063), rate (p = 0.316) and duration of drug action (p = 0.068) could be excluded as statistically insignificant. Multinomial logistic regression analysis demonstrated that in patients with GERD there is a significant dependence of the adherence to therapy on the patient's metabolic rate and personality traits (p = 0.006).

During calculating the observed and predicted frequencies (cell probabilities), the probability of high or low adherence to therapy was determined depending on metabolism rate and personality traits:

- in patients with hyperthymic type of the accentuation of personality traits, the probability of high adherence to therapy (11+ points) was 66.5 % for fast metabolizers, 65.3 % for intermediate metabolizers, and 100 % for slow metabolizers;
- in patients with mixed types of the accentuation of personality traits and fast metabolism, the probability of high adherence to therapy was 21.9 %, in patients with intermediate metabolism — 29.0 %, in slow metabolizers — 100 %;
- in patients with an emotionally labile type of the accentuation of personality traits, the probability of low adherence to therapy was 100 %, regardless of metabolism rate.

Thus, high adherence to therapy should be expected in patients with GERD, with a hyperthymic type of the accentuation of personality traits and with different phenotypes of oxidative metabolism, as well as in patients with mixed types of the accentuation of personality traits and slow metabolism. At the same time, patients with an emotionally labile type of the accentuation of personality traits have a high probability of low adherence to therapy, regardless of metabolism rate.

Table 3. *Observed and predicted frequencies of the influence of the level of metabolism on the severity of pain syndrome*

Metabolitic rate	Pain assessment on the VAS	Frequency			Percentage	
		Observed	Predicted	Pearson residual	Observed	Predicted
Quick	2,00	11	11	0	26,8 %	26,8 %
	3,00	6	6	0	14,6 %	14,6 %
	4,00	9	9	0	22,0 %	22,0 %
	5,00	12	12	0	29,3 %	29,3 %
	6,00	3	3	0	7,3 %	7,3 %
	7,00	0	0	0	0 %	0 %
	8,00	0	0	0	0 %	0 %
Intermediate	2,00	4	4	0	6,5 %	6,5 %
	3,00	6	6	0	9,7 %	9,7 %
	4,00	9	9	0	14,5 %	14,5 %
	5,00	16	16	0	25,8 %	25,8 %
	6,00	12	12	0	19,4 %	19,4 %
	7,00	9	9	0	14,5 %	14,5 %
	8,00	6	6	0	9,7 %	9,7 %
Slow	2,00	2	2	0	12,5 %	12,5 %
	3,00	1	1	0	6,3 %	6,2 %
	4,00	3	3	0	18,8 %	18,7 %
	5,00	6	6	0	37,5 %	37,5 %
	6,00	2	2	0	12,5 %	12,5 %
	7,00	2	2	0	12,5 %	12,5 %
	8,00	0	0	0	0 %	0 %

Table 4. Factors affecting adherence to therapy

Name of indicator	Data		
Total points — adherence to therapy Me (MQR, min-max)	13 (IQR 11-13, min9-max 13)	10 (IQR 9-10, min 8-max 12)	9 (IQR 6-9, min 5-max 12)
Type of accentuation of temperament properties	Hyperthymic type 29 (19 %)	Mixed types 61 (42 %)	Emotion allyunstable type 66 (39 %)
Metabolitic rate			
Fast metabolizers n=51 (32,7 %)	12(7,7 %)	23(14,7 %)	16(10,3 %)
Intermediate metabolizers n=82 (52,6 %)	9(5,8 %)	31(19,9 %)	42(26,9 %)
Slow metabolizers n=23 (14,7 %)	8(5,1 %)	7(4,5 %)	8(5,1 %)
The daily cost of the drug, rubles		от 3 до 50 Me 6 (IQR 3-10)	
Frequency rate of admission per day, number of times		от 1 до 6 Me 2 (IQR 1-6)	
Performance (number of people who answered YES)		116 (74,3 %)	
The effectiveness and duration of the drug (number of people who answered YES)		121 (77,6 %)	

Note: The cost of the administered drug product was calculated per one day during the month preceding the study

Discussion

In this study, for the first time, the psychophysiological characteristics of patients with GERD were analyzed using the accentuation of personality traits test, as well as the effect of the metabolic rate and personality traits on clinical presentation and adherence to therapy.

Evaluation of the clinical presentation in patients with GERD with different phenotypes of oxidative metabolism and different types of the accentuation of personality traits demonstrated the following patterns: a direct dependence of the level of pain syndrome on metabolism rate was established (p = 0.014); in fast metabolizers the perceived pain syndrome, assessed using VAS scale, was lower than in intermediate and slow metabolizers. However, personality traits of examined subjects had no effect on the perception of pain syndrome (p = 0.263).

These patterns can be explained by the fact that in patients with GERD, due to the chronic damage to esophageal mucosa by gastric contents, there is not only a nociceptive, but also an inflammatory component of pain [2]. In response to inflammation, immune cells release histamine in blood that binds to its receptors, and the subsequent cascade of biochemical interactions triggers membrane depolarization and conduction of pain impulse. Histamine can be metabolized in two ways: by oxidative deamination with diamine oxidase produced by the apical membrane of enterocytes, and by methylation with histamine-N-methyltransferase [15]. In fast metabolizers, histamine can be more rapidly destroyed in the liver with a decrease in its blood concentration, thereby, it can lead to a decreased intensity of pain syndrome.

It should be noted that the authors of APTT method describe individuals with hyperthymic type of the accentuation of personality traits as individuals with the following behavior pattern: extraversion, sociability, cheerfulness, good mood most of the time, free movements, activity, quick thinking. Such individuals are subjective and have adequate self-regulation in order to monitor their health [11]. At the same time, signs of emotional lability in patients with GERD, i.e. psychovegetative instability, somatic distress, aggressive reactions and self-doubt, can be associated with inadequate self-regulation and low self-control that can lead to the patient's poor attention to follow the physician's recommendations [11]. In this regard, our study, with the help of multinomial logistic regression analysis, revealed the following patterns: in patients with a hyperthymic type of the accentuation of personality traits, regardless of metabolism, high adherence to therapy should be expected (probability from 65 to 100 %, p = 0.006); in patients with an emotionally labile type of the accentuation of personality traits and with different phenotype of oxidative metabolism low adherence to therapy is observed (p = 0.006). Similar results on patients with emotional lability and viral hepatitis C (CVHC) were obtained by Maksimova M.Yu. et al. (2014). In this study, it was found that 69.66 % of the examined patients with chronic hepatitis C have pronounced personality deviations that in 39.3 % of cases reached the level of personality disorder, and in 30.33 % of patients corresponded to the level of accentuations. At the same time, patients with emotional lability demonstrated low adherence to therapy, and patients with a high level of adherence to therapy predominated in the group of CVHC patients with anxiety disorders [16].

Our study demonstrated that metabolism rate also affected the adherence to therapy: the highest adherence to therapy can be expected in slow metabolizers with hyperthymic and mixed types of the accentuation of personality traits. In intermediate and fast metabolizers, the probability of high adherence to therapy is observed only with hyperthymic type of the accentuation of personality traits ($p = 0.006$). Apparently, this is due to the fact that the effectiveness of drugs in standard doses was pronounced in slow metabolizers, and patients did not refuse to take drugs.

These factors (personality traits and metabolism) are unchangeable ones, however, the effect of temperament can be changed by psychological methods, and the dosage of proton pump inhibitors can be increased in order to increase their effectiveness. These assumptions require further analysis and confirmation. Training physicians in the ability to develop trusting relationships with the patient can also play a not unimportant part.

Conclusion

1. Clinical signs of gastroesophageal reflux disease in the form of pain in patients with fast metabolism are less pronounced than in patients with GERD and intermediate or slow phenotype of oxidative metabolism.

2. High adherence to therapy should be expected in GERD patients with hyperthymic type of personality traits accentuation and different oxidative metabolism phenotypes, as well as in the patients with mixed types of personality traits accentuation and slow metabolism, regardless of other factors (the price of drugs, administration frequency, the rate and duration of action).

3. In patients with GERD with emotionally labile types of accentuation, regardless of metabolism rate, a decrease in the possible fulfilling physician's prescriptions should be expected.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

Калугин А.А. (ORCID ID: https://orcid.org/0000-0002-8339-3369): участие в разработке дизайна, сбор, анализ и интерпретация данных, окончательное утверждение рукописи к публикации, создание критически важного интеллектуального содержания, готовность принять ответственность за все аспекты работы

Степченко А.А. (ORCID ID: https://orcid.org/0000-0001-5672-9341): разработка дизайна исследования, математический анализ и интерпретация данных

Степченко М.А. (ORCIDID: https://orcid.org/0000-0002-7105-7501): участие в разработке дизайна, анализ и интерпретация данных

Author Contribution

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Kalugin A.A. (ORCID ID: https://orcid.org/0000-0002-8339-3369): participation in design development, basic collection, data analysisand interpretation, final approval of the manuscript for publication, creation of critical intellectual content, willingness to accept responsibility for all aspects of the work

Stepchenko A.A. (ORCID ID: https://orcid.org/0000-0001-5672-9341): design development, mathematical analysis and data interpretation

Stepchenko M.A. (ORCID ID: https://orcid.org/0000-0002-7105-7501): participation in design development, data analysis and interpretation

Список литературы / References:

1. Лазебник Л.Б., Машарова А.А., Бордин Д.С. и др. Результаты многоцентрового исследования «Эпидемиология гастроэзофагеальной рефлюксной болезни в России» («МЭГРЕ»). Терапевтический архив. 2011; 83(1): 45-50.
Lazebnik L.B., Masharova A.A., Bordin D.S. et al. Results of a multicenter trial «Epidemiology of Gastroesophageal Reflux Disease in Russia» («MEGRE»). Therapeuticarchive. 2011; 83(1): 45-50[In Russian].
2. Ивашкин В.Т., Маев В.И., Трухманов А.С. и др. Клинические рекомендации Российской гастроэнтерологической ассоциации по диагностике и лечению гастроэзофагеальной рефлюксной болезни. Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2017; 27(4): 75-95. doi: 10.22416/1382-4376-2017-27-4-75-95.
Ivashkin V.T., Mayev V.I., Trukhmanov A.S. et al.Diagnostics and treatment of gastroesophageal reflux disease: clinical guidelines of the Russian gastroenterological association. Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2017; 27(4): 75-95. doi: 10.22416/1382-4376-2017-27-4-75-95 [In Russian].
3. Patti M.G. An Evidence-Based Approach to the Treatment of Gastroesophageal Reflux Disease. JAMA surgery. 2016; 151(1): 73-78. doi: 10.1001/jamasurg.2015.4233.
4. Маев И.В., Белый П.А., Лебедева Е.Г. Влияние полиморфизма гена CYP2C19 на эффективность использования ингибиторов протонной помпы в лечении гастроэзофагеальной рефлюксной болезни. Лечащий врач. 2011; 7: 93-95.
Maev I.V., Belyj P.A., Lebedeva E.G. Effect of CYP2C19 gene polymorphism on the efficacy of proton pump inhibitors in the treatment of gastroesophageal reflux disease. Lechashchijvrach. 2011; 7: 93-95. [In Russian].
5. Waring R.H. Cytochrome P450: genotype to phenotype. Xenobiotica. 2020;50(1):9-18. doi: 10.1080/00498254.2019.1648911.
6. Качмарская Л.М. Изучение индивидуальной вариабельности биотрансформации теофиллина. В кн.: Актуальные вопросы экстренной специализированной медицинской помощи. Орел, 1996; 246-247.
Kachmarskaya L.M. Study of individual variability of theophylline biotransformation. Aktual'nye voprosy ekstrennoj specializirovannoj medicinskoj pomoshchi. Orel, 1996; 246-247 [In Russian].
7. Mirijanyan G. Peculiarities of quality of life in patients with gastroesophagealreflux disease. Georgian medical news. 2018; (274): 88-92.
8. Циммерман Я.С., Вологжанина Л.Г. Приверженность больных к соблюдению врачебных рекомендаций как действенный фактор повышения эффективности лечения. Клиническая медицина. 2015; 93(3): 5-13.
Tsimmerman Ya.S., Vologzhanina L.G. Compliance of patients with prescribed medication as an important factor of treatment efficiency. Klinicheskaia Meditsina. 2015; 93(3): 5-13 [In Russian].
9. Новик А.А., Ионова Т.И. Руководство по исследованию качества жизни в медицине. Москва, **ОЛМА Медиа Групп.** 2007;315 с.

Novik A.A., Ionova T.I. Guidelines for Quality of Life Research in Medicine. Moscow, OLMA Media Grupp. 2007; 315 p. [In Russian].

10. Лукацкий М. А., Остренкова М. Е. Психология: учебник. 2-е изд., испр. и доп. Москва, ГЭОТАР-Медиа.2013; 262-312.
Lukackij M. A., Ostrenkova M. E. Psychology: Textbook. 2nd ed. Moscow, GEOTAR-Media. 2013; 262-312[In Russian].
11. Плотников В.В., Северьянова Л.А., Плотников Д.В., и др. Тест акцентуаций свойств темперамента (ТАСТ): методическое руководство. Изд. 3-е. Санкт-Петербург, ИМАТОН, cop. 2016; 74 с.
Plotnikov V.V, Sever'yanova L.A., Plotnikov D.V., et al. Temperament property accentuation test (TPAT): methodological guide. 3rded. St. Petersburg, IMATON, cop. 2016; 74p. [InRussian].
12. Кайбышева В.О., Кучерявый Ю.А., Трухманов А.С. идр. Результаты многоцентрового наблюдательного исследования по применению международного опросника GerdQ для диагностики гастроэзофагеальной рефлюксной болезни. Российский журнал гастроэнтерологии, гепатологии и колопроктологии. 2013;23(5):15-23.
Kajbysheva V.O., KucheryavyjYu.A., Truhmanov A.S. et al. Results of a Multicenter Observational Study of the GerdQ International Questionnaire for the Diagnosis of Gastroesophageal Reflux Disease. Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2013;23(5):15-23 [In Russian].
13. Колесникова И.Ю., Беляева Г.С., Леонтьева В.А. О соотношении между качеством жизни, комплаенсом пациентов и течением язвенной болезни. Клиническая медицина. 2005;83(10):33-36.
Kolesnikova I.Yu., Belyaeva G.S., Leont'eva V.A. The relationship between quality of life, patient compliance, and the course of peptic ulcer disease. Klinicheskaia Meditsina. 2005;83(10):33-36 [InRussian].
14. Информатика и медицинская статистика, под ред. Г. Н. Царик. Москва, ГЭОТАР-Медиа.2017; 304 с.
Computer science and medical statistics, ed. G. N. Carik. Moscow, GEOTAR-Media. 2017; 304 p. [In Russian].
15. Obara I., Telezhkin V., Alrashdi I.et al. Histamine, histamine receptors, and neuropathic pain relief. British Journal of Pharmacology. 2020; 177(3):580–599. doi: 10.1111/bph.14696.
16. Максимова М.Ю., Поддубная Т.В., Богомолов П.О. и др. Личностные характеристики и структура внутренней картины болезни как предикторы комплаенса пациентов, страдающих хроническим вирусным гепатитом. Психиатрия. Психические расстройства в общей медицине. 2014;03-04:31-38.
Maximova M.Yu., Poddubnaya T.V., Bogomolov P.O., et al. Personality characteristics and the structure of the internal picture of the disease as predictors of compliance in patients with chronic viral hepatitis. Psihiatriya. Psihicheskie rasstrojstva v obshchej medicine. 2014;03-04:31-38 [In Russian].