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ASSOCIATIONS OF GENERAL MENTAL HEALTH SYMPTOMS WITH SUBJECTIVE SLEEP QUALITY AND INDIVIDUAL DAYTIME SLEEPINESS*

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Abstract

Purpose: Sufficient sleep quality plays a significant role for long-term physical and mental health. The aim of this study was to examine the associations of general mental health symptoms with sleep quality and daytime sleepiness. **Materials and Methods:** A cross-sectional survey with 84 included participants (female: n = 42, male: n = 42) was conducted. General mental health symptoms were assessed using the 12-item General Health Questionnaire (GHQ-12), sleep quality was measured with the Pittsburgh Sleep Quality Index (PSQI), and daytime sleepiness was evaluated with the Epworth Sleepiness Scale (ESS). Statistical differences were calculated using two-sample t-test and Mann–Whitney U test. For correlation analyses Spearman's rank correlation was used. **Results:** Subjects with poor sleep quality reached higher scores in the GHQ-12 and in the ESS than subjects with good sleep quality, but the difference regarding the ESS was not significant. Higher GHQ-12 scores were associated with higher PSQI scores but not with higher ESS scores. **Conclusions:** Major findings show strong evidence of an association between general mental health symptoms and sleep quality with poor sleepers having a more disturbed mental health than good sleepers. Further evidence of the interrelationship between subjective sleep quality and general mental health symptoms was found.

Keywords: *Mental health, Work ability, Stress, Sleep, Insomnia.*

Introduction

Restorative sleep is important for performance, productivity, and efficiency at the workplace as well as for work ability and mental well-being [1]. However, modern society demands permanent flexibility, mobility, and accessibility of the employee. As a consequence, psychological strain at the workplace appears to be an ever larger health hazard. The number of absences due to mental disorders increased sharply compared to other diseases [2].

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Psychological strain leads to an increased physiological and psychological activation [3]. This matter is in contrast to the physiological and psychological reduction of the activation as a main characteristic of sleep [1]. Sleep satisfaction is reduced by social stress [4]. Several studies could find associations between increased work-related psychosocial stress and poor sleep quality [5–8]. Perceived unfair treatment at the workplace is also associated with an increased risk for poor sleep quality in the long run [9].

Disturbed sleep is a symptom of various mental illnesses including bipolar disorder [10] and psychosis [11]. Some sleep problems even form part of the diagnostic criteria of certain psychic illnesses, e.g. major depression or post-traumatic stress disorder [12, 13]. Moreover, for example, regarding clinical depression and anxiety disorder the association between psyche and sleep

appears to be bidirectional [14–16]. Studies have also shown that sleep disturbances raise the risk for certain mental conditions, e.g. a first episode of psychosis [17], transition to major depression [18], paranoia [19], manic symptoms [20], and burnout [21]. On the other hand, improving sleep problems seem to reduce mental health problems [22].

2. Purposes, subjects and methods:

2.1. Purpose

The purpose of the present study was to further investigate the consequences of poor sleep quality on general mental health symptoms and the other way round. We hypothesised that: (1a) bad sleepers have a higher level of daytime sleepiness; (1b) reduced sleep quality is accompanied by higher daytime sleepiness; (2) poor sleep quality is accompanied by reduced general mental health symptoms.

2.2. Subjects & Methods

Participants and Design

Participants were recruited through the occupational health out-patient department of the Institute of Occupational Medicine of Otto von Guericke University Magdeburg within the context of regular preventive medical examinations of the employees and via advertisement (distribution of leaflets) both on Health Days and among local undergraduate students. In Germany Health Days are regularly offered in companies within the scope of the operational health management. On these days all employees are invited to participate in various health activities. The recruited participants collected the questionnaires in German at the out-patient department and completed them at home receiving a feedback after handing them in again. All participants except for one were native speakers. Exclusion criteria included shift work, chronic medication intake with influence on the heart rhythm, reported diabetes mellitus, untreated thyroid diseases and treated thyroid diseases with thyroid blood parameters outside the normal range, cardiac diseases, use of nocturnal oxygen or nightly continuous positive airway pressure, and reported diseases of the central or peripheral nervous system resulting in a final study sample of 84 participants of various occupational groups. All subjects provided informed consent prior to participation in the study. Participants' anonymity with consideration for data protection was fully ensured. The study was approved by the ethics committee of Otto von Guericke University Magdeburg (registration no. 50/16) in May 2016. The experimental part of the study was carried out until October 2017.

Questionnaires

Socio-Demographical and Medical Data

In the beginning participants were asked to give details about age, height and weight (for body mass index; BMI), waist and hip circumference (for waist-hip ratio; WHR), physical activities, job profile, and tobacco consumption. Furthermore, arterial systolic blood pressure (RR sys) and diastolic blood pressure (RR dias) were taken after a 3 to 5-minute stationary phase.

12-Item General Health Questionnaire (GHQ-12)

The GHQ-12 [23, 24], a short version of the GHQ, is an instrument to evaluate general mental health symptoms. It consists of 12 questions screening for recently experienced dysfunctional symptoms and behaviour on a four-stage answer-scale. There are 4 different possibilities for scoring [25]. In this study the Likert-scoring (0–3 scale; sum score ranging from 0–36) and the dichotomous GHQ-scoring (0–1 scale, 0 in the case of 0 or 1 in the Likert scale or 1 in the case of 2 or 3 in the Likert scale; sum score ranging from 0–12) [26] were used in which a higher value indicates a more disturbed state of psychological health. The cut-off value for disturbed mental health depends on population-specific factors [26–28]. Regarding the GHQ-scoring following Ustun and Sartorius [27] and like in Linden et al. [29] and Seibt et al. [30] a cut-off value of ≥ 5 was used. With regard to diagnostic validity the GHQ-12 has a sensitivity of 83.4 % and a specificity of 76.3 %. The internal consistency is indicated by a Cronbach's alpha coefficient of 0.85 [26].

Pittsburgh Sleep Quality Index (PSQI)

The PSQI [31] is a self-assessment questionnaire capturing subjective sleep quality of the preceding month. It consists of 19 self-rated questions and 5 questions for third-party evaluation not counted in the scoring of the PSQI. The 19 items generate 7 component scores (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, daytime dysfunction), each weighted equally on a 0–3 scale. The sum of the component scores yields the global PSQI score (range of 0–21) in which higher values indicate worse sleep quality. The cut-off value recommended by Buysse et al. [31] to distinguish between good and bad sleepers is > 5. Regarding diagnostic validity the original study shows a sensitivity of 89.6 % and a specificity of 86.5 %, the internal consistency is indicated by a Cronbach's alpha coefficient of 0.83 [31].

Epworth Sleepiness Scale (ESS)

The ESS [32] is a self-administered questionnaire assessing daytime sleepiness in recent times. It consists of 8 questions describing different degrees of soporific daily situations for each to be rated the probability to doze off or fall asleep on a scale of 0–3. If some situations have not been experienced recently subjects are asked to estimate how they might affect them. The 8 selected values are summed to a score (range 0–24) in which higher values indicate a higher level of daytime sleepiness. The determined cut-off value for excessive daytime sleepiness is > 10 [32–35]. The internal consistency determined by the original author of the ESS is indicated by a Cronbach's alpha coefficient of 0.88 [36]. Referring to diagnostic validity for instance in narcolepsy the ESS has a sensitivity of 93.5 % and a specificity of 100 % [37].

Statistical Analysis

Regarding descriptive statistics means (M) and standard deviations (SD) as well as medians and ranges were calculated. To test for normal distribution the Kolmogorov–Smirnov test was used. In case of normal distribution and interval-scaled data the two-sample t-test for independent samples was applied. If variables were ordinal-scaled or interval-scaled but not normally distributed Mann-Whitney U test was used. When comparing groups for outcomes of interest differences in mean or median are reported with the 95 % confidence interval (95%CI) in addition to the p value. Pearson's χ^2 test was applied if all variables involved were categorial. For correlation analyses we used Spearman's rank correlation since the correlated variables were not normally distributed. The significance level for all analyses was set to $p < 0.05$. All analyses were conducted with the statistical software IBM SPSS Statistics 24, IBM, Armonk, USA.

3. Results

On the basis of the reached global PSQI score the participants (n = 84) were divided into the two groups "Good sleepers" (n = 53) and "Bad sleepers" (n = 31) forming the foundation of the examination with regard to the associations of general mental health symptoms with subjective sleep quality and individual daytime sleepiness.

Socio-Demographical and Medical Data

The participants had a mean age of 37.3 ± 15.6 years (median 33 years, range 19 – 71 years), among them 42 females (mean age 38.2 ± 14.5 years, median 38.5 years, range 20 – 71 years) and 42 males (mean age 36.4 ± 16.7 years, median 28 years, range 19 – 71 years). The good sleepers consisted of 52.8 % males and 47.2 % females, the bad sleepers of 45.2 % males and 54.8 %. Table 1 depicts means and standard deviations of the examined socio-demographical and medical variables for both groups separately and the total sample. The 12 current or former smokers of the good sleepers (23.1 %) smoked an average dose of 10.5 py ± 9.5 py while the 8 current or former smokers of the bad sleepers (26.6 %) on average smoked a dose of 17.5 py ± 12.9 py. [*Table 1* near here].

Sleep Quality

Table 2 shows descriptively the average global PSQI scores and the 7 separate component scores with standard deviations as well as the medians and ranges of both groups and the total sample. [*Table 2* near here].

The good sleepers needed an average time of 12:13 min ± 07:55 min to fall asleep (median 10 min, range 2 ? 45 min) and actually slept 07:17 h ± 00:50 h per night. In comparison the bad sleepers needed on average 35:00 min ± 42:04 min to fall asleep (median 23 min, range 2 – 240 min) and the actual sleep duration was 05:41 h ± 01:03 h.

Daytime Sleepiness

Although the bad sleepers reached higher scores in the ESS no significant difference between the two groups was found ($p = 0.113$) (*table 2*). Applying the determined cut-off value for excessive daytime sleepiness of > 10 [32, 33] no significant distribution was found either ($p_{\chi 2} = 0.331$) (*table 3*). [*Table 3* near here].

While 9 good sleepers (17.0 %) were categorized as having excessive daytime sleepiness there were 8 bad sleepers (25.8 %), so in total 17 participants scored above the ESS cut-off value.

Correlations between Subjective Sleep Quality and Individual Daytime Sleepiness

Correlating the global PSQI score with the global ESS score no significant association was found ($r = 0.184$, $p = 0.094$) (*table 4*). [*Table 4* near here].

Regarding the 7 separate PSQI component scores only the component daytime dysfunction correlated significantly in terms of a very strong evidence with the global ESS score ($r = 0.365$, $p < 0.001$).

Mental Health Symptoms

With regard to the global scores in the GHQ-12 a significant difference between the two groups which shows strong evidence was found ($p = 0.004$). The bad sleepers on average reached higher scores (*table 2*). The distribution after applying

Table 1

Depiction of the socio-demographical and medical data of both groups

	Good sleepers (n = 53)	Bad sleepers (n = 31)	Total (n = 84)
	M ± SD Median (range)	M ± SD Median (range)	M ± SD Median (range)
Age [years]	35.2 ± 14.3 29 (19 – 64)	40.9 ± 17.2 47 (19 – 71)	37.3 ± 15.6 33 (19 – 71)
BMI [kg/m^2]	24.37 ± 3.94 23.46 (17.63 – 38.57)	24.84 ± 4.20 24.13 (19.33 – 34.36)	24.55 ± 4.02 23.89 (17.63 – 38.57)
WHR	0.88 ± 0.11 0.89 (0.68 – 1.29)	0.89 ± 0.11 0.88 (0.70 – 1.20)	0.89 ± 0.11 0.89 (0.68 – 1.29)
RR sys [mmHg]	125.9 ± 10.8 125 (90 – 158)	124.4 ± 15.6 121 (99 – 167)	125.3 ± 12.7 124 (90 – 167)
RR dias [mmHg]	79.3 ± 8.7 80.5 (60 – 105)	78.8 ± 11.0 78 (57 – 102)	79.1 ± 9.6 79 (57 – 105)
Sport [times/week]	2.3 ± 1.9 2 (0 – 6)	1.8 ± 2.0 1 (0 – 8)	2.1 ± 2.0 2 (0 – 8)
Sport [no. of years]	12.0 ± 12.2 10 (0 – 45)	8.7 ± 8.9 6 (0 – 30)	10.8 ± 11.1 10 (0 – 45)
	Number (%)		
Occupation			
mainly intellectual	40 (75.5)	23 (74.2)	63 (75.0)
mainly physical	5 (9.4)	1 (3.2)	6 (7.1)
physical and intellectual	8 (15.1)	6 (19.4)	14 (16.7)
pensioner	0 (0.0)	1 (3.2)	1 (1.2)
Smoker			
former	8 (15.4)	7 (23.3)	15 (18.3)
current	4 (7.7)	1 (3.3)	5 (6.1)
non-smoker	40 (76.9)	22 (73.3)	62 (75.6)

Table 2

PSQI global and component scores, global ESS scores and global GHQ-12 scores of both groups

	Good sleepers (n = 53)	Bad sleepers (n = 31)	Total (n = 84)	Significance
	M ± SD Median (range) 95%CI	M ± SD Median (range) 95%CI	M ± SD Median (range)	p-value 95%CI
PSQI Global PSQI score	 3.5 ± 1.3 4 (0 – 5) 3.15 – 3.92	 9.0 ± 2.6 8 (6 – 14) 8.08 – 10.06	 5.5 ± 3.3 5 (0 – 14)	
Subjective sleep quality	0.83 ± 0.47 1 (0 – 2)	1.61 ± 0.56 2 (1 – 3)	1.12 ± 0.63 1 (0 – 3)	
Sleep latency	0.58 ± 0.50 1 (0 –1)	1.58 ± 0.93 1 (0 – 3)	0.95 ± 0.84 1 (0 – 3)	
Sleep duration	0.32 ± 0.51 0 (0 – 2)	1.58 ± 0.96 2 (0 – 3)	0.79 ± 0.94 1 (0 – 3)	
Sleep efficiency	0.13 ± 0.40 0 (0 – 2)	1.29 ± 1.11 1 (0 – 3)	0.56 ± 0.93 0 (0 – 3)	
Sleep disturbances	0.92 ± 0.34 1 (0 – 2)	1.35 ± 0.49 1 (1 – 2)	1.08 ± 0.45 1 (0 – 2)	
Sleeping medication	0 ± 0 0 (0 – 0)	0.26 ± 0.73 0 (0 – 3)	0.10 ± 0.46 0 (0 – 3)	
Daytime dysfunction	0.72 ± 0.61 1 (0 – 2)	1.35 ± 0.84 1 (0 – 3)	0.95 ± 0.76 1 (0 – 3)	
ESS Global ESS score	 7.1 ± 3.3 7 (1-14) 5.89 – 8.16	 8.8 ± 4.8 8 (0 - 20) 6.68 – 10.08	 7.7 ± 4.0 7 (0-20)	 0.113 0,040 – 3,475
GHQ-12 Global GHQ-12 score	 9.1 ± 3.7 9 (3-18) 8.45 – 10.88	 12.9 ± 6.1 11 (7 - 26) 10.43 – 14.81	 10.5 ± 5.0 9 (3-26)	 **0.004** 1,360 – 6,182

p-value: Mann–Whitney U test.

Table 3

Classification of both groups by applying the ESS cut-off value

		Good sleepers	Bad sleepers	Total	
		Number (%)			*p*-value
ESS	normal	44 (83.0)	23 (74.2)	67 (79.8)	0.331
	increased	9 (17.0)	8 (25.8)	17 (20.2)	

p-value: Person's χ^2 test.

Table 4

Correlations of PSQI global and component scores with ESS global score and GHQ-12 global score

		PSQI components							
		Global PSQI score	Subjective sleep quality	Sleep latency	Sleep duration	Sleep efficiency	Sleep disturbances	Sleeping medication	Daytime dysfunction
Global ESS score	r	0.184	0.115	0.017	0.066	0.070	0.211	0.011	0.365
	p	0.094	0.300	0.880	0.550	0.530	0.054	0.921	**< 0.001**
Global GHQ-12 score	r	0.414	0.401	0.263	0.226	0.186	0.304	0.113	0.380
	p	**< 0.001**	**< 0.001**	**0.016**	**0.039**	0.090	**0.005**	0.304	**< 0.001**

r: Spearman's rank correlation.

the cut-off value for disturbed mental health of ≥ 5 with regard to the GHQ-scoring [27] shows *table 5*. [*Table 5* near here].

was correlated with the global GHQ-12 score a positive and significant association indicating very strong evidence was found (r = 0.414, p < 0.001).

Table 5

Classification of both groups by applying the GHQ-12 cut-off value

		Good sleepers	Bad sleepers	Total
		Number (%)		
GHQ	stable	51 (96.2)	22 (71.0)	73 (86.9)
	disturbed	2 (3.8)	9 (29.0)	11 (13.1)

The subjects categorised as being good sleepers with stable mental health reached on average a score of 1.1 ± 1.3 in the GHQ and 3.5 ± 1.3 in the PSQI while the subjects categorised as being bad sleepers with disturbed mental health reached on average a score of 7.7 ± 2.3 in the GHQ and 11.0 ± 2.2 in the PSQI. Categorised good sleepers with disturbed mental health reached on average a score of 7.0 ± 0.0 in the GHQ and 4.0 ± 1.5 in the PSQI, categorised bad sleepers with stable mental health reached on average a score of 1.0 ± 1.0 in the GHQ and 8.2 ± 2.3 in the PSQI.

Correlations between General Mental Health Symptoms and Subjective Sleep Quality as well as Individual Daytime Sleepiness

Correlation analyses were performed to find further associations of general mental health symptoms with subjective sleep quality and daytime sleepiness. When the global PSQI score

Apart from the components sleep efficiency and sleeping medication the component scores correlated significantly with the global GHQ-12 score as well (*table 4*). However, correlating the global ESS score with the global GHQ-12 score no significant relation was found (r = 0.118, p = 0.285).

4. Discussion

There is a rise of mental strain in the world of work [2]. Sleep disturbances and problems falling asleep are often associated with occupational stress as well as problems and social conflicts at the workplace [5–9].

Restorative sleep plays a significant role for health, subjective well-being, and quality of life [38, 39]. Due to the unconscious experience sleep and its quality can subjectively only be assessed in retrospect [40]. In this study the PSQI was used for that which distinguishes between good and bad sleepers. This distinction was used to

divide the total sample into two groups ("Good sleepers" and "Bad sleepers").

General mental health symptoms assessed with the GHQ-12 differed significantly in terms of a strong evidence between both groups whereby the bad sleepers had a worse psychological state in form of higher scores in the GHQ-12. In the correlation analyses significant positive associations between the global GHQ-12 score and the global PSQI score as well as most PSQI component scores were found, too. These associations were both of weak, strong, and very strong evidence.

Given the cross-sectional design of this study it is not possible to draw any conclusions regarding the causality of the associations. It might both be conceivable that subjective sleep quality had an influence on mental health and that mental health influenced subjective sleep quality. It is probable that there is a bidirectional relationship since on the one hand disturbed sleep is symptom of various psychic illnesses [16], but on the other hand it also causes psychic illnesses [14, 15]. Short sleep duration is associated with burnout [41], depression, and suicidal tendency [42, 43]. Kahn–Greene et al. [44] could show that there is an increase of depressive symptoms already after 56 hours of sleep deprivation. The association of psyche and sleep could also be illustrated by the fact that behavioural therapy procedures are superior to hypnotics in the treatment of particular sleep disorders [45, 46]. Cognitive behavioural therapy for insomnia also improves comorbid anxiety and depression [22, 47]. Mental health can be influenced by work-related psychosocial stress. Various studies found a significant association between social stress as well as work-related psychosocial stress and sleep quality [4–6, 8]. A specific problem could be the current development towards permanent availability of the employee. After regular work working is virtually continued due to permanent availability what leads to qualitative and quantitative disturbance of sleep [48]. The results of this study show that poor mental health is associated with reduced sleep quality. Improving sleep might enhance mental health and thus the work ability of the employee. On the other hand, improving mental health could lead to better sleep and thus to a better recovered and more efficient employee.

A possibility of distortion of the described associations in this study could be that a subject with poor mental health or poor subjective sleep quality might have a negative and pessimistic general attitude and therefore estimates the respective other factor intentionally or unintentionally worse than it actually is. In comparison the subject with good psychological health or good subjective sleep quality possibly could have a positive and optimistic general attitude and evaluates the respective other factor intentionally or unintentionally better than it actually is.

The GHQ-12 is an instrument to assess recently experienced mental dysfunctional symptoms and behaviour. A further more precise psychopathological exploration was not performed. Therefore, it cannot be estimated if psychological health was disturbed before recent times or since when it was damaged. That is why we are not able to say from what period of time the association of mental health and sleep quality might possibly exist.

To our knowledge there are few studies which examine the associations of subjective sleep quality and daytime sleepiness with the GHQ score or the GHQ classification. One study which examined students in southern Thailand confirmed the association between poor sleep quality and mental health problems in their sample [49]. The prevalence of poor sleep quality in this study was 42.4 %. Sepehrmanesh [50] also showed that sleep quality might play a significant role in various aspects of mental health. There were significant correlations between general mental health symptoms, physical symptoms, states of anxiety, depression and sleep quality. Both studies used a relatively young sample.

Limitations of this study are the cross-sectional design and the relatively small sample size, especially for the categorical group comparisons. Moreover, the study relied on self-report questionnaires which were completed at home. The clinical relevance of the 95%CI of the results of this study is small. Extended diagnostics (e.g. sleep laboratory) might be necessary to evaluate them sufficiently. Further research on this topic including studies with longitudinal design and larger sample sizes is required. On the whole the findings of this study might provide further evidence of the inter-relationship between subjective sleep quality and mental health and could emphasise the important role of restorative sleep for psychological well-being and the other way round.

Declaration

The authors report no conflicts of interest.

Data Availability

The data that support the findings of this study are available from the corresponding author, RSS, upon reasonable request.

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NEURO-HUMORAL MEDIATORS IN PROGRESSION OF CORONARY ARTERY DISEASE WITH CONCOMITANT OBESITY (REVIEW)

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Abstract

Cardiovascular diseases are the main cause of death worldwide. Priority in the structure of the cardiovascular diseases belongs to coronary artery disease (CAD) and especially to its acute form - acute myocardial infarction. AMI largely determines mortality, economic losses in most countries of the world. Modern epidemiological studies have shown the relationship between obesity and cardiovascular diseases, as well as between obesity and individual cardiovascular risk factors such as hypertension and hyperlipidemia. Cardiac troponin is a biomarker of choice for the diagnosis of acute myocardial infarction. However, after reperfusion therapy the actual level of Tn may be misleading due to the phenomenon of washout and the 12-hour expectation of peak levels remains the Achilles heel of this biomarker. Activation of neurohumoral systems in the acute period of the myocardial infarction promotes the expansion of the necrosis zone, the development of myocardial ischemia, bnormal heart rhythm and acute heart failure. Despite the large number of detected and studied neurohormones, our knowledge of the role of these peptides in the development of myocardial infarction and its complications is very limited. That is why studying of new biomarkers, such as copeptin and midregional proadrenomedullin, is perspective and interesting for scientist all over the world.

Keywords: *acute myocardial infarction, coronary artery disease, obesity, copeptin, MRproADM.*

Cardiovascular diseases are the main cause of death worldwide [1–6]. Priority in the structure of the cardiovascular disease belongs to coronary artery disease (CAD) and especially to its acute form - acute myocardial infarction (AMI), which is an urgent clinical condition, due to necrosis of the area of the heart muscle as a result of disturbance of its blood supply [6–7].

In most economically developed countries, cardiovascular diseases rank first among the causes of morbidity, disability and mortality, although their prevalence varies considerably in different regions [8–9]. This represents half of all deaths and 2.5 times more than all malignant neoplasms taken together. The annual economic losses due to death from the cardiovascular disease in the US amount to 56900 million dollars. In Ukraine, these diseases are the main cause of mortality and morbidity of the population. If in 1939 cardiovascular diseases accounted only for 11% in the general structure of the causes of mortality, in 1980 this number increased by more than 50%, and in 2010 – 76%.

Since 1995 in Ukraine a progressive increase in mortality due to cardiovascular diseases has been observed, reaching one of the highest levels in Europe – 63.6%. Coronary artery disease is ranked first (66.8%) in the structure of mortality from cardiovascular diseases. At the same time, in our country there are significantly lower rates of hospitalization of patients with AMI (109 per 100 thousand population, compared with 295 per 100 thousand population in the USA). In turn, the hospital mortality rate for AMI in Ukraine exceeds the European indicators (12.9% vs. 8–8.4%). In Ukraine the mortality rate is 10063 out of 594796 persons.

AMI largely determines mortality, economic losses in most countries of the world [10–11].

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The cause of each second mortality among adults is AMI and cerebral stroke. Implications of AMI are marked in months and years. Thus, according to the American Heart Association, 18% of men and 35% of women undergo recurrent MI during 6 years after acute coronary syndrome, moreover 22% of men and 46% of women become disabled due to development of severe heart failure (HF), and 30–40% of patients develop left ventricular (LV) dysfunction [12].

This problem affects the low and middle income countries [13–16]. More than 80% of deaths from cardiovascular diseases occur in these countries almost equally among men and women. By 2030, it is projected that about 23.6 million people will die due to heart attacks and mainly from heart disease and stroke. In the world 17.5 million people die due to cardiovascular diseases annually, and 1.2 million of them are our compatriots. The leading nosological form in the structure of the coronary artery disease is the AMI with elevation of ST segment (STEMI) for many years [17].

The present peculiarity is that 40% of deaths are attributed to people of working age, 25–64 years old, and Ukraine is no exception in this matter. The prevalence of heart and vascular diseases mainly depends on lifestyle and risk factors. Lifestyle changes and risk factors may slow down the development of the disease both before and after the onset of clinical symptoms [18–19].

In European countries there is a trend towards reduction in mortality from myocardial infarction (MI). In Ukraine, on the contrary, an intensive index is 6–8 times higher than that in countries of Europe, Japan, and the USA [20–21].

Modern studies show that the main causes of the high prevalence of coronary artery disease are risk factors such as hypertension, smoking, diabetes mellitus, dyslipidemia, age, family history, alcohol consumption, and obesity, whose pace of growth has become threatening scales [22, 23].

According to the World Health Organization (WHO), obesity is recognized as a non-infectious "epidemic of the 21st century" and is one of the five major risk factors for death. Epidemiological studies indicate a rapid increase in the number of obese patients in all countries of the world. Obesity (body mass index (BMI) more than 30 kg/m^2) affects from 9 to 30% of the population in the developed countries of the world [24–25]. Annually, about 2.8 million people die because of overweight or obesity [26]. Obesity is a heterogeneous disease. There are various factors contributing to obesity: features of the genotype, dysregulation of lipolysis and lithogenesis, disorders of the hypothalamic-pituitary adrenal system, dysfunction of various peptides and neurotransmitters, impaired functions of appetite centers [26–28].

Modern epidemiological studies have shown the relationship between obesity and cardiovascular diseases, as well as between obesity and individual cardiovascular risk factors such as hypertension and hyperlipidemia. In obesity, a number of hemodynamic changes occur, in particular, an increase in the volume of circulating blood and cardiac output with relatively normal vascular resistance [29]. It is believed that high blood pressure in obese patients is mainly due to increased cardiac output with "inadequately normal" peripheral resistance [29, 30].

As a result of the INTERHEART study, it has been shown that obesity is an independent risk factor for coronary artery disease [31]. The incidence of coronary artery disease in both sexes and at any age is directly proportional to BMI. Some authors have shown that the ratio of the waist circumference to the hips circumference (WC/HC) is a better dependence of obesity and development of cardiovascular complications than BMI [32–35]. With excessive body weight, the relative risk of coronary artery disease is statistically insignificant, but with the progression of obesity, the risk increases by 1.5–2 times. For example, in women with MI, patients with excess body weight and obesity are seen in 74.6%, and with normal body weight – only in 25.4%.

Despite the existence of a close relationship between obesity and cardiovascular disorders, the molecular genetic bases remain not fully defined. It is known that adipose tissue secretes a large number of biologically active substances – adipocytokines, which can provide either local auto- and paracrine effects or systemic endocrine effects, as well as to promote and counteract the development of cardiovascular disease. Obesity is not only an independent factor in the risk of cardiovascular complications, but also a trigger mechanism for the development of cardiovascular disease.

Presence of obesity is accompanied by the changes of the structure and functions of the heart. The effect of obesity on cardiovascular mortality can be explained by its effect on the compensatory change in the structure and function of the myocardium, aimed at satisfying higher metabolic needs. In obese people, adaptation of cardiac activity leads to eccentric left ventricular hypertrophy, which is an important

prognostic factor for AMI development, sudden death and congestive heart failure, regardless on the presence of hypertension. Left ventricle hypertrophy is also an important risk factor for sudden cardiac death.

In foreign sources, the concept of "adipose pathology" has appeared, which implies anatomical and functional deviations in adipocytes and adipose tissue, which can directly contribute to the development of cardiovascular disease through pericardial and perivascular effects on myocardium and blood vessels [36].

The rapid growth of the prevalence of obesity among persons of working age, the relationship of excess body weight with cardiovascular disease, and the effect of obesity on an increase in the percentage of patients with cardiac event, such as acute coronary syndrome are forced to more deeply study the problems of comorbidity in this cohort of patients and determined the relevance of the chosen problem.

The assessment of the patient's health is carried out using standard biological parameters that act as indexes, the main criteria of which are visibility, ease of implementation and early appearance. The latter position is especially important in the diagnosis of urgent conditions, such as AMI. That is why in 2000, cardiac troponin (Tn) replaced creatinine kinase MB-fraction (CK-MB) as a biomarker of choice for the diagnosis of AMI. Strengthening the position of cardiac troponins as the desired biomarkers for the diagnosis of AMI today is evident for both researchers and practitioners. The current international document containing the criteria for diagnosis of AMI, calls cardiac troponins "predominant biomarkers for the diagnosis of AMI" [37, 38]. Creation of new generations of highly sensitive tests for measurement of serum cardiac Tn can reveal the majority of cases of AMI already at the arrival of patients into the hospital [39, 40].

Tn is a protein that is released from myocytes when irreversible damage to the myocardium occurs. The main structural contractile unit of the myocyte is the sarcomer who forms ordered thick and thin fibers. Thin fibers contain actin fiber and troponin-tropomyosin complex. Troponins (I, T and C) in the 1:1:1 ratio are part of the troponin complex, which is associated with tropomyosin. Tn together with actin forms the thin filaments of myocytes - a very important component of contractile apparatus of striated muscle cells. All three troponins are involved in calcium-dependent regulation of the reduction-relaxation act [41]. Tn I is an inhibitory subunit of this complex that binds actin during the relaxation and inhibitory ATPase activity of an actomyosin, thus preventing muscle contraction in the absence of calcium ions. Tn T is a regulatory subunit that attaches the troponin complex to the thin filaments, and thus participates in a calcium-regulated act of contraction.

Tn I and T are found in three isoforms unique in structure for each type of transverse striped muscle (fast, slow and cardiac), since they are encoded by different genes. Cardiac isoform Tn I is significantly different from isoform Tn I, which is localized in skeletal muscle. About 44% of the amino acid sequence of the cardiac isoform Tn I is specific for this protein. In addition, Tn I contains an additional N-terminal polypeptide consisting of 31 amino acid residues. Thus, Tn I is a completely specific myocardial protein. The molecular weight of Tn I is about 24,000 daltons. The cardiac form of Tn T also significantly differs according to its molecular structure from the two types of Tn T that are localized in the skeletal muscle (fast and slow muscle): there are 43% differences in the amino acid sequence of heart muscle Tn T and the slow skeletal muscle and 56% of the difference from fast skeletal muscle. Thus, Tn T is a completely specific protein for the heart. The molecular weight of Tn T is 34500 daltons. cTn I and Tn T can be differentiated from similar skeletal muscle proteins immunochemically with monoclonal antibodies, which is used in their immunoassay methods [41].

Cardiac Tn C in contrast to Tn I and Tn T is absolutely identical to the structure of muscle Tn C and, consequently, is not a cardiospecific protein.

In case of damage of the myocardium, after 4–6 hours due to the development of irreversible necrotic changes, Tn enters the peripheral blood flow, peak concentration is reached in the first 12–24 hours from the onset of AMI. Cardiac isoforms of Tn for a long time retain their presence in peripheral blood: Tn I is determined for 5–7 days (0–0.5 ng/ml), Tn T is determined up to 14 days (0–0.1 ng/ml). It is advisable to study Tn I when examining patients both in the early and late terms, after the manifestation of clinical symptoms. Even a slight increase in Tn levels suggests an additional risk for the patient, since there is a clear correlation between the level of growth of Tn in blood and the size of the damage zone of the myocardium [41]. Positive troponin is associated with an increased risk of an adverse outcome for 30 days (HR 1.96, P = 0.003). This

test is useful in addressing the issues of choosing tactics for the management of patients with acute coronary syndrome, including patients with unstable angina pectoris. Tn has never detected in the peripheral blood flow of healthy individuals. His appearance is an alarm signal about necrotic damage of the myocardium. In acute coronary syndrome, elevated levels of Tn I are considered as a sign of myocardial ischemia caused by platelet activation and aggregation and leading to necrosis. Increasing the concentration of Tn I in patients with unstable angina suggests an unfavorable prognosis and the risk of developing an MI within the next 4–8 weeks. The specificity of the determination of cardiac Tn I in the blood is 95% and exceeds the specificity for CK-MB and myoglobin. The development of AMI is accompanied by a large destruction of cardiomyocytes and a significant release of cardiac Tn T in blood, which can increase by 20–400 times [42]. The amount of cardiac Tn T in blood increases in proportion to the volume and depth of MI. The absolute diagnostic sensitivity range of AMI for cardiac Tn T is 125–129 hours, for CK-MB and lactate dehydrogenase – 22 and 70 hours, respectively. The level of heavy chains of myosin begins to increase only from the middle of second day, exceeding the initial values in 5–6 times, and decreases in one week after the occurrence of AMI.

However, after reperfusion therapy the actual level of Tn may be misleading due to the phenomenon of washout. Peak level of Tn occurs after 12 hours and remains elevated for 10 days or more. Despite the fact that the use of Tn for the diagnosis of AMI and risk stratification should be helpful for management of patients with chest pain, the 12-hour expectation of peak levels remains the Achilles' heel of this biomarker. More sensitive forms of Tn [43] and new biomarkers were introduced to correct this disadvantage. The activation of circulating (plasma) and local (myocardial) neurohormonal systems plays an important role in the pathogenesis of the MI and its complications. This is initially compensatory in nature to maintain an adequate pumping function of the heart in response to hemodynamic overload and decrease the mass of the functioning myocardium, but may subsequently become maladaptive. Most neurohumoral shifts are mediated by vasoconstrictor and vasodilator responses. The first ones are implemented through the sympathetic adrenal system (SAS), renin-angiotensin-aldosterone system (RAAS), vasopressin, antidiuretic hormone, serotonin, endothelin, thromboxane A2; the other - through the calicrein-kinin system, the system of brain natriuretic peptide (BNP), prostaglandins I2 E2, endothelium-dependent relaxing factor, and others.

Activation of neurohumoral systems in the acute period of the MI promotes expansion of the necrosis zone, development of myocardial ischemia, heart rhythm and acute heart failure (AHF) [44]. The increase in the activity of neurohormonal systems, which is stored at a later date after a myocardial infarction, leads to the development of pathological cardiac remodeling, manifested by the syndrome of chronic heart failure, left ventricle myocardial dysfunction and heart rhythm disorders [44]. Despite the large number of detected and studied neurohormones, our knowledge of the role of these peptides in the development of MI and its complications is very limited. Mechanisms of the effect of neurohormones on the forecast are also not fully understood. In most studies, end points are used for lethality or major cardiovascular complications, as they are easy to determine, but they can all be the result of various pathophysiological processes [44].

The current recommendations of the European Society of Cardiology for the treatment of acute coronary syndrome without ST elevation in 2015 say that there is possibility to use novel biomarkers such as midregional pro-adrenomedullin (ADM) and copeptin for diagnostic and prognostic purposes [38].

Copetin was first described by Holwerda in 1972 [45]. The detection of the glycopeptide was amazing. The glycoprotein of such a relatively low molecular weight (extract from the posterior lobe of the pituitary gland containing a glycopeptide with a molecular weight of about 3200) has never been isolated before [90]. The precursor for vasopressin and copetin is pre-provasopressin, which consists of 164 amino acids, including the signal peptide, vasopressin, copetin and neurophysin II.

The process of synthesis is primarily carried out due to the endocrine mechanism in the nucleus of the hypothalamus (paraventricular and supraoptic in the cerebellar neurons). Pro-vasopressin enters the posterior part of the gland through the pituitary funnel. Mature vasopressin excretes in the next stage with the enzymatic transformation with the help of copeptin and neurophysin II. The secretion of neurohypophysis occurs in response to osmotic and hemodynamic changes [46]. Another way of synthesis passes

through hormone-producing neurons in the hypothalamus, where it is synthesized in the corticotrophin-releasing hormone. In this case, vasopressin directly affects the endocrine cells of the pituitary gland through portal circulation. The elimination of adrenocorticotropin and cortisol in response to stress stimulation reveals significant synergism between corticotrophin-releasing hormone and vasopressin, which confirms the importance of stress as an important factor in the startup of vasopressin production, which then stimulates the release of adrenocorticotropin [47].

Copeptin is a more stable vasopressin surrogate with known effects of osmoregulation and cardiovascular homeostasis. Vasopressin is believed to contribute to [46] increased peripheral vasoconstrictive resistance, thus increasing the load and tension of the ventricle; an increase in protein synthesis in myocytes, which leads to hypertrophy and [47] vasoconstriction of the coronary arteries. These effects are mediated by the receptor V1, while the effect on V2 receptors causes water retention in the renal tubules. Vasopressin acts on three types of receptors: V1, which is responsible for vasoconstriction; V2, which has antidiuretic effect; and V3 which is involved in the release of adrenocorticotropin [46]. V1 receptors are most often located within smooth muscle of the arterial wall and cause vasoconstriction due to intracellular influx of calcium ions via G-protein [46]. V1 receptors are also located in the cells of the heart muscle, but their effectiveness has not been clarified. V2 receptors are in the renal tubules and, by increasing intracellular cyclic adenosine monophosphate (cAMP), have a double action on water: they contribute to the synthesis of matrix ribonucleic acid encoding aquaporin 2 – a protein that forms membrane channels; and they are also involved in the transport of this protein in the renal collecting canal that allows water to be absorbed from the urine [48]. These receptors are currently targets for pharmacological therapy [49, 50].

There are several hypotheses that explain the rapid release of vasopressin/copeptin after destabilization of CAD. Vasopressin reacts quickly as part of the endocrine stress axis, which results in the release of adrenocorticotropin and cortisol. Copeptin is considered a quick and immediate biomarker of an individual stress response [50]. An alternative to the secretion of the vasopressin/ copeptin trigger from the posterior lobe of pituitary gland may be stimulation of the baroreceptors by the threat of hypotension as a result of MI or direct damage of the cardiac baroreceptors. The above-mentioned possibility is confirmed by the fact that the highest increase in the level of copeptin after AMI is observed in patients with acute coronary syndrome (ACS) with elevation of ST segment [51].

Copeptin is a glycosylated, 39-amino acid-length C-terminal portion of the hormones of vasopressin and is produced together with vasopressin in the process of treating the precursor after hemodynamic or osmotic stimulus (hypovolemia, hyponatremia, osmotic pressure, pain, stress, hypoxia and acidosis). Copeptin is also known as a hormone of endocrine stress. Unlike vasopressin, copeptin is very stable in plasma at room temperature, which makes it possible to reliably measure. An increase in the concentration of copeptin after AMI was first reported by Kahn et al. [52] with the highest values registered at first day and further decrease within the next 2–5 days. Copeptin concentrations were higher in patients who died or had a heart failure compared with the rest. Copeptin is stable and easily studied. Taking into account that several studies focused on the participation of copeptin in various pathologies (AMI, cardiomyopathy, stroke, sepsis), the use of that parameter was well-known as an appropriate marker [52, 53]. Previously published data showed the diagnostic and prognostic value of copeptin in combination with cardiac Tn in patients with AMI [54–56]. Copetin, in addition to negative Tn T, may exclude MI [108]. In the case of copeptin levels <14 pg/ml and Tn T level less than 0.01, it is possible to exclude AMI with an area under the ROC curve of 0.97 (negative predictive value of 99.7%), eliminating the need for monitoring and serial blood tests in most patients. There is also evidence that measurment of copeptin allows rapid elimination of AMI in patients with suspected acute coronary syndrome [55, 56]. In the study of 487 patients in the intensive care unit [56], the level of copeptin increased (more than 14 μmol/L) within 4 hours after the onset of symptoms, despite the fact that the levels of cardiac Tn T did not increase (less than 99th percentile of the upper range of the task) These studies indicate that adding copeptin can be helpful in excluding AMI in patients with suspected ACS.

Interestingly, there is a question about the participation of copeptin in the pathogenesis of obesity and the metabolism of adipose tissue. According to Enhörning, increased levels of copeptin associated with an increase in BMI [56, 57].

Copeptin was found to be a prognostic marker of mortality or HF within 60 days of AMI. In

addition, the effect of copeptin on LV dysfunction persists for a long period after an acute event [56].

ADM, a 52-amino acid peptide, was first isolated from human pheochromocytoma cells by a group of Japanese scientists who have screened these cells for peptides that increase cAMP levels in platelets [58]. Physiologically, this hormone has natriuretic, vasodilating and hypotensive effects. ADM can be found in many tissues and organs, including cardiovascular, renal, pulmonary, brain vessels, gastrointestinal tract and endocrine tissue, where it functions as a circulating hormone, as well as a local autocrine and paracrine effector. ADM is a hemodynamically active vasodilator peptide with a potent hypotensive effect [59]. It also exhibits an acute inotropic, vasodilating, diuretic, and natriuretic effect, and it inhibits the production of aldosterone. There is evidence that ADM is one of the most important agents in the development and regulation of fatty metabolism [59].

Also, ADM has antihypertrophic, antiapoptotic, antifibrotic, antioxidant effects and angiogenesis effects. Biological activity of ADM in cardiovascular system consists in expansion of vessels [60] through production of nitric oxide, increase of cardiac output and induction of diuresis [61].

ADM, which is synthesized as part of a larger molecule of the precursor, is called preproadrenomedulin. In humans, this precursor consists of 185 amino acids [61]. However, the exact measurement of ADM until recently was hampered by its very limited stability in the test-tube. Thus, there was no a complete understanding of its diagnostic and therapeutic potential. However, a new method of immunoassay was developed. It measures the concentration of an inactive stable protein fragment that is released into the systemic bloodstream during the synthesis of ADM. Being called mid-regional proADM (MRproADM), it is a stable fragment of pro-ADM, which is produced in a ratio of 1:1 with active ADM. ADM is difficult to measure in plasma because it partially forms a complex with the factor of complement H and is rapidly removed from the bloodstream [62]. Thus, measurement of serum levels of MRproADM accurately reflects the level of ADM [62], and allows conducting functional clinical samples to determine the concentration of ADM [61–64]. According to this strategy, promising studies have evaluated the importance of ADM determining in emergency department patients. In the recently published study BACH (biomarkers in AHF), the main prognostic endpoint was the use of MRproADM compared with the B-type BNP to predict 90-day mortality in patients with a diagnosis of AHF [65]. The prediction of survival for 90 days for MR-proADM was 73% (95% confidence interval [CI]: 70% to 77%), while for BNP – 62% (95% CI: 58% to 66%) ($p<0.001$). In addition to Tn [66], copepin and ADM have not yet spread as prognostic markers that accurately predict short-term mortality. Finally, while an elevated ADM level is associated with an increased risk of short-term mortality, the low level allows it to be equated with a low mortality risk. In addition, it should be noted that MRproADM is a non-specific hemodynamic marker. Regardless of the presence of AHF, its high level indicates the severity of the underlying disease and the need for appropriate intervention. Ultimately, ADM may be similar to Tn in a marker that predicts short-term mortality. Nevertheless, a recent study using MRproADM showed that after AMI, an increase in MRproADM was associated with death and HF [66].

It has been shown that the level of ADM in plasma is significantly increased in patients with acute forms of CAD. Thus, it was noted that in patients with AMI, the concentration of ADM in blood plasma on the 2nd day after the onset of the disease significantly increased (12.3±8.8 versus 4.9±1.0 mmol/l, $p<0.001$) compared with healthy people [67]. Increased ADM level in blood of patients with LV dysfunction was noted. It has been experimentally established that cytokines, in particular, interleukin-1β and tumor necrosis factor (TNF)-α, whose content in AMI increases in parallel with myocardial damage, is stimulated by the in vitro ADM synthesis [68]. These results suggest that both LV dysfunction and peripheral vascular resistance changes are involved in ADM concentration increasing in patients with AMI. High values of the ADM are due to severe LV dysfunction. A connection between increased ADM level in blood and the presence of HF, which complicates the AMI [69], has been established. In addition, a negative correlation between the plasma content of ADM and LV ejection fraction [168] was demonstrated. This data became the reason for estimating the predictive value of ADM in patients with AMI. A correlation was found between plasma concentration of ADM for 2–4 days of AMI and mortality. However, since plasma ADM concentration in patients with AMI is noted in the earlier period (1st–2nd day from the onset of the disease), the predictive value of the concentration of ADM in blood for second day

of AMI is shown [69]. In an additional analysis in patients with severe LV dysfunction, it was noted that the ADM content in blood on the 2nd day was significantly higher in patients who died later than those who survived. At the same time, LV ejection fraction did not significantly differ between the two groups. The authors concluded that the concentration of ADM in blood on the 2nd day of AMI may complement ejection fraction as a prognostic marker, especially in patients with systolic dysfunction.

Thus, copeptin and MRproADM together with cardiac Tn occupy an important and promising place in the diagnosis of CAD, especially its acute forms, but the role of these factors in the course of CAD in the presence of metabolic disorders remains unexplored, as well as their possible influence on dynamics of these indicators, which requires further research.

Conflict of interests

The authors declare that they have no competing interests.

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CLINICAL MANIFESTATION OF GASTROESOPHAGEAL REFLUX DISEASE ASSOCIATED WITH AUTOIMMUNE THYROIDITIS IN YOUNG PERSONS

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Abstract

Background. Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal disorders worldwide, with relevant impact on the quality of life and health care costs. The prevalence of GERD in Western Europe and North America is 30–40 % of the adult population, 10 % of them with daily heartburn as main symptom of GERD. The statistic data of GERD in Ukraine ranges from 11.1 % to 30 %. **Purpose.** To investigate the clinical features of gastroesophageal reflux disease which associated with autoimmune thyroiditis in young patients. **Subjects & Methods.** 165 patients have been studied. All patients were divided in two groups: first group consists of 120 patients with GERD associated with autoimmune thyroiditis (AIT), second group included had 45 patients with isolated GERD. Groups were matched in age (21.9 ± 2.7 and 21.2 ± 2.4 years, respectively), sex (77.5 % and 75.5 % women, respectively), education and disease duration. **Results.** The main clinical symptom of GERD in patients with comorbid pathology and isolated GERD was heartburn, which was recorded in all cases, but its manifestations had different intensity, frequency, time of occurrence and duration. Patients of the group with the combined course of GERD and AIT significantly often noted the appearance of heartburn at night (65 %) in comparison with isolated GERD (31.1 %). Belching was observed in 62 patients (51.7 %) in the group with comorbid pathology and at 6 examined (13.3 %) in group with isolated GERD ($p<0.05$). **Conclusions.** Patients of the group with the combined course of GERD and AIT significantly more often had the night heartburn at – 65 % versus 31.1 % in the group with isolated GERD ($p<0.05$). Belching was observed in 52.5 % of patients with comorbid pathology and in 13.3 % of patients with isolated GERD ($p<0.05$). Assessment of other symptoms of GERD: epigastric discomfort, epigastric pain, dysphagia, nausea, vomiting, belching, satiety after meal, flatulence, hoarseness, cough did not have a significant difference between the groups, but there was a tendency to increase the incidence of symptoms in patients of the GERD group associated with AIT.

Key words: *gastroesophageal reflux disease, autoimmune thyroiditis, clinical characteristics.*

Introduction

The beginning of the 21st century is characterized by growing prevalence of the main socially significant diseases of internal organs. Gastroesophageal reflux disease (GERD) is considered one of these diseases [1].

The 2014 review based on data of 16 studies of GERD showed that in North America prevalence of GERD was 18.1–27.8 %, 23.0 % in South America, 8.8 %-25.9 % in Europe, 2.5–7.8 % in East Asia, 8.7–33.1 % in the Middle East, 11.6% in Australia; in the general population of the United Kingdom and the United States the incidence of GERD rate per 1000 population was approximately 5 persons [2].

According to more recent epidemiological data, the prevalence of GERD in Western Europe and North America is 30–40 % of the adult population, 10 % of them with daily heartburn as main symptom of GERD, but only 2 % of patients receive treatment [3]. Due to screening data of the endoscopic examination of the upper gastric tract in Japanise population esophagitis is detected

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in 16.5 % of all examined persons [4]. In Australia 11.3 % of patients visiting a general practitioner reveal GERD of chronic condition [5].

Recently endoscopic findings have shown an increase in erosive forms of GERD from 3.1 % to 16.0 % [6]. It was previously believed that the incidence of GERD increases with age, and its complications are usually found in patients older than 50 years. But epidemiological evidences suggest that now there is tendency to rising GERD rate in the young population [7,8]. In children, the prevalence of GERD, according to different observations is from 2–4 % to 8.7–49 % and the data is growing annually [9,10].

The prevalence of GERD in Ukraine ranges from 11.1–30% [11]. But clinicians emphasize that the given statistical results do not correspond with reality: such patients are much more, because almost a quarter of patients with complaints of GERD (usually heartburn) do not visit the doctors [12]. This is explained both to the young age of patients who first had the disease, and the lack of knowledge about the symptoms and signs of the disease [13]. The appearance of heartburn is often considered as a temporary unfavorable symptom of overeating or eating spicy food and the like ones. In this case, the disease for a long time remains uncontrolled, which contributes to its progression and the occurrence of complications.

Another unfavorable sign in the course of the disease is the addition of another nosological form, the pathogenic links of which intersect with the underlying disease. Among such diseases, the occurrence of which at a young age is quite common, is autoimmune thyroiditis (AIT). The prevalence of AIT in the world among the adult population is 20-30 % [14]. And there is data that confirms constant increase in incidence of AIT in young persons [15].

The provoking factors of AIT formation in young patients are: viral infection and its uncontrolled and inadequate treatment, acute or chronic diseases that preceded AIT and had a significant load on the immune system [16].

The combination of diseases of the internal organs is very typical for young persons who are in a specific environmental condition (students). A student's life consists of two parts – end-of-term exams and the period between exams. This has its equivalent of load: chronic stress and a period of complete relaxation. Such a distribution of time is one of the factors in the formation of the disease: during the exams "there is no time to get sick", and after they end – a long period of rest without attention to the health [17].

There were a few studies assessing the combined course of GERD and AIT but they mainly related to patients of older age groups. Currently, there are some studies about the role of thyroid hormones in the formation of motor and secretory disorders in young patients with GERD [18]. But main links of pathogenesis combination of GERD and AIT is unknown. This is the argument for further scientific research and clinical observations of young patients with a combination of these diseases. Determination of the phenotype of the clinical picture of GERD and AIT, the searching for common provoking factors play an important role in the clinic of internal diseases. Determination of the clinical features of GERD and AIT in this case very important for prevention the manifestation of complications.

2. Purposes, subjects and methods:

2.1. Purpose. To investigate the clinical features of gastroesophageal reflux disease associated with autoimmune thyroiditis in young patients.

2.2. Subjects & Methods. The study involved 165 patients. All patients were divided in two groups: first group consisted of 120 patients with GERD associated with AIT, second group included 45 patients with isolated GERD. Groups were matched in age (21.9 ± 2.7 and 21.2 ± 2.4 years, respectively), sex (77.5% and 75.5% women, respectively), education and disease duration.

Clinical examination of patients included: presentation, past and present history, physical examination, laboratory and instrumental methods of examination. The form of the disease was established taking into account visual changes in the mucous membrane of the esophagus (non-erosive or erosive) according to the video esophagogastroduodenoscopy data (Fuginon system) and recommendations of the Los Angeles Classification. Histomorphological studies of biopsy specimens have been performed for all patients.

The recommendations of the Montreal Consensus (2006), "Protocols for Patient Management ..." and the International Classification of Diseases of the 10th revision were used in establishing the diagnosis of GERD.

The presence of AIT was proved on the basis of palpatory examination of the thyroid gland, levels of antibodies to thyroperoxidase and thyroglobulin in blood serum, ultrasound data of the thyroid gland (apparatus Mindray DC-60 Exp).

The thyroid gland function was determined by the results of thyroid-stimulating hormone (TSH), free thyroxine (T4) and free triiodothyronine (T3). The diagnosis was proved with reference to the "Protocols of patient management ..." of the International Classification of Diseases of the 10th revision.

The study was conducted according to Medical-diagnostic standards and requirements for the ethical component of clinical trials (GCP, 1997). Patients were informed about the study, its purpose and possible results. Written consent to conduct the study was obtained from each patient who was involved, according to the recommendations of the ethical committees on biomedical research, the legislation of Ukraine on health, the Helsinki Declaration 2000 and European Society Directive 86/609 on the role of people in biomedical research.

Patients with diabetes mellitus, cardiovascular diseases, kidneys, oncological diseases of any localization, with mental illnesses, pregnant women and minors were not included in the study.

Standard statistics for the medical studies was used for the data analysis.

Conflict of interests.

There is no conflict of interests.

3. Results and discussion

The main clinical symptom of GERD in patients with comorbid pathology and isolated GERD was heartburn. In our study heartburn was recorded in all examined, but its manifestations had different intensity (*Figure 1*).

Patients with severe heartburn prevailed in both groups: 21 examined (17.5 %) in the first group and 4 (8.9 %) in the second group, but there were no significant differences between the groups.

Frequency, time of onset and duration of heartburn had the following distribution into groups (*Table 1*).

Daily incidence rate increased by 1.2 times and significantly frequent occurrence of this symptom at night in 78 patients (65 %) with a combination of GERD and AIT as compared to 14 persons (31.1 %) with isolated GERD.

The duration of the heartburn symptom was different: from 30–40 minutes to 2–3 hours and quite often its occurrence was stopped by taking medications in both groups.

Other symptoms of GERD included epigastric discomfort, epigastric pain, dysphagia, nausea, vomiting, belching, satiety after a meal, flatulence, hoarseness, cough (*Table 2*).

The prevalence of belching was significantly higher and occurred in 52.5 % (63 examined) of the group with GERD and AIT and in 6 patients (13.3 %) with isolated GERD. Among the other symptoms, there were no significant differences, but there was a tendency to increase the frequency of symptoms in patients with combined pathology.

The duration of the GERD history in the group of patients with combined course of diseases was as follows: the diagnosis was first established in 43 cases (35.8%); in other patients it ranged from 1 to 3 years. In the comparison group, the diagnosis of GERD was first established in 17 people (37.8%). The first visit to the doctor was from 7–8 months to 1.5 years after the onset of the first symptoms. According to the explanation of students the reasons of late visits to doctor were: either moderate clinical symptoms, "lack of time during the session" or a careless attitude toward oneself when clinical signs were considered temporary, associated with "the use of poor-quality food or drinks".

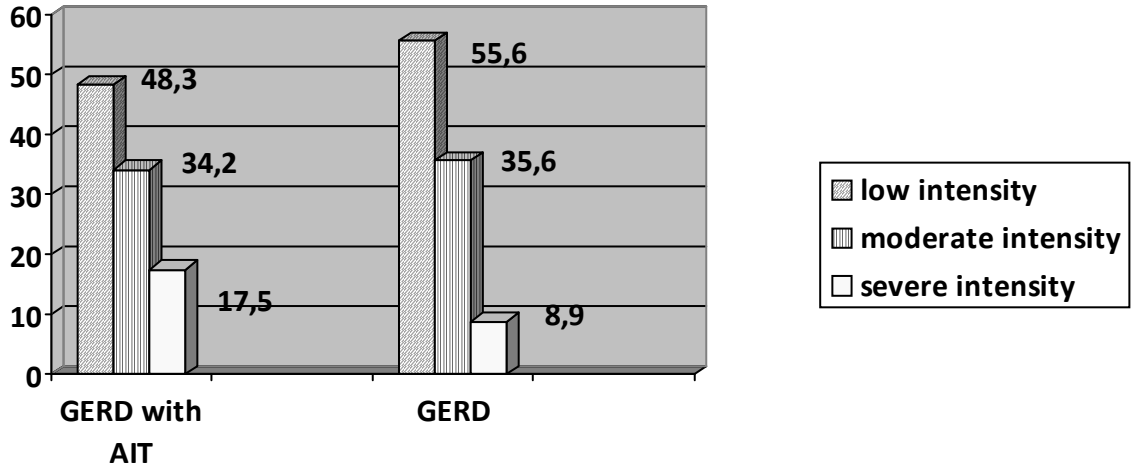

Fig. 1. Intensity of heartburn in examined patients with GERD and GERD associated with AIT, percentage

Table 1

Frequency and time of occurrence of heartburn in patients with GERD and AIT and isolated GERD, abs. (%)

Heartburn	GERD with AIT, n=120	GERD, n=45
Frequency of the heartburn (abs., %)		
Everyday	76 (63.3)	23 (51.1)
More than 2 times a week	44 (36.7)	22 (48.9)
Time of the episodes of the heartburn (abs., %)		
During the day	85 (70.8)	31 (68.9)
At night	78 (65.0)	14 (31.1)*

Note: * – the difference is statistically significant between groups p <0.05.

Table 2

Frequency clinical symptoms of GERD occurrence in examined patients, abs. (%)

Clinical sign	GERD with AIT, n=120	GERD, n=45
Epigastric discomfort	27 (22.5)	6 (3.3)
Epigastric pain	19 (15.8)	6 (13.3)
Dysphagia	8 (6.7)	2 (4.4)
Nausea	14 (11.7)	4 (8.9)
Vomiting	8 (6.7)	3 (6.7)
Belching	63 (52.5)	6 (13.3)*
Satiety after meal	41 (34.2)	11 (24.4)
Flatulence	47 (39.2)	14 (31.1)
Hoarseness	9 (7.5)	1 (2.2)
Cough	11 (9.2)	3 (6.7)

Note: * – the difference is statistically significant between groups p<0.05.

Among the all examined, 18 patients were smokers with smoking history from 7–10 cigarettes per day to half a pack. Smoking experience ranged from 6–7 to 3–4 years. The abuse of strong drinks was rejected by all groups, but they noted the use of low-alcohol drinks, such as beer. Also, almost all patients indicated frequent use of fizzy drinks.

Among the 165 students, 87 lived at home, the rest lived in a hostel or rented apartment. However, despite the different places of residence, there was practically no dietary and daily regime.

An additional survey of patients with GERD allowed to determine that almost all students did not adhere to the time of eating, volume and quality of food. Abuse of dry and spicy food, pastry, sweets were noted; and in most cases, the meal was taken on the go; between snacks there were different periods of time taking food and the first courses were practically not used. The feeling of hunger was often suppressed by smoking and drinking.

Ñonducted research of gastroesophageal reflux symptoms among Italian university students showed that 26.2% of the respondents had typical GERD symptoms occurring at least weekly [19].

According to statistic data GERD in combination with AIT is quite often registered in young patients. Such comorbidity contributes to unbalanced diet, stress, abuse of dry food and gas drinks, frequent viral infections and smoking [20].

Patients turned to the doctor in the delayed period, which can be explained by the "richness" of the life of young people and the lack of alertness for the occurrence of the disease.

The GERD on the background of autoimmune inflammation concerns with the worsening and increasing in the frequency of individual clinical symptoms (intensity of heartburn and its registration at night, belching), which can be considered as unfavorable factors for the progression of the disease and its chronicity.

Comparison of the clinical symptoms of patients with isolated GERD and GERD associated with AIT in our study revealed that all patients had heartburn with different intensity in our study. Low intensity of heartburn was registered in 17.5 % cases, moderate in 34.2 % and severe intensity in 48.3 %. Research that was conducted among medical students from southern India has shown that heartburn with low intensity was in 58.6 % of examined, 38.6 % had moderate and 2.8 % had severe GERD [21].

Night heartburn was registered in 78 patients of the first group and in 14 examined of the second group GERD ($p<0.05$). Belching occurred significantly more often in the group with comorbid pathology (63 patients versus 6 persons in group with isolated GERD).

I.V. Baranov and T.V. Maikova showed in their study the relationship between the level of thyroid hormones and the severity of the atrophy and inflammatory changes in the mucous membrane of the esophagus. However, the authors did not investigate the features of secretion in this group of patients, as well as the clinical course of GERD, depending on the presence of AIT [22].

V.T. Ivashkin and I.V. Maev analyzed in detail the characteristics of GERD therapy taking into account the clinical picture of the disease, the characteristics of the secretion and morphological state of the GERD mucosa. However, the features of the course of GERD in the presence of concomitant thyroid pathology during the course of GERD and the formation of motor-secretory disorders were not studied [23].

Considering the above, it can be speculated that associated AIT produced a negative impact on the course of GERD, but pathogenic relationship between these diseases are not well defined and requires further research.

4. Conclusions

1. Patients of the group with the combined course of GERD and AIT significantly more often had night heartburn in 65% versus 31.1% in the group with isolated GERD ($p<0.05$).

2. Belching was observed in 52.5% of patients with comorbid pathology and in 13.3% of patients with isolated GERD ($p<0.05$).

3. Assessment of other symptoms of GERD: epigastric discomfort, epigastric pain, dysphagia, nausea, vomiting, belching, satiety after meal, flatulence, hoarseness, cough did not have a significant difference between the groups, but there was a tendency to increase the incidence of symptoms in patients of the GERD group associated with AIT.

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EVALUATION OF 3-YEARS COURSE OF SUBLINGUAL IMMUNOTHERAPY WITH EXTRACTS OF CAT EPITHELIUM IN PRE-SCHOOL CHILDREN

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Abstract

The article presents the results of a 3-year course of sublingual allergen immunotherapy with a lyophilized extract of cat epidermal allergens in preschool children with allergic rhinitis, rhino-conjunctivitis and bronchial asthma. New possibilities of component diagnostics were found, and in particular, the definition of the major *Fel d 1* molecule as a direct indication for the start of therapy and use to assess the achievement of tolerance to the causative allergen. It was found that a 3-year course of sublingual allergen immunotherapy with lyophilized epidermal cat allergens for children with allergic rhinitis and/or bronchial asthma was characterized by a significant improvement in the clinical symptoms of the disease and a decrease in the level of *Fel d1*. A comparative analysis of the results of observing children with SLIT and without therapy proved that SLIT in children with allergic pathology associated with sensitization to cat epidermal allergens reduces the number of exacerbations and prevents the development of symptoms of bronchial asthma in preschool children. In addition, once again, high safety allergen immunotherapy efficacy in children has been proven.

Key words: *preschool children, sublingual allergen immunotherapy, prevention, asthma, major allergens Fel d 1.*

Introduction

Sublingual allergen immunotherapy (SLIT) is effective and safe treatment for children with allergic rhinitis, rhino-conjunctivitis and asthma. The efficacy of SLIT in the prevention of asthma in patients with seasonal allergic rhinitis is described. At the same time, to date, there is not enough information in the literature about the possibilities of prescribing SLIT in children less than 5 years of age, despite the fact that the start of the "atopic march" falls even at an earlier age. The "atopic march" well described in the medical scientific literature requires a further study. [5, 14]. In addition to food allergens, its development involves aero- or inhalant allergens, that are increasingly being considered as a significant etiological factor. Among them, a rather significant role belongs to animal epidermal allergens. The cat allergens have a special role among them. Modern date show that the prevalence of allergic reactions associated with allergens in cats and dogs is 10–20% [4]. First of all, this is due to the annual increase the number of animal owners. In the scientific literature, allergens of animals and the properties of their vital products are already well defined. The main allergic component responsible for the development of allergic reactions in more than 90% of patients with clinical manifestations of allergy is *Fel d 1*. This is an uterokinin-like protein with a molecular weight of 38 kDa, which is found in the hair, dandruff, saliva, and lacrimal fluid of a cat, secretion of the anal glands, but absent in its urine and serum. Its secretion depends on the hormonal status and testosterone level - in males it is more than in females, and after castration the secretion of this protein decreases. The high activity of cat allergens and the high risk of allergic reactions after short-term contact, as well as data on the high activity of this allergen and the possibility of its transmission through contact with the owner of the animal, have been proven [1, 3, 6, 7, 13]. Moreover, the analysis of modern literature data indicates a significant lack of information regarding the treatment of this type of allergy, the possibility

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of using sublingual allergen-specific therapy (SLIT), especially in children [11].

2. Purposes, subjects and methods:

2.1. Purpose. To evaluate the efficacy of sublingual immunotherapy with extracts of cat epithelium in pre-school children and possibilities of component allergy diagnostics using SLIT.

2.2. Subjects & Methods. As part of a prospective cohort study, the analyzed sample included 302 children aged 6 months to 7 years with clinical manifestations of allergic rhinitis (AR), rhino-conjunctivitis (ARC), bronchial asthma (BA), which depended on the allergens of a cat and / or dog.

Inclusion criteria: 1) Sensitization confirmed by skin prick test (SPT) and serum level of allergen-specific IgE measured using ImmunoCAP® (ThermoFisher Scientific, Uppsala, Sweden). The presence of a papule ≥3 mm in size and a serum level of specific IgE for *Can f1, Fel d 1* ≥0.35 kU / L molecules were considered proven sensitization. 2) Complaints of the development of symptoms of rhinitis, rhino-conjunctivitis, cough, shortness of breath in contact with animals.

Children with polyvalent sensitization to various inhalation and food allergens were excluded from the study.

Due to the fact that in patients with true sensitization to major allergens, Can f 1 there were no severe allergic manifestations in clinical history, SLIT was not recommended for these children. Sublingual allergen immunotherapy with lyophilized extracts of cat epithelium was performed in 16 patients with positive skin prick-tests and confirmed sensitization to major cat allergens *Fel d 1*. These children were included in the 1st observation group. 10 children who did not receive SLIT were included in the comparison group (2nd group). Children in both groups also received protocol-based basic therapy. If necessary, 2nd generation antihistamines, inhaled beta-agonists, IHCs and anti-leukotriene drugs were added to control respiratory symptoms.

The efficacy of the therapy was evaluated using a visual analogue scale (VAS) and the level of sIgE *Fel d 1*, that were determined before the start of therapy and during the 3-year follow-up.

Clinical and laboratory characteristics of children of the 1st and 2nd examined groups are presented in *Table 1*.

STATISTICAL ANALYSES

The Statistical analyses of the means were evaluated using the software package "Statistica-2014" and "Excel-2010". Nonparametric variables were analyzed using the Mann-Whitney paired test, while categorical variables were analyzed using the Fisher test.

Conflict of interests

The authors of the article declare no conflict of interest.

3. Results and discussion

The results of a three-year evaluation of the SLIT clinical efficacy of according to VAS indicators are presented in *Table 2*.

The analysis of the results showed that in patients of the 1st group means of the upper symptoms were significantly decreased: sneezing by 5.7 times (p = 0.041), rhinorrhea by 4.5

Table 1

Clinical and laboratory characteristics of the examined children

Marks	1st group, n=16	2nd group, n=10
Gender, n (%)		
– male	4 (66.7%)	7 (70.0%)
– female	2 (33.3%)	3 (30.0%)
Age (M±m), year	4.7±0.5	4.2±0.4
Keeping the cat in the house	2 (33.3%)	3 (30.0%)
Clinical symptoms, n (%) *		
– nasal congestion	6 (100.0%)	8 (80.0%)
– conjunctivitis	6 (100.0%)	10 (100.0%)
– shortness of breath	5 (83.3%)	8 (80.0%)
– sneezing	4 (66.7%)	6 (60.0%)
– itching	4 (66.7%)	7 (70.0%)
– cough	4 (66.7%)	8 (80.0%)
– rhinorrhoea	1 (16.7%)	3 (30.0%)
– skin symptoms	1 (16.7%)	3 (30.0%)
Monosensitized children, n (%) after SPT	3 (50.0%)	4 (40.0%)
SPT with extracts "Cat", "Dog" (M±m), мм	8.3±2.7	8.5±1.4
sIgE, kU/l (M±m)		
– *Fel d 1*	12.8±3.1	15.1±4.2

Table 2

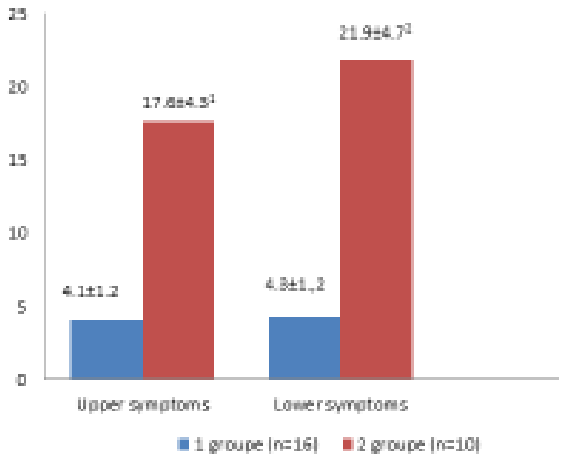
Means of VAS scale during the treatment of SLIT

Marks, mm (0–100)	1st group, n=16					2nd group, n=10				
	Before treatment	6 mo.	12 mo.	24 mo.	36 mo.	Before treatment	6 mo.	12 mo.	24mo.	36 mo.
Upper symptoms										
Sneezing	29.6±12.7	18.7±5.9*	12.8±3.2*	8.4±1.7*	5.2±0.5*	27.4±6.2	20.9±6.8*	19.3±5.3*	19.8±6.3	21.3±8.5^
Rinorrhea	15.8±3.8	9.0±1.6*	5.8±1.0*	4.3±0.7*	3.5±0.2*	10.6±1.5	7.2±2.1	10.3±3.8	8.5±1.8	9.3±2.5^
Itchy nose	25.1±7.5	17.3±4.2*	9.1±1.3*	7.8±2.1*	3.2±0.5*	27.4±6.8	17.1±3.6	16.7±4.2	15.8±5.9	18.5±5.1^
Nasal congestion	49.1±10.4	28.3±7.5*	19.1±4.2*	11.5±2.9*	4.8±0.7*	47.9±11.8	28.4±6.9	19.6±4.3	25.9±4.9	21.4±7.2^
Itchy eyes	26.1±5.8	15.3±4.3	10.2±2.2	7.8±1.7	4.7±0.3	23.7±4.7	19.2±4.3	15.8±4.9	15.2±8.3	18.9±5.7^
Conjunctival hyperemia	48.1±8.4	31.2±5.9*	22.1±5.1*	14.2±3.1*	5.3±1.2*	46.3±10.8	28.3±5.9	26.2±7.3	23.9±6.1	26.1±11.3^
Watering	24.3±8.5	18.3±4.3	12.4±3.2	8.1±2.5	2.9±0.5	28.3±7.6	11.8±4.3	14.5±3.2	17.6±5.3	20.8±4.5^
Lower symptoms										
Dyspnea	56.1±18.3	31.8±13.4	19.5±7.2	11.2±3.3	6.5±1.6	54.2±13.7	37.1±10.4	26.8±10.9	33.2±11.1	30.4±10.9^
Cough	39.4±9.2	22.8±6.3*	17.1±5.0*	11.2±2.3*	4.1±1.9*	42.3±10.4	35.1±12.7	29.6±11.9*	32.4±13.1	32.9±7.8^

(p = 0.027), itching by 7.8 (p = 0.01) and nasal congestion 10.2 (p = 0.013) times to compare with the initial level (*Table 2*). During the therapy in the group of children with SLIT the symptoms of "itchy eyes" significantly decreased in 5.5 (p = 0.033), "conjunctival hyperemia" in 9.1 (p = 0.028) and "watering" in 8.4 (p = 0.036) times, respectively, compared with the initial values.

Figure 1 presents a general follow-up description of the upper and lower symptoms in children of both groups and a significant improvement is recorded secondary to SLIT.

Significant differences of the clinical symptoms, especially the fact of the development



1 – p = 0.032 compared with the initial means;
2 – p = 0.015 compared with the initial means.

Figure 1. Comparative characteristic of the results of a 3-year treatment in study groups with sensitization to pet allergens according to VAS indicators

of bronchial asthma in 4 (40%) children of the 2nd group, despite the basic therapy, demonstrated the high effectiveness of SLIT as a method of preventing the progression of allergic pathology and the development of allergic asthma. It coincides with own observations among children of this age group who used SLIT with a mixture of house dust mites and data from foreign literature regarding older children [6, 10, 11]

In our opinion, an important factor, that shows SLIT efficacy, is "frequency of respiratory virus diseases". It decreased in the 1st group during the SLIT in the 2nd and 3rd year, 3.0 (p = 0.042) and 3.4 (p = 0.037) times accordingly (*Fig. 2*). This fact confirms that SLIT has a preventive value in the development of upper respiratory tract infections.

Besides improvement VAS parameters in children of the first group compared with children of the second group, were recorded significantly decreased levels of the specific IgE for *Fel d 1* by 17.9% (p = 0.011), 28.1% (p = 0.009) and by 50.8% (p = 0.003), respectively, compared with the initial values. In the children from the comparison group, there were no significant differences between the initial means and the means fulfilled after 3 years.

SAFETY REPORTING

Taking into account the age-specific characteristics of the examined children (3–7 years), the safety of SLIT is a priority in assessing this method According to the World Allergy Organization (WAO) guidelines during the study was not registered any systemic adverse events. Rare (6 %) local adverse events in the form of oral allergic syndrome (OAS) have been reported.

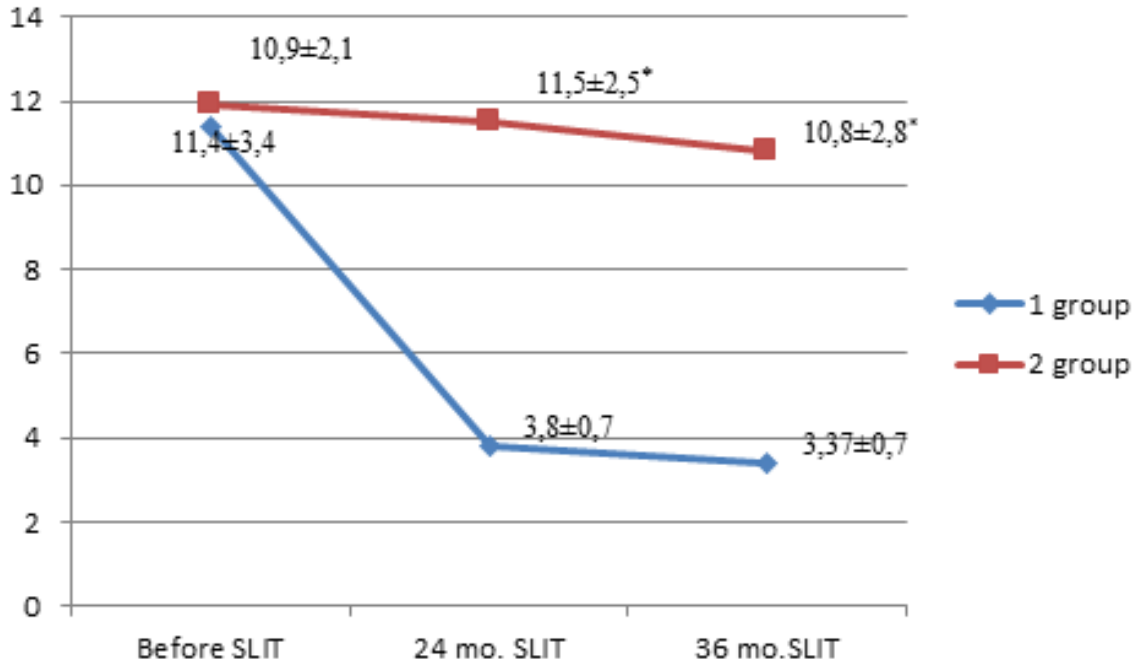


Figure 2. The number of respiratory virus diseases in children of the 1st group after two and three years of SLIT
* p > 0.05 compared with indicators of children of group 2

4. Conclusions

1. A 3-year course of sublingual allergen immunotherapy with lyophilized epidermal cat allergens in children with allergic rhinitis and / or bronchial asthma was characterized by a significant improvement of the clinical symptoms and a decrease the level of *Fel d1*.

2. The use of SLIT in children with allergic pathology associated with sensitization to cat epidermal allergens reduces the number of exacerbations and prevents the development of symptoms of allergic asthma in the preschool children.

3. Sublingual allergen immunotherapy in this study showed high safety and efficacy in 3-year-old children.

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PROINFLAMMATORY CYTOKINES IL-8 AND TNFα IN HENOCH-SCHONLEIN PURPURA IN CHILDREN

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Abstract

Background. Henoch-Schonlein purpura (HSP) belongs to a group of systemic vasculitis with predominant damage to small caliber vessels (EULAR/Pres, 2006). Difficulties in diagnosis in the early stages and the likelihood of developing complications leaves HSP in the top of the current issues of pediatrics today. Kidney damage is observed in 20–50% of patients with HSP and leads to complications. In recent years, the question of prognostic markers of progression of HSP remains open. **Subjects&methods.** The study involved examination of total of 83 HSP patients aged between 2 and 17, divided into two groups: patients with HSP without nephrotic syndrome (HSPWN, n = 58.35 of which were boys and 23 – girls) and a group of patients with HSP with renal syndrome (HSPN, n = 25.14 of them boys and 11 girls) in acute and remission periods. **Results.** The Kraskal-Wallis analysis recorded a highly statistically significant H criterion for IL-8 in the acute period (H = 17.421, p = 0.0002) and the remission period (H = 13.035, p = 0.0015). IL-8 levels in both groups of patients with HSP WN and HSPN were significantly higher in the acute period than in the control group, and the difference was statistically significant (p = 0.0004 and p = 0.0002, respectively). No significant difference was found between the medians in both periods regarding TNF-α level (H = 4.136, p = 0.1264; H = 0.133, p = 0.9356). **Conclusions.** In the group HSPN in the acute phase, a high IL-8 level in serum has been recorded compared to the group HSPWN. There was no significant difference in TNF-α level in both groups.

Keywords: *children, Henoch–Schonlein purpura, Ig-A vasculitis, nephritis.*

Introduction

Henoch–Schonlein purpura (HSP) belongs to a group of systemic vasculitis with predominant damage to small caliber vessels (EULAR/Pres, 2006). Clinical presentation is characterized by the presence of hemorrhagic rash on the skin, which is combined with the joint damage and nephrotic syndromes. HSP develops more often in children and occurs between the ages of 4 and 8 years. Difficulties in diagnosis in the early stages and the likelihood of developing complications leaves HSP in the top of the current issues of pediatrics today. Kidney damage is observed in 20–50% of patients with HSP and leads to complications [1]. The progress to chronic renal failure observed in 25–30% of patients who had nephritis due to HSP [2]. Long-term prognosis of HSP is determined by the severity of kidney damage, which varies significantly from patient to patient [3].

In recent years, the question of prognostic markers of progression of HSP remains open. In particular, the IL-10 levels were determined, IgA-IgG complexes [4], IL-6, serum amyloid A [5], antistreptolysin Î , C-reactive protein, antibodies to anticardiolipin [6], (IL)-17, IL-18, IL-23 [7, 8] . Many studies have identified some changes to different indicators, but no specific marker has been found.

Increase in the level of tumor necrosis factor a (TNFα) in the acute phase of HSP induces a series of functional and morphological changes in the nephrons and can be used as a marker of activity in renal dysfunction [9].

TNF-α is a cytokine with multiple immune response functions. Many studies have found that TNF-α plays a major role in many systemic

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inflammatory diseases, including systemic vasculitis [10].

Recent studies have suggested that TNFα hyperproduction causes severe pathological reactions in the body. Further study of the biological activity of TNFα will allow the use of this predictor of the acute phase of inflammation in the complex diagnosis of early manifestations of complications in diseases [11].

Many cells can produce IL-8 under the influence of many factors, which include proinflammatory cytokines, such as TNF-α or IL-1 [12].

2. Purposes, subjects and methods:

2.1. Purpose was to study the levels of proinflammatory cytokines IL-8 and TNFα as specific markers of nephrotic syndrome in children with HSP.

2.2. Subjects & Methods

The research was conducted in Kharkiv City Clinical Children's Hospital No. 16 from 1 January 2015 to 1 November 2018. A total of 83 HSP patients aged between 2 and 17 were examined. Patients with HSP were divided into two groups: patients with HSP without nephrotic syndrome (HSPWN, n = 58.35 of which were boys and 23 – girls) and a group of patients with HSP with renal syndrome (HSPN, n = 25.14 of them boys and 11 girls). The control group consisted of 20 healthy children, underwent a planned medical examination or received vaccination in the Kharkiv City Clinical Children's Hospital No. 16.

The diagnosis of HSP has been established according to the criteria defined by the European League against Rheumatism and Pediatric Rheumatology European Society [13]. The criteria for inclusion in the study were the established diagnosis of HSP, the presence of informative consent on the part of patients and / or parents. Criteria for exclusion from the study were the refusal of patients and / or parents to take a part in the study; the presence in patients of hereditary diseases of the blood system and other acute or chronic inflammatory diseases.

The main methods of examination were assessment of presentation, past history and present history, examination findings, clinical, laboratory and instrumental data. Major syndromes were identified, such as skin and joint pain. Detection of hematuria (erythrocyte amount > 5 / mm 3) and / or proteinuria, nephritis during the first month of PSH was diagnosed as nephrotic syndrome. Standard tests included routine clinical blood and urine tests, acute inflammation proteins. Clinical examination was performed twice: upon admission to the hospital (without nephrotic syndrome) and during remission (after disappearance of the skin syndrome). TNFα, IL-8 levels were studied upon the admission to hospital and remission period in patients with HSP and once in the control group. The proinflammatory markers of TNFα, IL-8 were determined by enzyme-linked immunosorbent assay using standard VECTOR BEST kits, Russia (A-8756, A-8762). All samples were frozen at - 40 ° until the time of the study.

Ethical aspects. All participants and / or their parents were informed about the goals, objectives and scope of the study and gave written informed consent. The study was approved by the Ethics Committee of Kharkiv National Medical University (Ethics Committee Protocol No. 8 as of 5.10.2016) and conducted in accordance with the recommendations of the Declaration of Helsinki (1975).

Statistical analysis. Statistical analysis was performed using StatSoft STATISTICA Version 8 (Tulsa, OK). Gauss's law on distribution was performed using the Shapiro-Wilk test. Nonparametric variables were represented as median (Me), interquartile range (Lq – lower quartile; Uq – upper quartile). A Kruskal-Wallis analysis of variance (ANOVA) was used to determine the statistically significant difference between the medians across all groups. A nonparametric Mann-Whitney test was used to compare the two independent variables; non-parametric Wilcoxon test was used to compare two dependent samples (T). All p-values were two-sided and values <0.05 were considered statistically significant. The relationship between the series of indicators was assessed using Spearman's rank correlation methods (r).

Conflict of interests

The authors of the article declare no conflict of interest.

3. Results

The study involved examination of 83 children between the ages of 2 and 17. The distribution of children by gender among the total number of patients did not show a statistically significant difference: boys – 49 and girls – 34 (59.04%, 40.96% respectively, ð= 0.1105). HSP in children was significantly diagnosed at the age of 12 years 86.6% ± 4.3% (p = 0.003). An analysis of HSP clinical presentations showed that skin syndrome was recorded in 100% of cases and represented by symmetric palpatory purpura. In 83.13% (69/83) patients, skin syndrome was combined with articular syndrome with signs of arthritis and

arthralgia. Representation of the abdominal syndrome were distinguished by abdominal pain, nausea and vomiting and were recorded in 43.37% (36/83), and nephrotic syndrome appeared in 30.12% (25/83).

There was no significant difference between sex and age, in terms of leukocyte and platelet levels, fibrinogen (*Table 1*). There was a significant decrease in ESR (erythrocyte sedimentation rate) in group HSPN compared to group HSPWN (p = 0.009).

was significantly higher in patients with HSPN compared to the HSP WN and control group (p = 0.0327 and p = 0.0005, respectively), and higher IL-8 level in the HSPN group compared to the group of patients with HSPWN (p = 0.0375). The Wilcoxon test showed that IL-8 levels were significantly higher in groups during both the acute and remission periods (T = 0.00; p = 0.00006 and T = 16.0, p = 0.00247).

On the contrary, no significant difference was found between the medians in both periods

Table 1

Clinical and laboratory data of children with HSP in the acute period

Indicator	HSPWN, n=58	HSPN, n= 25	p
Age, years	6.9 (3.2;15.5)	7.1 (3.8;9.8)	0.43
Boys	35 (60.34 %)	14 (56 %)	0.714
Girls	23 (39.66%)	11(44%)	0.713
Leukocytes, $\times 10^9$/L	6.5 (5.3;9.6)	6.3 (5.0;10.3)	0.813
ESR, mm / h	15.0 (9.0;20.0)	9.0 (5.0;15.0)	0.009
Fibrinogen, mg/dL	3.5 (2.6; 4.0)	3.9 (2.4;4.4)	0.127
Platelets, $\times 10^9$/L	211 (187.0;253.5)	194.5 (161.0;280.0)	0.547

The Kraskal–Wallis analysis determined a highly statistically significant H criterion for IL-8 (*Table 2*) in the acute period (H = 17.421, p = 0.0002) and the remission period (H = 13.035, p = 0.0015), which indicated the difference between the medians in all groups.

IL-8 levels in both groups of patients with HSP WN and HSPN were significantly higher in the acute period than in the control group, and the difference was statistically significant (p = 0.0004 and p = 0.0002, respectively), but no significant difference was observed between groups of patients with HSPWN and HSPN (p = 0.1087). During remission period, IL-8 level

regarding TNF-α level (H = 4.136, p = 0.1264; H = 0.133, p = 0.9356). TNF-α level tended to increase in the acute period in patients with HSPN compared to the patients with HSP WN and control group, but was not statistically significant (p> 0.05). The level of TNFα in both HSP periods in all groups did not change significantly. During the remission period, TNF-α level was close to correspondent level of the control group and was statistically unreliable (p> 0.05). The Wilcoxon test showed that TNF-α levels were significantly higher in groups both in acute and remission periods (T = 0.00, p = 0.007 and T = 0.00 p = 0.0002).

Table 2

*TNFa, IL-8 * levels in the acute and remission period in children with HSP WN and HSPN and the control group*

Indicators' levels		HSPWN n=22	HSPN n= 18	Control group n= 20	P
Acute period					
IL-8, (pg/ml)	Me Lq Uq	19.5 9.6 36.4	27.8 14.5 77.5	8.8 6.2 9.1	$p_{HSP\ WN-HSPN}$ = 0.1087 $p_{HSP\ WN-c}$ = 0.0004 p_{HSPN-c} = 0.0002
TNFα, (pg/ml)	Me Lq Uq	6.9 5.4 9.1	7.5 4.6 13.3	4.9 3.6 6.3	$p_{HSP\ WN-HSPN}$ =0.5497 $p_{HSP\ WN-c}$ = 0.0574 p_{HSPN-c} = 0.0849
Remission period					
IL-8, (pg/ml)	Me Lq Uq	11.4 6.8 23.9	24.1 10.8 56.4	8.8 6.2 9.1	$p_{HSP\ WN-HSPN}$ =0.0375 $p_{HSP\ WN-c}$ = 0.0327 p_{HSPN-c} = 0.0006
TNFα , (pg/ml)	Me Lq Uq	4.8 3.4 6.7	4.4 3.7 10.3	4.9 3.6 6.3	$p_{HSP\ WN-HSPN}$ =0.7034 $p_{HSP\ WN-c}$ = 0.8879 p_{HSPN-c} = 0.8676

* TNFa, IL-8 was studied in HSPWN group (22 patients), HSPN group (18 patients).

There was a direct correlation between IL-8 and TNF-α in patients with HSPN during acute period ($r = 0.527$, $p \leq 0.05$) and remission period ($r = 0.658$, $p = 0.05$), $p \leq 0.05$, respectively. A direct correlation between IL-8 and TNF-α was observed in the acute phase of HSP ($r = 0.396$, $p \leq 0.05$).

4. Discussion

The study showed that non-invasive biomarkers could be used to safely diagnose nephrotic syndrome in children with HSP. Many studies have found that HSP is not a self-curable disease and can transform in chronic kidney disease (CKD) in childhood. [14]. The pathogenic mechanism underlying HSP is still not fully understood, so it is important to find specific markers for the development of kidney complications in HSP patients, because many researchers consider HSP as one of the serious and common causes of kidney damage in children [15].

With regard to pro-inflammatory cytokines, it has recently been found that serum IL-8 levels are significantly increased in cases of kidney damage [6] and our study confirmed these results. Our patients were found to have an increased level of IL-8 in serum, not only in the HSP group with nephritis, but also without kidney damage in comparison with the control group, the same data was obtained by French researchers. IL-8 concentrations were higher in patients with HSP WN and HSPN than in the control group [4]. Based on our results, IL-8 level may be useful as a marker for monitoring the progression of nephrotic syndrome in children with HSP.

We have not determined a significant difference between the median levels of TNF-α in both groups of patients in the acute and remission periods compared to the control group, which has been also confirmed in studies by our colleagues. A slight increase in TNF-α level during the acute period in the nephrotic syndrome group compared to the group without nephrotic syndrome indicates that increased TNF-α level in serum causes a number of functional and morphological changes in the glomerular cells in the acute phase and cannot be used as a marker to monitor the activity of HSP disease with severe kidney damage, which is in contrast to the studies of our colleagues. [16]. Thus, it can be stated that in addition to TNF-α, in serum of active HSP there may be other major factors that can activate endothelial cells to produce IL-8 [17].

The activation of inflammation leads to the activation of the coagulation system, which also markedly affects inflammatory activity. This is considered important in the pathogeneses of vascular diseases [18, 19].

Conclusions

1. In the group with nephrotic syndrome in the acute phase, a high IL-8 level in serum was detected as compared to the group without nephrotic syndrome and the control group.

2. There was no significant difference in TNF-α level in both groups in the acute phase as compared to the control group.

3. In the follow-up, the IL-8 level was decreasing in both groups of the study, but still remained high in the group with nephrotic syndrome in remission period, which can indicate accurate prognostic effectiveness in the detection of patients with HSP with kidney damage at the time of diagnosis.

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THE CURRENT STATE OF THE PROBLEM OF PERINATAL PSYCHOSOMATIC DISORDERS IN PREGNANT WOMEN

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Abstract

Purpose: to study the characteristics of the psychosomatic state of women during pregnancy using the Edinburgh Postpartum Depression Scale (EPDS). **Subjects&methods.** Sixty pregnant women in the III trimester of pregnancy were tested using the EPDS questionnaire, a 10-point self-assessment scale that covers the general symptoms of depression. To determine the internal consistency and reliability of this scale, the Cronbach alpha indicator, a statistical indicator that allows evaluation of whether the features included in the questionnaire measure the same thing (high internal agreement), or different things (low internal agreement), was calculated. **Results.** Subjectively, all pregnant women noted simplicity, unambiguity and clear wording of the questions, which indicated good acceptability of this questionnaire for the use in the complex of standard monitoring of pregnant women in an antenatal clinic. The Cronbach alpha coefficient was 0.775, which corresponds to a sufficient degree of consistency of the internal elements of the scale. Screening for depressive disorders using EPDS during pregnancy revealed psychosomatic problems of the perinatal period. Data obtained using this scale demonstrate high rates of depressive manifestations in pregnant women. Psychopathological disorders were detected in 40% of women, while in 23% the symptoms of the current "major" depression were identified. The frequency of development of depressive symptoms increases significantly in the presence of a high obstetric risk, characteristic of the current pregnancy (threat of premature birth, hypertensive disorders during pregnancy, intrauterine infection of the fetus, retardation of the fetus development), as well as compromised obstetric and gynecological history. EPDS can be used as a reliable diagnostic tool to prevent pregnancy-related adverse outcomes. **Conclusions.** Sdentifying the risk factors of pregnancy, screening and examining psychosomatic symptoms with EPDS, and timely referral for psychiatric care are key issues for reducing the risk among women with psychosomatic disorders during pregnancy and the postpartum period.

Keywords: *pregnancy, psychosomatic disorders, Edinburgh postpartum depression scale.*

Introduction

The health of future generations in recent years has become one of the priority medical-social areas of modern obstetrics and gynecology in Ukraine and in the world. At the same time, the perinatal period is unique in its significance for the establishment of the foundations of national health. Improvement of methods for the integrated study of physiological and pathological manifestations of gestational adaptation in the mother and fetus during this period will make it possible to identify new reserves for improving the quality of medical care [1, 2]. It is very important to assess a huge number of factors under the influence of which the so-called "high risk" pregnancy is formed. Among these factors a special place is occupied by chronic psycho-emotional stress, which is formed against a background of socio-economic, family, professional negative effects on the modern person and of course including pregnant women who are one of the vulnerable parts of society [3, 4]. Based on historically oriented, illuminated scientific works from philosophers of antiquity to modern medical forums, the concept of unity in a person's mental and somatic, unfavorable psychological condition of the future mother adversely affects the course and outcome of pregnancy, childbirth,

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fetus, newborn and child health. Prolonged and intense exposure to stress factors leads to development of a significant number of psychosomatic diseases of pregnancy [5, 6].

The term "psychosomatic disorder" identifies psychological and emotional effects as the leading etiological element of the manifestations of diseases in which it is impossible to find any organic pathological causes, and which appear to be the result of emotional states, such as anger, anxiety, depression and guilt. At the present stage, given the high incidence of mental disorders, psychosomatic medicine has been recognized as a special area of psychiatry, which provides psychological support and psychiatric care to patients with various complex medical and obstetric conditions [7]. In the presented report, we tried to highlight the epidemiological aspects of the most important psychosomatic disorders during pregnancy, as well as the main directions of diagnosis and prevention of common types of this pathology.

Most studies of psychosomatic disorders during pregnancy focus on major postpartum depression, however, according to literary data and our own observations, most women who have been diagnosed in this way have symptoms of depression in the antenatal period. And despite the fact that the Psychiatric Diagnostic and Statistical Manual of Mental Disorders (DSM-5), developed by the American Psychiatric Association, identifies only depressive disorders in women between 4 weeks and 3 months after childbirth, it is the antenatal depressive symptoms that are the source of postpartum problems and are detected in most patients [8, 9].

The results of a study conducted in the United States showed that 33% of postpartum depression begins during pregnancy and 27% before pregnancy. In the first, second and third trimesters the frequency of depressions was 7.4, 12.8, and 12%, respectively. It is important for clinicians to solve this problem that antenatal monitoring and timely identification of groups of pregnant women at high risk of developing postpartum depression should be the basis of effective preventive measures [2, 10].

The perinatal period is also critical for development of anxiety disorders in pregnant women and puerperas; cohort studies conducted by European scientists showed that anxiety occurred in 30% of women in the second trimester and in 16% in the postnatal period, two categories of anxiety were described: subsyndromic state anxiety (intensity indicator experiences, which arises in relation to typical events) and clinically significant comorbid anxiety (social phobias, generalized and mixed-depressive states I), which occurs in approximately 50% of women with depression during pregnancy and the postpartum period. The anxiety symptoms have a negative impact on the outcome of pregnancy, form a negative attitude towards motherhood and violate the processes of perinatal adaptation [11].

Psychological problems, anxiety, lack of social and family support are known risk factors for the occurrence of post-traumatic stress symptoms associated with childbirth. Postpartum post-traumatic stress disorder occurs more often after instrumental delivery through the birth canal or emergency caesarean section, while the risk is minimal after elective caesarean section. Spontaneous abortion and perinatal death also lead to postpartum post-traumatic stress disorder, in 29% of women it develops after stillbirth. The risk of major depression, appearance of generalized anxiety disorder, increases 5 and 3 times, respectively, about a third of women report suicidal thoughts. Early identification and prompt psychiatric care remain the main therapeutic and preventive measures for such patients [12, 13].

It is necessary to note the increased risk of psychosomatic clinical manifestations and obstetric complications in pregnant women with eating disorders. According to the current data, anorexia nervosa and bulimia nervosa occur in 0.2–0.7% of the population and in 0.8–2.3% women, however, a significant proportion of women with eating disorders before pregnancy note recurrence of symptoms after childbirth, however, the risk of postpartum depression is significantly increased in these women compared with the women with a history of eating disorder, but without active symptoms [14, 15].

Despite the high frequency of perinatal psychosomatic disorders, research in this direction is still insufficient. In particular, the question about the optimal timing and clinical efficacy of diagnostic tests, the need to use psychometric questionnaires as a tool for perinatal screening remains unresolved. The most commonly used screening method is the Edinburgh Postpartum Depression Scale (EPDS), which is a ten-point questionnaire (including the issue of self-harm), adopted in many countries for both antenatal and postnatal use. According to the recent studies, the test has a sensitivity of 88% and a specificity of up to 92.5% while, combined with the general health questionnaire (GHQ), the predictive value of an integrated approach is increased compared

to using each method separately. At the same time, as many international guidelines emphasize, screening methods are not so much aimed at diagnosing depressive disorders, but rather aimed at identifying women for whom further comprehensive psychosocial and clinical evaluation is needed [16, 17].

Thus, at present, there is a need for additional studies aimed at investigation of the clinical features, nosological affiliation of psychosomatic symptoms in the perinatal period and development of integrated approaches to the diagnosis, correction and prevention of psychosomatic perinatal disorders.

2. Purposes, subjects and methods:

2.1. Purpose: to study the features of the psychosomatic state of women during pregnancy using the EPDS.

2.2. Subjects & Methods

Sixty pregnant women were examined in the third trimester of pregnancy, who were tested according to the Edinburgh scale of postpartum depression in the conditions of antenatal clinic; then they were tested 2–3 days and 6 weeks after the delivery.

The Edinburgh Postpartum Depression Scale (EPDS) is a 10-point self-assessment scale that was developed to screen a wide population for postnatal depression (Cox et al., 1987). This scale covers the overall symptoms of depression; this excludes somatic measurements, such as fatigue and changes in the appetite, which are normal before and after childbirth. Each item is rated on a 4-point scale (from 0 to 3) with a minimum total score of 0 and a maximum of 30.

After signing a written informed consent, the pregnant women who agreed to participate filled out the EPDS questionnaires.

To determine the internal consistency and reliability of the specified scale, the Cronbach alpha indicator, a statistical indicator was calculated. This allows evaluation of whether the characteristics included in the questionnaire measure the same thing (high internal agreement, or different things (low internal agreement). are not related in meaning to each other, then the alpha indicator is 0, but if all the signs measure the same thing, then the alpha value is 1.0, the internal agreement is considered satisfactory with an alpha value of more than 0.7.

The statistical methodology of factor analysis was also used a comprehensive and systematic study and measurement of the impact of factors on the value of the effective indicator, the factors as a result of the analysis receive a quantitative and qualitative assessment, in order to highlight in the totality of the signs of those that really affect the change in the dependent variable.

The obtained data were subjected to statistical processing using Student's criterion, the Spearman correlation coefficient.

Conflict of interests

The authors of the article declare no conflict of interest.

3. Results and discussion

The average age of the surveyed was 29.7±4.6 years. According to the history, there was no significant difference in parity, frequency of concomitant somatic and gynecological pathology among pregnant women. The inclusion criteria were pregnant women from pregnancy 28 to 37 weeks and at least 18 years old. Exclusion criteria were mental disorders in pregnant women.

The analysis of the socio-demographic and clinical-anamnestic data of the pregnant women are presented in *Table 1*. All women were married or lived with the father of the child, most of them were born in Ukraine, all levels of education are equally represented among the examined.

Twenty-four (40%) of the examined were multiparous, one third of the examined were hospitalized during the previous 2 weeks, 12 (20%) were treated for infertility, 3 (5%) had a history of preterm delivery, 15 (25%) had previously been artificial abortion, 13 (22%) – spontaneous abortion, one (2%) had an ectopic pregnancy.

Women found the EPDS quite acceptable, filling out the questionnaire took no more than 10 minutes, subjectively, all pregnant women noted simplicity, unambiguity and clear wording of questions. Each questionnaire was completely filled in. Therefore, it should be concluded about the good acceptability of this questionnaire for the use in the complex standard monitoring of pregnant women in female counseling.

Of the 60 women, 16 (23%) had symptoms of "major" depression, none had ongoing manic or hypomanic episodes. Average ratings according to the EPDS scale were 9.3±6.1 (minimum 0, maximum 28), while statistical analysis showed high sensitivity and specificity for choosing a threshold value of 11.5 points as an indicator of the level of the Edinburgh scale for pregnant women with serious depressive disorders.

To assess the internal consistency of the EPDS, adapted for our study, the Cronbach alpha coefficient was calculated, and a value greater than 0.8 was chosen as a sufficient level for assessing the reliability of the scale. In our study,

Table 1

Socio-demographic characteristics and complications of pregnancy

	No	%
Family status		
Married	44	73
Lives with the baby's father	59	98
Single	16	27
Place of birth		
Ukraine	46	77
Other countries	14	23
Education		
School education	12	20
College	24	40
Higher education	24	40
Profession		
Office workers	47	78
Manual workers	4	7
Not working	9	15
Complications of current pregnancy		
Hypertensive disorders	5	8
Polyhydramnios	2	4
The threat of preterm birth	38	63
Gestational diabetes	2	4
Retardation of the fetus	4	6
Intrauterine infection of the fetus	3	5

the value of this coefficient was 0.857, which showed a sufficient degree of consistency of the internal elements of the scale and its reliability in assessing psychosomatic disorders in pregnant women. Correlation analysis, components of the questionnaire with the total value of the EPDS, revealed statistically significant correlations ($p < 0.01$).

A factor analysis allowed us to obtain a two-factor model for the EPDS during pregnancy: one factor consists of "depression" elements (F1) and the other factor consists of elements reflecting depression and other disorders, including anxiety (F1) (*table 2*), the first factor F1 includes the following items: 3 (fault), 4 (alarm), 5 (panic attacks), 6 (congestion) and 10 (suicide ideas), the second factor F2 consists of points 1 and 2 (angedonia), 7 (sleep disorders), 8 (sadness) and 9 (tearfulness). Items 7 and 9 are included in both factors.

The average total F2 score was significantly different (Student's t test, $p<0.001$) among depressed (according to DSM IV criteria) and non-depressed women. For F1, the difference in mean total scores between the two groups (depression = no depression) was not significant.

Internal consistency, as measured by the Cronbach alpha scale, was 0.76 for the global EPDS scale, 0.77 for the F1 subscale, and 0.85 for the F2 subscale.

Retesting was carried out in 23 pregnant women who were in the same clinical condition during the test. The average duration between tests was 4.7±1.7 days (minimum 1 day, maximum

Table 2

Characteristics of the factor analysis of the EPDS scale on the Cronbach alpha scale

	F1	F2
Sections of the EPDS scale		
Section 1(angedonia)		0,898
Section 2(angedonia)		0.667
Section 3(guilt)	0,743	
Section 4 (anxiety)	0,635	
Section 5 (panic attacks)	0,806	
Section 6 (overwhelmed)	0,714	
Section 7 (sleep disorders)	0,564	0,675
Section 8 (sadness)		0,836
Section 9 (tearfulness)	0,622	0,614
Section 10 (suicidal ideas)	0,853	

5 days). The correlation coefficient was 0.83 ($p<0.05$), which indicates high reliability of retesting.

Discussion. Thus, the results obtained indicate a sufficiently high level of "major" depression and high dysphoria in the examined group of pregnant women, among whom 40% had a high-risk pregnancy. It should be noted that the frequency of development of depressive symptoms increases significantly in the presence of a high obstetric risk characteristic of the current pregnancy (threat of premature birth, hypertensive disorders during pregnancy, fetal infection of the fetus, fetal retardation), as well as burdened obstetric and gynecological anamnesis.

The results of the assessment of the consistency of the questionnaire, as well as the factor analysis carried out confirm the good reliability of the used scale for screening pregnant women who may have depressive disorders.

Our study shows that the value of the EPDS score, 11.5, gives good sensitivity (0.80) and specificity (0.80) for screening women who may have depressive disorders during pregnancy, confirms good internal consistency of the scale and its good short-term reliability when re-testing. Factor analysis involves a model with two subscales (F1 and F2).

Our data are in good agreement with the literature data, since many medical associations, such as the American Academy of Pediatricians, the European Association of Gynecological Obstetricians strongly recommend screening for depression with the EPDS and do it during pregnancy, immediately after birth, and 1–2 months after giving birth [18, 19]. The prospect of our further research on the diagnostic and therapeutic aspects of the psychosomatic problems of the perinatal period will be to obtain more accurate diagnostic criteria for screening testing, as well as for an objective assessment of the effectiveness of therapeutic interventions in high-risk pregnant women.

4. Conclusion

Identifying risk factors of pregnancy, screening and examining psychosomatic symptoms with the EPDS, and timely referral for psychiatric care are key issues for reducing risk among women with psychosomatic disorders during pregnancy and the postpartum period.

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THE LEVEL OF ORGANISM FUNCTIONING AS AN INDICATOR OF PREMORBID CONDITIONS (REVIEW)

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Abstract

The state of the organism is the consequences of interaction with the environment, that is, the result of adaptation or maladaptation of the organism to the environment. The transition from health to illness can be seen as a process of gradually reducing the ability of a person to adapt to changes in social, educational, and production environments and surrounding conditions. Achievement of any level of functioning of an organism or its separate systems is provided through the activity of regulatory mechanisms. The mobilization of reserves occurs as a result of changes in the level of activity of regulatory systems. This is primarily due to an increase in the tone of the sympathetic department of the autonomic nervous system. In those cases where the body constantly has a deficit of functional reserves to support homeostasis, there is a state of functional stress, which is characterized by the displacement of the autonomic balance in favor of the adrenergic mechanisms and the corresponding changes in the hormonal state. In the state of functional stress, all of the basic functions of the body are within physiological norm, but the organism spends functional reserves to maintain the normal level of functioning. The process of adaptation precedes the development of a disease that results from the lack of adaptation mechanisms, their reduction and disruption. The development of maladaptation is preceded by the state of adaptability, and after the maladaptation the state of the disease develops, i.e. all the conditions that precede the disease, that is, the failure of adaptation, are united in the premorbid state. The process of identifying the states that border between the norm and the pathology, when it does not yet have signs of the disease, that is, the premorbid states, is called premorbid diagnostics. The diagnosis of premorbid states takes into account the use of methods and equipment that are designed for processing information in the range of relative functional stability of the organism with the definition of the vector of adaptation processes and that is an integral part of preventive medicine.

Key words: *Premorbid condition, functional state of an organism, functional reserves of an organism, premorbid diagnostics, preventive medicine.*

The state of the organism (its health or disease) is the consequences of interaction with the environment, that is, the result of adaptation or maladaptation of the organism to the environment. The transition from health to illness can be seen as a process of gradually reducing the ability of a person to adapt to changes in social, educational, and production environments and surrounding conditions. According to the theory of general adaptation syndrome, developed by H. Selye in 1961 [1], the reaction of the organism to any influence contains two main components - specific and nonspecific. At the same time, the nonspecific component predominates. The leading process is the mechanism of mobilization of functional reserves, which provides the release of additional energy and compensation of energy consumption of an organism in achieving the final useful adaptive result. As noted by F. Meerson in his works, the energy links of adaptive reaction are basic and implemented at the cellular level in the form of activation of the genetic apparatus of

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the cell, increase in the number and activation of mitochondria, and increase of intensity of the functioning of cell structures [2]. Achievement of any level of functioning of an organism or its separate systems is provided through the activity of regulatory mechanisms. The mobilization of reserves occurs as a result of changes in the level of activity of regulatory systems. First of all, this is due to an increase in the tone of the sympathetic department of the autonomic nervous system. In those cases where the body constantly has a deficit of functional reserves to support homeostasis, there is a state of functional stress, which is characterized by the displacement of the autonomic balance in favor of the adrenergic mechanisms and the corresponding changes in the hormonal state. In the state of functional stress, all of the basic functions of the body are within physiological norm, but the organism spends functional reserves to maintain the normal level of functioning. The process of adaptation precedes the development of a disease that results from the lack of adaptation mechanisms, their reduction and disruption [3, 4].

The development of maladaptation is preceded by the state of adaptability, and after the maladaptation the state of the disease develops, i.e. all the conditions that precede the disease, that is, the failure of adaptation, are united in the premorbid state. The premorbid state leads to an increase in the energy consumption of the human body [3, 5].

The term premorbid condition was first proposed by R. M. Baievskiy in 1974 [3]. The doctrine of the premorbid status has evolved due to researches in the field of prophylactic medicine, age-related physiology, epidemiology, which control the health of the organism, focus on its ability to adapt to new unusual environmental conditions, rather than the development of diseases in the body. The premorbid state of the organism is characterized by its normal functioning, which traces the dynamics of reducing the level of adaptive capacity of the organism. Theoretical analysis of scientific data points to a small number of researches of the premorbid states of the individual and a practical absence of models for the evaluation and correction of the premorbid states of the human body by prophylactic means and physical education and recreation classes [6, 7]. Some scientific researches about the problem of diagnostics of the level of somatic health are found in the articles [6, 7]. The premorbid state develops due to a certain set of factors having a different contribution to its structure. According to number of authors, various factors of the premorbid state development, namely, anthropometric, physiological and others [3, 7, 8, 9], are noted. However, the results of most studies do not allow complete interpretation and usage of them in preventive measures and physical education and wellness activities, which allows to conclude that this problem needs further research [5, 8].

The process of identifying the states that border between the norm and the pathology, when it does not yet have signs of the disease, that is, the premorbid states, is called premorbid diagnostics. Diagnostics of the premorbid states takes into account the use of methods and equipment that are designed for processing information in the range of relative functional stability of the organism with the definition of the vector of adaptation processes [3, 4, 10].

Premorbid diagnostics is an integral part of preventive medicine. The current analysis of the premorbid diagnostics, the deterioration of the health of children, adolescents and people of working age in Ukraine shows the relevance of this problem and emphasizes its main task that is to define the ways to manage human health [2, 6]. However, despite a large number of studies, most of the existing methods are based on the definition of the functional capabilities of the body, which is insufficient to measure the amount of health, and even more so for the determination of the premorbid state of the organism [3, 7–10]. For a comprehensive assessment of the health of an organism, it is important to know not only the functional capabilities of the organism (the level of capacity of the organism), but also qualitative indicators of health (level of well-being, period of recovery of the organism). According to the results of various researchers, about 80% of children of junior school, high school and people of working age are in the premorbid states [3, 4, 7]. There is a large number of studies devoted to the early detection of children's premorbid conditions, which confirms the relevance of this problem [3, 4, 6–8].

So in many studies for the purpose of correction of the premorbid state it is suggested to use means of physical fitness, which influence the optimization of functional reserves of the cardiovascular and respiratory systems of the organism. Research results of R.M. Baievskiy, T.G. Omelchenko, M.V. Malikova, N.V. Bogdanovskaya and others show the priority factors in the structure of the premorbid states

and require the development of typical correctional health programs [3–6, 8].

This diagnosis is based on the fact that the transition from health to disease passes through a series of successive stages, during which the body adapts to new conditions of existence, changing the level of functioning and tension of regulatory mechanisms. They can be characterized as:

1) normal adaptation reactions;

2) the tension of the adaptation mechanisms (short-term, or unstable adaptation);

3) overloading and failure of adaptation processes.

In the case of long-term adaptation, the number of mitochondria increases, that is the main way of adaptation is the change of energy metabolism. It is the lack of energy that determines regulatory, metabolic and structural changes. Compensation mechanisms are starting to work, which are, in fact, markers before illness. Then comes the phase of reversible changes, and only after it morphological damage to structures occurs.

There are three parameters describing the stage of adaptation of an organism, according to the opinion of many authors:

1) the level of functioning of the system;

2) the tension level of regulatory mechanisms;

3) the amount of the functional reserves.

In the premorbid diagnosis, the classification of functional states of the organism is used [6, 10].

The norm is a class of functional states with sufficient functional (adaptive) capabilities of the organism. An assessment of the functional state of the body is impossible without the use of concept of norm. The methodological aspect of the norm allows to approach its definition in the applied, scientific sense as an expression of a functional optimum, as pointed out by R. M. Baievsky in 1979. In this regard, it is often believed that the optimum is consistent with the average data. But biological systems are always characterized by instability, which manifests itself in the variability of their functional characteristics. Therefore, the individual norm is always concrete and specific, which is established depending on the conditions in which a person exists. There are four main types of norm, such as statistical, clinical, ideal and physiological. The statistical norm is described by the corresponding deviations from the mean value. Clinical norm characterizes the importance of indicators in individuals without manifestations of the disease. The ideal norm reflects the state of a person, which is in the best of pleasant conditions. The physiological norm indicates the maintenance of a sufficient level of functional capabilities of the organism [5].

Therefore, the norm for any indicator includes not only the average value, but also a series of deviations from it. These deviations are connected with the nature of biological indicators, and with individual variability, specificity. The individual optimum of the organism does not always (or rather, very rarely) coincides with the average indicators. Individual norm is always concrete and specific. However, the set of individual indicators gives only a static image of the current state of the organism, which by comparison can be attributed to a certain class of states. The notion of norm includes the ability of an organism to adapt to certain effects of factors of the environment. Human organism constantly adapts to changes in the environment associated with the time of day, working environment, and so on. The adequacy of the response of the organism to the action of one or another factor is the one of the important components of the norm [4, 5, 9].

The premorbid states are the states in which optimal adaptive capabilities of the organism are provided with higher than normal tension of regulatory systems. This leads to increased expenditure of the functional reserves of the body, the increase of energy-information provision of the interaction of physiological systems of the body to support homeostasis. A characteristic feature of the premorbid states is the presence of increased functional tension of adaptation mechanisms. It is possible to distinguish three stages of functional tension: moderate, expressed and sharply expressed [7, 8, 9].

Examination and forecasting of the premorbid states of health of people of working age are based on the analysis of physiological mechanisms ensuring the activity of a person. The spectrum of modern researches is based on a number of scientific fields, including the study of parameters of psychophysiological potential of a person. In these studies, premorbid diagnostics takes a first place as a marker for possible physical and psycho-emotional stresses [7].

The deterioration of health of population occurs due to an increase in the number of premorbid states. This requires the development of techniques that allow to predict them. Currently there are three main criteria of the premorbid state commonly accepted such as the level of functioning of organs and systems, the state of functional reserves and the measure of tension of regulatory mechanisms [10, 11].

Thus, the formation of premorbid state most often occurs in a non-specific way depending on the individual characteristics and adaptive capabilities of the organism, which significantly reduces the possibilities of the methods of parametric statistics [4–6]. In this case, it is recommended to study the correlation between the investigated features, the calculation of nonparametric statistical criteria processing [4–6].

Conceptual definition of the concept of "cause-effect relationship" implies the existence of functional (or correlation) relationships, which consider the role of causative factors and risk factors in the manifestations of morbidity [6, 12, 14]. Changing the frequency and quality of one of the factors entails a change to another. The change in the first part of the interacting phenomena is considered a cause, and the change in the second is a consequence. The causal link between the health determinants and health is a statistical connection [13, 14].

The causal nature of the epidemiological link is expressed by the difference in the rates of morbidity, depending on the revealed correspondences with one factor or another. The presence of this is evidenced by the quantitative relationship between the strength of the hypothetical risk factor (level and duration of exposure) and the severity of the effects (level of morbidity) by the type of dose-effect [4, 5].

Thus, the study of the intensity of regulatory mechanisms is the study of the dynamics and interconnection of indicators of homeostasis, the influence of factors on the development of the premorbid state. For forecasting, the following statistical methods can be used: correlation, regression and dispersion analysis [4, 5].

Another perspective way of the premorbid diagnosis is the application of the principles of information theory and the calculation of indicators of information analysis of entropy (IEA). The possibility of using the IEA to measure the tension of regulating mechanisms is confirmed in the study of the peculiarities of the lifestyle of modern youth [6]. Separation of subjects under regular physical activity allowed to identify the risk factors that are most pronounced in the group of people not engaged in physical culture. The calculation of the relative entropy indicators allowed establishing a hierarchy of risk factors that increase the regulation level and form an unhealthy lifestyle. Thus, the use of statistical methods allowed assessing the process of formation of the premorbid status [4, 6, 15–17].

In turn, a significant increase in tension, which leads to a decrease in functional resources, makes the biological system unstable, sensitive to various actions and requires additional mobilization of reserves [6, 7, 19, 20]. This condition, associated with the tension of regulatory mechanisms, was called the state of poor adaptation. In this state, specific changes of individual organs and systems become more significant [21–23]. Therefore, it is entirely permissible to speak about development of initial manifestations of premorbid conditions, when changes already indicate a manifestation of a possible pathology. Premorbid conditions are conditions characterized by a decrease in the functional capacity of the body and manifest in the form of two stages, namely: 1) with the predominance of non-specific changes while maintaining homeostasis of the main vital systems of the body, including the cardiovascular system; 2) with the predominance of specific changes on the part of certain organs and systems, homeostasis of which is violated, but due to the mechanisms of compensation the manifestation of the disease can be expressed or it is in the initial phase and is compensatory in nature. An essential feature of this class of functional states is that they develop and flow with overloading of regulatory mechanisms [24–26].

Maladaptation is a state with a sharp decline in the functional capabilities of the body in connection with the violation of compensation mechanisms. In this state, as a rule, there are various diseases in the stage of subcompensation or decompensation [5, 6, 10]. This majority of violations is manifested by the cardiovascular, respiratory, digestive, excretory systems [6].

I.M. Sechenov noted that the existence of organism without an external environment is impossible; according to I.P. Pavlov, the animal organism as a system exists among the surrounding nature only due to the continuous equilibrium of this system with the external environment, provided by certain reactions of the living system to external stimulation. In general, the doctrine of health can be defined as a science of the laws of the harmonious unity of biological, physical-chemical and informational exchange processes both within the body and with the environment surrounding it [26, 32, 33].

The human organism facing modern scientific and technological progress with continuous stress (social, psycho-emotional, etc.) must be considered as a dynamic system that continuously adapts to environmental conditions by changing the level of functioning of individual systems and the

corresponding tension of regulatory mechanisms [29–32]. Adaptation to new conditions is achieved by the expenditure of functional resources of the organism. An organism constantly spends its vital resources and constantly refills them during rest and sleep [33–35]. The state of an organism is determined by the optimality of actions that control the ability of mechanisms to balance the organism with the environment, its adaptation to the environment. Support of the normal level of functioning of the basic systems of the body is the main task of mechanisms of homeostasis. In order for the fluctuations of the homeostatic parameters to be kept within normal limits, constant work of functional regulatory systems is required. The activity of adaptation mechanisms requires a certain tension of regulatory system which is a level of stress depending on the functional reserves of the body [29, 36–38]. The more are the functional reserves, the lower tension of regulatory systems is required to maintain homeostasis [29, 39, 40].

Adaptation reactions to a large extent depend on the individual characteristics of the organism (sex, age, type of regulation), and also on environmental conditions. The state of an organism, as a result of the activity of various functional systems and organs, is determined by the optimality of the managing actions, their ability to balance the organism with the environment, its adaptation to the conditions of existence, and the adequate level of functioning of the basic systems and organs to the requirements of the environment [4–7, 41, 42].

Functional reserves of regulatory systems can be explained by the equation (R. M. Baievsky, 2017): level of functioning = tension level x functional reserves. This equation shows that in various actions to maintain an adequate level of functioning of the organism as a whole or its separate systems, an increase in the amount of stress is required, which is pronounced the more, the lower are the functional reserves [5]. Maintenance of homeostasis within the body and between the organism and the environment is the main condition for the existence of a living system. The homeostatic properties of an organism are the result of the simultaneous action of numerous and complex organizational mechanisms, among which one of the important central places is autonomic regulation of the body, its organs and tissues. After researches made by K. Bernard, I. M. Sechenov and W. Cannon, a new step in the development of the idea of homeostasis was made by N. Wiener, who proposed to apply the theory of control in the modeling of homeostatic systems. The ability to balance with the environment, or the adaptive capacity of the body, is one of the most important features of the living system. It should be noted that the reduction of the adaptive capacity of the organism, associated with changes in physiological functions, in particular, with the change myocardial-hemodynamic homeostasis, is characterized by an increase in blood pressure, a decrease in the external work of the heart [46]. However, in the premorbid conditions observed changes in physiological parameters, as a rule, do not go beyond the so-called clinical norm and therefore usually remain out of the attention of doctors during the preventive medical examination of the population. As a result, as it is known that only the failure of adaptation with the development of specific disease becomes the basis for medical treatment. In the best case, with the earlier detection of the initial signs of the disease, specific measures of secondary prevention may be applied. To assess the level of functioning of the cardiovascular system which is the leading homeostatic system of the organism, a special indicator is developed that is the index of functional changes (IFC). It is calculated in points according to the following formula: IFC = 0.011 * HR + 0.014 * SAP + 0.008 * DAP + 0.014 * A + 0.009 * BM – 0.009 * H-0.27, where HR is the heart rate (bpm), SÀP and DAP – systolic and diastolic blood pressure (mm Hg), A – age (years), BM – body weight (kg), H – height (cm). Interpretation of IFC is carried out according to the following scheme: satisfactory adaptation – up to 2.59; tension of adaptation mechanisms – 2.60–3.09; unsatisfactory adaptation – 3.10–3.49; maladaptation – 3.50 and above [14, 18].

Even small changes in the traditionally measured parameters of pulse rate, blood pressure, body mass change the value of this integral index, indicating the direction of change in the functional state of the organism. The action on the organism of the environmental factors is constant, systematic and, being a stressor, leads to the development of the tension of regulatory systems of the body [10, 43].

Normally, this tension has a working character and ensures that the body achieves an individual functional optimum. It does not cause negative consequences, and after rest the complete recovery of initial normal functional state is marked. By reducing the adaptive capacity of the body in response to normal activity loads, there is an increased functional tension of the adaptation

mechanisms [44, 45]. Gradually, in the absence of adequate preventive measures, moderate functional tension converts into expressed, and then sharply expressed. In the case where ordinary activity loads are inadequate or with a significant reduction in the adaptive capacity of the organism (for example due to a disease) and insufficient recovery, a sharp increase in functional tension leads to overloading of regulatory mechanisms and then to their exhaustion. In this case, the premorbid conditions develop, as the initial stage of occupational diseases. But traditional occupational pathology practically begins with the second stage of premorbid conditions, when specific changes of certain organs and systems whose homeostasis are violated are already appearing. In this case, due to the mechanisms of compensation, the manifestation of the disease may be slightly expressed or it is in the initial phase and is compensatory in nature [6, 8, 9]. It is clear that it is fundamentally important to discover the signs of the disease at the first stage of premorbid conditions, when non-specific changes are predominant in preserving the homeostasis of the vital systems of the organism, including the cardiovascular system [46].

The central place in the diagnostics is the study and evaluation of the organism's response to the stressful environmental effects and the determination of the tension of regulatory systems and functional reserve. The leading method for determining the tension of regulatory systems is the analysis of cardiac rhythm variability (HRV), which is now widely used worldwide [5, 13, 14]. It is possible to analyze the degree of tension of regulatory systems by many methods: by studying the blood levels of the hormones of adrenaline and norepinephrine, by changing the diameter of the pupil, by the amount of sweating, and so on. But the most simple and accessible method, and most importantly, that allows continuous dynamic control, is a mathematical analysis of the heart rhythm [46]. It is known that changes of heart rhythm are a universal operational response of an organism to any action of the factors of the environment. However, the traditionally measured mean pulse rate only reflects the final effect of numerous regulatory influences on the blood circulation apparatus, characterizing the features of the already existing homeostatic mechanism. One of the important tasks of this mechanism is to balance the sympathetic and parasympathetic parts of the autonomic nervous system [47, 48]. One and the same heart rate may correspond to various combinations of activity of the system's links that controls the equilibrium of the autonomic system. This provides the basis for considering the SA node as a sensitive indicator of adaptive reactions of the organism in the process of its adaptation to environmental conditions. If the body is represented as a cybernetic system, the blood circulation system can be considered as the one of the main executive mechanisms acting as an intermediary between the leader (central nervous system, autonomic nervous system, system of humoral and hormonal regulation) and controlled (locomotor apparatus, muscular system, internal organs) contours [46, 49, 50]. This allows considering the activity of the cardiovascular system as a process of interaction between autonomic and cardiovascular homeostasis [51, 52]. Cardiovascular homeostasis is aimed at providing adequate blood supply to organs and tissues. Informational processes in cardiovascular homeostasis are determined by chrono- and inotropic effects on the myocardium, carried out inside and outside the heart reflex mechanisms, vascular reactions, cardiopulmonary actions. Comparison of the results of a large number of clinical and clinical-physiological observations and studies shows that some violations of normal functioning of the body can be regarded as a special type of pathology – "disease of homeostasis", according to the definition of Kassil. These include states caused by insufficiency, excess or inadequacy of the adaptive systems of the body. With a certain condition they can be attributed to disorders of the functions associated with the process of aging, some functional disorders, depletion of the nervous system, endocrine apparatus, diseases such as autonomic dysfunction, and so on [53–57].

For operational evaluation of the functional state of the body, an analysis of the following indicators is carried out in next steps: 1) filling out a short questionnaire on health, complaints and lifestyles; 2) registration of ECG in 3 standard leads; 3) dispersion ECG mapping; 4) analysis of heart rhythm variability; 5) measurement of height and weight of the body; 6) measurement of blood pressure; 7) psychophysiological testing (measuring the speed of a simple and complex visual-motor reaction). All these surveys are carried out at rest, without any testing loads. Dispersion mapping of the electrocardiogram (ECG) is performed using three electrocardiograms and special software programs. The research is conducted in the sitting position with maximum psychological and physical comfort [6, 15].

The concept of health includes not only medical, biological and psychological aspects, but also social, economic and environmental components, therefore the degree of tension of regulating systems reflects the integral response of the human body to the whole complex of factors that affect it [58]. A healthy organism, in the conditions of a high level of functionality, responds to the effect of stimuli on the normal, working tension of regulatory systems. However, the degree of tension of regulatory systems in healthy individuals may fluctuate, where the higher intensity of stress depends on the functional reserves, which leads to an increase in the tone of the sympathetic ANS and the stability of the heart rate [59, 60]. Prevalence of sympathetic tone leads to the activation of the hypothalamic-pituitary-adrenocorticotropic system, which implements the response of the organism to the effect of stress exposure.

Therefore, an increase in the tension level of adaptation mechanisms is the initial stage of the state between health and disease. On the one hand, the functional tension is characterized by a high degree of development of elements of the stage of resistance, but on the other hand, adaptive activity proceeds on the limit of the capabilities of the organism and is accompanied by the development of relevant violations. In the state of functional tension of adaptation mechanisms there is an increase in the degree of the structural and functional organization of the biosystem [55, 61]. At the same time, the high content of corticosteroids indicates an increase in the level of functionalization, which is supported by the intensive tension of regulatory systems, where the amount of reserves is sufficient, but due to constant spending, functional reserves are not sufficiently replenished, and if there is no replenishment of reserves, the achievement of equilibrium in regulatory mechanisms becomes impossible [62]. One of the ways in which the disorder of energy and metabolic processes occurs is a shift in the autonomic balance towards sympathetic prevalence.

Human body continuously experiences the effect of factors that reject the balance of regulatory processes. At the same time, regulatory mechanisms are introduced to prevent or compensate for possible or existing shifts, i.e. adaptive mechanisms are closely related to homeostasis. That is, the state of functional stress of adaptation mechanisms reflects the maximum mobilization of the mechanisms of short-term and long-term adaptation that occurs at the limit of the possibilities of the organism.

Thus, as stated in the scientific works of V. Lisovy, V. Kapustnik and V. Korobchansky, the development of clinical forms of diseases is preceded by well-defined violations of the functional state of the organism, having a boundary character. At the same time, the timely detection of premorbid states, the establishment and elimination of risk factors for their occurrence can prevent the development of pathological process. The premorbid conditions arise from the dysfunction of those adaptive systems that are now called to ensure the stable functioning of the organism, which is why the premorbid diagnosis is based on the definition of qualitative and quantitative indicators of the adaptation process, which are measured and / or calculated as a result of the preventive examination. As a rule, border mental states are diagnosed on the basis of presence of neurotic disorders in situations and periods of risk, the precursors of somatic diseases are diagnosed on the basis of dysfunction of the relevant regulatory systems (pro- and antioxidant, thermoregulation, etc.) [8].

Conclusions. Based on the discussed above, it becomes possible to conclude that stress response is a necessary link in adaptation. It should be emphasized that during the action of extremely strong factors, the adaptive response becomes inadequate, however, in some cases, even when the normal environmental factors influence the organism, inadequate adaptive reactions may occur, which is the main example of the transition of the adaptive reaction to pathological one. Adequacy and adaptation efficiency depend on the state of adaptation mechanisms, that is, the level of functionality, the degree of regulatory mechanisms tension and functional reserves.

Conflict of interests

There is no conflict of interests.

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COMPARATIVE MORPHOLOGICAL CHANGES IN SMOOTH MYOCYTES AND MACROFAGES CD16 IN PULMONARY ARTERY AND AORTA IN FETUSES AND NEWBORNS EXPOSED TO CHRONIC INTRAUTERINE HYPOXIA

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Abstract

Background. Oxygen deficiency, both acute and chronic, causes a variety of pathological changes in a number of organs and systems of fetuses and newborns. In particular, there are morphological changes in the vessels. Information in the available literature regarding the morphological state of smooth myocytes (SM) and cells expressing CD16 in the pulmonary artery (PA) and aorta of fetuses and newborns under such conditions of pregnancy is various and insufficient. **Subjects and methods.** The results of complex pathomorphological research of SM and macrophages CD16 of fetuses and newborns PA and aorta in chronic intrauterine hypoxia with the use of histological (staining with hematoxylin and eosin), immunohistochemical (MCA to Anti-Human Smooth Muscle Actin and MCA to CD16), morphometric, statistical methods are presented in the article. The investigation was performed on WAG line rats, observing all ethical norms and rules of handling of laboratory animals. The location of SM and macrophages CD16 in the wall of the PA and aorta in normal pregnancy and under oxygen deficiency, the density of their location in the field of vision (SM – ×1000, CD16 – ×600) was calculated. A comparative analysis of the morphological characteristics of the studied cells between mentioned vessels was also carried out. **Results.** The macroscopic examination of the wall of PA and aorta in the group of fetuses and newborns from mothers with physiological pregnancy with a magnifier (×3, 8 diopters) revealed that it was elastic, had a smooth ivorish intima. Smooth muscle cells in PA and aorta during immunohistochemical identification are determined in intima and media, as well as in the adventitial vessels of vessels. With hypoxic effect their number decreased in comparison with control group, and the number of macrophages – increased in both described vessels. **Conclusions.** The density of smooth myocytes (SM) location in the thickness of the wall of PA and aorta in the fetuses and newborns during the physiological course of pregnancy differs significantly from each other with dominance in the first vessel. Under the influence of experimental chronic intrauterine hypoxia in PA and aorta of fetuses and newborns a significant ($p<0.05$) decrease in the density of smooth muscle cells location in the field of vision compared to control group without a significant difference between the studied vessels can be observed, as well as the tendency to increase the macrophages number, which expresses the marker CD16. The latter fact can be regarded as an increase in the macrophage reaction under the described conditions.

Key words: *aorta, CD16 cells, chronic intrauterine hypoxia, experiment, pulmonary artery, smooth myocytes.*

Introduction

According to the WHO, cardiovascular pathology is the first among the causes of death of our planet population [1]. It is a long-known fact that mother's health and the course of pregnancy affect the fetus development [2]. A marked negative effect of oxygen deficiency on posterity during pregnancy, which is manifested especially in the second and third trimesters has been reported [3, 4]. Morphological studies devoted to the effects of chronic intrauterine hypoxia (CIH) on the state of the heart [5], the pituitary gland, the hematoencephalic barrier [6], the liver [7], the adrenal glands [8], the organs of the urinary system [9] of fetuses and newborns have been performed. The state of pulmonary

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artery (PA) and aorta has been investigated under conditions of acute postnatal hypoxia [10].

There are different points of view regarding the morphological changes of smooth myocytes (SM) under the oxygen insufficiency influence. Sjundjukova E.G. and others, (2013), Zamechnik T.V. and Rogova L.N. (2012) have noted their proliferative activity decrease in this state [11, 12]. At the same time, other authors have demonstrated PA SM multiplying with insufficient oxygenation [13–15]. It should be also marked that severe oxygen deficiency and anoxia are the causes of proliferative activity decrease of smooth muscle cells in a given vessel [16–18].

The lack of a single point of view on the effect of intrauterine hypoxia influence on SM PA and aorta of fetuses and newborns, as well as the limited information in the available literature about the morphological features of CD16 macrophages in these blood vessels, determine our research relevance.

2. Purposes, subjects and methods:

2.1. Purpose of the study was to determine the difference in the morphological changes in the population of smooth myocytes (SM) and CD16 macrophages in the pulmonary artery (PA) and aorta in fetuses and newborns exposed to chronic intrauterine hypoxia (CIH), based on a complex pathomorphological investigation.

2.2. Subjects & Methods

This research was carried out within the research work of Pathological Anatomy Department of KhNMU: "Pathomorphological peculiarities of the fetus and the newborn formation under the influence of the mother's pathology" (state registration number 0110U001805, 2010–2014) and "Influence of maternal and fetal infection on embryogenesis and fetogenesis of progenies (clinical morphological study)" (state registration number 0115U000987, 2015–2019).

Pregnant female rats of the WAG line were subjected to altitude effects of hypoxia (7.500 m above sea level) from the pregnancy registration time and until the delivery for 20 minutes every day at the same time. Pregnant females (19–21 days of gestation) and females after giving birth were deduced from the experiment by intravenous injection of 2–2.5 % solution of sodium thiopental (7–10 mg per 1 kg of body weight), and then subjected to decapitation. Newborn rats 24 hours after birth 2–3 minutes were inhaled with 80 % CO2 concentration under the cap, followed by decapitation.

The pathomorphological material was divided into control group (C) – fetuses and newborns from mothers with physiological pregnancy, and the study group (CIH) – the fetuses and newborns who were exposed to HIC. The first group had 18 cases (7 fetuses, 11 newborns), the group of CIH had 16 cases (6 fetuses, 10 newborns).

All manipulations with animals and their withdrawal from the experiment were done in accordance with the requirements of the normative documents (European Convention for the Protection of Vertebrate Animals (Strasbourg, 18.03.1986), Council of the European Economic Community for the Protection of Vertebrate Animals (Strasbourg, 24.11.1986.), the Law of Ukraine "On Medicinal Products", 1996, Articles 7, 8, 12, Guidelines of the CCI GSP (2008), GLR (2002), in accordance with the requirements and norms, the standard provisions on the ethics of the MoH of Ukraine No. 690 dated September 23, 2009).

PA and aorta were studied macroscopically (elasticity of the wall, color and intima status) using magnifier (×3, 8 diopters). After that, one piece from the vessel wall in the supravalvular region, was cut, fixed in 10 % neutral formalin solution to standard paraffin processing of tissue for conducting a morphological examination. Serial sections of $4–5\times10^{-6}$ m thickness have been made from the prepared blocks on the Microtome cryostat MK-25. Histologic and morphometric studies were performed on Olympus BX-41 microscope (Japan) using Olympus DP-Soft (Version 3: 1), Microsoft Excel 2010 and the luminescence microscope Axiskop 40 (FS) (Carl Zeiss, Germany). The methods of the study were histological (staining with hematoxylin and eosin), immunohistochemical, morphometric, statistical. Morphometric parameters of PA, aorta (density of the SM location in the vessel wall in the field of vision (×1000), the number of cells expressing CD16 receptors in the field of vision (×600)) were described under microscopic examination. Immunohistochemical studies were performed according to the indirect Coons method in the Brosman M. (1979) modification (to determine the location of macrophages in the vessel wall with MCA to CD16 (Novocastra Laboratories Ltd, UK.) and the indirect streptavidin-peroxidase method using MCA to Anti-Numan Smooth Muscle Actin ("DAKO", Denmark) (for typing smooth muscle cells). Indicators of markers expression, both quantitative and qualitative, were investigated in 8–10 randomly selected fields of vision of the microscope of histological sections at of ×600 and ×1000 magnification. The statistics were processed on a personal computer using

the IBM SPSS Statistics (IBM Corp.) and Portable Statistica 8.0 (Statsoft, Inc) licensed software packages. Methods of variational, alternative and correlation analysis were used. Statistical significance of the differences in the comparable characteristics was evaluated by calculating the Student's t-criterion for groups with a normal distribution of the sign. Non-parametric U-test Mann–Whitney was used for small selections. Differences were considered statistically significant at a significance level of $p<0.05$, which corresponds to 95 % probability of sure prognosis.

Conflict of interests

There is no conflict of interests.

3. Results and discussion

The macroscopic examination of the wall of PA and aorta in the group of fetuses and newborns from mothers with physiological pregnancy with magnifier (×3, 8 diopters) revealed that it was elastic, had a smooth ivorish intima. Microscopically with hematoxylin and eosin staining, all three layers of the vessel were detected: internal, medium and external. SM had elongated star shape and were determined by MCA to Monoclonal Anti-Human Smooth Muscle Actin staining with moderate intensity expression marker in the cytoplasm. They were located in tunica intima, tunica media, and tunica adventitia, mostly in the vessels of the vessels. The density of these cells location in the thickness of the PA wall was 28.20±0.63 cells in the field of vision (×1000), and in aorta – 24.62±0.76 cells in the field of vision (×1000). These figures differed significantly from each other, probably due to the peculiarity of the blood flow of the fetus and the newborn in the early post-birth period [19]. Macrophages were identified using the CD16 marker, their number in the vascular wall of PA was 26.35±1.42 cells in the field of vision (×600), and in aorta - 26.00±1.36 cells in the field of vision (×600).

Consequently, the morphological state of the wall of PA and aorta in the fetuses and newborns of the control group corresponded to the generally accepted notion of the physiological norm [20].

The wall of PA and aorta in the group of fetuses and newborns under the CIH influence in a macroscopic study using magnifier (×3, 8 diopters) was elastic with smooth, whitish-gray intima. In microscopic study, all three vessel layers were determined in hematoxylin and eosin staining: tunica intima, media and adventitia.

In this group, the smooth muscle cells in both vessels were also elongated, with moderate intensity expression of brown color marker in the cytoplasm in immunohistochemical staining. They were present mostly in intima and medium, as well as in the adventitial vessels walls. The density of the SM location in PA in the field of vision (×1000) was 20.00±0.35 cells, these values were lower than the control ones (*table*). Similar changes in the density of investigated cells location were observed in aorta – 18.67±0.56 cells in the field of vison (×1000), which is lower than the control group.

Investigation of the number of macrophages in the PA wall using the CD16 marker revealed 29.45±0.84 cells in the field of vision (×600), and in aorta – 28.45±0.68 cells in the field of vision (×600). As it can be seen, their number in conditions of hypoxic effect increased.

As it is shown in t*able*, the amount of SM in PA is bigger than in aorta during normal pregnancy ($p<0.05$), while in groups with hypoxia, their number in investigated vessels is significantly decreased ($p<0.05$) without significant difference between PA and aorta ($p\geq0.05$). Our data are confirmed by a few literary reports, which inform about SM proliferation decrease in PA with severe oxygen deficiency, anoxia [17]. In this case, studies about SM peculiarities in vessels under acute hypoxia have different results. Some investigators report an increase in their proliferation [21] directly in the PA [15], while others report a decrease in the reproduction of these cells in the PA under such conditions [18].

The density of the smooth myocytes (SM) and cells expressing the marker CD16 location in the wall of pulmonary artery (PA) and aorta in the fetus and newborns

	The density of the SM location in the field of vision (×1000)		Density of cells expressing the marker CD16 location in the field of vision (×600)	
	PA	Aorta	PA	Aorta
C	28.20±0.63	24.62±0.76 $p_2<0.05$	26.35±1.42	26.00±1.36 $p_2\geq0.05$
CIH	20.00±0.35 $p_1<0.05$	18.67±0.56 $p_1<0.05$; $p_2\geq0.05$	29.45±0.84 $p_1\geq0.05$	28.45±0,68 $p_1\geq0,05$; $p_2\geq0.05$

Note. p_1 is the veracity of the difference of two averages between the control and studied groups; p_2 is the veracity of the difference of two averages between PA and aorta in one group.

Study of the quantitative characteristics of macrophages expressing the CD16 marker in the examined vessels wall under the chronic hypoxia influence has tended to increase the density of their placement in both vessels compared with the control ($p \geq 0.05$), without differences between them ($p \geq 0.05$).

These indications may evidence that macrophage reaction occurs when exposed to the CIH. This fact is confirmed in the literature about the presence of the described cells in hypoxic regions, including inflammatory and tumor processes [22–24].

Conclusions

1. Density of placement of SM in the field of vision (×1000) in the thickness of the walls of PA and aorta in the fetuses and newborns during the physiological course of pregnancy significantly differs from each other with domination in the first vessel (PA – 28.20±0.63 cells, aorta – 24.62±0.76 cells).

2. Under the influence of experimental CIH in PA and aorta in fetuses and newborns, there is a significant ($p < 0.05$) decrease in the density of smooth muscle cells location in the field of vision compared with control, but without significant difference between the examined vessels ($p \geq 0,05$).

3. Fetal chronic oxygen deficiency is manifested in the tendency to increase the number of macrophages expressing the CD16 marker in the wall of PA and aorta in the fetuses and newborns as compared with the control parameters ($p \geq 0.05$).

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DIAGNOSTIC CRITERIA OF COGNITIVE IMPAIRMENTS IN PATIENTS WITH MIXED DEMENTIA COMPLICATED BY HALLUCINATORY-PARANOID DISORDERS

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Abstract

The study involved 72 patients with mixed dementia complicated by hallucinatory-paranoid disorders (main group) and 61 patients with mixed dementia not complicated by psychotic disorders (control group). It was established and proved that patients with mixed dementia complicated by psychotic disorders were characterized by more expressed cognitive impairments, which were manifested in impairments of praxis, gnosis, memory, skills of counting, attention process, thinking and orientation.

Key words: *mixed dementia, diagnosis, hallucinatory-paranoid disorders, cognitive dysfunctions.*

Introduction

An older age is a risk factor for cognitive impairment development with different levels of manifestation. The peculiarities of changes in cognitive functions in the age aspect and in neurological diseases are given considerable attention [1]. The changes in cognitive activity in the elderly persons may develop against a background of dementia [2]. According to the data from the WHO, there are around 35.6 million persons with dementia in the world, which is a significant burden for the health care system and economics, even in highly developed countries [3].

Dementia, despite a considerable amount of researches, remains one of the most problematic pathologies [1, 3, 4]. On the base of the data from various studies, it has been noted that cognitive impairments of a different severity are found in 40–70% of patients with mixed dementia (MD) [2, 5, 6]. The main causes of dementia are neurodegenerative processes (the first place among them belongs to Alzheimer's disease), brain vascular diseases and their combination [4, 7]. Based on the WHO data concerning a rising incidence of dementia, scientists are forced to review their previous strategies and to find new ways of solving the problem [3, 8]. However, no progress has been made in the recent years regarding a timely diagnosis and treatment of dementia and related cognitive impairments [5, 6]. Risk factors for dementia are being actively investigated, but there are no clear recommendations to prevent its development at the moment [2, 4, 7, 8]. Particular problems in this respect arise in situations where dementia is complicated by psychopathology of the psychotic level.

2. Purposes, subjects and methods:

2.1. Purpose of the study was to determine the peculiarities of cognitive impairment in the structure of neurodegenerative processes in patients with mixed dementia complicated by hallucinatory-paranoid disorders.

2.2. Subjects & Methods

The study of cognitive disorders was performed in 72 patients with MD (F00.1 (1–2); F01.3 (1–2)) complicated by hallucinatory-paranoid disorders (the main group). Sixty-one patients with MD without hallucinatory-paranoid disorders (HPD) (F00.1; F01.3) participated in the study as the control group.

To investigate the main cognitive impairments (memory, attention, psychomotor coordination, language, gnosis, praxis, counting, thinking, orientation, planning and control of higher mental

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activity) in patients with MD complicated by HPD, such methods were used: clinical-psychopathological method (a structured interview conducted within the framework of clinical-phenomenological and psychopathological approaches in psychiatry); elementary neuropsychological examinations of basic cognitive functions in patients with dementia (compilation of pictures, understanding of narratives and plot pictures, establishment of sequence of events, classification, elimination of redundant, determination of a significant features, search of analogies, definition and comparison of concepts, formation of artificial concepts, selection of words), conducted during the structured interview process; the Mini-Mental State Examination (MMSE) Mental Status Scale [9]; Montreal Cognitive Assessment Scale (MoCa) [10].

Standard statistics used for evaluating results of the study.

Conflict of interests

The authors of the article declare no conflict of interest.

3. Results

Analysis of results of the investigation, carried out using the scales MMSE, MoCa and elementary neuropsychological examinations, to study the main cognitive impairments in patients with MD complicated by HPD in comparison with patients with MD from the control group, is presented in *Table 1*.

According to the results presented in *Table 1*, in patients with MD complicated by HPD, as compared with patients with MD without psychotic disorders, predominated cognitive impairments were: impaired visual-constructional skills (58.3±6.7% of cases, p<0.05) and writing (41.7±4.7% of cases, p <0.05); difficulties in understanding of instructions (61.1±6.9% of cases, p <0.05); impairments of a serial counting (77.8±9.5% of cases, p<0.05); a decreased level of delayed reproduction related to impairment of encoding (83.3±10.4% of cases, p <0.05); decreased concentration (70.8±8.3% of cases, p<0.05); errors in the sentence repetition (69.4±8.1% of cases, p<0.05); impaired orientation in the own personality (31.9±3.7% of cases, p<0.05).

More manifested impairments of intellectual activities in patients with MD complicated by HPD were: impairments of generalization (79.2 ± 9.9% of cases, p<0.05), formal-logical operations (84.7 ± 10.6% of cases, p<0,05), making of conclusions (83,3 ± 10,4% of cases, p<0,05), motivational component of thinking (80,6 ± 10,0% of cases, p <0,05) and criticism (90.3 ± 11.1% of cases, p<0.05).

The analysis of informativeness of highlighted by, the main cognitive impairments, identified by means of MMSE, MoCa scales and elementary neuropsychological examinations, in patients from the main group with MD, as compared with patients with the MD from the control group, is presented in *Table 2* (values are presented in order of a decreasing level of informativeness).

According to the results of the statistical analysis presented in *Table 2*, in patients with MD complicated by HPD (the main group), the most informative cognitive function impairments were: impairments of a motivational component of thinking (heterogeneity, paralysis, inconsistency, disconnectivity, symbolism) (DC = - 2.14, MI = 0.34, p<0.0001); impairments of criticism (DC = - 1.85, MI = 0.29, p<0.00002); impairments of generalization (insufficiency of the level of generalization, its distortion) (DC = - 1.65, MI = 0.21, p <0.001); impaired orientation in the own personality (DC = - 2.48, MI = 0.17, p <0.03). Also, in patients with MD complicated by HPD, significant cognitive function impairments, which increased a level of diagnostic informativeness, were: an impaired making of conclusions (DC = - 1.38, MI = 0.16, p<0.002); impairments of praxis (impairments of writing) (DC = - 2.01, MI = 0.16, p<0.03); impairments of formal-logical operations (DC = - 1.34, MI = 0.15, p<0.002); an impaired concentration (DC = - 1.44, MI = 0.14, p<0.009); impairments of counting (DC = - 1.20, MI = 0.11, p<0.01); delayed reproduction impairments related to impairments of encoding (DC = - 1.15, MI = 0.11, p <0.006); impaired visual-constructional skills (DC = - 1.20, MI = 0.10, p <0.04); impairments of gnosis (difficulties in understanding of instructions) (DC = - 1.09, MI = 0.10, p <0.04); speech impairments (errors in repetition of sentences) (DK = - 1.22, MI = 0.10, p <0.02).

Therefore, in patients with MD complicated by HPD, more pronounced cognitive impairments were identified, in comparison with the patients with MD without psychotic disorders. These impairments were manifested as impairments of praxis, gnosis, memory, counting skills, attention, thinking, and orientation.

The revealed peculiarities of cognitive decline in MD confirm the data of other researchers that in these cases of the disorder there are specific cognitive impairments characteristic of diseases associated with frontal lobe dysfunction: this is a decrease in concentration, impaired ability to plan one's actions, and mental retardation works [13,

Table 1

Number of patients with mixed dementia complicated by hallucinatory-paranoid disorders, which had impairments of cognitive function (% ±m)

Cognitive function and methods of their diagnosis	Main group	Control group
1	2	3
Impairments of praxis (impaired ability to acquire, retain and use various motor skills)		
Errors in creating alternate path (MoCa)	48.6 ± 5.3	39.3 ± 5.1
Visual-constructional impairments (MoCa and MMSE)	37.5 ± 4.3	37.7 ± 5.0
Impairments of visual-constructional skills (MoCa)	58.3 ± 6.7 *	44.3 ± 5.4
Impairments of writing (MMSE)	41.7 ± 4.7 *	26.2 ± 4.1
Gnosis impairments (impairments of the function of perception of information, its processing and synthesis of elementary sensory sensations into holistic images, inability to holistic perception, recognition)		
Errors in naming objects, animals, etc. (MoCa and MMSE)	44.4 ± 4.9	34.4 ± 4.7
Problems with understanding of instructions (MMSE)	61,1 ± 6,9 *	47,5 ± 5,7
Impairments of counting		
Errors in a serial subtraction (MMSE)	77.8 ± 9.5 *	59.0 ± 6.7
Memory impairments (impaired ability to absorb, store and reproduce the information needed for a current activity)		
Delayed reproduction impairments related to impairments of retrieval (MoCa)	88.9 ± 11.0	75.4 ± 8.2
Delayed reproduction impairments related to impairments of encoding (MoCa)	83.3 ±10.4*	63.9 ± 7.1
Impairments of attention		
Impairments of stability (mobility (distraction, inertness) and exhaustion) of attention (MoCa)	55.6 ± 6.2	45.9 ± 5.6
Impairments of concentration (MoCa and MMSE)	70.8 ± 8.3 *	50.8 ± 6.0
Language impairments (impaired ability to communicate by means of sentences)		
Errors in sentence repeating (MoCa and MMSE)	69.4 ± 8.1 *	52.5 ± 6.1
Impairments of the speech speed (MoCa)	65.3 ± 7.5	54.1 ± 6.2
Impairments of reading (MMSE)	48.6 ± 5.3	37.7 ± 5.0
Impairments of thinking		
Impairments of generalization: insufficiency of a level of generalization, its distortions (understanding of plot pictures, understanding of a series of plot pictures, tasks for classification)	79.2 ± 9.9 *	54.1 ± 6.2
Impairments of detection of similarities and differences (the exception task – redundant the third, classification of geometric figures)	61.1 ± 6.9	59.0 ± 6.7
Impairments of formal-logical operations (ending of a series of pictures, selection of analogies, tasks for classification, search for essential features)	84.7 ±10.6*	62.3 ± 7.0
Impairments of associative links (tasks to determine essential features, definition and comparison of concepts, comparison of analogies)	63.9 ± 7.2	60.7 ± 6.9
Impaired making of conclusions (understanding of stories and plot pictures, establishing of sequence of events, understanding of a figurative meaning of proverbs, metaphors, sayings)	83.3 ±10.4*	60.7 ± 6.9
Impairments of abstract thinking (MoCa, method of artificial concepts formation, relationships establishing)	73.6 ± 8.8	68.9 ± 7.6
Impairmentsof the dynamics of thinking: acceleration, deceleration, delay, lability / inertness, perseveration, inconsistency (clinicalpsychopathological method)	61.1 ± 6.9	62.3 ± 7.0
Impairments of a motivational component of thinking: heterogeneity, paralogism, inconsistence, disconnection, symbolism, autism, resonance (clinical-psychopathological method)	80.6 ±10.0*	49.2 ± 5.9
Impairments of criticism (clinical-psychopathological method)	90.3 ±11.1*	59.0 ± 6.7
Orientation		
Impairments of the time orientation (year, month, date, and day of the week) (MoCa and MMSE)	66.7 ± 7.7	65.6 ± 7.3
Impairments of space or locational orientation (country, city, street, institution) (MoCa and MMSE)	51.4 ± 5.7	42,6 ± 5.3
Impairments of orientation in the own personality (clinical-psychopathological method)	31.9 ± 3.7 *	18.0 ± 3.6

Symbols: * – differences are statistically significant at $p < 0.05$.

Table 2

Diagnostic coefficients and measure of informativeness of main cognitive impairments identified in patients with MD from the main group

Cognitive impairments	Manifestation (points)	DC *	MI**
Impairments of the motivational component of thinking	–	-2.14	0.34
Impairments of criticism	–	-1.85	0.29
Impairments of generalization (insufficiency of generalization, its distortion)	–	-1.65	0.21
Impairment of orientation in the own personality	–	-2.48	0.17
Impairments of making of conclusions	–	-1.38	0.16
Impairments of praxis (impairments of writing)	= 0	-2.01	0.16
Impairments of formal-logical operations	–	-1.34	0.15
Impairments of attention (concentration)	= 0	-1.44	0.14
Impairments of the counting (errors in a serial subtraction)	³ 1	-1.20	0.11
Memory impairments (delayed reproduction impairments related to impairments of encoding)	³ 1	-1.15	0.11
Impairments of praxis (impairments of visual-constructional skills)	³ 2	-1.20	0.10
Gnosis impairments (impairments of understanding of instructions)	³ 1	-1.09	0.10
Speech impairments (errors in repetition of sentences)	³ 1	-1.22	0.10
Total set of the signs		-20.15	2.14

Symbols: * – diagnostic coefficient; ** – Kullback measure of informativeness.

16, 17]. It has been noted by a number of authors that in mixed-type dementia, the greatest cognitive differences are observed in the visual-spatial sphere, working memory, but no significant differences in regulatory functions and episodic memory were found [14, 15, 17]. Violation of regulatory functions is considered an essential sign of the contribution of the vascular factor to the picture of cognitive decline in MD [14]. The results of a neuropsychological assessment of cognitive impairment in MD complicated by HPD obtained in this study show that cognitive impairment in this disorder is more pronounced.

Thus, the data obtained should be taking into account in the diagnosis and treatment of patients with MD complicated by HPD.

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SUBSTANTIATION AND CONTENT OF PSYCHO-EDUCATION OF PATIENTS WITH ALCOHOL DEPENDENCE

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Abstract

Subjects & methods. On the basis of the Kharkiv Regional Clinical Narcological Hospital No. 9 and the Military Medical Clinical Center of the Northern Region, a comprehensive examination of 150 male patients aged 20 to 55 years with alcohol addiction syndrome was conducted. **Results.** According to the results of the study, among the examined patients, persons with a persistent alcohol abuse were prevalent, the average AUDIT score in the main group was 4.0, indicating that there were serious alcohol problems; the style of alcohol abuse of patients of the main group was correlated with issues of the presence of danger for physical, psychological, and mental health. Dangerous alcohol consumption was found in 35.2%, high probability of alcohol dependence was found in 60.1%. The system of rehabilitation of patients with alcohol dependence with the use of psychoeducation has been developed and tested. Against the background of psychoeducational activities, positive dynamics of stress-coping behavior was observed. After conducting rehabilitation measures, coping strategies aimed at solving problems were noted in 45.1% of the examined patients of the main group and 32.6% of people of the control group, coping strategies aimed at emotions were in 31.4% and 22.4% respectively, 15.9% and 32.6% respectively – at avoidance, 6.7% and 12.4% – at distraction. **Conclusions.** Thus, the study identified the foundations and principles of psycho-education for the system of complex rehabilitation of patients with alcohol dependence

Keywords: *alcohol addiction syndrome, alcohol dependence, psychoeducation, coping strategies, rehabilitation.*

Introduction

In recent years, among the population of Ukraine there has been a significant increase in the consumption of alcoholic beverages and as a consequence an increase in the number of patients with alcohol dependence [1, 2].

According to the WHO data for 2010, the average annual consumption of alcohol in Ukraine is about 13.9 liters of pure ethanol per year (more than 2 liters of spirits per month) per capita, including all persons 15 years and older. The criteria for severe episodic use of alcohol in Ukraine correspond to about 35.2% of men and 12.1% of women (consuming 60 grams and more of pure alcohol in one case over the past 30 days) [3, 4].

The modern period of development of our country is characterized by a considerable amount of destructively-destabilizing and socially predetermined stress factors, which results in a significant increase in the long-term stress load in which the Ukrainian population lives. This forms a number of adverse factors in increasing the level of use of psychoactive substances, in particular, alcohol [5, 6].

Low indicators of the effectiveness of treatment for patients with alcohol dependence necessitate the search for certain criteria for their effective use and the development of complex differentiated therapeutic programs on this basis that include various combinations of modern pharmacological and psychotherapeutic approaches. Analyzing the literature data, it has to be noted that despite the large arsenal of means and methods, available to the addiction medicine,

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the effectiveness of alcohol dependence treatment continues to be insufficient [7–9].

Modern scientific research on alcohol dependence is devoted to updating the concept of psychosocial rehabilitation of patients, their social reintegration and improvement of quality of their life. In this regard, the relevance of finding new psychotherapeutic approaches to the treatment of alcohol addiction and development of effective schemes that meet current standards of treatment is increased. Psycho-education can be considered one of such approaches. Its increasing importance in world psychotherapeutic practice is gaining more and more recognition as for increasing the intensity, efficiency and effectiveness of psychotherapeutic assistance to patients with alcohol dependence [10–13].

The foregoing stipulated the relevance and necessity of this study.

2. Purposes, subjects and methods:

2.1. Purpose: To develop and evaluate the effectiveness of psycho-educational programs in the system of psychosocial rehabilitation of patients with alcohol dependence.

2.2. Subjects & Methods

To achieve this goal, a comprehensive survey of 150 male patients aged 20 to 55 years was conducted on the basis of the Kharkiv Regional Clinical Narcological Hospital No. 9 and the Military Medical Clinical Center of the Northern Region (with the informed consent in compliance with the principles of bioethics and deontology). The patients were diagnosed with a syndrome of alcohol dependence according to the diagnostic criteria of the ICD-10 (F 10.2õ) and grouped: F10.20, currently abstinent – 31.9 %; F10.24, currently using the substance (active dependence) – 22.6 %; F10.25 continuous use – 29.2%; F10.26, episodic use (dipsomania) – 16.3 %.

All respondents who were included in the study gave voluntary consent to participation, were fluent in Russian and Ukrainian languages. This allowed to perform a complete clinico-psychopathological and psycho-diagnostic survey. The contingent of the surveyed persons was homogeneous in baseline. This allowed the results of the study to be considered as representative of the general population.

All patients received regulated psychopharmacotherapy according to the standards of the Ministry of Health of Ukraine within the limits of the provision of the medical institution. The main group consisted of 105 subjects, control group comprised 45 patients who received standard regulated therapy in the hospital. The patients in the main group participated in the psycho-educational program, based on our own research.

The study implied clinico-psychopathological and psychodiagnostic methods of examination. The clinico-psychopathological research was based on generally accepted approaches to psychiatric and narcological examination by interviewing and observation, which was supplemented with the use of the Alcohol Use Disorders Identification Test (AUDIT) [14]. This test is used to detect disorders associated with alcohol abuse and to determine the extent of its use. The survey was conducted using diagnostic and research criteria of the ICD-10.

Psychodiagnostic study included the study of the features of stress-breaking behavior "Methods of coping" (in the adaptation of T. A. Kryukova, 2002) [15].

Standard statistics used for evaluating study results.

Conflict of interests

The authors of the article declare no conflict of interest.

3. Results and discussion

The research was conducted in three stages. At the first stage, the definition of biological and psychosocial predictors of alcohol dependence, clinical psychopathological phenomenology and personality traits of patients were made. Based on this, the rationale and development of the psycho-education system of patients with alcohol dependence was carried out. At the second stage, the actual psycho-educational effects were realized, the effectiveness of which was evaluated at the third stage of the study, particularly 6 months after the start of treatment.

According to the results of the study, the surveyed patients were mainly persons with a constant style of alcohol abuse, the average score for AUDIT in patients with the main group was 4.0. This indicated that there were serious alcohol problems. The style of alcohol abuse by patients of the main group with a high degree of reliability correlated with the issues of the danger to physical ($p \leq 0.001$), psychological ($p \leq 0.001$) and mental health ($p \leq 0.001$).

In the clinical picture of alcohol disorders, alcohol abuse was permanent in nature, with loss of situational control, palimpsests.

In the clinical picture of alcohol dependence, dysphoria was observed in 38.1% of the patients. Its features included irritability (65.9%), anger (69.1%), aggression (42.3%); affective reactions (27.3%) which were manifested by pronounced

irritability (72.1%), distraction (51.4%), impatience (49.2%); anxiety-depressive disorders (34.6%) that were characterized by a feeling of tension (38.9%), anxiety, internal tension with the inability to relax (54.8%), asthenic manifestations (29.1%), hyperesthesia (45.1%).

In 53.2% of surveyed patients with alcohol addiction, coping strategies were focused on avoidance, in 31.3% on distraction, in 11.3% on emotions, in 4.4% on solving problems.

Based on the data obtained, we have developed and tested a system of rehabilitation of patients with alcohol dependence using psycho-education, aimed at improving the ability of patients to solve their own problems. That is, on the disclosure and the ability to apply the skills of self-regulation and self-actualization of the patient, which is deformed in patients with alcohol dependence.

The psycho-educational effect was directed to the following features: focus on the alcohol problem and on the patient; structuring and use of methods of activating consciousness, changes in the habitual patterns of thinking, behavioral changes, activation of experience and expression of emotions, patient support.

The main tasks in conducting psycho-educational lessons were: filling in the informational specific (narcological) knowledge deficiency available to patients and their families; awareness of a patient of a morbid condition, formation of motivation for treatment; development of behavioral skills in the "crisis"; correction of "alcohol" patterns of behavior, correction of alcohol dependence of patients' social positions; counteract the possibility of relapse of the disease.

Psycho-educational classes were held in closed groups (i.e., after the beginning of the cycle, new participants are not accepted), with the number of participants from 10 to 15 people. Psycho-educational intervention consisted of 4 modules: increasing the level of special (narcological) knowledge of the patient and his family; development of skills for solving life problems; training of communication skills; coaching skills training.

Implementation of modules was carried out in the form of lectures, discussions, using auxiliary visual information (photos, video materials) and printed materials (leaflets, booklets, brochures). In addition, patients and their relatives were given hometask (for example, self-preparation of their ideas about some topics from among those discussed in the group lesson). As a monitoring tool, patients were invited to keep a diary in which they reflect the time course and practical application of the knowledge gained.

The basis of psycho-education of patients with alcohol dependence is the patient's awareness of a morbid condition, an analysis of their own personality characteristics and peculiarities of their perception in society; formation of patient motivation for treatment; development of skills of adequate behavior in a psycho-traumatic situation; correction of "alcohol" patterns of behavior.

The effectiveness of the developed complex rehabilitation of patients with alcohol dependence with the use of psycho-education was carried out in comparison with traditional measures on the basis of evaluation of the time course of clinico-psychopathological and pathosychological characteristics of patients and quality of life. Catamnesis was 6 months.

Analysis of the clinical results of the use of the developed system showed that in the main group for the AUDIT test, in 65.3% of the examined, relatively safe (or complete absence) alcohol consumption was detected (0-7 points), in 23.1% of the surveyed, risky use of alcohol was maintained (8–15 points). Among the surveyed control groups, 55.1% had a dangerous alcohol use (16–19 points), and 25.8% had a high probability of alcohol addiction (20 points or more). In the clinical picture of alcohol disorders in patients in the control group, alcohol abuse was permanent with a loss of situational control and palimpsests.

In the analysis of the duration and quality of remission was established (after 6 months): 70.1% of the surveyed in the main group noted a complete remission of alcohol dependence compared with 41.5% of patients in the control group; incomplete remission, respectively, in 26.2% and 49.1% of the surveyed accordingly; persistent alcohol abuse in 3.7% of the surveyed in the main group and 9.4% of the control group.

Perception of their own dependent status and understanding of the need for therapeutic work was formed in 77.6% of the surveyed in the main group.

A positive follow-up of stress-breaking behavior was noted following psycho-educational events. After carrying out rehabilitation measures, 45.1% of the surveyed in the main group and 32.6% in the control group noted coping strategies aimed at solving problems. In 31.4% and 22.4% respectively, coping strategies were aimed at

emotions. In 15.9% of the surveyed in the main group and in 32.6% in the control group, the coping strategies were aimed at avoidance, in 6.7% and 12.4%, respectively, at the distraction.

The study showed effectiveness of psychoeducation in therapy and psychosocial rehabilitation of patients with alcohol dependence, correlating with the data of modern researchers [16, 17] and indicating the need for further development of rehabilitation measures for patients with alcohol addiction, which will improve the quality and duration of remission, contribute to successful social adaptation of patients and significantly improve their quality of life.

Conclusions

Thus, the study identified the foundations and principles of psycho-education for the system of complex rehabilitation of patients with alcohol dependence, the main purpose of which is to develop the patient's ability to independently solve their own problems of alcoholic origin and prove their effectiveness.

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