ANNOTATION

of the dissertation work of

Mustapayeva Aigerim Abdymazhitovna

on the topic **"Improving the radiological diagnosis of cystic echinococcosis of the liver"**, submitted for the degree of Doctor of Philosophy (PhD) on the specialty "6D110100-Medicine"

The relevance of the research topic

Cystic echinococcosis (CE) is a zoonotic biohelminthiasis caused by Echinococcus granulosis, characterized by the formation of parasitic cysts, with a predominant destructive lesion of the liver (with possible involvement of the biliary tract), lungs and other organs with a long asymptomatic and manifest chronic course (Duisenova A.K., 2017).

Echinococcosis is a serious medical and social problem in many countries of the world, including Kazakhstan, where large endemic foci among farm animals persist, and in a subordinate connection there is an increase tendency in the number of cases among human (Suleymenov M., 2014). In Kazakhstan, the incidence of echinococcosis of people has increased more than 5 times since 1994: from 1.4 to 6.7 per 100 thousand population. A particularly high increase in the incidence is observed in the Southern regions of the republic (Ordabekov S.O., 2011). The deterioration of the epidisituation for echinococcosis in Turkestan, Zhambyl, Kyzylorda, Almaty regions is alarming. It should be noted that the proportion of morbidity among urban and rural residents is almost the same (in 2008, 48% and 52%, respectively) (Duisenova A.K., 2017).

Diagnosis of cystic echinococcosis of the liver is difficult due to the prolonged asymptomatic course of the disease (Brunetti E., 2018). Patients, as a rule, seek medical help late, when the parasitic cyst reaches a significant size, that is why CE is often called “parasitic cancer”. The prognosis of the disease can be extremely unfavorable when complications requiring emergency surgical intervention are diagnosed (cyst suppuration, breakthrough into the bile ducts, abdominal or pleural cavities, bronchi). Therefore, the leading importance for a favorable prognosis of the disease is its diagnosis at an early stage. (Romig T., 2017).

Serological methods traditionally used for the diagnosis of infectious diseases are not confirmatory tests of cystic echinococcosis (Deplazes P., 2017). These samples can be both false negative and false positive as a result of more than 15-25% of cases (Vola A., 2019).

Therefore, for the diagnosis of echinococcosis of the liver, radiological diagnostic methods such as ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) are traditionally used (Rinaldi F., 2014). CT and MRI are clarifying research methods in the diagnosis and differential diagnosis of liver CE, and are also used in complex diagnostic cases. It is mandatory to conduct a CT study with intravenous contrast. Accumulation and leaching of contrast agent in different phases of contrast allows differential diagnosis of formations (Stojkovic M., 2012).

CT is the method of choice when ultrasound has limitations, such as obesity, excess gases in the intestine, abdominal wall deformation due to previous surgical interventions and small cysts (Juan, L. B. S., 2019).

Due to the lack of radiation exposure and detailed visualization of the internal structure of the cyst, MRI with contrast is currently the leading and informative diagnostic method, allows to specify the size and localization, visualize small cysts, and is also used for preoperative evaluation of relationships with large vascular and ductal structures of the liver (Yu XK, 2021).

Ultrasound is a highly informative, accessible, non-invasive method of diagnosing liver echinococcosis. In international practice, several classifications of the ultrasound pattern of echinococcal cysts are used, of which the most common are the Gharbi classification and the WHO classification (WHO-IWGE), which are not used mainly in Kazakhstan (Gharbi N., 1981, WHO-IWGE, 2003, Brunetti E., 2010). The WHO classification (WHO-IWGE) meets the requirements of practical healthcare, according to which echinococcal cysts are distributed at stages depending on the ultrasound picture: CL (cystic lesion) – cystic formation; CE1 and CE2 - active stages, cysts with the presence of viable parasites; CE3a and CE3b – transitional, intermediate stages; CE4 and CE5 – inactive stages, cysts with the presence of non-viable parasites (Brunetti E., 2010).

On the basis of this WHO classification, a differentiated therapeutic tactic has been developed: 1) observation; 2) conservative therapy with antiparasitic drugs; 3) percutaneous puncture of the cyst under the control of ultrasound or CT (PAIR: puncture-aspiration-infusion-reinspiration); 4) surgical treatment in combination with antiparasitic drugs (Rinaldi F., 2014). When detecting the CL stage, observation is recommended. At CE1 (active) and CE3a (transitional) stages – conservative tactics (with cyst size < 5 cm - prescribing of antiparasitic drugs) and minimally invasive interventions – PAIR (with cyst size 5-10 cm in combination with antiparasitic drugs) or continuous drainage-catheter (with cyst size >10 cm) (Dietrich C., 2017). Only at the CE2 (active) and CE3b (transitional) stages, surgical intervention in combination with antiparasitic drugs is indicated. In the absence of the effect of conservative treatment with ultrasound control, namely: if there is no reduction in the size of the cyst and the transition of stages CE1 and CE2; CE3a and CE3b in CE4 - CE5, or the development of complications, further therapeutic tactics should be determined in favor of surgical treatment after consultation with the surgeon. Patients with inactive stages – CE4 and CE5 - are subject only to dynamic observation for 5 years (F. Tamarozzi, 2015). While in Kazakhstan, surgical intervention is traditionally performed in the diagnosis of liver CE regardless of the stage of cysts (Brunetti E., 2018).

Thus, the ultrasound picture of the echinococcal cyst of the liver allows not only to diagnose the disease, but also to determine the phase of development of the process, which determines the differentiated tactics of management, treatment and, ultimately, its prognosis (Dietrich C.F., 2017).

In connection with the above, there is a need to study the incidence of echinococcosis in the Republic of Kazakhstan in order to determine the need to introduce the WHO ultrasound classification (WHO-IWGE) into healthcare practice and to determine the prevalence of various ultrasound stages of CE in regions with the highest incidence.

The aim of the study is to improve the ultrasound diagnosis of cystic echinococcosis of the liver with the standardization of the conclusion in the Republic of Kazakhstan on the basis of determining the stage of activity of an echinococcal cyst.

Research objectives:

1. To study the incidence of cystic echinococcosis in the Republic of Kazakhstan by region, localization, age and gender structure of registered cases.

2. To conduct an ultrasound examination of the abdominal organs of the population of regions with high morbidity for the diagnosis of cystic echinococcosis of the liver with the determining and description of the ultrasound stages of the activity of echinococcal cysts.

3. To estimate the semiotics of the ultrasound picture depending on the stage of activity of the echinococcal cyst and to determine the informative value of the ultrasound method in the diagnosis of cystic echinococcosis of the liver.

4. To standardize the conclusion of radiological specialists on the basis of pathognomonic ultrasound signs of different stages of activity of the echinococcal cyst of the liver for making a clinical decision.

The object of the study:

1. Data of 8443 registered cases of cystic echinococcosis from the register of the Scientific and Practical Center for Sanitary and Epidemiological Expertise and Monitoring for 2007-2016.

2. Ultrasound data of abdominal organs of 4072 conditionally healthy residents of the regions of the Republic of Kazakhstan with a high incidence of cystic echinococcosis (7 villages of Almaty region and 6 villages of Turkestan region).

3. Data of ultrasound examination of the abdominal organs of 441 patients with 803 focal liver formations.

The subject of the study: the incidence of cystic echinococcosis of the liver in the Republic of Kazakhstan, diagnosis of cystic echinococcosis, ultrasound semiotics of cystic echinococcosis of the liver in comparison with the results of a pathomorphological study.

Research methods: epidemiological; radiological (ultrasound); morphological (histological examination); statistical analysis.

Scientific novelty:

The incidence of cystic echinococcosis of the liver in the Republic of Kazakhstan was studied with the determination of regions with high incidence, localization of echinococcal cysts and the age, sex structure of affected individuals **(article in the journal Web of Science, Scopus - 60th percentile, Q2)**

For the first time, a continuous ultrasound examination of the abdominal organs of the conditionally healthy population of Almaty and Turkestan regions with the diagnosis of cystic echinococcosis of the liver with the definition and description of ultrasound signs depending on the stage of activity according to the WHO classification (WHO-IWGE) **(article in the journal Web of Science, Scopus - 40th percentile, Q3)**

For the first time in the Republic of Kazakhstan, ultrasound semiotics of cystic echinococcosis of the liver was described with the determination of new pathognomonic ultrasound signs of echinococcal cysts in the form of ultrasound signs of the unevenness of its contours: local unevenness and bypass.

The informative value of the ultrasound diagnostic method according to the criteria of sensitivity, specificity and accuracy of the method depending on the stage of activity according to the WHO classification (WHO-IWGE) is determined.

The main provisions submitted for protection:

Retrospective analysis of the incidence of cystic echinococcosis in the Republic of Kazakhstan for 2007-2016 revealed a downward trend with consistently high rates in the Southern region with the highest level of population involvement in South Kazakhstan, Zhambyl and Almaty regions with a predominant lesion of people of working age with a significant predominance of women and localization of echinococcal cysts in the liver. According to WHO (2022) at the global level incidence of CE in Republic of Kazakhstan belongs to hyperendemic region.

A field continuous study of a conditionally healthy population of endemic regions using an ultrasound method revealed for the first time all stages of activity with a predominance of neglected inactive stages of echinococcal cysts.

Ultrasound semiotics of cystic echinococcosis in endemic regions is characterized by pathognomonic ultrasound signs of echinococcal cysts depending on the stage of activity with the identification of new pathognomonic ultrasound signs.

Ultrasound examination is a highly informative method of diagnosing cystic echinococcosis with determination of the stage of activity of echinococcal cyst and characterized by high sensitivity, specificity, accuracy, with low rates of false positive and false negative results according to pathomorphological verification of the diagnosis

Practical significance:

For the first time in the Republic of Kazakhstan, the ultrasound classification of CEs (WHO-IWGE) has been introduced, which allows clinicians to choose differentiated management tactics depending on the stage of the disease (conservative treatment, percutaneous puncture of a cyst under the control of ultrasound or CT (PAIR), surgical treatment or observation).

Methodological recommendations on the radiological diagnosis of cystic echinococcosis of the liver have been developed for radiologists and introduced into clinical practice using modern ultrasound classifications to standardize the results of the study, which makes it possible to standardize the conclusions of specialists in visual diagnostics (Methodological Recommendations).

An innovative Clinical protocol for the diagnosis and treatment of "Cystic echinococcosis of the liver in adults" (2016) has been developed and a consensus has been reached for the management of patients depending on the ultrasound stage of an echinococcal cyst between therapeutic and surgical specialists, in connection with which the CP has been revised in the Republic of Kazakhstan ("Cystic echinococcosis of the liver of adults", dated 17.07.2020).

Conclusions:

1. A retrospective analysis (2007-2016) of the incidence of cystic echinococcosis in the Republic of Kazakhsta reveled steady downward trend with an increase/decrease rate over 10 years between the extremes of the average annual standardized incidence rates T = -15.4%. Although at the global level, the Republic of Kazakhstan (5.19‰) belongs to the hyperendemic region (WHO, 2022). Moreover, high average annual standardized morbidity rates were found with a significant excess of the national

average values in South Kazakhstan (10,76‰), Zhambyl (8,73‰) and Almaty (7,43‰) regions (p=0,004, p=0,024 and p=0,571 respectively).

2. The highest average annual incidence of cystic echinococcosis throughout the study period was in the Southern region (7,98‰, p=0,019) with the peak incidence at the most able-bodied age of 30-39 years (1,35‰) with a significant predominance of women of reproductive age (p=0.017). The average long-term ratio of morbidity rates between men and women was 1:1.15.

Localization of cysts was diagnosed in the liver - 72.3%, in the lungs - 21.8%, in other organs - 5.9%.

3. Ultrasound examination of the abdominal organs of the conditionally healthy population of endemic regions for the first time revealed echinococcal cysts in 0.98% (40/4072) of the examined residents of Almaty and Turkestan regions. CE was detected in women 2.6 times more often than in men in Almaty region (72.2%, 27.8%, respectively) and 1.5 times – in Turkestan region (59.1%, 40.1%, respectively). At the same time, neglected stages of development of echinococcal cysts prevail with a predominance of inactive stages (CE4-CE5) over active (CE1-CE3) (78.9% vs. 21.1% in Almaty region) ($p<0.001$) and 75.8% vs. 24.2% in Turkestan) ($p<0.001$). There is a prevalence of persons under the age of 20 years compared to other age categories – 7/18 (38.9%) in Almaty region ($p>0.05$) and at the age of 41-60 years compared to other age categories - 9/22 (40.9%) in Turkestan region ($p>0.05$).

4. In the ultrasound semiotics of cystic echinococcosis of the liver, pathognomonic ultrasound signs of echinococcal cysts were revealed: in the active stage – oval/rounded shape (93.3%), uneven contours (70.6%), the presence of a capsule (59.8%); in the inactive stage – hyperechogenicity (100%), irregular shape (39.8%), uneven contours (94.9%), the presence of a capsule (86.4%) and partitions (49.4%) ($p<0.001$).

5. Echinococcal solitary cysts (CL) are characterized by uneven contours (65.1%) and heterogeneity of the internal signal (19.5%), in contrast to a simple single liver cyst, which was visualized as an anechoic formation with smooth contours (84.7%) and a homogeneous internal signal (100%). The irregularity of the contours of the parasitic cyst in CE was characterized by local irregularity (25.9%) and two-contour (70.3%) ($p<0.001$).

6. Ultrasound is a highly informative method of diagnosing cystic echinococcosis with sensitivity of 94.9%, specificity – 90.8%, accuracy – 93.0% with high rates of true–positive – 50.3% and true–negative – 42.6% of results, with low rates of false-positive - 4.3% and false-negative - 2.7% of ultrasound results.

Practical recommendations:

In the regions of the Republic of Kazakhstan with a high incidence of cystic echinococcosis, it is necessary to conduct an ultrasound examination of the abdominal organs with standardization of the conclusion of a radiologist in accordance with the WHO classification, which makes it possible to identify CE with the determination of the stages of activity, which is important in timely diagnosis and, accordingly, the choice of an adequate method of treatment by clinicians and determining the prognosis of the disease **(Guidelines)**.

Personal contribution of the PhD student: all the results presented in the dissertation work and having scientific novelty were obtained by the author. The author analyzes the retrospective data of registered cases of CE for the period 2007-2016. All ultrasound examinations of abdominal organs were carried out by the author (the PhD student completed training at the WHO Collaborating Center for Clinical Management of Cystic Echinococcosis, Pavia, Italy). A statistical analysis of the data was carried out. In the departments of radiological diagnostics of the I.S. Zhekenova City Clinical Infectious Diseases Hospital (Almaty) and the Regional Consultative and Diagnostic Center (Shymkent), the ultrasound classification of CE (WHO-IWGE) has been introduced, with the developed differentiated tactics of management and treatment depending on the ultrasound stage of CE. Methodological recommendations have been developed for the radiological diagnosis of liver cystic echinococcosis using modern ultrasound classifications to standardize the results of the study.

Approbation of the dissertation results:

The main provisions and results of the dissertation are reported in:

1. V International Congress "Central Asian Gastroenterological Week - 2017", Almaty, Kazakhstan, 2017 (oral report);
2. International Scientific and Practical Conference "Tropical infections of Central Asia: management of infectious diseases at the stage of primary health care", Astana, Kazakhstan, 2017 (oral and poster presentations);
3. Scientific and practical conference with international participation "Parasitic and infectious diseases in the regional pathology of the Central Asian region". Samarkand, Uzbekistan, 2018 (oral report and thesis);
4. International Scientific and Practical Conference "Tropical infections of the Southern regions of Kazakhstan", Shymkent, Kazakhstan, 2018 (oral report and thesis);
5. 29th European Congress of Clinical Microbiology & Infectious Diseases (ECCMID), Amsterdam, Netherlands, April 2019 (oral report and thesis);
6. 30th European Congress of Clinical Microbiology & Infectious Diseases (ECCMID), Paris, France, 2020 (online, thesis);
7. The 40th Anniversary & 51st Annual Congress of the Korean Society of Ultrasound in Medicine (KSUM 2020) November 16-17, 2020, Seoul, Korea (online, poster report);
8. IX Eurasian Radiological Forum, October 7-9, 2021, Nur-Sultan, Kazakhstan (oral report and thesis).

Publications:

The author has published a total of 15 scientific articles, 4 of them on the topic of the dissertation, 1 in the List of publications, in an international peer–reviewed scientific journal with an impact factor according to JCR data (indexed in the Web of science Core Collection database, science Citation Index Expanded, CiteScore percentile index at least 50 in the Scopus database) - 3, 8 abstracts are presented at international conferences, 3 of them in English language.

1. Mustapayeva A., Zholdybay Zh., Duisenova A. et al. Incident Rates of Surgically Managed Cystic Echinococcosis in Kazakhstan, 2007-2016. Am J Trop Med Hyg. 2020;102(1):90-95. doi:10.4269/ajtmh.19-0572 (article in the journal Web of Science, Scopus - 60th percentile, Q1).

2. Mustapayeva A. One Patient (and One Physician) at a Time. Am J Trop Med Hyg. 2020;102(6):1170-1171 (article in the journal Web of Science, Scopus - 60th percentile, Q1).

3. Mustapayeva A., Zholdybay Zh., Duisenova A. at al. Ultrasound-based evaluation of the prevalence of abdominal cystic echinococcosis in the Turkestan region of Kazakhstan. Trans R Soc Trop Med Hyg. 2022 Mar 2;116(3):222-226 (article in the journal Web of Science, Scopus - 60th percentile, Q2; 51st percentile, Q2).

4. Mustapayeva A.A., Zholdybay Zh.Zh., Duisenova A.K. Radiological diagnosis of cystic echinococcosis of the liver: WHO recommendations // Medicine (Almaty). – 2017. – No 9 (183). – P. 172-174.

5. Mustapayeva A.A., Zholdybay Zh.Zh., Duisenova A.K. Methodological recommendations on the topic "Echinococcosis of the liver: radiological diagnosis, principles of treatment". - 2020. page 29.

The dissertation work was carried out within the framework of the educational grant of the WHO Special Program in the field of research and training of specialists in tropical diseases (TDR/WHO) "Implementation of the scientific and educational program for the study of echinococcosis on the model of Kazakhstan".

The scope and structure of the dissertation work:

The dissertation work is presented on 106 pages of computer text, consists of an introduction, a literature review, a description of the material and methods of research, own research results, discussion of the results, conclusions, a list of references from 143 sources. The work is illustrated with 24 figures and 24 tables.