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The authors declare that they have no conflicts of interest

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MODERN APPROACHES IN THE DIAGNOSTICS AND TREATMENT OF CYSTIC LIVER ECHINOCOCCOSIS. LITERATURE REVIEW

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Abstract

Liver echinococcosis is a severe zoonotic disease of cosmopolitan nature caused by cestodes of the genus Echinococcus from the family Taeniidae that leads to cystic and alveolar echinococcosis that forms a significant problem in public health worldwide.

***The purpose** of this work is to analyze a literature review of modern approaches in the diagnostics and treatment of liver cystous echinococcosis*

***Material and methods.** We systematically searched the literature and selected sources from MEDLINE, PubMed, Scopus, Elsevier, E-library, Google Scholar as well as research papers and online educational publications in various languages. Forty three papers that met the inclusion criteria were included.*

***Results.** The review article presents epidemiology, methods of diagnosis and treatment of cystic liver echinococcus.*

***Conclusion.** Thus, among the modern approaches in diagnostics of cystic liver echinococcosis, ultrasound is the method of choice, also CT, MRI, ERCP are methods used for identifying complications. Morever, various surgical methods in combination with antiparasitic therapy decrease the risk and recurrence of cystic liver echinococcosis.*

Бауырдың кистозды эхинококкозын анықтау мен емдеудің қазіргі заманауи тәсілдері. Әдебиет шолуы.

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Аңдатпа

Бауыр эхинококкозы - космополитикалық сипаттағы ауыр зоонозды ауру, taeniidae тұқымдасының Echinococcus цестодтарынан туындайды, және де кистозды және альвеолярлы эхинококкозға шалдықтыратын бұл ауру бүкіл әлем бойынша денсаулық сақтауы саласындағы өзекті мәселе болып табылады.

***Жұмыстың мақсаты –** бауырдың кистозды эхинококкозын диагностикалау мен емдеудің заманауи тәсілдеріне әдеби шолу.*

***Материал және әдістер.** Біз жүйелі түрде әдебиеттерді іздедік және MEDLINE, PubMed, Scopus, Elsevier, E-library, Google Scholar дереккөздерін, сондай-ақ әртүрлі тілдердегі зерттеу жұмыстары мен онлайн білім беру басылымдарын таңдадық. Қосылу критерийлеріне сәйкес келетін қырық үш құжат енгізілді.*

***Нәтижелер.** Бұл мақалада бауыр эхинококкының эпидемиологиясы, диагностикасы және емдеу әдістері берілген.*

***Қорытынды.** Осылайша, бауырдың кистозды эхинококкозын диагностикалаудағы заманауи әдістердің ішінде УДЗ таңдау әдісі болып табылады, сонымен қатар КТ, МРТ, ERCP асқынуларды анықтау үшін қолданылатын әдістер болып табылады. Сонымен қатар, әртүрлі хирургиялық әдістер антипаразиттік терапиямен біріктірілген бауыр эхинококкозының қаупін және қайталануын азайтады.*

Мүдделер қақтығысы
Авторлар мүдделер қақтығысының жоқтығын мәлімдейді

Түйін сөздер:
эхинококкоз кистасы, бауыр гидатидозы, PAIR, Альбендазол, перицистэктомия.

Современные подходы в диагностике и лечении кистозного эхинококкоза печени. Обзор литературы

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Аннотация

Эхинококкоз печени – тяжелое зоонозное заболевание космополитической природы, вызываемое цестодами рода Echinococcus семейства Taeniidae, приводящее к кистозному и альвеолярному эхинококкозу, формирующему значительную проблему здравоохранения во всем мире.

Цель работы – *анализ литературного обзора современных подходов в диагностике и лечении кистозного эхинококкоза печени.*

Материал и методы. *Мы систематически искали литературу и выбрали источники из MEDLINE, PubMed, Scopus, Elsevier, E-library, GoogleScholar, а также исследовательские работы и образовательные онлайн-публикации на разных языках. Были включены 43 статьи, отвечающие критериям включения.*

Результаты. *В обзорной статье представлены эпидемиология, методы диагностики и лечения кистозного эхинококка печени.*

Вывод. *Таким образом, среди современных подходов в диагностике кистозного эхинококкоза печени методом выбора является УЗИ, а для выявления осложнений используются КТ, МРТ, ЭРХПГ. Кроме того, различные хирургические методы в сочетании с антипаразитарной терапией снижают риск и рецидивы кистозного эхинококкоза печени.*

Конфликт интересов
Авторы заявляют об отсутствии конфликта интересов

Ключевые слова:
эхинококковая киста, гидатидоз печени, PAIR, альбендазол, перицистэктомия

Introduction

Liver echinococcosis (LE) is a severe zoonotic disease caused by cestodes of the genus *Echinococcus* from the family *Taeniidae*, affecting both humans and animals, consisting of eight currently recognized species and one genotypic cluster - *Echinococcus canadensis*. This pathology has a cosmopolitan nature and occurs in all continents of the globe except Antarctica [1]. The most dangerous and serious problem for public health are: *Echinococcus granulosus* and *Echinococcus multilocularis*, which cause cystic and alveolar echinococcosis, respectively [2].

Alveolar echinococcosis (AE) or alveococcosis, caused by *Echinococcus multilocularis*, causes a tumor-like liver disease that is widespread throughout the northern hemisphere of the globe, in parts of Asia and in southern regions of Tibet, and is an extremely serious disease that is associated with significant loss of life mainly due to the lack of treatment options. The life cycle of this pathology is associated with wildlife, with carnivorous canids, usually foxes, as the definitive hosts and various rodent species as intermediate hosts. However, dogs and cats can also serve as competent definitive hosts [3-4].

Cystic liver echinococcosis (CE) or hydatidosis is a cosmopolitan parasitic disease of humans and animals caused by infection with *Echinococcus granulosus*, the main sources of which are canines [5]. Like other cestodes, CE has intermediate and definitive hosts. Dogs are the definitive hosts, and mammalian ruminants are intermediate carriers of this tapeworm [6].

Studies have shown that CE is a serious problem in the Mediterranean countries with high prevalence in Spain, parts of Italy, Greece and Turkey [7], as well as Central Asian countries: Kyrgyzstan, Tajikistan, Turkmenistan and Uzbekistan [8]. In Africa, there is an active transmission of *Echinococcus granulosus* between humans and animals (including wild animals) in countries: Libya, Tunisia, Algeria and Morocco [6]. In the countries of South America: in Argentina, Brazil, Chile, Peru and Uruguay, 5 thousand cases of CE are diagnosed every year [9].

Echinococcal cysts can be localized in almost any human tissue and organs, but most often affect the liver [10]. The lethal outcome from this pathology is associated with the development of many complications which accounts for 2-4% [11]. Due to the paucity of manifestations of clinical signs, CE is detected incidentally, mostly during routine check-ups [12].

Complications of CE include: allergic and anaphylactic reactions to dissemination of contents into the abdominal cavity; breakthrough into the biliary system with cholangitis and with or without obstructive jaundice; into the pleural cavity or into the lung, causing pleural echinococcosis or bronchial fistula [13].

Despite wide range of diagnostic and treatment modalities, there is yet no standardized protocol. This review aims to provide up-to-date information on the diagnosis and treatment of hepatic cystic echinococcosis in light of the available data.

Microbiology of the parasite:

Echinococcus granulosus is a small sized tape-

worm with various genotypes. Molecular biology has identified 10 genetic types within *E. granulosus* [14]. These are G1 and G2 - two lines of sheep; G3 and G4 - two lines of cattle; G4 horse line; G6 - camel line; G7 - pig line; G8 - cervid line; G9 - genotype in pigs in Poland; G10 - a line of reindeer in Eurasia. Of these, G1 is the most dangerous and endemic, most often associated with human infections [14].

There are two hosts in the life cycle of all Echinococcus species. The first is the definitive host, and the second is the "intermediate host" where the hydatid arises. The definitive hosts include cats, dogs, wolves and foxes. The adult worm is present in the intestines of the definitive hosts, causing intestinal parasitosis, the lifespan of which in the intestines of dogs is about 5 months and is excreted in the faeces [15]. Sheep and other herbivores become "intermediate hosts" when they eat grasses infested with these eggs. Humans are incidental hosts and do not play a significant role in the life cycle of Echinococcus, being an "intermediate host" for the parasite when they eat food contaminated with these eggs. The oncosphere, which comes out of the egg taken through the gastrointestinal tract, attaches to the intestinal wall with its hooks, then entering the bloodstream reaches the liver first. Thus, the most common site of injury in humans is the liver, which accounts for 50–70% of cases, followed by the lungs (20–30%), less often the spleen, kidneys, heart, bones, central nervous system, etc. organs [13-15]. The embryo loses its scolex when it enters the organ and takes the form of a cyst consisting of an exocyst and an endocyst. Inside the cyst there is a sterile transparent liquid, and outside there is fibrous capsule which is a granulomatous inflammatory reaction, that leads to the cyst being blocked by fibrous tissue [16].

Epidemiology in the world

Developed natural livestock farming, low socio-economic status, regional climate, as well as uncontrolled and unhygienic slaughter of animals increase morbidity. According to the World Health Organization (WHO), E. granulosus is endemic in South America, Eastern Europe, Russia, the Middle East and China, where the incidence rate among humans reaches 50 per 100,000 population [10, 13]. CE is also endemic in the Mediterranean countries with a high prevalence in Spain, Italy, Greece and Turkey, and in Central Asia: Kyrgyzstan, Tajikistan, Turkmenistan and Uzbekistan. In Africa, there is an active transmission of *Echinococcus granulosus* between humans and animals (including wild animals) in the countries: Libya, Tunisia, Algeria and Morocco. In South American countries: in Argentina, Brazil, Chile, Peru and Uruguay, 5,000 cases of CE are diagnosed annually [17].

Epidemiology in Kazakhstan

The Republic of Kazakhstan is an endemic region for echinococcosis with high incidence rates. It is estimated that in Kazakhstan, the prevalence of infection among sheep ranges from 20% to 25% among sheep aged 1 year and 74%-80% among sheep aged 6 years and older. Among wild and rural dogs, the prevalence of infection is 23% and 6%, respectively. Human infection has increased since the mid-1990s [17, 18]. The average yearly incidence in the country from 1974 to 1994 went up from 0.9 to 1.4 per 100,000 population. From 1995 to 2000, it increased from 1.4 to 5.9 cases.According to the results of research for the period from 2007 to 2016, in most regions of Kazakhstan, the incidence of CE dropped from 5.6 to 4.7 per 100 thousand population, respectively. A higher incidence was noted in the south of Kazakhstan, with the incidence rate from 7.0 to 10.5 cases per 100,000 population. We analyzed the primary incidence of liver echinococcosis in the Republic of Kazakhstan for 2018 – 2020. During the study period, 2,248 patients with LE aged 15 to 70 years were registered. The analysis revealed a decrease in morbidity over 3 years by 2.03 = from 5.77 to 3.74, however in the south of the country, morbidity rates remain at a high level [19].

Ultrasound in diagnostics

Liver CE is mainly diagnosed by ultrasound examination (ultrasound). It is the simplest method due to its accessibility and the safest due to its noninvasiveness and lack of radiation, and is also preferred for determining the stage, differential diagnosis and follow-up of most cystic lesions of the abdominal cavity [20-22]. Ultrasound is also an imaging tool for minimally invasive percutaneous interventions in interventional treatment of CE [23].

The particular significance of ultrasound is that portable ultrasound is important as a screening tool [24].

For questionable cysts, serology may be useful for differentiation. Although ultrasound is the method of choice for determining the stage and number of cysts, as well as the degree of the disease, computed tomography (CT) and magnetic resonance imaging (MRI) are useful under certain circumstances [25].

Computed tomography (CT)

CT is indicated in cases where there are difficulties in diagnosis by ultrasound in patients with excessive subcutaneous fat, and is also effective for assessing postoperative changes - calcification of cysts [25]. Calcification of the cyst occurs not only in inactive cysts in the late stage, but can develop in all stages.

CT with contrast is crucial in the differential diagnosis of focal liver lesions [26]. CT is often used to monitor the effectiveness of PAIR (Puncture, Aspiration, Injection of protoscolicidal agent and Reaspiration) in remote periods [19, 25].

Magnetic resonance imaging (MRI)

In complications associated with the breakthrough of echinococcal cysts into the bile ducts, MR cholangiography is the most preferable, moreover MRI can be used when ultrasound is not informative enough, and CT is contraindicated [19. 25]. MRI has a high sensitivity for detecting CE, especially for identifying the number of cysts, their size, location and relationship with neighboring structures. MR cholangiography is comparable to endoscopic retrograde cholangiography, for the assessment of cystobiliary fistulas [27].

Drug therapy

Antiparasitic therapy and CE surgical treatment complement each other and require an individual approach. Drug therapy is required for all patients after surgical treatment to prevent relapses.

Nowadays, albendazole (ABZ) is used in clinical

practice as the main drug for drug therapy of echinococcosis [28]. The daily dose ranges from 10 to 20 mg / kg. The duration of one continuous treatment cycle is from 21-60 days to several years, the number of cycles is 1-20 or more, the intervals between cycles are from 21 to 30 days. Also, this drug is used to reduce the risk of dissemination in PAIR and prevent relapse [19].

Operative method of treatment

In the modern world, minimally invasive interventions are becoming increasingly used in clinical practice: laparoscopic pericystectomies, percutaneous with ultrasound navigation and mini-access operations [19].

PAIR (punction, aspiration, injection, reaspiration).

Percutaneous puncture method of CE treatment under ultrasound guidance is designated by the abbreviation PAIR. This method is performed under endotracheal anesthesia due to the potentially high risk of anaphylactic reaction [28]. The advantages of PAIR are low traumatism, the possibility of numerous repetition of the procedure, the possibility of performing the procedure under local anesthesia in certain cases, and a shorter stay of patients in the postoperative period [19, 28].

The disadvantages of the percutaneous PAIR method are: the difficulty of evacuating the dense contents of the cyst in the presence of daughter cysts; the difficulties of complete fragmentation and removal of the chitinous membrane, the inability to remove the fibrous membrane, the danger of hemorrhagic complications during puncture [29].

Contraindications to PAIR:

• cyst infection;

• superficially located cysts,

• biliary fistulas;

• cysts localized in dangerous or hard-to-reach areas of the liver.

Injection of antiparasitic agents with PAIR includes the following solutions: 30% NaCl solution and 95% ethyl alcohol. Prevention with albendazole before and after PAIR is mandatory [19, 30].

According to Smego et al [31], 769 patients treated with ABZ + PAIR were compared with 952 patients treated surgically only. The conclusion from this study is that PAIR + ABZ is more effective than surgery and is associated with lower morbidity and mortality rates, reduced risk of relapse and shorter hospital stay.

Laparoscopic cholecystectomy

Laparoscopic surgery with CE is a technically complex surgical procedure. These surgical interventions are carried out only in specialized hepatopancreatobiliary centers with properly adapted equipment for this. For the first time, a laparoscopic approach for liver CE was applied in 1992 [32].

Advantages of laparoscopic access:

• shorter stay in the postoperative period;

• low risk of wound infections;

• less need for analgesics in the postoperative period [6].

Disadvantages:

• difficulties with access to cysts localized in the posterior sector;

• increased risk of contamination leakage [33]. Systemic allergic and anaphylactic reactions, sometimes up to coma, are not uncommon in the case of hydatid fluid on the peritoneum [34].

Open echinococcotomy (endocystectomy)

Radical operations aimed at liver CE repair include pericystectomy and liver resection, whereas endocystectomy is the removal of cyst contents and sterilization of the residual cavity with scolexide solutions in combination with partial cystectomy [19].

Endocystectomy is performed mainly with large cysts adjacent to large tubular structures, when it is impossible to perform pericystectomy, as well as in cases where there is suppuration of the cyst with abscessing [34]. Leaving a fibrous capsule increases the risk of postoperative complications and the risk of relapse of the disease [19, 34].

Many methods of treatment of the residual cavity are described: omentoplasty, capitation and external drainage, or synthetic fibrin. In a retrospective study of Baliket al with 304 patients [35], it was shown that external drainage has a significantly higher level of complications, such as infection of the residual cavity and the formation of bile fistulas.

We found only one randomized trial that compared radical surgery with conservative surgery. The conclusion was that conservative surgery leads to a significantly higher frequency of early relapses compared to radical surgery [36].

Pericystectomy

Pericystectomy is the total removal of an echinococcal cyst with a fibrous capsule [19, 36-37]. When the echinococcal cyst is mobilized and the fibrous capsule is isolated from the liver parenchyma in order to prevent complications, all tubular structures are carefully ligated and clipped. Excision of a parasitic cyst with a fibrous capsule (pericystectomy) is indicated for complicated forms of echinococcosis, especially with significant calcification of the fibrous capsule of the parasite. Complete removal of a cyst with a fibrous capsule is a more radical intervention, for it more reliably prevents relapses of the disease, and modern methods of hemostasis during surgery allow for intervention with minimal blood loss [37].

Total pericystectomy has long been considered the “gold standard” of CE treatment [38]. Radical resection of the liver for CE in comparison with partial cystectomy is safer in terms of complications and relapses [39].

Liver resection

Liver resection in echinococcosis is the most radical operation that provides the best guarantee against the occurrence of relapses of the disease [34]. Resection interventions have their advantages and disadvantages, the choice of technique is made by a specialist. In atypical operations, when only the affected area is excised and most of the liver is preserved, there is still a risk of bleeding.

Complications

Intraperitoneal rupture and breakthrough is the most common complication of CE and occurs in 3-17% of cases [40], as well as a breakthrough into the bile ducts [41]. Endoscopic retrograde cholangiopancreatography (ERCP) determines the presence of a cystobiliary fistula for choosing the treatment in the

pre- and postoperative periods. Endoscopic sphincterotomy for surgical treatment of large-diameter cysts can lower the frequency of postoperative biliary fistulas from 11.1% to 7.6% [41], and in the postoperative period it can also provide possibility to treat postoperative biliary fistulas [42].

Postoperative period

Follow-up in the early and late postoperative period is recommended for the first month, third month, sixth month and twelfth month in the first year, and then every six months for the following two years, and then once a year, depending on the relevant clinical conditions. With CE, it is challenging to estimate the frequency of relapses. Therefore, ultrasound monitoring is sometimes carried out for up to ten years, during which relapses have been reported, despite the treatment [23].

Conclusion

Antiparasitic therapy surpasses the placebo effect, but monotherapy is not effective with a separate application for each. Uncomplicated active cysts in stages C1 and C E3 a can be treated with PAIR + ABZ before and after surgery. Uncomplicated, inactive cysts (deceased echinococcosis) can be treated with a “watch and wait” strategy. Surgery is the primary choice in multivesicular cysts, as well as in the presence of cystobiliary fistulas. The combination of ABZ + surgical treatment is more advantageous in terms of relapse and complications [42].

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