

Abstract
of the thesis work
of **BATYRBEKOVA LAZAT SARSENBAEVNA**
on the topic "Condition of the hepatobiliary system of the Sub-Aral area
population"
for the degree of Doctor of Philosophy (PhD)
in the specialty 6D110100 "Medicine"

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Timeliness

Currently, the pathology of the hepatobiliary system remains an urgent problem. According to the World Health Organization (WHO), there are more than 2 billion people suffering from liver diseases in the world [A.A.Ilchenko. - 2011]. Only in the CIS countries there are annually registered from 500 thousand to 1 million people suffering from one or another liver pathology [V.T.Ivaschkin - 2012]. According to WHO experts, one in five women and one in ten men in Europe suffer from pathology of the liver and biliary tract [WHO. News bulletin #328 – 2009].

In etiology of a dysfunction of the hepatobiliary system, the share of environmental factors can make from 14 to 36%. In areas with unfavorable environmental conditions, hepatobiliary pathology occurs 3-4 times more often than in relatively “clean” areas [A.A.Baranov – 2012; A.S.Faustov, S.V.Popov - 2014].

One of the unfavorable regions in Kazakhstan is the Sub-Aral area. In the works of domestic and foreign researchers, environmental pollution (the Syrdarya River) it was determined that was contaminated by sulfates, nitrates and magnesium and salts of heavy metals (copper, cadmium, zinc, lead and nickel) exceeding the MAC several times [A.Sh.Alnazarova – 2010; L.Zh.Orakbay – 2010; Sh.Rakhmatullaev - 2017]. When entering into the body, heavy metal salts can lead to an imbalance of microelements. The most aggressive route of polluting chemicals is respiratory tract in the form of salt - dust aerosols. The total load of the imbalance of bioelements can be the cause of diseases of the hepatobiliary system, which performs the main detoxification function in the body [O.I.Aksenova – 2011; Y.A.Rakhmanin - 2004].

Therefore, a comprehensive study of the state of the hepatobiliary system in the adult population of the Sub-Aral area and in the experiment with an imbalance of bioelements is an urgent problem and allows us to reveal the mechanism of the appearance of the pathology of the hepatobiliary system in this region.

Purpose of the study: To establish the features of clinical and functional changes in the hepatobiliary system and the microelement composition of blood of

adults living in environmentally unfavorable areas of the Sub-Aral area, and to evaluate the morphological changes in the liver during experiment when exposed to fine-dyspersated dust in the Sub-Aral disaster zone.

Objectives of study:

1. To conduct clinical and functional studies of the hepatobiliary system and to determine it's structure, prevalence at the population of Sub-Aral area.
2. To evaluate the microelement composition of blood in the pathology of the hepatobiliary system Sub-Aral area population living in the crisis and catastrophe zone.
3. To study morphological changes in the liver and microelement composition in experimental animals under subacute and chronic inhalation exposure with finely dispersed precipitated dust from the air of of Sub-Aral disaster zone.
4. To develop a prognostic model for the development of chronic cryptogenic hepatitis in adults living in environmentally unfavorable areas of Sub-Aral area.

Scientific novelty of the work:

1. A comprehensive clinical and functional study of adults living in environmentally unfavorable areas of Sub-Aral area showed a high risk of developing chronic cryptogenic hepatitis with persistent flow with a minimal degree of activity and changes in the microelement composition of the blood — lowering of zinc and increasing of copper.
2. An experimental study showed that the chronic exposure to fine-dyspersated dust of air in the Sub-Aral disaster zone causes inflammatory changes in hepatocytes and moderate liver fibrosis of the periportal area, decrease of zinc and increase of copper in the blood and parenchyma in liver of animals.
3. The developed mathematical model made it possible to determine the risk group for the development of chronic cryptogenic hepatitis among the adult population living in the zones of crisis and catastrophe of the Sub-Aral area.

Materials and methods:

The work was carried out in 2 stages.

At the first stage, a clinical and functional study of the adult population of the selected areas of the Sub-Aral area of the Kyzylorda region was carried out: disasters – Aralsk city and Aiteke-bi village; crisis – village Zhosaly, Zhalagash village and Shieli village. The control zone is defined at Atasu village of Karaganda region. There were examined 4381 people.

The inclusion criteria were: 1) living time of the adult in the environmentally unfavorable zone was more than 5 years; 2) age from 18-69 years; 3) a practically healthy population of the Sub-Aral area living in areas of disaster and crisis;

The exclusion criteria were: 1) the presence of contact at the workplace with production factors above the 2 hazard class and hazard; 2) patients registered with a hepatobiliary system (viral hepatitis, alcoholic hepatitis, autoimmune hepatitis, non-alcoholic fatty liver disease, cysts and liver cancer);

- patients with socially significant diseases.

The medical examination included a consultation with the therapist and analysis of outpatient cards of the examined persons, questionnaires on a scale of CAGE, ultrasound examination of the abdominal cavity and ECG. Biochemical studies of blood: alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transpeptidase, alkaline phosphatase, cholesterol, bilirubin, total protein, albumin, gamma globulin, glucose, triglycerides and ceruloplasmin. Biochemical analysis were carried out on a StarDust MC-15 semi-automatic analyzer using reagents of "Ordamed".

Chemical studies were carried out to identify the concentration of 5 microelements in the blood - copper (Cu), zinc (Zn), selenium (Se), iron (Fe), iodine (I) on atomic absorption spectrometer MGA-915 of "Lumex" company.

The second stage is an experimental study of the hepatobiliary system of animals during inhalation inoculation of finely dispersed precipitated dust in the Sub-Aral disaster zone (Aralsk city), with determination of liver biochemical parameters, microelements (copper, zinc, selenium, iron, iodine) in the blood and liver of animals of atomic absorption method. After the end of the experiment, a morphological study of the liver of animals was carried out on a specialized computerized complex of the company "Leica mycrosystems" (Sweden) with a microscope "Leica DM1000", specially designed for the study of histological preparations at 100, 200 and 400-fold magnifications with color microphotography.

In order to assess the nature of pathomorphological changes in the liver of animals used histological criteria for the degree of activity of the process, recommended by R.G.Knodel et al.

The main provisions to be defended:

1. The adult population of the Sub-Aral area living in the disaster zone is 1.5 and in the crisis zone is 1.4 times more likely to suffer from the pathology of the hepatobiliary system than in the control zone. The calculation of the odds ratios (OR) showed that the risk of developing chronic cryptogenic hepatitis in the adult population living in the crisis zone is 4.1 times and in the catastrophe zone is 13.3 times higher than in the control zone.

2. A feature of the clinical and functional development of chronic cryptogenic hepatitis at adult population living in a crisis and catastrophe zone has a persistent course with a minimal degree of activity and a change in trace elements — a decrease in zinc and an increase in copper.

3. The chronic exposure to fine precipitated dust in Sub-Aral disaster zone in experimental animals causes inflammatory changes in hepatocytes with minimal cytolytic and cholestatic activity and moderate periportal liver fibrosis, accompanied by a decrease in zinc and an increase in copper.

4. The performed logistic regression analysis established indicators that make it possible to determine the risk group for the development of chronic cryptogenic hepatitis among the adult population of the Sub-Aral area living in the zone of ecological crisis and catastrophe: place of residence (unfavorable region), residence time, cytolysis and cholestasis enzymes (alanine aminotransferase,

gamma-glutamyl transpeptidase, alkaline phosphatase), copper and zinc in the blood.

Practical and theoretical significance

Based on calculations of the odds relations, a high risk of developing chronic cryptogenic hepatitis in the adult population of the Sub-Aral area living in the crisis and catastrophe zone has been established.

The developed predictive mathematical model, including 7 predictors: place of residence (unfavorable region), residence time, cytolysis and cholestasis enzymes (alanine aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase), copper and zinc in the blood, with 85% probability, it allows to determine risk groups for the development of chronic cryptogenic hepatitis among the adult population of Sub-Aral area, which will improve the quality of not only early diagnosis, but also preventive measures.

Putting Results Into Practice

The results of the research work were introduced in the research work of the “Institute of Public Health and Occupational Health” and the practical work of the “MSE Polyclinic #5 of the city of Karaganda”, which allowed us to expand our understanding of the state of the hepatobiliary system under the influence of the environmental load on the population and the effect of sedimentary dust on liver in experimental studies. Acts of implementation for the certificate of state registration of rights to the copyright object #1879 dated February 20, 2019 “Criteria for assessing liver damage in an adult population of the ecological unfavorable area of Sub-Aral” and guidelines for doctors “An algorithm for determining the structure of therapeutic morbidity in an adult population of Sub-Aral area of Kyzylorda region” were received.

Connection of the dissertation with other research works.

The thesis was carried out at KSMU as part of the program-targeted research work “Integrated approaches to managing the health status of the Sub-Aral area population”.

Approbation of work.

The main provisions and results of the work were reported at the III International Scientific and Practical Conference with the participation of “New Tasks of Modern Medicine” (St. Petersburg, Russia, December 26, 2015), the International Scientific and Practical Conference of Young Scientists with the participation of “World of Science and Youth: Achievement and prospects” (Karaganda, February 26, 2015), the International scientific-practical conference “The development of science in the 21st century” (Kharkov, Ukraine, April 11, 2015), the International forum “Modern methodological problems of study, evaluation and regulation environmental factors affecting human health” (Moscow, RF, December 15-16, 2016), International Congress of Epidemiologists” (June 25-27, 2015), the scientific forum “Medicine, Chemistry and Biology” (Moscow, RF, 2019).

The results of the thesis were reported to the non-profit joint-stock company “Medical University of Karaganda” at a meeting of the department “General

Medical Practice #2” protocol #11 dated May 6, 2019 and at a meeting of the “Scientific Expert Council” protocol #5 dated 04.12.2019.

Publications:

Based on the materials of the dissertation, 25 works were published, including in publications, 8 articles were recommended by the Committee for Control in Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan and the Higher Attestation Commission, including 2 intellectual property of copyright, state registration #0313 of February 17, 2016 and #1879 of February 20, 2019, 1 methodological recommendation, 2 articles in the journal included in the Scopus database “Occupational medicine and industrial ecology”, “Biomedical and Pharmacology Journal”. The remaining 15 articles are published in collections of materials from regional and foreign conferences and magazines.

Conclusions:

1. The frequency of diseases of the hepatobiliary system in the adult population of the Sub-Aral area, living in the disaster zone exceeds the control zone by 1.5 times, in the crisis zone by 1.4 times.

The structure of hepatobiliary pathology in the Sub-Aral disaster zone is represented by chronic non-calculous cholecystitis (59,0%), chronic cryptogenic hepatitis was 9,0%, and Non alcoholic fatty liver disease was 8,0%.

Chronic cryptogenic hepatitis in the catastrophe zone has a probability (OR) of development 13.3 times higher than in the control zone, in the crisis zone the probability is 4.1 times higher than the control zone.

2. Chronic cryptogenic hepatitis in an adult population living in the zone of crisis and catastrophe of the Sub-Aral area has a persistent course with a minimal degree of activity (ALAT $54,4 \pm 1,7$ and $55,7 \pm 1,2$, ASAT $53,1 \pm 2,6$ and $53,5 \pm 1,4$, alkaline phosphatase $158,8 \pm 7,9$ and $119,2 \pm 3,1$). In patients with chronic cryptogenic hepatitis in these territories, a significant increase in copper ($1463,7$ and $1467,2 \mu\text{g/l}$), a decrease in zinc (3519.4 and $3543.8 \mu\text{g/l}$) and a slight decrease in selenium (48.7 and $48, 2 \mu\text{g/l}$), iron (267.2 and $296.2 \mu\text{g/l}$) and iodine (3.8 and $3.9 \mu\text{g/l}$).

3. The chronic exposure of experimental animals to fine precipitated dust in the Sub-Aral disaster zone, containing 74% sulfates and heavy metals (lead, copper and cadmium), exceeding the standard value, causes inflammatory changes with lymphoid hepatocyte infiltration and moderate periportal liver fibrosis. Inflammatory changes in the liver are characterized by minimal cytolytic (ASAT 4.8 times higher than standard indicators) and holistic (alkaline phosphatase 3.1 times higher than standard indicators) activity. An increase in copper in the blood and in the liver parenchyma by 1.3 times, a decrease in zinc in the liver parenchyma by 2.6 times from the reference values was established.

4. The developed mathematical model makes it possible to predict with 85% probability the risk group for the development of chronic cryptogenic hepatitis among the population living in the disaster and crisis zones of the Sub-Aral area of Kyzylorda region, with the following predictors established: place of residence

(unfavorable region), residence time, cytolysis and cholestasis enzymes (alanine aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase), copper and zinc in the blood, that allows to improve early diagnostics and timely preventive measures.

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