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Differential diagnosis of sleep disorders in the presence of chronic mercury intoxication

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ABSTRACT. Insomnia is a widespread pathological condition in the general population, which has numerous social and medical consequences. Sleep disorders in patients with chronic mercury intoxications are much more common than in the general population. This study aimed to determine the most significant differential diagnostic criteria for sleep disorders in patients with chronic mercury intoxications for their further effective treatment. In this regard, we examined 30 patients with chronic mercury intoxications, whose age averaged 56 ± 0.71 years, and 30 patients of the control group, whose age averaged 54 ± 0.66. All patients underwent clinical, neurological, polysomnographic, and psychological examinations, and neurotransmitters were determined in the blood. Discriminant analysis based on polysomnography, psychological testing and neurotransmitter metabolism revealed significant differences in the examined groups of patients for the following indicators: total sleep time (decreased in the chronic mercury intoxication group) and wake within sleep (increased in the chronic mercury intoxication group) based on polysomnography, blood dopamine level (increased in the chronic mercury intoxication group) as well as reactive anxiety level according to the Spielberger-Khanin scale (increased in the chronic mercury intoxication group). Taking into account the data obtained, it is possible to improve approaches to the diagnosis and treatment of insomnia in the presence of chronic mercury intoxication.

Keywords: sleep, insomnia, chronic mercury intoxication, dopamine, reactive anxiety

1. Introduction

Metallic mercury is an industrial poison that primarily affects the central nervous system. In the Irkutsk Region, this neurotropic poison was used in the production of caustic soda at chemical enterprises in the cities of Usloye-Sibirskoye (Usolyekhimprom) and Sayansk (Sayanskkhimplast).

According to the previous data, in the case of occupational chronic mercury intoxication (CMI), the following structures of the central nervous system are gradually involved in the pathological process: nonspecific structures of the midbrain, the limbic system and reticular formation, which provide basal emotions and vital functions, maintain a certain level of wakefulness and regulate muscle tone (Lakhman et al., 2014). Therefore, sleep disorders occur already at the early stages of occupational CMI characterised by the presence of functional disorders of the nervous system in the form of asthenic and autonomic defects. Further development of organic disorders in the central nervous system is accompanied by an increase in the severity of mental and sleep disorders (Lipenetskaja et al., 2004).

Insomnia is a widespread pathological condition in the general population, which has numerous social and medical consequences. According to various social surveys, the prevalence of this condition among the adult population reaches 15% (Schutte-Rodin et al., 2008). There is a direct relationship between the severity of sleep disorders and a decrease in physical performance, cognitive functions and life expectancy of an individual (Poluektov, 2016). At the same time, this problem is one of the least studied among various specific diseases.

Currently, insomnia is known to have a high comorbidity with various somatic and neurological diseases (Lichstein et al., 2016). Sleep disorders are much more common among patients with CMI than in the general population. Based on our surveys, 88% of these patients complained of sleep disturbances; 100% had difficulties in maintaining sleep, and 60% – early

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final awakening. According to the questionnaire data on subjective sleep characteristics, a decrease in the total assessment of sleep quality was observed among 100% of the respondents (Katamanova et al., 2016).

According to the State Service for Medical and Social Expertise, in the Irkutsk Region, over the past five years, occupational neurotoxicosis has been ranked third or fourth in the structure of disability causes associated with occupational diseases, after vibration disease, sensorineural hearing loss and respiratory diseases (Boklazhenko and Bodyenkova, 2019). Therefore, the characterisation of occurrence and development of sleep disorders, as well as methods of their objective diagnosis in patients with occupational neurotoxicosis, are of great clinical and social significance.

Neurotransmitters such as serotonin, acetylcholine, catecholamines, histamine, and dopamine that are involved regulating the above vital functions play an important role in the CMI pathogenesis (Katamanova et al., 2010). At present, the dopaminergic system is known to be associated with strong emotions and stress (Kovalzon, 2012). Previously, we determined that with the predomination of organic personality disorder with psycho-emotional disorders of anxiety and depression nature in the CMI clinical picture, there was a significant increase in the level of reactive anxiety based on the data on the psychological condition of the patients.

Therefore, the aim of the study was to identify the most significant differential diagnosis of sleep disorders in patients with occupational CMI for their further effective treatment.

2. Materials and methods

Two groups were included in the study. The first group consisted of 30 patients (men) with occupational CMI, who worked at Ulsoyekhimprom and were aged on average 56 ± 0.71 years. The second group (control) consisted of 30 male patients aged on average 54 ± 0.66 years, who complained of sleep disorders but had no contact with toxic production factors.

Sleep disorders were diagnosed using a Neiron-Spektr-4 electroencephalograph manufactured by Neirosoft (Ivanovo, Russia), followed by evaluation of the resulting hypnogram.

The concentration of dopamine (DA) was determined in blood plasma obtained with EDTA as anticoagulant by a solid-phase competitive enzyme immunoassay on microplates using the 3Cat ELISA test kits (LDN, Germany) on a BioTek enzyme immunoassay reader (USA). DA was preliminarily extracted from blood samples using an affinity gel specific for cis-diol groups, then acidified to N-acyl-dopamine and subjected to enzymatic conversion to N-acyl-3-methoxytyramine during the detection procedure. The evaluation of the physiological condition of the examined patients included determination of anxiety level, asthenic condition and depression. The levels of reactive and trait anxiety were assessed based on the Spielberger-Khanin scale; the level of asthenic condition – based on the asthenic condition scale (Akhmedzhanov, 1995), and the level of depression – using the V. Zung scale adapted by T.N. Balashova (Krylov, 1990).

Statistical processing of the material was carried out with Statistica for Windows v.6 Ru (license No. AXXR004E642326FA; license holder East-Siberian Institute of Medical and Ecological Research). The median value and the interquartile range (25^{th} and 75^{th} percentiles) were calculated for the indicators. Discriminant analysis was used to determine the differential diagnosis of insomnia. Step-by-step procedures determined the information content of the indicators. The initial installation parameters were made according to the recommendation of V. Borovikov (2001). $F \geq 3.5$ was chosen as the threshold value.

This study does not infringe on the rights or jeopardise the well-being of the examined patients according to the requirements of biomedical ethics imposed by World Medical Association Declaration of Helsinki (2000) and the Order of the Ministry of Health of the Russian Federation No. 266 (dated 19 June 2003).

3. Results

In the first group of patients, for the long-term period of occupational CMI, in 97.7% of cases, we recorded stage II of the disease, and in 2.3% of cases – stage III. The frequency of encephalopathy in this group was 90% [95% CI 78–95]. Asthenic disorder was identified in 30% of cases [95% CI 19–45]; vegetative dysfunction – in 55.6% of cases [95% CI 35–70]. Patients with CMI complained of non-systemic headaches and dizziness, difficulty remembering current events, increased irritability, and fatigue. Complaints about sleep disorders were recorded in 100 % of cases.

Based on the clinical examination of the patients in the control group, the detection frequency of gastrointestinal tract diseases (chronic gastritis) was 36%, diseases of the organs of vision (myopia and hypermetropia) – 40% and vertebrogenic pathology – 36%. Complaints about sleep disorders were recorded in 47% of the patients.

As psycho-emotional disorders of anxiety and depression nature prevailed in the clinic picture of patients with CMI, both groups underwent psychological tests to detect anxiety, asthenic condition and depression. Analysis of the indicators of the psycho-emotional domain in the two groups indicated the presence of astheno-depressive syndrome with an anxious component in the CMI group and its absence in the control group. Comparative analysis of the psychological indicators revealed the statistically significant differences ($p < 0.05$) characterising levels of depression (67.4(59-70) and 37.9(32-45) points, in the first and second group, respectively), trait anxiety (58.7(55-62) and 37.0(31-46) points in the first and second group, respectively), reactive anxiety (54.7(49-60) and 36.4(29-41) points in the first and second group, respectively), and asthenic condition (84.1(78-92) and 23.5(19-28) points in the first and second

group, respectively).

For an objective diagnosis of nocturnal sleep disorders, patients in both groups underwent full in-lab polysomnography (gold standard of sleep studies, Level 1 study). Polygraphic registration of biopotentials with subsequent assessment of the resulting hypnogram revealed in patients with CMI an increase in falling asleep time (35.0 (30.5 to 47.0) min), a decrease in sleep duration (total sleep time 339.5 (305.0 to 374.0) min), an increase in the number of activations (2.9 (1.9 to 3.6) % of total sleep time) and total wake within sleep (11.3 to 23.5) %), a decrease in the number of sleep cycles (3.0 (2.0 to 4.0)) as well as a decrease in the sleep efficiency index, SEI (70.95 (60.7 to 78.2) %) and an integrative sleep quality index, SQI (17.8 (13.4 to 27.5)).

The results of polysomnographic study of the patients in the control group revealed the following changes in quantitative and qualitative indicators of nocturnal sleep structure: an increase in the total wake within sleep (12.2 (8.4 to 18.6) %), an increase in the latent period of REM-stage (93.0 (72.0 to 117.0) min), a decrease in the number of sleep cycles (3.0 (3.0 to 4.0)) as well as a decrease in SEI (78.4 (73.9 to 81.5) %) and SQI (14.1 (10.9 to 20.6)).

For a more detailed study of sleep disorder mechanisms in patients with CMI, we studied the concentration of the DA transmitter in the blood. In the CMI group, the DA concentration was elevated in the blood of the patients. In the control group, the DA concentrations in the blood of the patients were within the reference values.

To determine the differential diagnosis of insomnia in patients with occupational CMI, we carried out a discriminant analysis for 26 indicators of polysomnography, psychological testing and neurotransmitter metabolism in both groups. As a result of statistical analysis, we obtained four most significant diagnostic criteria, in which F inclusions and confidence level were statistically significant (Table).

Table. Results of the analysis of discriminant functions in the examined groups

No	Indicator	F inclusions	p
a1	total sleep time (min)	4.7	0.03
a2	wake (%)	5.3	0.02
a3	DA level (pg/mL)	3.6	0.04
a4	reactive anxiety level, (points)	142.2	0.000000

4. Discussion

Based on an objective technique for studying sleep disorders, we identified that patients with occupational CMI had more manifested qualitative and quantitative changes in the indicators of nocturnal sleep structure than in the control group.

The results of psychological testing that revealed significant changes in the emotional domain (increase in depression level, reactive and trait anxiety, and asthenic condition compared to the control group) confirmed the presence of a more manifested form of insomnia in patients with occupational CMI.

The limbic-hypothalamic-reticular complex maintains the level of attention and muscle activity, regulation of the sleep-wake cycle, basal emotions and autonomic reactions. These processes occur in the body during the normal functioning of transmitter metabolism (Andreeva et al., 2002). In the presence of CMI, the transmitter system showed elevated DA concentrations in the blood. The identified changes corresponded to the currently existing theory of chronic neurotoxicosis pathogenesis as well as to the disorders detected in the psycho-emotional domain and from polysomnography of patients with CMI.

The discriminant analysis based on the polysomnography, psychological testing and transmitter metabolism revealed significant differences in the examined groups of patients for the following indicators: total sleep time (decreased in the CMI group) and wake within sleep (increased in the CMI group) based on polysomnography, blood DA level (increased in the CMI group) as well as reactive anxiety level according to the Spielberger-Khanin scale (increased in the CMI group). Taking into account the data obtained, it is possible to improve approaches to the diagnosis and treatment of insomnia in the presence of CMI.

5. Conclusions

1. The resulting set of diagnostic indicators is specific for sleep disorders in the presence of occupational CMI.
2. A certain set of diagnostic criteria can be used for differential diagnosis of insomnia in the presence of occupational CMI.

Conflict of interest

The authors (Korchuganova E.N., Katamanova E.V., Slivnitsyna N.V., Kudaeva I.V., and Kazakova P.V.) are the inventors of the patent “Method for diagnosing dyssomnia associated with chronic mercury intoxication”.

The authors declare no conflict of interest.

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