

# MECHANISMS OF AUTONOMIC DYSFUNCTION REALIZATION DURING COMORBID GASTROESOPHAGEAL REFLUX DISEASE AND NEUROCIRCULATORY DYSTONIA WITH INSOMNIA AMONG YOUNG PEOPLE

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## Abstract

**The aim of the study:** to optimize diagnostics and treatment of comorbid gastroesophageal reflux disease (GERD) and concomitant neurocirculatory dystonia (NCD) with insomnia among young people by studying autonomic dysfunction and mechanisms of its realization.

**Methods.** The study was conducted in three groups of patients, homogeneous by gender and age. The first group included patients with GERD and insomnia, the second group counted those with NCD and insomnia, and the third group consisted of GERD with NCD and insomnia. We studied the quality of life (SF-36), quality of sleep (PSQI), the presence and severity of depression (PHQ-9), psychosomatic condition (Spielberger-Khanin scale), and determined the presence and severity of autonomic dysfunction syndrome (Wayne questionnaire), acidity of the stomach, ultrasound examination of the esophagus and stomach.

**Results.** The first group revealed sympathicotonia and increase of gastric juice aggression (in the stomach body  $0.89 \pm 0.05$ ) and reactive (47.2 points) and personal anxiety (52.7 points), which suggests the advisability of use PPI (omeprazole 20 mg 2 times a day for 5 weeks), and melatonin 3 mg per night during 3 weeks. The second group showed parasympathicotonia predominant, a more pronounced decrease in vitality scale ( $31.5 \pm 4.2$ ), and a moderate increase in indicators of reactive (44.0 points) and personal anxiety (46.5 points), which suggests the advisability of use 3 mg of melatonin per night during 3 weeks. The third group demonstrated predominance of parasympathicotonia, motor disorders, a decrease in alkalizing function of antrum ( $5.4 \pm 0.17$ ), depression (81.8 %), and the greatest decrease in indicators of sleep quality (11.7) and quality of life, which suggests the advisability of use PPI (omeprazole 20 mg 2 times per day during 5 weeks), with prokinetics (domperidone 10 mg 3 times per day during 5 weeks), and melatonin 3 mg per night during 3 weeks.

**Conclusions.** Autonomic dysfunction has a key influence on the main pathogenetic factors in the formation of both GERD and NCD and insomnia, and the type of autonomic tone determines the features of the clinical course of both isolated and combined pathology.

**Keywords:** gastroesophageal reflux disease, neurocirculatory dystonia, autonomic dysfunction, insomnia.

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## 1. Introduction

Gastroesophageal reflux disease (GERD) is one of the most common diseases and it occurs among both out-patients and in-patients [1]. At the same time, reflux and heartburn are typical symptoms of GERD. They reduce daytime activity [2], performance efficiency, disrupt sleep and, as a result, significantly reduce the quality of life of the patient [3, 4]. In recent times, there has been a significant rejuvenation of this pathology and it is increasingly diagnosed in young and middle-aged people [5]. In its turn, it is in this age group that autonomic tone is most pronounced.

As far as it is known, autonomic nervous system (ANS), which consists of sympathetic and parasympathetic divisions, regulates the activity of internal organs, blood vessels and endocrine glands, as well as the activity of metabolic processes, ensuring homeostasis. Taking into account the above mentioned, the ANS is one of the leading systems that regulates processes of secretion and motility. Their mis-function leads to the formation of GERD [7].

Thus, the ANS is a kind of first “performer” in psychosomatic disorders, that is, when a person experiences a stressful impact, the central nervous system affects the ANS, activating the endocrine glands.

At the same time, it was noted that GERD usually has a comorbid course, and neurocirculatory dystonia (NCD) is one of the most frequent diseases that accompanies GERD [6]. More often this pathology affects young people who do not have an organic myocardial lesion, and therefore one of the leading places in pathogenesis also belongs to autonomic disorders.

Also nowadays insomnia [8, 9] is a frequent condition accompanying both GERD and NCD [10, 11]. Taking into account the fact that the vast majority of young patients do not have severe organic pathology, i.e. heart and lung diseases, therefore, violations of the ANS also have an important place in the formation of insomnia.

Taking into account that autonomic dysfunction syndrome (ADS) is a trigger for the development of these pathologies, its study in students suffering from GERD and concomitant NCD with sleep disorder is of great practical importance for providing timely treatment and prevention measures.

**The aim of the study:** to optimize diagnostics and treatment of comorbid GERD and concomitant NCD with insomnia among young people by studying autonomic dysfunction and mechanisms of its realization.

## 2. Materials and methods

There was a study conducted in 2017–2019 on the basis of the gastroenterological department of the Municipal Non-Commercial Enterprise “City Student Hospital”, Kharkiv, Ukraine, in which 81 patients and 20 practically healthy students took part.

Prior to the study, all sick and healthy students of the control group were informed of its aims. A voluntary consent for the study was obtained. All procedures performed in the study comply with the Declaration of Helsinki and current legislation of Ukraine in the field of bioethics of medical research (order of the Ministry of Health of Ukraine No. 281 of 01.11.2008 “On approval of instructions on clinical trials of drugs and examination of clinical research materials and model regulations on Ethics commissions”). It was approved by ethics committee at Kharkiv Medical Academy of Postgraduate Education (protocol No. 8 of 27.09.2017)

The criteria for inclusion of patients into this study group were: persons of both sexes from 18 to 35 years, the existence of a non-erosive form of GERD with concomitant NCD and insomnia. GERD was diagnosed according to ICD-10 and the recommendations of the 2006 Montreal Consensus. The diagnosis of NCD is made according to the standard protocol (Decree No. 436 of the Ministry of Health of Ukraine on 03.07.2006) and ICD-10. The duration of the history of both pathologies is from 1 to 5 years. Insomnia in these patients was diagnosed by the Pittsburgh Sleep Quality Index (PSQI) with an overall average score of more than 6.0.

The exclusion criteria were as follows: the combination of GERD with structural gastrointestinal disorders, in particular, peptic ulcer, neoplasms of the stomach and esophagus, Barrett’s esophagus, as well as the existence of concomitant pathology of other systems in these individuals and an increased average score of self-assessment of psychosomatic status on any of the scales of questionnaires, which is an indication for a psychotherapist advice.

The first group included 25 patients of 18–25 years old, 20.6 average (13 women and 12 men) with isolated GERD and insomnia, who received proton pump inhibitors (PPI) (omeprazole 20 mg 2 times per day for 5 weeks) and melatonin 3 mg per night for 3 weeks. The second group consisted of 25 patients of 18–25 years old, 21.5 average (13 women and 12 men) with isolated NCD and insomnia, who received melatonin 3 mg per night for 3 weeks. The third group comprised 31 patients of 18–25 years old, 21.1 average (16 women and 15 men) suffering from GERD with

concomitant NCD and insomnia, who received PPI (omeprazole 20 mg 2 times a day for 5 weeks) with prokinetics (domperidon 10 mg 3 times per day during 5 weeks) and melatonin 3 mg per night for 3 weeks. The control group included 20 almost healthy students of 18–25 years old, 20.2 average (10 women and 10 men).

Life quality was assessed using the unified SF-36 questionnaire, which includes assessment of the physical health scale and the mental health scale. The level of complete health corresponds to 100 points. The lower is the overall score, the worse is the quality of life.

The PHQ-9 (Patient Health Questionnaire) was used to determine the presence and severity of depression. According to the survey results, you can score from 0 to 27 points, which allows you to interpret the severity of depression from the absence of this violation to high-grade depression.

The psychosomatic condition of patients was assessed according to the Spielberger-Khanin scale to determine personal and reactive anxiety. When analyzing the results, the total indicator for each of the sub-scales can be in the range from 20 to 80 scores. When interpreting the indicators, the following anxiety assessments are used: up to 30 scores – low, 31–44 scores – moderate; 45 and more – high.

Based on the Wayne questionnaire the availability and severity of ADS was determined, as well as the type of autonomic status (sympathicotonia, vagotonia, and eutonia (vegetative tone)) was established. The questionnaire consists of 11 questions. As a result, a healthy person can score up to 15 points. If more than 15, then we can talk about the presence of VDS.

Patients were tested for the acidity of gastric juice by intragastric pH-meter method using IKZh-2 apparatus (produced in Ukraine). Motor function of the esophagus and stomach was identified using an ultrasound examination conducted on ALOKA SSD-650 machine (produced in Japan) and Ultima pro-30 machine (produced in Ukraine) – in the patient's left side and on the back; in epigastric region and projections at esophageal hiatus; fasted and 5, 10 and 15 minutes after drinking 0.5 l of liquid. The study measured the thickness of the esophagus wall, the esophagus width in the lower third, the diameter of esophageal hiatus, the presence of fluid regurgitation, and its duration. The organic and functional state of myocardium was studied with the help of pulse wave Doppler sonography with color mapping on the device ALOKA SSD-650 (manufactured in Japan) and ULTIMA pro-30 (manufactured in Ukraine).

To process statistical data, we used Microsoft Office Excel 2007 and the statistical data processing system Statistica 6.0. Under normal distribution, Student's t-test was used; in case of deviation from the normal distribution, nonparametric methods were used. The mean value (M), Student's t-test was assessed. The differences were considered significant at  $p < 0.05$ . The results were presented as  $M \pm m$ , where M is the median and m is the standard deviation.

### 3. Results

The study found that patients in groups 1 and 3 presented typical GERD complaints of heartburn, which bothered them more than twice a week, as well as at night, they often felt a sour taste in their mouth. Patients in groups 2 and 3 had typical NCD complaints: they were concerned about heart failure, sometimes pain in the lower third of the sternum, a decrease in blood pressure to 90/60 or an increase in it to 135/85. According to the results of pulse wave Doppler sonography with color mapping, no organic heart pathology was detected in patients of groups 2 and 3. On ECG, some of the patients in these groups showed a slight violation of the repolarization processes, while all the others showed no pathological changes.

When studying the sleep quality index in patients of the study and control groups according to the Pittsburgh questionnaire (PSQI), the following results were found (**Table 1**).

It was found that sleep disorders were observed in all groups under control, however, insomnia ( $p < 0.05$ ) was more pronounced in patients of group 3 because all the indicators of this questionnaire were significantly higher in comparison not only with the control group, but also with patients of groups 1 and 2.

The quality of life indicators in accordance with the unified SF-36 questionnaire are shown in **Table 2**.

**Table 1**

Characteristics of sleep quality indicators in treatment and control groups

Indicators	Group 1 n=25	Group 2 n=26	Group 3 n=30	Control group n=20	p
Sleep duration	0.95	1.19	1.46	0.3	p<0.05
Sleep disturbance	1.16	1.0	1.52	0.25	p<0.05
Duration of falling asleep	50±10 min	45±14 min	60±15 min	13±3,5 min	
Sleep latency	2.4	1.95	2.7	0.32	p<0.05
Daytime dysfunction	1.27	1.53	2.01	0.15	p<0.05
Sleep efficiency	1.05	1.04	1.54	0.24	p<0.05
Subjective sleep quality	1.86	1.84	2.47	0.53	p<0.05
Use of sleep medication	0	0	0	0	
Average total score	7.74	7.55	11.7	1.8	p<0.05

**Table 2**

Characteristics of quality of life in treatment groups and control group individuals

Indicators	Group 1	Group 2	Group 3	Control group	p
Physical functioning	43.5±3.8	40.1±3.9	41.7±3.2	84.5±4.0	p>0.05
Role-physical functioning	27.0±3.3	34.9±3.9	36.7±4.0	71.4±3.0	p<0.001
Bodily pain	41.2±3.6	36.5±3.1	23.1±3.8	76.3±4.0	p<0.001
General health	35.5±3.9	34.3±3.6	32.2±3.9	74.9±4.1	p>0.05
Vitality scale	45.5±3.2	31.5±4.2	40.4±3.2	80.5±3.2	p<0.001
Social functioning	45.2±3.5	44.1±3.4	43.6±3.3	81.4±4.2	p>0.05
Role-emotional functioning	48.3±3.1	43.4±3.5	31.7±3.6	78.6±3.5	p<0.001
Mental health	44.5±3.3	38.4±3.9	30.5±2.7	75.4±3.7	p<0.001

Patients of all three groups compared to the control group showed a significant decrease in quality of life on all scales. At the same time, the lowest indicators are observed in patients with combined pathology, but on the role-physical functioning scale, the lowest indicator is observed in patients with GERD and insomnia, the vitality scale indicator is most reduced in patients with NCD and insomnia. On the other hand, unreliable differences ( $p>0.05$ ) were found on the scales of physical, social functioning and general health.

Data from the PHQ-9 questionnaire is presented in **Table 3**.

**Table 3**

Characteristics of indicators in patients of treatment groups and control groups according to the PHQ-9 questionnaire

Indicators	Group 1	Group 2	Group 3	Control group	p
Absence of depression (1–4 points)	13.04 %	5.66 %	4.55 %	96.7 %	p<0.05
Mild depression (5–9 points)	21.74 %	20.11 %	13.65 %	3.3 %	p<0.05
Moderate depression (10–14 points)	65.22 %	74.23 %	81.8 %	0	p<0.05

Patients in all three follow-up groups were found to have moderate depression, but the highest percentage was observed in group 3 patients.

According to the results of the Spielberg-Hanin questionnaire, both personal and situational anxiety were higher in patients of groups 1, 2 and 3 than in the control group. Situational anxiety was higher in group 1 and averaged 47.2 points ( $p<0.05$ ), in group 2 this indicator was 44.0 points ( $p<0.05$ ), in group 3 – 41.5 points ( $p<0.05$ ), in the control group – 22 points ( $p<0.05$ ). Personal anxiety was higher in group 1 patients than in group 2 and 3 and was 52.7 points ( $p<0.05$ ), 46.5 and 44.9 points, respectively ( $p<0.05$ ), in the control group – 27 points ( $p<0.05$ ).

During the study, it was found that according to the Wayne questionnaire, patients in groups 1, 2 and 3 have a syndrome of autonomic dysfunction. In students with GERD and insomnia, the results ranged from 19 to 37, with an average of 33. In patients with NCD and insomnia, the indicators ranged from 23 to 40, with an average of 35. In patients with combined pathology, the indicators were from 25 to 45, with an average of 39. Students in the control group had scores from 5 to 13, with an average of 8. Thus, ADS was most pronounced in patients with combined pathology. The type of autonomic tone is shown in **Table 4**.

**Table 4**

Type of tone autonomic nervous system in the treatment groups and the control group

Type of tone autonomic nervous system	Group 1	Group 2	Group 3	Control group	p
Eutonic	11.1 %	10.5 %	14.4 %	61.2 %	$p<0.05$
Vagotonic (parasympathicotonia)	12.5 %	48.5 %	45.5 %	13.7 %	$p<0.05$
Sympathicotonic	76.4 %	41.0 %	40.1 %	25.1 %	$p<0.05$

Thus, in patients with GERD with insomnia, sympathicotonia prevails, while in patients with NCD and insomnia and GERD with NCD and insomnia, parasympathotonia prevails, although it is not reliable.

When studying the secretory function of the stomach in the study groups, as well as in the control group, the following results were obtained (**Table 5**).

**Table 5**

Indicators of pH-metry in the treatment groups and the control group

Indicators of pH-metry	Group 1	Group 2	Group 3	Control group	p
The stomach body	0.89±0.05	1.60±0.1	1.32±0.05	1.61±0.1	$p<0.05$
The antrum	6.12±0.15	7.22±0.13	5.4±0.17	7.21±0.12	$p<0.05$

In the study of secretion in patients with isolated GERD and insomnia, indicators of increased aggression of gastric juice came to the fore, while in patients with GERD with concomitant NCD and insomnia, indicators of a decrease in the alkalizing function of the antrum came to the fore. In patients with NCD, the results are within the normal range.

When examining the motor function of the esophagus and stomach in patients of the study groups, as well as in the control group, the following results were found (**Table 6**).

In patients with combined pathology, changes in motility were most pronounced, compared not only with the control group, but also with patients with isolated GERD and insomnia. Patients with NCD and insomnia had results comparable to the control group.

Thus, for patients with GERD and insomnia given the prevalence of increased aggression of gastric juice, it is reasonable to use PPI (omeprazole 20 mg 2 times a day for 5 weeks), and melatonin 3 mg per night during 3 weeks. For patients with NDC and insomnia, given the noticeable decrease vitality scale, it is reasonable to use melatonin 3 mg per night during 3 weeks. For patients with comorbid GERD, NCD and insomnia, given the prevalence of motor-evacuation disorders in them, it is reasonable to use PPI (omeprazole 20 mg 2 times per day during 5 weeks), with prokinetics (domperidone 10 mg 3 times per day during 5 weeks), and melatonin 3 mg per night during 3 weeks.

**Table 6**

Indicators of ultrasound examination of the esophagus and stomach with water load in the treatment groups and the control group

Indicators	Group 1	Group 2	Group 3	Control group	p
The esophagus width in the lower third	2.57±2.1 cm	2.10±0.2 cm	2.63±2.8 cm	2.11±0.1 cm	p<0.05
The diameter of esophageal hiatus	1.83±0.25 cm	1.52±0.14 cm	1.93±0.27 cm	1.51±0.12 cm	p<0.05
The presence and duration of gastroesophageal reflux	7 minutes ± 1.3	5 minutes ± 1.5	9 minutes ± 1,3	5 minutes ± 1.1	p<0.05
The thickness of the esophagus wall	0.40±0.03 cm	0.30±0.07 cm	0.46±0.05 cm	0.31±0.07 cm	p<0.05

Analyzing the obtained data, it was found that in all study groups there is a autonomic dysfunction, which is directed towards sympathicotonia in patients of the first group, or parasympathicotonia in patients of the second and third groups. Autonomic dysfunction has a key influence on the main pathogenetic factors in the formation of both GERD and NCD and insomnia, and the type of autonomic tone determines the features of the clinical course of both isolated and combined pathology. Determination of autonomic tone opens up new opportunities for prevention and treatment of these groups of patients.

#### 4. Discussion

Analyzing the obtained data, they are in close relationship with the main world trends in the study of this pathology [13, 14] and at the same time have a number of fundamental features. So, to date [15, 16] students studied the clinical picture of isolated GERD and GERD with combined pathology [17], however, we have studied the clinical features in the combination of GERD with NCD and insomnia.

At the same time, [18, 19] studied the role of autonomic dysfunction in various pathologies, however, the present study is devoted to the analysis of the role of autonomic dysfunction in the combination of GERD with NCD and insomnia, which have not yet been the subject of scientific consideration.

The relationship between GERD and psychosomatic disorders is shown in a number of works [21]. The level of depression and anxiety among students suffering from GERD was analyzed [7, 16]. The relationship between GERD, psychological stress and insomnia is shown in works [12, 22]. In its turn, this article studied and revealed the presence of a higher level of depression in patients with comorbid pathology compared to isolated one, and anxiety – in GERD with insomnia. In addition, the quality of life in patients with GERD was studied [2, 23]. At the same time, we have shown that the combination of GERD with NCD and insomnia significantly reduces the indicators of the SF-36 scale, in comparison with isolated pathology. At the same time, motor-secretory changes in students with GERD and GERD with concomitant obesity were studied [20]. We supplemented this study by reviewing these indicators in students with GERD in combination with NCD and insomnia.

**Study limitations.** The study was not conducted in case of identified concomitant pathology of other organs and in case of patients refuse to participate in the study.

**Prospects for further research.** Further study of the tone of the ANS in patients with both isolated GERD and GERD with combined pathology is important for the formation of treatment and prevention regimens for a particular patient, and at the same time it outlines new directions in approaches to both diagnosis and treatment of this pathology.

#### 4. Conclusions

It is shown that patients with GERD and insomnia have more pronounced sympathicotonia and indicators of increased aggression of gastric juice (in the stomach body 0.89±0.05) and reactive (47.2 points) and personal anxiety (52.7 points) come to the fore, which suggests the advisability of use PPI (omeprazole 20 mg 2 times a day for 5 weeks), and melatonin 3 mg per night during 3 weeks.

It was found that in patients with NCD and insomnia, parasympathicotonia prevails, although it is unreliable, with a simultaneous more pronounced decrease in vitality scale ( $31.5 \pm 4.2$ ) compared to other treatment groups, with a moderate increase in the indicators of reactive (44.0 points) and personal anxiety (46.5 points), which suggests the advisability of use 3 mg of melatonin per night during 3 weeks.

In patients with GERD NDC and insomnia often prevails parasympathicotonia but it is unreliable and at the forefront compared to other therapeutic groups are to be released motor disorders, lower rates alkalizing function of the antrum ( $5.4 \pm 0.17$ ), the highest rates of depression (81.8 %), as well as the worst indicators of quality of sleep (11.7) and quality of life, which suggests the advisability of use PPI (omeprazole 20 mg 2 times per day during 5 weeks), with prokinetics (domperidone 10 mg 3 times per day during 5 weeks), and melatonin 3 mg per night during 3 weeks.

Autonomic dysfunction has a key influence on the main pathogenetic factors in the formation of both GERD and NCD and insomnia, and the type of autonomic tone determines the features of the clinical course of both isolated and combined pathology.

### Conflict of interests

The authors declare that they have no conflicts of interest.

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