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Hydatid cyst and treatment

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ABSTRACT

Echinococcosis also known as hydatid cyst disease (HD) is caused by the transmission of *Echinococcus granulosus (E. granulosus)* from animals to humans. Transmission is by fecal-oral contact, usually from infected domestic dogs or their stools containing eggs. *E. granulosus* forms unilocular cysts, particularly in liver and lungs in humans following infection. Although the most common location is the liver, hydatid cyst formation can be seen almost everywhere in the body. In patients with liver cysts, abdominal pain and anorexia are the most common manifestations. It can compress the bile ducts, leading to jaundice. Cysts in the lungs present with symptoms as chronic cough, dyspnea, pleuritic chest, pain and hemoptysis. Ultrasound is a rapid and accurate method to detect liver lesions with a precision up to 90 to 95%. Hydatid cyst usually has the appearance of a simple fluid-filled cyst on ultrasound; however, the appearance and characteristics may change depending on the development stage of the disease. Computed tomography (CT) scan and magnetic resonance imaging (MRI) are more sensitive and specific in the detection and characterization of HD. Surgical treatment has long been accepted as the definitive treatment method for hydatid cyst. It can be performed in about 90% of patients, if the disease has not progressed excessively. In addition, the puncture, aspiration, injection, and re-aspiration (PAIR) technique, which is a less invasive approach, is an alternative treatment performed by aspirating the cystic fluid with ultrasound or CT. In addition, two medications as mebendazole and albendazole, are used for the treatment of hydatid cyst in patients, if necessary. The management and treatment approach of hydatid cyst depends on the affected organ, the number of cysts, the presence of cystic-biliary communication, secondary bacterial infection, and hemorrhage. Therefore, it is of utmost importance to evaluate each case thoroughly and carefully to achieve the best possible outcome.

Keywords: Daughter vesicles, echinococcosis, *E. granulosus*, hydatid cyst, treatment.

HYDATIC CYST *(ECHINOCOCCOSIS)*

Echinococcosis or hydatid cyst disease (HD) is a disease transmitted from animals to humans caused by the larval stages of taeniidcestodes belonging to the genus *Echinococcus*. Six species of *Echinococcus* are known; however, four of them are responsible for human diseases: *Echinococcus granulosus (E. granulosus), Echinococcus multilocularis (E. multilocularis), Echinococcus Oligarthrus (E. oligarthrus), Echinococcus vogeli (E. vogeli).* Additional two new non-pathogenic species for humans have been described in recent studies as, *Echinococcus felidis (E. felidis)* and *Echinococcus shiquicus (E. shiquicus)*.[1] Among these four pathogenic species, *E. granulosus* causes the vast majority of cases in humans. *E. granulosus* causes hydatid cyst (cystic echinococcosis), the pastoral form that is widely distributed worldwide and concentrated in sheep breeding areas. Humans are less frequently infected by *E. multilocularis*, resulting in alveolar echinococcosis. In general, *E. multilocularis* infestation occurs in colder regions and is associated with wild ecosystems, particularly animals such as foxes. *E. vogeli* and *E. oligarthrus* are rare species and cause polycystic echinococcosis.[2] The control of the hydatid cyst caused by *E. granulosus* is largely based on expert opinion. The complexity of the disease particularly in advanced stages, requires interdisciplinary management.[3]

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ECHINOCOCCUS GRANULOSUS

Life cycle

The hydatid cyst formed by *E. granulosus* develops as a unilocular cyst in the internal organs of humans and other intermediate hosts, particularly in the liver and lungs.[4] Although the most common location is the liver, there are cases of hydatid cysts developing almost all over the body in the literature. The life cycle of *E. granulosus* in animals and humans is quite complex (Figure 1).[5]

Adult *E. granulosus* are 3 to 6-mm long and are found in the small intestine of dogs or wild canids; however, they do not harm the dog. The definitive host in the cycle is the dog.[1] *E. granulosus* eggs in the dog's feces are released and these eggs are transmitted to a suitable intermediate host. The intermediate hosts are sheep, goat, pig, cattle, horse or camel under natural conditions. In the small intestine of the intermediate host, the egg hatches and an oncospheres emerge, which penetrates the intestinal wall and passes through the circulatory system to various organs, particularly the liver and lungs.[2,3]

The oncosphere transforms into a cyst that gradually expands, proctoscopically, and produces daughter vesicles, particularly in the lung and liver.[4] Human as an aberrant intermediate host, becomes infected when consumes the cyst-containing organs from the infected intermediate host. After release from the sheath, proctoscopics proliferate within 32 to 80 days, attach to the human intestinal mucosa and continue to develop.[4-6]

Epidemiology

The *E. granulosus* has a worldwide distribution and the highest prevalence is seen in Mediterranean countries, Russia and China.[6] Other hyperendemic regions are North and East Africa with a prevalence of >3%, South America and Australia.[7] It is transmitted to humans by fecal-oral contact, usually from infected domestic dogs or their feces containing eggs. *Echinococcus* eggs attach to animals' flesh, mouth, paws, and particularly the hair around the anus.[8] It is possible for *Echinococcus* eggs to contaminate water, vegetables and other nutrition through wind, flies, birds or insects. This spreading would result in greater contamination.[1]

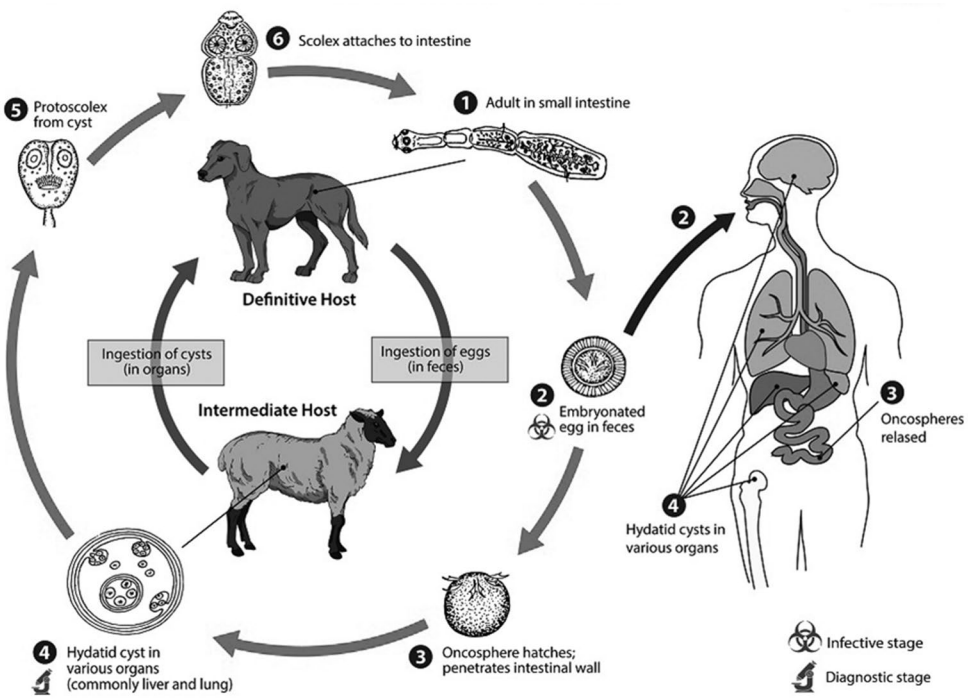

Figure 1. Life cycle of *Echinococcus granulosus*.

The global distribution of the disease varies depending on factors such as contact with the dog, geographical climate, frequency of dogs, nourishment behavior (water consumption, food and raw vegetables contaminated with parasite eggs), residence (urban, rural or nomadic), education level, occupation, etc.[9-16] According to the World Health Organization (WHO), *E. granulosus* is endemic in regions such as South America, Eastern Europe, Russia, the Middle East, and China, where incidence rates reach up to 50/100,000 individuals per year. In some areas, such as slaughterhouses in South America, the prevalence ranges from 20 to 95%.[9] The most common intermediate hosts are livestock such as sheep, goats, pigs, camels, horses and cattle. Small ruminants such as sheep and goats are the most affected. Sheep are most commonly associated with human hydatid cysts.[10,11] Factors such as agricultural livelihood, low socio-economic situation, regional climate and uncontrolled and unhygienic slaughter increase the incidence.[12]

Hydatid cyst is a neglected disease and causes economic resource loss, which is one of the important public problems in the Middle East.[13,14] The result of a study showed that the seroprevalence of hydatid cysts in the Middle East was 7.4% (95% CI: 4.8-10.6) and 10.7% (95% CI: 7.6-14.3) in the population with suspected hydatid cysts and those at risk, respectively. Enzyme-linked immunosorbent assay (ELISA), a method that determines the antigen-antibody relationship while investigating hydatid cysts, has been used in most of the studies since this method is easy, efficient and has high-sensitivity.[15-19]

Studies have revealed that the seroprevalence of the infection is similar in both sex and there is no statistically significant difference between the sex according to the results of the Iranian authors.[20] Regarding residence, a significant difference was observed among the urban, rural and nomadic populations, with seroprevalence rates of 4.3%, 6.5% and 13.8%, respectively. This research reveals that nomadic individuals are more likely to get hydatid cyst infection than urban and rural populations. This higher rate of seroprevalence may be related to the lifestyle and cultural characteristics of nomads who lived in close contact with their dogs as well as the wandering dogs among nomadic communities.[21]

Studies have shown that there is no significant relationship between hydatid cyst seropositivity and the age group. Hydatid cyst is a chronic disease and develops very slowly in humans. It takes years for individuals to develop clinical disease. Therefore, hydatid cyst infection is detected at further ages. However, this is not related to the age group; it is a chronic and slowly progressing disease.[22]

Etiology and pathogenesis

Humans can become infected as a result of consumption of infected sheep meat or internal organs. However, they are mainly infected either through direct contact with a dog contaminated with egg-bearing feces, or through direct contact with a dog contaminated with water, food, or the like. Oncospheres emerge from the eggs and penetrate the human intestinal wall. These oncospheres enter the portal venous system, which provides access to the liver, lungs, and various other organs.[11,23-25]

Later on, the oncospheres begin to cyst development. Cysts are usually unilocular and can range from 1 cm to 15 cm in diameter. They also tend to affect the right lobe more often than the left lobe, due to the nature of the portal blood flow. Cysts consist of two membrane layers: an inner, nucleated, germinal membrane and an outer, acellular, laminated layer. The immune system responds to cysts by forming a calcified fibrous capsule. This capsule is the most common visualizing layer in imaging studies. The cyst expands to form a combination of proctoscopic and additional cysts. *E. granulosus* infections are usually seen as solitary cysts and have single organ involvement. Depending on the specific geographic region and parasite strain, two organ involvement may occur in 10 to 15% of patients.[11,25,26]

CHARACTERISTICS OF HYDATIC CYST AND LOCALIZATION IN HUMAN ORGANS

In the human host, hydatic cysts may localize in many anatomic sites following oral ingestion of *E. granulosus* (primary echinococcosis) eggs. Secondary echinococcosis occurs as a result of the spread of *E. granulosus* metacestodes from primary sites to distant organs through blood

vessels or the rupture of cysts into the peritoneum, pleura, bronchial tree or bile ducts. Secondary echinococcosis can manifest as a result of invasive effects. Unlike *E. multiloculuris* infection, larval development invading adjacent structures such as the diaphragm or retroperitoneum is rare in *E. granulosus* infection.[27]

Most patients with *E. granulosus* infection have single organ involvement and contain a solitary cyst. According to Australian Hydatid Registry, locations of 1802 cysts recorded as; 63% liver, 25% lungs, 5% muscles, 3% bones, 2% kidneys, 1% brain, 1% spleen, less than 1% heart, breast, prostate, parotid gland and pancreas.[28]

Similar numbers were reported in a study conducted with 459 patients in Switzerland.[29,30] In this study, 13% of the patients had simultaneous multiple-organ involvement. Most patients have a solitary cyst. Cysts vary in size; however, they are usually between 1 and 15 cm. Also, much larger cysts larger than 16 cm in diameter and giant cysts containing 48 Liter of hydatid fluid were recorded.[31]

In the WHO classification published in 2001, hepatic hydatid cysts observed on ultrasound consist of several layers.[32] In the active stages of the infection, these cysts consist of three layers. The outer pericist is formed by a reaction of compressed host tissue and a fibrous tissue, the middle layer consists of acellular ectocysts, and the innermost endocyst is where the larval *Echinococcus* is produced.[33]

CLINICAL DIAGNOSIS

Studies have shown that liver hydatid cysts in humans grow very slowly, with more than half of the cysts differ in size within 10 years, and one-third are growing less than 3 cm. The average cyst growth in patients with long-term follow-up is 0.7 cm.[34] Various clinical findings such as cholangitis with bile rupture, portal hypertension, bile obstruction, fistula and abscess formation are observed depending on the cyst localized organ and the environment it affects.[1]

Symptomatic patients with liver cysts most often present with abdominal pain and anorexia. Compression of the bile ducts can result in jaundice. During the palpation phase of the physical examination, a tumor-like mass, hepatomegaly or abdominal distension may be found.[35] Cysts in the lungs present with chronic cough, dyspnea, pleuritic chest pain and hemoptysis.[11,36]

The majority of cases are incidentally diagnosed by imaging studies. In the clinic, histories as contact with wildlife, vegetables not properly washed, travel to endemic areas, etc. suggest HD. Abdominal ultrasound examination is requested in high-risk patients. If the history and radiological findings are significant, most physicians start treatment without further investigations.[37]

However, additional special tests are available when diagnosis is unclear. Detection of *E. granulosus*-specific antigen and immune complexes by ELISA confirms the diagnosis with a sensitivity of 93.5% and a specificity of 89.7%. However, the risk of secondary hydatid cyst formation due to the procedure is high, and therefore, oral albendazole should be administered four days before the procedure and should continue for one month following the intervention, which aims to reduce the risk of anaphylactic shock during the aspiration procedure.[38]

Ultrasonography is a fast and accurate method to detect liver lesions with a sensitivity up to 90 to 95%.[39] Hydatid cyst usually has the appearance of a simple cyst filled with fluid on ultrasound; however, its appearance and characteristics may change depending on the developmental stage of the disease. Computed tomography (CT) scan and magnetic resonance imaging (MRI) are more sensitive and specific in the detection and characterization of HD.[37] The CT scanning is used in the rapid detection of cyst rupture, precise definition of the location and type of rupture, and in emergency situations.[40] Typical morphological features of *E. granulosus* cysts in the lungs or liver are different.[40]

Lung cysts

The non-ruptured cysts are well-defined in chest X-ray. They are homogeneous round structures with a diameter of 1 to 20 cm. They can also be seen as thin-walled empty cysts.[41] On the other hand, cysts can be seen as single or multiple cysts anywhere in the lungs. Simultaneously, liver cysts are quite common as in 38% of 37 cases in Switzerland cases.[30] Lung cysts are usually non-calcified, and the formation of the daughter vesicles is rare.[41]

Cysts in the lung may rupture before diagnosis. Air entering the space between the pericyst and endocyst is a sign of cyst rupture. When larger uninterrupted cysts rupture, localized compression atelectasis and reactive changes may occur around the rupture. Cyst rupture may be associated with transient eosinophilic pulmonary infiltration, abscess formation, or pneumothorax with or without pleural effusion.[27]

Hepatic cysts

The liver is the most frequently involved organ in hydatid cysts, and 60 to 85% of cysts are located in the right lobe. Ultrasonography and CT are the standard methods for the diagnosis of hepatic and other abdominal cysts located in the kidney, urogenital system, spleen or peritoneal cavity (Figure 2).[27,42]

HYDATIC CYST AND TREATMENT

Surgical approach

Surgical treatment of echinococcal cysts with partial and total cystectomy has long been accepted as the definitive and the most common treatment for hydatid cysts.[43,44] If the disease has not excessively progressed, it can be performed in approximately 90% of patients.[45] According to the WHO guidelines, treatment with albendazole or mebendazole should be started four days before surgery and continued with albendazole at least one month and mebendazole for three months.[9] There are many approaches to surgical removal; however, all must achieve two objectives: resection of the cyst and obliteration of the cavity. This can be achieved with the help of intraoperative fluorescent dyes and careful disconnection of present cyst-biliary communication.[46]

Other approaches range from a radical approach, such as incision of cystic fluid, drainage, injection of the scoliocidal agent, and aspiration of the cyst contents, to a conservative approach, such as resection of pericystic tissue. Open pericystectomy is performed by resecting pericystic tissue and contents after using protoscolicidal agents to sterilize the cyst. In contrast, a laparoscopic, total pericystectomy involves resection of the cyst without rupturing it.[46]

A recent surgical approach called subadventitial cystectomy has been developed for liver HD.[47,48] In a study by Chen et al.,[49] subadventitial cystectomy resulted in fewer complications than perisectomy (partial/complete) and hepatic resection, shorter hospitalization period, and parasite burden in serum immunoglobulin levels decreased when followed for one year after surgery. Intraoperative mortality was 2% or less.[45] However, when a redo and further operation is required, the mortality rate increases significantly.[27]

In conclusion, in terms of surgical treatment, the main options available for liver hydatid

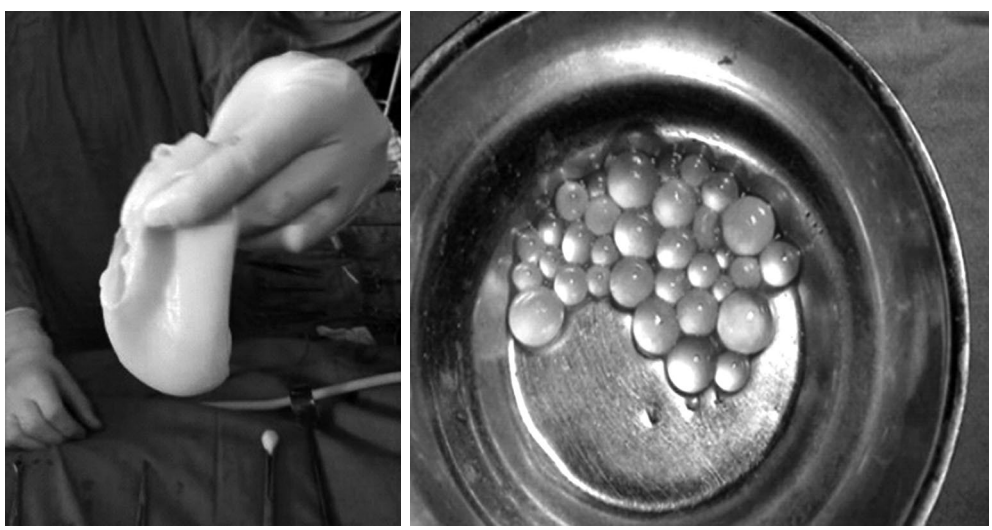

Figure 2. Liver cysts.[12,44]

cyst are partial liver resection, pericystectomy, and cystectomy. For pulmonary hydatid cyst, it is extrusion of cysts (Barrett's technique), pericystectomy and lobectomy.[27]

Puncture-aspiration-injection-reaspiration (PAIR) Method

The PAIR method has been defined as an alternative treatment. This is a less invasive approach and is the aspirating of cystic fluid with ultrasound or CT guidance. It plays an important role both in confirming the diagnosis and for therapeutic intervention. However, PAIR is not suitable for all cyst types. With this strategy, it is very important to determine the number of compartments and the presence of daughter cysts in advance for a successful treatment.[50]

Khuroo et al.,[51] PAIR treatment was supported by albendazole treatment programs in the treatment of 33 hepatic cysts. The combination of PAIR with albendazole is effective in the treatment of hepatic cysts.[51,52] Today, the efficacy and safety of PAIR has not been sufficiently proven. Therefore, this technique needs further evaluation in properly controlled trials. PAIR cannot be considered as an established alternative to surgery before more data are available. However, it appears to be a promising alternative method.[27]

Percutaneous treatment can be used in single compartment cysts smaller than 5 cm without complications.[18] Divided complex cysts, cysts communicating with the biliary system, and inaccessible cysts are contraindicated in this procedure. In this method, aspiration of cystic fluid is performed using an ultrasound or CT-guided multi-purpose drainage catheter. A protoscolicidal agent is then injected into the cavity through the catheter. The contents are aspirated over after about 15 minutes.[9]

Chemotherapy

For the treatment of human hydatid cyst, two mainly benzimidazole compounds are used: mebendazole and albendazole. The main difference between the two is that the degradation metabolites are different. Albendazole metabolite is a potent prodrug with excellent anthelmintic properties, while mebendazole is broken down into metabolites with very poor activity.[53] The primary mechanism of action is to deplete the glycogen in *E. granulosus*' intracellular organelles, leading to be glucose free. Studies have revealed that the effects of albendazole are superior to mebendazole.[54,55]

If the primary lung and liver cyst is multiple cysts and peritoneal involvement inoperable, drug therapy should be applied. In addition, drug therapy is required to reduce cyst pressure and the risk of recurrence in preoperative and pre-ruptured cases.[46]

Drug treatment is contraindicated in large cysts with the possibility of rupture, inactive or excessively calcified cysts, early pregnancy, chronic liver diseases with treatment adverse effects and bone marrow suppressive disorders. For a typical 70-kg individual, the treatment dose is 400 mg BID for 28 days.[9] The most common toxic effect is elevation of liver enzymes during long-term treatment.[54,55]

In recent studies, another broad-spectrum anthelmintic agent, praziquantel, has been found. However, this drug alone is not sufficient for hydatid cyst treatment. It is recommended in combination with albendazole, particularly in the preoperative period.[56]

Mebendazole

Mebendazole is weakly absorbed (<10%) after oral administration. The rate of absorption is significantly increased when the drug is administered during a fat-rich meal compared to administering the drug on an empty stomach. Serum levels are highly variable between individuals and this variability is not related to the oral dose.[57,58] In patients with normal liver function, mebendazole is rapidly metabolized in the liver and excreted via urine and bile. The elimination half-life is short, between 1.5 and 9 hours.[58] WHO recommends monitoring serum drug levels following one month of chemotherapy, followed by three-month intervals to adjust drug dosage, control patient compliance, and avoid toxic side effects.[61]

Albendazole

Albendazole is rapidly metabolized in the liver after absorption from the intestine.[59,60] The intestinal absorption rate is low, like mebendazole. For safety reasons, a therapy regimen of four

weeks of therapy duration and two weeks of drug-free was recommended.[27]

According to WHO records, chemotherapy of a hydatid cyst should be administered for patients who are inoperable or after an incomplete surgery. It prevents the formation of secondary echinococcosis after spontaneous or traumatic (perioperative) cyst rupture.[61,62] Benzimidazoles should not be given to pregnant individuals due to the potential risk of embryotoxicity and teratogenicity that observed in early pregnancy in some laboratory animals. Adverse reactions to medications are usually mild and temporary. Increased serum transaminases and gastrointestinal disturbances are most common, while hair loss, insomnia and leukopenia are less common. Discontinuation of treatment due to adverse reactions was required in only 2.6% of cases.[62]

Watch-and-wait approach

Additional treatment method is the watch-and-wait method. In this approach, the patient should not be treated; however, he/she should be follow-up closely. This treatment is sometimes beneficial as some cysts are excessively calcified and transform into quite non-pathological structures.[63]

Follow-up

It is recommended that patients be followed up every six months for the first two years and, then, once a year.[64] It is difficult to evaluate the frequency of recurrence in hydatid cyst.[46] Therefore, regular ultrasound monitoring should be performed up to 10 years, when relapses are reported.[38,64]

In conclusion, the management and treatment approach of hydatid cyst depends on the involved organ, the number of cysts, the presence of cystic-biliary communication, secondary bacterial infection and hemorrhage. Thus, it is very important to evaluate each case thoroughly and carefully to achieve the best possible outcome. Surgical treatment has long been considered the definitive treatment for hydatid cyst. If the disease has not progressed too far, it can be performed in about 90% of patients. In addition, it is a less invasive approach and the PAIR method, which is performed by aspirating the cystic fluid with ultrasound or CT, is an alternative treatment and two main drugs, mebendazole and albendazole, are used for the treatment of hydatid cysts in patients, if necessary.

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