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ANXIETY AND ITS SIGNIFICANCE IN THE STRUCTURE OF SOMATOFORM DISORDERS IN CHILDREN AND THE ROLE OF SEROTONINE AND TRIPTOPHAN IN THEIR NASCENCE

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The work was aimed to study the confidence and significance of anxiety in the occurrence of somatoform disorders (SD) in children, to establish the role of serotonin and tryptophan in its development. 111 children were diagnosed with SD. In 109 (98,2%) children were diagnosed with excessive anxiety. Serotonin levels in children with personality and reactive anxiety were 1,16 ± 0,33 μmol/l and 1,17 ± 0,33 μmol/l, respectively and were lower compared to the control group, where its level reached 1,35 ± 0,34 μmol/l ($p<0,004$ and $p<0,008$, respectively). The level of serotonin in patients with anxiety in combination with depression was lower compared with patients with anxiety without depression ($p<0,0001$). It is possible to suspect the existence of several subtypes of SD, where one can occur as a variant of depression with somatic manifestations and secondary anxiety in which serotonin metabolism may play a key role, whereas the second variant of SD can arise as a variant of anxiety disorder with somatic manifestations and somatic manifestations and secondary disorders as a personality response to a disease in which serotonin metabolism does not play a key role in the development of pathology.

Key words: somatoform disorder, anxiety, serotonin, tryptophan, children.

The paper is a fragment of the research project "Physiological and hygienic assessment of the features of adaptation of children, adolescents and young people to the conditions of study in modern educational institutions and scientific bases of university hygiene: vocational aspects, problems of introduction of health-saving technologies and creation of preventive educational environment", state registration No. 0116U000038.

A study of mental health disorders in primary care by the World Health Organization has found widespread anxiety among pediatric outpatients [2].

It is difficult for children to express emotions and feelings through language, so psychological stress and anxiety can be expressed as somatic symptoms [10].

Somatization can be characterized as a tendency to express psychological dysphoria with bodily symptoms. Somatic symptoms are known to be associated with many psychiatric disorders, but are usually accompanied by anxiety and depression [11].

Somatization of emotional disorders in ICD-10 is considered in the heading F45.3 as "Somatoform dysfunction of the autonomic nervous system" or "Somatoform disorder" (SD) [1].

Somatoform disorder brings together a group of psychogenic diseases characterized by pathological symptoms reminiscent of somatic disease, but in which, according to the survey results, there aren't detected morphological manifestations, although there are often nonspecific functional disorders [1, 4]. These symptoms lead to numerous medical consultations, additional unnecessary research and manipulation and in children cause family and social maladaptation, impaired educational functioning [8].

With the release of DSM-5, the SD was renamed "Somatic Symptoms Disorder" [9].

It is known that serotonin deficiency in the brain and the impact of psychosocial stress play an important role in the development of depression and anxiety disorders [14].

Serotonin is an amine that is synthesized in the gut (95%) by enterochromaffin-like cells and it is stored in platelets and it is only minimally contained in the brain (5%) as a neurotransmitter [12, 13].

Dysfunction of the serotonergic system is involved in the etiology of many psychiatric (depression, schizophrenia, alcoholism) and neurological (migraine, epilepsy, Alzheimer's disease) pathologies, including the development of anxiety disorders [12].

Unfortunately, data on the mechanisms and factors of development of SD and anxiety, especially the role of serotonin in their onset and other pathogenesis chains in children are rather limited and need further investigation.

The purpose of the work was to study the presence, severity and significance of anxiety in the occurrence of somatoform disorders in children, to establish the role of serotonin and tryptophan in its development.

Materials and methods. The studies were performed on the clinical basis of the Department of Pediatrics, Obstetrics and Gynecology Faculty of Postgraduate Education, Vinnytsia National Pyrogov Memorial Medical University in the gastroenterological, cardiological, nephrological and neurological departments of Khmelnytskyi regional children's hospital in Khmelnitskyi.

Following the informed consent of parents and children, 111 patients diagnosed with SD were included in the study. The average age of children was 13.6±2.3 years (M±σ), of which boys were 37.8%

(n = 42) and girls were 62.2% (n = 69). In the gastroenterology department 39 children with SD were examined, in the cardiology - 26 children, in the nephrological - 16 children and in the neurological - 30 children. Also 33 children with average age of 13.2±2.0 years (M±σ) were treated in somatic wards and did not have emotional disorders, who were in the control group were examined.

The selection of children and the diagnosis of SD were performed after a general clinical examination and according to the criteria of SD ICD-10. For identifying the presence of depression and its clinical symptoms in a selected group of children with somatoform disorders, the Children's Depression Inventory (M. Kovacs) was used to assess the affective and cognitive symptoms of depression.

For investigation of the anxiety we used the Spielberger (STPI - State Trait Personal Inventory) questionnaire modified by A. D. Andreeva.

In all 111 children diagnosed with SD blood samples were taken to determine serum concentrations of serotonin and tryptophan, which were determined in the certified laboratory of "Diagnostics Plus", Kharkiv.

Serotonin was investigated by a biochemical method. The tryptophan was examined by liquid chromatography using the Milchrom-6 microcolonial liquid chromatography.

Statistical analysis was performed using Statistica 8.0.360, MedCalc.7.4.4.1. Quantitative features are given as M±σ (arithmetic mean ± mean deviation). The likelihood of differences was assessed using a two-tailed Student's t-test and plotting a 95% confidence interval (CI) for the mean difference. Values at $p<0.05$ were considered significant.

Results of the study and their discussion. In our study of SD by the gastrointestinal tract in children was predominantly manifested as functional dyspepsia (FD) - in 30 (27.0%) children, irritable bowel syndrome - in 8 (7.2%), SD by other organs and systems manifested with various pain syndromes (headache, fibromyalgia, arthralgia, dorsalgia) - in 10 (9.0%), violation of thermoregulation - 7 (6.3%), SD by the cardiovascular system cardiac and hyperventilation syndromes - 39 (35.1%), extrasystolic arrhythmia - in 1 (0.9%) case, SD by the urinary systems neurogenic dysuric disorders - in 16 children (14.5%).

Anxiety is an individual psychological trait that involves an increased tendency to feel anxious in a wide variety of situations. There are two types of anxiety - situational, or reactive, and personal. Reactive anxiety is an indicator of the intensity of experiences that occur in relation to typical events. Reactive or situational anxiety is characterized by tension, anxiety, nervousness. Personal anxiety - the readiness of a person to experience fear and anxiety about a wide range of subjectively significant phenomena [3].

According to the questionnaire, among 111 children in 2 (1.9%) cases there were no personal anxiety disorders, 39 (35.1%) children had moderate personal anxiety, and 70 (63.0%) children had severe personal anxiety (fig. 1). Also, 5 (4.0%) children reported no reactive anxiety, moderate reactive anxiety was detected in 70 (63.6%) children, severe reactive anxiety in 36 (32.4%) children (fig. 2).

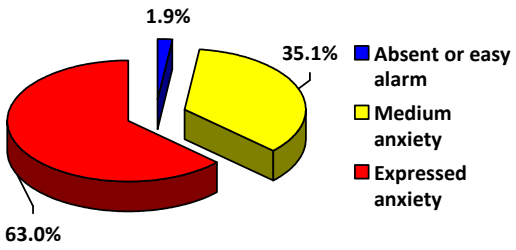

Fig. 1. General structure of personal anxiety in children with SD according to the questionnaire STPI.

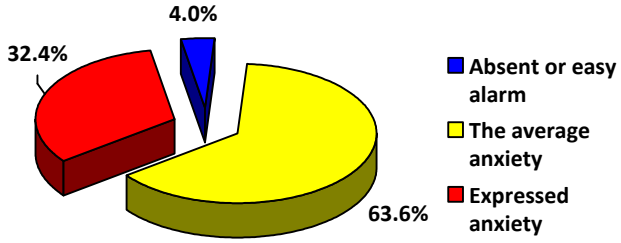

Fig. 2. General structure of reactive anxiety in children with SD according to the questionnaire STPI.

Thus, it should be noted that in all patients with SD significant anxiety disorders, both personal and reactive nature, which can be a factor in the propensity to develop SD and a key cause of their occurrence.

The average personal anxiety score for all children with anxiety disorders according to the questionnaire was 25.2±3.3 points, and reactive anxiety 23.8±4.3 points indicating the average severity of anxiety disorders in children with SD. In the general structure of adolescents signs of marked personal and reactive anxiety were found in 18 (16.2%) persons whose data significantly exceeded the average and reached submaximal figures (maximum 40), which is quite significant and needs appropriate attention, since they are the largest risk of development in the future of SD and other pathologies of the anxiety spectrum.

The mean age of children with anxiety symptoms was 13.6±2.3 years and was not significantly different from the mean age of children in the control group, who was 13.2±2.0 years.

Among patients with anxiety disorders a significant prevalence of girls was noted - 68 (61.8%). over boys - 42 (39.2%), their ratio was 1.6:1. The prevalence of female sex over male (75% vs. 25%) in SD in children was also noted in the study by Bujoreanu S. et al. (2014), with the mean age of 14.4 years [6].

Our findings also indicate that women are more likely to develop anxiety disorders and accordingly to develop of SD.

The highest incidence of severe personal anxiety disorders was observed in patients with SD by the cardiovascular system (73.1%), slightly lower in patients with gastrointestinal tract and SD by other organs and systems (66.6%, respectively) and the lowest was in the SD from the urinary system (56.3%).The available data also correlate with the incidence of SD which is also more commonly occurring on the part of the cardiovascular system and gastrointestinal tract, which may indicate the decisive value of personality disorders of the anxiety spectrum in the occurrence of SD.

The highest incidence of severe reactive anxiety disorders was observed in patients with SD by the urinary system (37.5%), slightly lower with SD by other other organs and systems (33.3%) and even lower with SD by the cardiovascular system (26. 9%) and gastrointestinal tract (20.5%).

Reactive anxiety is an indicator of the intensity of experiences that occur in relation to typical events [3]. Probably dysuric disorders have the greatest stressful effect on the child with complex formation, limitations and constant experiences and expectations, which forms the most pronounced reactive anxiety in response to the manifestation of the disease.

It is known that a decrease in serotonergic activity can lead to the development of anxiety disorders and depression, while the use of antidepressants lead to modulation of the serotonergic system and decrease the symptoms of anxiety and depression which indicates the important role of serotonin in their development [5].

In view of this we aimed to determine the role of serotonin and its precursor tryptophan in the development of anxiety disorders in patients with SD and its importance in the development of SD.

Serum serotonin levels in patients with children with excessive personal anxiety were 1.16±0.33 μmol/l and were significantly lower compared to children in the control group without SD and anxiety, whose level was 1.35±0.34 μmol/l (95% CI, 0.06 – 0.32 μmol/l, p<0.004) (fig. 3).

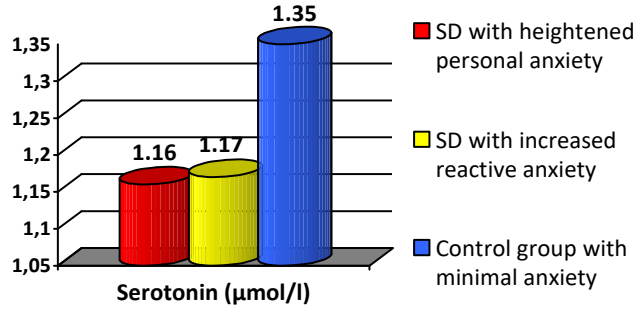

Fig. 3. The average serotonin levels in the serum of children with SD and high anxiety and minimal anxiety.

Also serum serotonin levels in patients with overactive reactive anxiety were 1.17±0.33 μmol/l and were also significantly lower compared with control children (95% CI, 0.05 – 0.31 μmol/l, p<0.008).

In contrast to serotonin serum tryptophan levels in patients with SD with excessive personality and reactive anxiety were 0.029±0.024 and 0.031±0.028 mmol/l, respectively and practically did not differ from the control group, whose level was 0.030±0.028 mmol/l (p>0.05).

Analyzing the levels of serotonin and tryptophan in patients with excessive anxiety depending on the manifestation of SD from the side of systems and organs, we can note certain features that are shown in table. 1.

Table 1

Levels of serotonin and tryptophan depending on the manifestations of SD from the side of organs and systems and excessive anxiety compared with the control group

	Serotonin (μmol/l)			Tryptophan (mmol/l)		
	n	M±σ	p	n	M±σ	p
SD by the gastrointestinal tract	39	1.18±0.25	<0.01	39	0.026±0.024	>0.05
Control	33	1.35±0.34		27	0.029±0.024	
SD by the cardiovascular system	26	1.21±0.31	>0.05	28	0.040±0.036	>0.05
Control	33	1.35±0.34		27	0.029±0.024	
SD by other organs and systems	30	1.31±0.33	>0.05	28	0.032±0.028	>0.05
Control	33	1.35±0.34		27	0.029±0.024	
SD by the urinary systems	16	0.87±0.46	<0.001	9	0.027±0.021	>0.05
Control	33	1.35±0.34		27	0.029±0.024	

The lowest levels of serotonin were observed in children with SD by the urinary systems and gastrointestinal systems which were significantly lower compared to the control group. Children with SD on the part of the cardiovascular system and SD on the part of other organs and systems also showed a

decrease in serotonin levels but the difference with the indicators of children in the control group is not statistically significant. No significant deviation in tryptophan concentration compared to the control group was found in any of the subgroups of children with SD.

The level of serotonin in children with SD by the urinary systems and excessive anxiety was significantly lower compared to patients with SD by other organs and systems and excessive anxiety (95% CI, 0.20 – 0.67 μmol/l. $p<0.0005$), compared with SD on the part of the cardiovascular system (95% CI, 0.10 – 0.58 μmol/l. $p<0.006$), and compared with SD by the gastrointestinal tract (95% CI, 0.11 – 0.50 μmol/l. $p<0.002$).

Serotonin levels in girls with SD and anxiety were slightly lower compared to boys – 1.15±0.34 μmol/l and 1.19±0.31 μmol/l, respectively, while at the same time tryptophan levels in boys compared to boys girls were higher – 0.032±0.031 and 0.029±0.028 mmol/l, respectively but these differences were not statistically significant. At the same time, in comparison with the control group the level of serotonin was significantly lower both in girls (95% CI, 0.057 – 0.343 μmol/l, $p<0.006$) and in boys (95% CI, 0.01 – 0.31 μmol/l, $p<0.03$). There were no significant deviations from tryptophan compared to the control group.

It is known that serotonin can play a significant role in the development of not only anxiety but also depression. Quite often anxiety and depression are comorbid to one another. Depression can be a factor of anxiety, while depression itself can be a reaction to the long-existing anxiety itself including during SD.

Somatic symptoms in SD are consistently associated with anxiety-depressive disorders in childhood. The likelihood of associated anxiety and depression increases with the number of somatic symptoms present [7].

In our study, 48 (43.2%) children with SD with excessive anxiety on the CDI scale were found to varying degrees of depressive disorders. Subsequently it was found that serotonin in patients with anxiety in combination with depression had the lowest rates in this study and was 1.03±0.37 μmol/l and was significantly lower than patients with excessive anxiety without depression, where the level was 1.30±0.27 μmol/l (95% CI, 0.15 – 0.39 μmol/l, $p<0.0001$) and compared to the control group where its level was 1.35±0.34 μmol/l (95% CI, 0.16 – 0.48 μmol/l, $p<0.0002$). At the same time patients with excessive anxiety without depression compared with the control group, serotonin levels were also lower but not significant. Tryptophan levels were slightly higher in patients with excessive anxiety and depression (0.035±0.031 mmol/l) compared with patients with excessive anxiety and without depression (0.026±0.026 mmol/l) but were not statistically different and compared with the control group, where the tryptophan level was 0.029±0.024 mmol/l.

Thus depression of both primary and secondary origin in relation to anxiety can significantly impair the course of SD. Considering the data obtained from the serotonin study, it can be noted that there are several subtypes of SD, where one variant of SD can occur as a variant of a depressive episode with somatic manifestations and secondary anxiety as a symptom of depression in which serotonin metabolism can play a key role and can occur as a variant of anxiety disorder with somatic manifestations and secondary depression, as a personality response to a disease in which serotonin metabolism may not be disturbed or play a key role a role in the development of disease. It is possible that in the second embodiment, other neurotransmitters (norepinephrine, dopamine, GABA and others) may play a key role in the development of SD. However, it is almost impossible to determine clinically a possible version of SD based on clinical symptoms alone. It is difficult to establish the basis on which SD occurs (primarily based on depression or anxiety disorder), but the detection of low levels of serotonin may be a predictor of a good response to the treatment of such conditions with serotonin-selective serotonin and serotonin inhibitors that occur on the basis of a depressive episode.

It should be noted that studies by Shidhaye R. et al. (2013), also indicate a strong association between SD and depression/anxiety (odds ratio 2.5 – 3.5). The authors also observed patients with SD without depression/anxiety. It is likely that these disorders may include common etiological factors can be variants of the same mental disorder and that one disorder may be a factor in the occurrence of another disorder [15].

We have not received conclusive data on the involvement of tryptophan and the involvement of the tryptophan-serotonin chain in the development of anxiety disorders in children with SD.

Although in our study the presence of anxiety and depression was associated with a decrease in serotonin concentration in the blood but their severity hadn't dependence on serotonin concentration including tryptophan concentration. The severity of depression and its various clinical manifestations can also depend on other brain mediators (norepinephrine, dopamine), the activity of enzyme systems and receptors and other factors that need further investigation.

Thus the high prevalence of excessive anxiety among children with SD (99.1%) indicates its importance in the course and development of the disease, its clinical manifestations and possibly prognosis. The question of the relationship between depression and SD, anxiety and SD, and depression and anxiety remains important. Probably SD can be a multifactorial pathology for the existence of different pathogenetic subtypes, however, with similar somatic symptoms, the detection of which will improve and improve treatment.

Conclusion

Excessive anxiety was evident in 98.2% of children with SD of whom severe personal anxiety was identified in 63.0% and severe reactive anxiety in 32,4% of children, indicating its widespread prevalence and significant role in the occurrence of SD. The prevalence of girls (61.8%) over boys (39.2%) was noted among patients with SD and excessive anxiety, which amounted to 1.6:1, indicating a greater tendency of women to develop anxiety disorders and, accordingly to SD development.

The highest frequent severe personal anxiety was observed in patients with SD by the cardiovascular system (73.1%) and the lowest in patients with SD by the urinary system (56.3%), which correlates with the highest number of patients with cardiac and hyperventilation manifestations syndromes (35.1%), where personal anxiety can be the basis for their development.

Serum serotonin levels in patients with SD with excess personality and reactive anxiety were lower compared to controls (95% CI, 0.06 – 0.32 μmol/l, $p<0.004$) and (95% CI, 0.05 – 0.31 μmol/l, $p<0.008$), respectively, indicating its importance in the development of anxiety disorders in SD. Low serotonin was also associated with excessive anxiety and SD from the urinary system (95% CI, 0.24 - 0.77 μmol/l, $p<0.0002$) and from the gastrointestinal tract (95% CI, 0.031 – 0.309 μmol/l, $p<0.01$), which confirms its special relationship and physiological function in the operation of these systems.

Given that the level of serotonin in patients with excessive anxiety in combination with depression was lower compared with patients with excessive anxiety without depression (95% CI, 0.15 – 0.39 μmol/l, $p<0.0001$), it is possible to suspect the existence of several subtypes of SD, where one subtype of SD may occur as a variant of a depressive episode with somatic manifestations and secondary anxiety as a symptom of depression, in which impaired serotonin metabolism may play a key role, while a second variant of SD may occur as a variant of anxiety disorder with somatic manifestations and layers of sec other depression, as a personality response to a disease in which serotonin metabolism may not be impaired.

We did not find conclusive evidence of involvement in the mechanisms of SD development with disturbing disorders of the serotonin precursor tryptophan and the tryptophan-serotonin chain.

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Реферати

ТРИВОГА ТА ЇЇ ЗНАЧЕННЯ В СТРУКТУРІ СОМАТОФОРМНИХ РОЗЛАДІВ У ДІТЕЙ, А ТАКОЖ РОЛЬ СЕРОТОНІНУ І ТРИПТОФАНУ В ЇХ ВИНИКНЕННІ

Пипа Л.В., Лисиця Ю.М., Свістільнік Р.В., Булат Л.М.

Метою роботи було дослідити наявність, вираженість та значення тривоги у виникненні соматоформних розладів (СР) у дітей, встановити роль серотоніну і триптофану в її розвитку. Обстежено 111 дітей, в яких було діагностовано СР. У 109 (98,2%) дітей діагностовано надмірну тривогу. Рівень серотоніну у дітей з особистісною і реактивною тривогою складав 1,16±0,33 мкмоль/л та 1,17±0,33 мкмоль/л, відповідно, і був нижчим, порівняно з контрольною групою, де його рівень сягав 1,35±0,34 мкмоль/л, ($p<0,004$ і $p<0,008$, відповідно). Рівень серотоніну у хворих на тривогу в поєднанні з депресією був нижчим у порівнянні з хворими на тривогу без депресії ($p<0,0001$). Можна запідозрити існування декількох підтипів СР, де один може виникати як варіант депресії з соматичними проявами і вторинною тривогою, в якому порушення обміну серотоніну може відігравати ключову роль, тоді як другий варіант СР може виникати як варіант тривожного розладу з соматичними проявами і вторинною депресією, як реакція особистості на захворювання, в якому обмін серотоніну не відіграє ключову роль в розвитку патології.

Ключові слова: соматоформний розлад, тривога, серотонін, триптофан, діти

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ТРЕВОГА И ЕЕ ЗНАЧЕНИЕ В СТРУКТУРЕ СОМАТОФОРМНЫХ РАССТРОЙСТВ У ДЕТЕЙ, А ТАКЖЕ РОЛЬ СЕРОТОНИНА И ТРИПТОФАНА В ИХ ВОЗНИКНОВЕНИИ

Пыпа Л.В., Лисица Ю.Н., Свистильник Р.В., Булат Л.М.

Целью работы было исследовать наличие, выраженность и значение тревоги в возникновении соматоформных расстройств (СР) у детей, определить роль серотонина и триптофана в ее развитии. Обследовано 111 детей, в которых было диагностировано СР. В 109 (98,2%) детей диагностирована высокий уровень тревоги. Уровень серотонина у детей с личностной и реактивной тревогой составлял 1,16 ± 0,33 мкмоль/л и 1,17 ± 0,33 мкмоль/л, соответственно, и был ниже по сравнению с контрольной группой, где его уровень достигал 1,35 ± 0,34 мкмоль/л, ($p<0,004$ и $p<0,008$, соответственно). Уровень серотонина у больных с наличием тревоги в сочетании с депрессией был ниже по сравнению с больными с тревогой но без депрессии ($p<0,0001$). Можно подозревать существование нескольких подтипов СР, где один может возникать как вариант депрессии с соматическими проявлениями и вторичной тревогой, в котором нарушение обмена серотонина может играть ключевую роль, тогда как второй вариант СР может возникать как вариант тревожного расстройства с соматическими проявлениями и вторичной депрессией, как реакция личности на заболевание, в котором обмен серотонина не играет ключевой роли в развитии патологии.

Ключевые слова: соматоформное расстройство, тревога, серотонин, триптофан, дети

Рецензент Крючко Т.О.

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EVALUATION OF HEALTHY LIFESTYLING LEVEL IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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In order to develop a personalized approach in patients with COPD - an individual and effective strategy to implement the recommendations, observance of the principles of healthy lifestyle in the first stage, the study of the main risk factors for the disease, on the basis of which developed for each patient an effective personalized strategy for observing the health of the elderly complex with the implementation of patients with curative respiratory gymnastics by Buteyko and hardening of the body - pouring cold water. The authors of the article prove that the observance by the patients with COPD of recommendations for the regulation of lifestyle, nutrition, systematic performance of therapeutic gymnastics by Buteyko and quenching of the body contribute to the achievement of long remission, improvement of quality of life.

Key words: healthy lifestyle (HLS), chronic obstructive pulmonary disease (COPD).

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Chronic Obstructive Pulmonary Disease (COPD) is one of the most important medical and social problems in Ukraine and in the world, according to the WHO, 0.8% of the world's population is affected today [3]. Due to the long-term effects of risk factors and the aging population around the world, an accelerated increase in COPD is observed [6]. Often severe exacerbations are associated with higher mortality. [3]. According to forecasts, by 2020, COPD will rank third among the leading causes of death