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The Role of Premorbid Background in Tanatogenesis of Acute Poisonings with Psychoactive Drugs in Gerontological Patients

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BACKGROUND Human aging is a universal and regular process characterized by uneven and steady progression, inevitably affecting to some extent all levels of biological organization. In the structure of acute exogenous toxicosis, patients of gerontological age range from 10.3 to 12.9%. After 60, with an increase of years, there is a growth of mortality rate from 9.8% in elderly patients to 25.5% in long-livers. A certain role in its genesis is played by the premorbid background, i.e. somatic diseases preceding and accompanying acute exogenous toxicosis.

AIM OF STUDY To identify the role of concomitant diseases in the course and outcome of acute poisoning by psychoactive drugs in patients over 60.

MATERIALS AND METHODS We retrospectively analyzed hospital records of 99 patients aged 60 to 90 years who died from poisoning with psychoactive drugs at the N.V. Sklifosovsky Research Institute for Emergency Medicine in 2013–2016, as well as their autopsy, forensic and histological research data.

RESULTS In gerontological patients with acute poisoning with psychoactive drugs, the main premorbid background (100%) is atherosclerotic lesion of the heart and vessels of different degree and extent. In case of lethal outcomes, in toxicogenic stage of poisoning on primary electrocardiograms, myocardial ischemia was revealed in 76.9% of cases, heart rhythm disturbances were detected in all patients, most often in the form of supraventricular extrasystoles (38.4%) and atrial fibrillation (23.1%). In the deceased patients during the somatogenic stage of poisoning, cardiac conduction disorders (31.3%) prevailed. Concomitant chronic lesions of the bronchopulmonary system, including terminal bronchi, contributed to the development of hypostatic pneumonia and its long, migratory course. In 50% of cases, large and small droplet fatty liver disease was detected, which could have a negative effect on the course of poisoning, altering biotransformation of toxicants.

CONCLUSION Atherosclerotic lesion of the heart and vessels, as well as chronic bronchopulmonary disease and fatty liver disease are the main premorbid background factors, which have a negative effect on the course and outcome of acute poisoning with psychoactive drugs.

Keywords: acute poisoning, psychoactive drugs, gerontological patients, premorbid background1

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LBB – left bundle branch
PPA – poisoning with psychoactive drugs
PD – psychoactive drugs
RBB – right bundle branch

A serious medical and social problem in the twenty-first century is a change in the demographic situation in many countries of the world, including Russia, such as redistribution of the population age structure due to an increase in the number of elderly and senile people. In Russia, their proportion is 20–25% [1].

Human aging is a universal and natural process, which is characterized by gradual, uneven and steady progression, inevitably affecting to some degree all levels of biological organization [2].

In recent years, there have been a significant part of gerontological age patient in various regions of the Russian Federation among patients receiving medical care for acute poisoning of chemical etiology, and their increase is now marked [3-5]. Each year 3,825±180 patients are admitted to the Department of Acute Poisonings Treatment of the N.V. Sklifosovsky Research Institute for Emergency Medicine, of whom patients over 60 comprise from 10.3 to 12.9%. With an increase in the age of victims, an increase in mortality is noted: in patients aged 60–74 years, on average, it is 9.8%; in the group of people from 75 to 89 years old it is 18.5%, and among long-livers it reaches 25.5% [6]. This is probably associated with a large number of somatic diseases in this group of patients prior to acute exogenous toxicosis, the so-called premorbid background. It is of great importance in the development of any pathological process, as it creates a certain level of organism reactivity.

The aim is to identify the role of comorbid diseases in the course and outcome of acute poisonings with psychoactive drug (PPD) in patients over 60.

MATERIAL AND METHODS

The material of the study were hospital records of 99 patients aged from 60 to 90 years who died of poisonings with psychoactive drugs at the N.V. Sklifosovsky Research Institute from 2013 to 2016, acts of autopsy, forensic chemical and histological studies.

In 20 cases, morphological and histological examination of the various lungs parts was performed: the root, pneumonic foci, peripheral sections from different lobes. Well-known histological methods were used: hematoxylin and eosin staining, van Gieson picrofuchsin, MSB for fibrin, oil red O. for fat.

The electrocardiograms of 51 patients, performed upon admission to hospital, were analyzed.

According to the WHO modern age classification, elderly age is 60–75 years, senile age is 76–90 years, and long-livers are elder than 90 [1].

In the conducted studies, elderly patients (52.6%) were the most numerous, then patients of senile age (44.4%) and long-livers (3%). Poisonings in women (79.8%) were noted 3.9 times more often than in men (20.2%), which is probably related to the general structure of the aging population, which is in favor of women aged 65 and older.

The overwhelming number of patients (88.9%) took drugs with suicidal intent, and in 7.1% of cases, poisonings occurred against the background of alcohol intoxication.

In all cases, the diagnosis of poisoning was confirmed by chemical and toxicological studies of the biological matrix of the body.

In 63.6% of cases, psychoactive drugs poisoning (PPD) occurred in case of taking one type of drugs, in 28.3% cases it was the combination of 2 items and 3 items in 8% of patients. Most often, patients took barbituric drugs in combination with benzodiazepines, carbamazepine, amitriptyline, and carbamazepines with benzodiazepines. It should be noted that in 25.2% of cases the time gap between the drug intake and the provision of specialized medical care exceeded 10 hours. During this period, the majority of drugs were able not only to be absorbed into the blood from the gastrointestinal tract, but also distributed and deposited in the body, and also partially undergo metabolic transformations [7].

According to the classification of E.A. Luzhnikov, the severity of poisonings among the patients was assessed as follows: mild in 10 cases (10.1%), moderate in 23 (23.2%) cases, severe in 66 cases (66.7%) [8]. The death of patients was registered in terms from 1 hour to 82 days.

Statistical data processing was performed using the Statistica 6 program. To compare the characteristics in the studied age groups, the $\chi 2$ criterion was used with the Yates correction [9]. For a statistically significant level $p \leqslant 0.05$ was taken.

RESULTS AND DISCUSSION

The retrospective analysis showed that the most frequent causes of death were pneumonia (77 cases, 77.8%) and intoxication (16 cases, 16.2%). Among other reasons were transmural myocardial infarction - 2; pulmonary embolism - 1; acute cerebrovascular accident - 1; brain aneurysm rupture - 1; gastrointestinal bleeding - 1.

Taking into account the presence of two leading causes of death, we found it reasonable to analyze the time of onset of death in elderly and senile patients with that causes (Table 1).

Table 1

The life expectancy of patients of elderly and senile age with psychoactive drugs poisonings, who died of intoxication and pneumonia

Age, years	Time of death of intoxication, hours	Time of death of pneumonia, days
60–75	17.9±13.3	22.51±11.7
76–90	15.8±12.1	20.19±6.61

It follows from the table that both in cases of intoxication and pneumonia, the timing of death in patients of the studied age groups did not have statistically significant differences, although in elderly people it was shorter by an average of 10%.

It is known that aging is accompanied by changes at all levels of vital activity of the organism: molecular and genetic, cellular, organ and regulatory [10]. This significantly affects the course of various pathological processes in gerontological patients. In morphological studies in elderly and senile patients who died of intoxication, signs of coronary and cardiac sclerosis were found in all cases, whereas death of pneumonia showed an average of 85% of patients (Table 2). Attention is drawn to the fact that, at early stages of death, obstructing coronary sclerosis was predominantly detected, and more often in people of senile age, which, as a rule, was combined with coarse or small focal atherosclerotic cardiosclerosis. In case of deaths that occurred later than 10 days, non-obstructing coronary sclerosis prevailed. According to the international classification of diseases of the tenth revision (ICD-10), such morphological changes correspond to a disease which belongs to section T.120-125, and this is coronary heart

disease. It is a myocardial damage caused by a disorder of the coronary circulation, resulting from an imbalance between the coronary blood flow and the metabolic needs of the heart muscle.

Table 2

The incidence of morphological signs in patients of gerontological age with acute poisoning with psychoactive drugs, died of intoxication and pneumonia

Morphological signs	Intoxication		Pneumonia	
Age, years	60–75	76–91	60–75	76–91
Number of patients	n=10	n=6	n=41	n=36
Atherosclerosis				
Coronary sclerosis	10/100%	6/100%	35/85.4%	31/86.1%
Myocardial dystrophy	8/80%	6/100%	29/70.7%	33/91.6%*
Aortal atherosclerosis	6/60%	2/33.3%	21/51.2%	18/50%
Atheromatous ulcer of the aorta	4/40%	4/66.6%	7/17.1%	15/41.6%*
Atherosclerosis of vessels of the base of the brain	4/40%	3/50%	21/51.2%	29/80.5%*
Essential hypertension				
Myocardial hypertrophy	8/80%	6/100%	27/65.8%	30/83.3%
Postinfarction cardiosclerosis	2/20%		6/14.6%	5/13.88%
Arteriolonephrosclerosis	6/60%	6/100%	26/63.4%	29/80.5%
Liver steatosis	5/50%	3/50%	22/53.65%	22/61.1%
Liver dystrophy	1/10%		4 / 9.7%	4/11.1%
Pancreatic lipomatosis	6/37.5%	3/50%	19/46.34%	16/44.4%
Cancer		1/16.5%	5/12.19%	7/19.44%
Chronic bronchitis	2/20%	3/50%	16/39.0%	4/11.1%*
Pneumosclerosis	1/10%	2/33.3%	9/21.9%	4/11.1%
Diabetes		1/16.5%	6/14.6%	4/11.1%
Hydrocephaly		2/33.3%	11/26.8%	9/25%
Brain atrophy	1/10%	2/33.3%	13/31.7%	9/25%

Notes: * — statistically significant differences in different age groups ($p<0.05$ χ^2 criterion)

Myocardial hypertrophy in the overwhelming majority of cases was recorded in senile patients. In this age group, arteriolonephrosclerosis was most often diagnosed, indicating that they had hypertension. At the senile age group, atherosclerosis of vessels of the base of the brain, atheromatous ulcer of the aorta, and myocardial dystrophy were found statistically significantly more often than in elderly patients (see Table 2).

Chronic bronchitis and pneumosclerosis with deaths of intoxication with the highest frequency (83.3%) were found in senile patients, and in elderly patients (60.9%) in cases of death of pneumonia (see Table 2). We have previously established that in gerontological patients with PPD, even of mild level, in a large percentage of cases hypostatic pneumonias develop, which are migrating and have a long course [11]. In our opinion, the basis for them is the premorbid background, represented by atherosclerotic lesions of the cardiovascular system and chronic lung diseases.

A morphological study of the lungs of the deceased in the early stages noted discirculatory disorders such as uneven blood filling of the vessels, erythrostasis, thrombosis, capillary plethora and interalveolar edema. Exudates with a predominance of granulocytes and a small admixture of pulmonary macrophages were found in the lumen of the alveoli.

All the deceased, who underwent morphological and histological examination of the lungs, had permanent signs of pneumosclerosis af varying degrees and types (diffuse, focal, reticular, peribronchial, perivascular). In all cases there was a lesion of the bronchial tree, often its terminal parts such as bronchiolospasms and purulent-desquamative bronchiolitis. According to S.V. Kolobov et al., inflammation in the lungs develops in the bronchi more often than in the respiratory part. An important element of the nonspecific protective reaction of the bronchioles, is the spasm of their muscular layer, which leads to the development of the obstructive syndrome [12].

Outside pneumonic focuses, a wide range of changes was noted: dystelectasis, atelectasis, edema, alternating with emphysema areas.

In these zones, as well as in individual pneumonic foci, air cyst-like structures were found in the form of optically empty spherical formations of various sizes. They differed from emphysematous formations by the shape, and from true cysts by the absence of a capsule or any lining. Their quantity and size differed (Fig. 1). Accumulations of small cystic formations were focal and combined with changes in bronchioles such as purulent-desquamative or desquamative bronchiolitis with lumen obstruction, as a rule, against the background of pneumosclerosis. Probably, these disorders are one of the factors contributing to the migration of inflammatory infiltrates in the lungs in elderly and senile people.

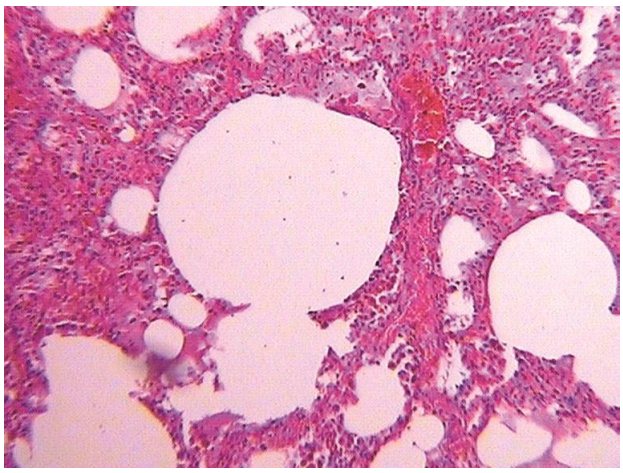

Fig. 1. Air cysts of various sizes in the lungs. Staining with hematoxylin and eosin. Magnification x100

E.A. Beresneva et al. (2012) describes the X-ray phenomenon of "mulberry" in the inhale thermal trauma: the appearance of small air bubbles as a result of violation of the act of exhalation and retention of air in individual alveoli, associated with the lesion of the terminal bronchioles [13]. The air cysts that we discovered may be the morphological equivalent of the radiological feature of the mulberry.

In 50% or more of patients who died at different times, total or focal liver steatosis was found, which mostly was mixed (Table 2). Large-focal steatosis, as a rule, was caused by long-term alcohol intake (more often in men) and long-term treatment with psychotropic drugs (in patients with endogenous diseases), and the microvesicular steatosis probably was drug induced as patients took certain drugs of different pharmacological groups or combined them with treatment of somatic or mental illness. These substances and their active metabolites have a negative effect on mitochondria, which leads to their damage and β-oxidation of fatty acids with the development of fatty degeneration of hepatocytes. It leads to violations of biotransformation of psychopharmacological drugs, having an adverse effect on the course of acute poisoning.

Almost 50% of deceased patients had pancreatic lipomatosis. Morphological signs of oncological diseases and diabetes mellitus were found in 11.1%-19.4% of observations. Up to 20% of patients had myocardial infarction in history.

Disorders on electrocardiograms recorded upon admission of patients with PPD to the hospital when compared with morphological studies indicate that they are nonspecific due to chronic cardiovascular pathology (Table 3).

The data presented in the Table 3, demonstrate that in patients who died of intoxication, the frequency of cardiac rhythm disturbances, subendocardial ischemia and myocardial ischemia was widespread, statistically significantly higher than in patients who died of pneumonia. This, in our opinion, could have an adverse effect on the course and outcome of poisoning in the toxicogenic stage. In patients who died later of pneumonia, rhythm disturbances in 39% of cases were sinus tachycardia. It is noteworthy that violations of cardiac conduction such as complete and incomplete right bundle branch block and left bundle branch block were detected only in the post-intoxication period against the background of hypoxic changes in the myocardium.

Table 3

Changes in the electrocardiogram in patients of gerontological age with acute poisoning with psychoactive drugs upon admission to hospital

Electrocardiographic signs	Causes of death	
	Intoxication	Pneumonia
Number of patients, n	13	38
Sinus rhythm		15 (39.4%)
Sinus tachycardia	3 (23.1%)	15 (39.4%)
Rhythm of the pacemaker	1 (7.69%)	1 (2.63%)
Atrial flutter	1 (7.69%)	
Atrial fibrillation	3 (23.1%)	2 (5.26%)
Supraventricular extrasystoles	5 (38.4%)*	3 (7.8%)
Incomplete RBB block		2 (5.26%)
Complete RBB block		3 (7.8%)
LBB block		4 (10.52%)
A-V conduction delay		3 (7.8%)
Hypoxic changes in the myocardium	8 (61.5%)	33 (86.8%)
Subendocardial ischemia	4 (30.76%)*	2 (5.26%)
Extensive myocardial ischemia	6 (46.15%)*	4 (10.52%)
Large-focal anterior myocardial infarction	1 (7.69%)*	1 (2.63%)
Transmural infarction of the anterior wall of the left ventricle and interventricular septum	2 (15.38%)	

Notes: * — statistically significant differences in age groups ($p<0.05$ χ^2 criterion). LBB — left bundle branch; RBB — right bundle branch

Arrhythmias and heart block are the most important problems of modern cardiology in geriatrics, since people over 60 are characterized by a high prevalence of cardiac rhythm disturbances and conduction. The increase in the prevalence of cardiac arrhythmias in the elderly is associated with a number of age-related changes in the body: a decrease in the automaticity of the sinus heart node, deterioration in the conductivity of the heart muscle, a weakening of nerve influences regulating the heart rate, myocardial hypertrophy and dilatation of the cardiac cavities, a decrease in coronary blood supply, microcirculation disorders, tissue hypoxia, increased sensitivity of the myocardium to catecholamines, a decrease in the content of intracellular potassium in the myocardium, a decrease in the energy exchange of the cardiac muscle, as well as the formation of disturbed metabolism foci [14, 15].

The reasons for extrasystoles in the elderly are not fully established. A.I. Martynov et al. (2000) believe that the prevalence of supraventricular extrasystoles may be partially explained by an increase in the diameter of the left atrium and pressure in its cavity with age, and the high frequency of ventricular extrasystoles appears to be associated with an increase in the mass of the left ventricle and the level of blood catecholamines [16].

Epidemiological data suggest that the prevalence of atrial fibrillation increases with age. At the same time, the incidence in men is 1.5 times higher than in women. The incidence of atrial fibrillation in people aged 60–90 years is about 1% per year [17].

CONCLUSION

Studies have shown that during the course and the outcome of acute psychoactive drug poisoning at different times of the disease, the negative role of disorders in the body caused by various chronic pathologies, primarily diseases of the cardiovascular and respiratory systems, cannot be excluded.

Revealed macrovesicular and microvesicular fatty degeneration of the liver can alter biotransformation of accepted toxicants, thereby exerting a negative influence on the course of acute exogenous toxicosis.

FINDINGS

1. The morphological study in gerontological patients who died of acute psychoactive drug poisoning, atherosclerotic lesions of the heart and vessels of varying degrees and length were detected in 100% of cases. At the same time, the incidence of atheromatous ulcer of the aorta, atherosclerosis of the vessels of the base of the brain, and myocardial dystrophy was significantly higher in senile people who died of pneumonia and myocardial dystrophy than in elderly patients.

2. On electrocardiograms made upon admission to hospital, myocardial ischemia was detected in 76.9% of patients with subsequent death in the toxicogenic stage of poisoning, in all cases rhythm disturbances were detected, most often in the form of atrial fibrillation (23.1%) and supraventricular extrasystoles (38.4%). In those who died in the somatogenic stage of poisoning on the initial electrocadiograms, cardiac conduction disturbances (31.3%) prevailed.

3. Chronic bronchopulmonary system lesions preceding poisonings with psychoactive drugs, including terminal bronchi in pneumosclerosis, contribute to the development of hypostatic pneumonia and its long-lasting migratory course in gerontological patients.

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