REVIEW / DERLEME

DOI: 10.4274/mjima.galenos.2021.2021.47
Mediterr J Infect Microb Antimicrob 2021;10:47
Erişim: http://dx.doi.org/10.4274/mjima.galenos.2021.2021.47

Echinococcosis

Ekinokokkozis

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Abstract

Echinococcosis is a zoonotic disease caused by Echinococcus species. The life cycle involves a definitive host (dogs, wolves, jackals, and foxes) and an intermediate host. It is not transmitted from human to human. The most frequent agents are *Echinococcus granulosus (E. granulosus)* and *Echinococcus multiloculoris (E. multiloculoris). Echinococcus vogeli (E. vogeli)*, and *Echinococcus oligarthus (E. oligarthus)* are more rarely seen. The disease is more widespread in rural areas in which animal husbandry and uncontrolled slaughter are common. The infection can remain asymptomatic for extended periods. *E. multiloculoris* infection has a greater probability of being symptomatic, and of mortality. It most frequently settles in the liver and lungs. Single organ involvement and cyst are detected in the majority of patients. Diagnosis is based on clinical, serological, imaging, and pathological findings. It is a preventable and treatable public health problem. Education and animal control are very important.
Keywords: Albendazole, echinococcosis, hydatid cyst, serology, treatment

Öz

Ekinokokkozis, ekinokok türlerinin etken olduğu zoonotik bir hastalıktır. Yaşam döngüsünde kesin konağı (köpek, kurt, çakal ve tilki) ve ara konağı (koyun, keçi, domuz) vardır. İnsandan insana bulaş olmaz. En sık *Echinococcus granulosus (E. granulosus)* ve *Echinococcus multiloculoris (E. multiloculoris)* etkendir. *Echinococcus vogeli (E. vogeli)*, *Echinococcus oligarthus (E. oligarthus)* daha nadir görülür. Hayvancılığın ve kontrolsüz kesimin yaygın olduğu kırsal kesimde hastalık yaygındır. Enfeksiyon uzun süre asemptomatik kalabilmektedir. *E. multiloculoris* enfeksiyonunun semptomatik olma ihtimali ve mortalitesi daha fazladır. En sık karaciğer ve akciğere yerleşmektedir. Hastaların çoğunluğunda tek organ ve bir kist tespit edilir. Tanı klinik, seroloji, görüntüleme ve patoloji ile konulur. Önlenebilir ve tedavi edilebilir bir halk sağlığı sorunudur. Eğitim ve hayvan kontrolü çok önemlidir.
Anahtar kelimeler: Albendazol, ekinokokkozis, kist hidatik, seroloji, tedavi

Introduction

Echinococcosis is a zoonosis caused by echinococcus species. It can cause disease in humans and animals. Four types cause infection in humans. These are *E. granulosus, E. multiloculoris, E. vogeli,* and *E. oligarthus*[1]. *E. granulosus* causes unilocular type, *E. multiloculoris* alveolar type disease[2]. The disease is common in rural areas where there is no sanitation, where people, cattle and dogs live close and conditions are bad[3].

Dog, jackal, wolf, fox are definite hosts; cattle, camels, sheep, goats, horses and pigs are intermediate hosts. The life cycle passes between the main host and the intermediate host. People are not part of the cycle. They randomly pick up the parasite. The adult parasite lives in the small intestine of the definitive

Cite this article as: Parlak E. Echinococcosis. Mediterr J Infect Microb Antimicrob. 2021;10:47.

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Received/Geliş Tarihi: 24.03.2021 **Accepted/Kabul Tarihi:** 13.08.2021 **ORCID ID:** orcid.org/0000-0001-8912-6360

Published: 17 August 2021

host (usually a dog, etc.). Thousands of eggs are thrown into the external environment with feces[4]. Eggs are very hardy and can remain infective for one year in a low temperature and humid environment. Eggs are sensitive to dryness. Oncospheres emerge when the egg is taken by the intermediate host or human. It enters the intestinal mucosa, blood and/or lymphatic system. It passes to the liver and other organs. A fluid-filled hydatid cyst occurs[5]. The aim of this review is to discuss the epidemiology, pathogenesis, clinical features, diagnosis, treatment, prevention and control of echinococcosis.

Epidemiology

Echinococcosis is an important public health problem in South America, the Middle East, the eastern Mediterranean, sub-Saharan African countries, western China, and the former Soviet Union[6]. It can often cause the disease in Mediterranean countries such as Turkey, France and Tunisia[7]. It is endemic in our country. It is reported more frequently in Southeastern Anatolia, Eastern Anatolia and Central Anatolia regions where animal husbandry is intense[8].

Echinococcosis is mostly seen in people dealing with animal husbandry. Hunters, farmers, shepherds, veterinarians, slaughterhouse workers and dog owners are risk groups. It is especially seen in areas where sheep are grown intensively. Dogs get cysts by eating the internal organs of slaughtered animals. The agent is transmitted to other animals with the eggs excreted in the feces of dogs. Contamination of water and vegetables by eggs is important in transmission. Transmission can also occur by contact between infected dogs and humans. Since different animal species are needed to complete the life cycle, human-to-human transmission of echinococcosis does not occur[4,5].

Pet dogs or cats can become infected when they eat wild rodents that are sick. People who ingest eggs laid from main hosts, such as foxes and coyotes, can also become infected. Humans are intermediate hosts. Rodents serve as intermediate hosts for *E. multilocularis*[9].

Its prevalence varies according to the density of animals (sheep, goats) raised by the countries. The disease is common in rural areas where animal husbandry and uncontrolled slaughter are carried out. Its epidemiology is influenced by socioeconomic status, climate, nutritional conditions and animal husbandry. In this high prevalence, the bond between human and dog is also very important[10].

The prevalence of hydatid cysts of the liver and the lung increases with age. It can occur at any age, in both genders. In a seroprevalence study conducted in our region, it was determined that it was more common in women (58.6%) and in the 31-45 age group[11]. The reason why it is seen more in women in the literature is attributed to the fact that they deal more with agriculture, animal husbandry and food preparation[4,12].

According to the data of the Ministry of Health, the number of patients who had echinoccosis and mortality rates for the years 2010-2019 are given in Table 1[4]. The increase in the number of patients is thought to be related to the increase in the number of notifications, not the actual increase[4].

Pathogenesis

Echinococcal eggs taken orally, pass the stomach and hatch in the duodenum. The released oncosphere form adheres to the small intestinal mucosa. It reaches the liver via the portal vein. It settles here and forms hydatid disease. Sometimes, it goes to the lungs, heart and other organs and causes disease[4,5,9].

Clinical Features

Primary infections are initially asymptomatic. It is usually acquired in childhood and causes symptoms in adulthood[11]. Cysts can be found in any part of the body. Clinical findings are seen according to the location and size in different organ involvements. The liver is involved in two-thirds of the patients,

Table 1. Distribution of the number of patients who had echinoccosis and morbidity/mortality rates between 2010-2019 by the Ministry of Health[4]

Years	Population	Number of patients	Morbidity rate	Number of deaths	Mortalite rate
2010	73.722.988	381	0.52	0	0.00
2011	74.724.269	579	0.77	0	0.00
2012	75.627.384	572	0.76	0	0.00
2013	76.667.864	616	0.80	0	0.00
2014	77.695.904	449	0.58	0	0.00
2015	78.741.053	544	0.69	0	0.00
2016	79.814.871	787	0.99	0	0.00
2017	80.810.525	1728	2.14	1	0.01
2018	82.003.882	1704	2.08	0	0.00
2019	83.154.997	1867	2.25	0	0.00

and the lung in 15-25%. Involvements such as heart, muscle, kidneys, bone, brain, spleen, breast, and pancreas constitute less than 10% of the patients[13,14].

Hydatid Disease of the Liver

Right lobe involvement is present in 60-85% of those with liver lesions. The cyst does not give any significant symptoms until its diameter reaches 10 cm. Right upper quadrant discomfort, weight loss, and malaise are most common. Hepatomegaly, right upper quadrant pain, nausea and vomiting occur in enlarged cysts. If the cysts open into the biliary tree, colic, obstructive jaundice, cholangitis or pancreatitis may be seen[1,4,9]. The cystic lesion in the liver on abdominal computed tomography (CT) is shown in Figure 1.

Hydatid Disease of the Lung

Cough, chest pain, hemoptysis or vomiting can be seen in bronchial tree involvement. In 60% of the patients with pulmonary hydatid disease, the right lung is affected. There is lower lobe involvement in 50-60% of the patients. There may be more than one cyst[15]. The most common symptoms in patients with pulmonary hydatid cysts are cough (53-62%), chest pain (49-91%), dyspnea (10-70%) and hemoptysis (12-21%)[16]. It may cause pleural involvement, pleural effusion, pneumothorax or empyema[17]. Pulmonary involvement is more common in children. At the same time, since the lung is a flexible organ, the cysts can reach larger sizes[18,19]. In a 15-year study conducted in Iran, lung involvement was reported in 279 (47.6%) patients and the most common involvement was in the right lung (64.9%)[20]. Approximately 20% of patients with lung cysts also have liver cysts[21]. Thick-walled cystic lesion in thorax CT is presented in Figure 2.

The heart is one of the rare areas where cysts can be found. Infection of the heart may cause mechanical rupture with extensive involvement or pericardial tamponade[22,23]. Central nervous system involvement may cause seizures or increased intracranial pressure. Spinal echinococcosis may cause spinal cord compression[24]. Cysts in the kidney may progress with hematuria or flank pain[25]. Immune complex-mediated disease, glomerulonephritis causing nephrotic syndrome, and secondary amyloidosis have also been reported[26,27]. Bone cysts usually remain asymptomatic until a pathological fracture develops. The growth of the parasite in bone tissue is a very slow process. The most commonly affected bones are the spine, pelvis and long bones[28,29]. Ocular cysts may also occur[30,31]. Rare but subcutaneous cysts thought to be tumors have also been described[32].

E. multilocularis causes severe infections in humans. It behaves like a malignancy that invades and destroys tissues, extends beyond organ boundaries to adjacent structures, and can metastasize to distant sites. It can spread to other organs including the lungs and brain from the primary focus in the liver or by hematogenous spread[1,2,9].

Infection due to this agent is usually symptomatic. Clinical manifestations are often nonspecific. The most common complaints are fatigue, weight loss, and discomfort in the right upper quadrant due to hepatomegaly. Cholestatic jaundice, cholangitis, portal hypertension, and Budd-Chiari syndrome may also occur. The clinical appearance may mimic hepatocellular

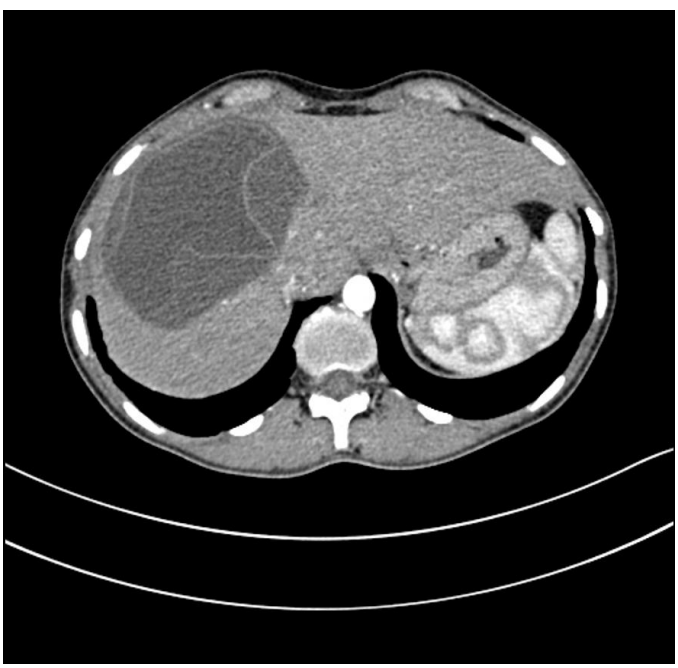

Figure 1. Cystic lesion in the liver on computed tomography

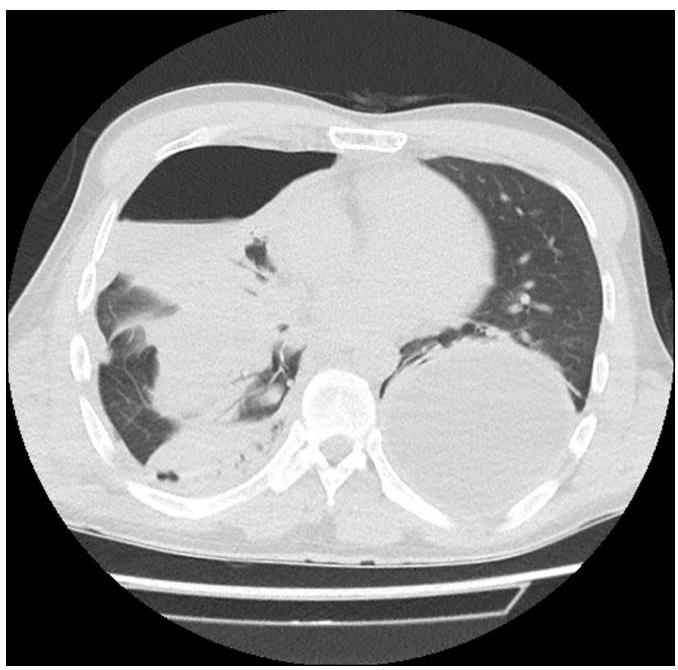

Figure 2. Cystic lesion in the right lung

carcinoma. Primary extrahepatic disease is seen in 1% of patients. Multiorgan disease, that is, involvement of the lung, spleen or brain in addition to the liver has been described in 13% of patients[33]. Immunodeficiency syndromes such as acquired immunodeficiency syndrome and transplantation may accelerate the onset of symptoms[34]. When the infection due to *E. multiloculoris* is left untreated, 90% of the patients died 10 years after the symptoms and all of them died after 15 years[35]. The survival rate of 117 patients who were treated appropriately and followed up for a long time in France was 88%[36].

Calcification of the cyst requires a long time (5-10 years). It is most commonly seen in liver cysts, less commonly in lung and bone cysts. Calcification of the entire cyst wall suggests that the cyst may be lifeless and unstable[37].

E. granulosus is a more common encountered causative agent. Single organ involvement was reported in 85-90% of patients and single cyst in 90%. In *E. granulosus* infection, clinical signs and symptoms occur according to the region and size of the cysts. Calcified and/or small ones may remain asymptomatic for many years. The diameter of the cysts grows to 1-5 cm per year. These growth rates and durations are very variable[37]. The clinical manifestation of *E. granulosus* infection depends on the location and size of the cysts. Small and/or calcified cysts may remain asymptomatic for life. They are sometimes diagnosed at autopsy[16,38].

Complications

Complications in Liver Involvement

As a result of fragmentation of echinococci, secondary cysts and bacterial infection may develop. Symptoms due to compression effect, obstruction of blood or lymphatic flow may be seen. Intra-abdominal abscess, secondary infection in cyst cavity, biliary fistula, sclerosing cholangitis, recurrence and anaphylaxis have been reported. Opening of cysts to the peritoneal cavity, opening of cysts to the digestive system and skin, vascular complications and acute abdomen have been detected[39-41].

Complications in Lung Involvement

The main complication in pulmonary echinococcosis is cyst rupture, which occurs when cyst material containing larval tissue and protoscolices spills into the bronchial tree or pleural space. Acute hypersensitivity reactions, including fever and anaphylaxis, may be the main manifestations of cyst rupture. Hypersensitivity reactions are related to immunological reactions and release of antigenic material. Complications such as intrapulmonary or pleural rupture, pleural thickening, infection of ruptured cysts, biliobronchial fistula, pneumothorax, pleural effusion and empyema have been described. Lung cysts may cause secondary infection and cause pulmonary abscess[4,42].

Diagnosis

Anamnesis and physical examination findings are helpful in diagnosis. Imaging and serology are used in diagnosis. Imaging methods are the most important diagnostic tools[2,4].

Although not diagnostic in *E. granulosus* infection, leukopenia, thrombocytopenia, mild eosinophilia and abnormalities in liver tests may be observed. Eosinophilia occurs in 25% of patients and is nonspecific. It usually occurs if there is leakage of antigenic material. Serum Ig E levels are high in 50% of the patients (Figure 3)[43].

Serology

Serological tests can be used for diagnosis. Depending on the location, size, integrity, and viability of the cyst, the results of serological tests may vary. Serological tests such as complement fixation, indirect hemagglutination (IHA), indirect immunofluorescence, latex agglutination, double diffusion immunoelectrophoresis, radioimmunoassay, enzyme-linked immunosorbent assay (ELISA), enzyme-linked immunoelectrodiffusion assay, and immunoblot can be used. These tests are useful both for primary diagnosis and for follow-up after treatment. The most commonly used methods for initial screening are ELISA and IHA. Enzyme-linked immunosorbent assay appears to be the most sensitive and specific of the tests available. Using the tests together increases the accuracy of diagnosis[4,8,9].

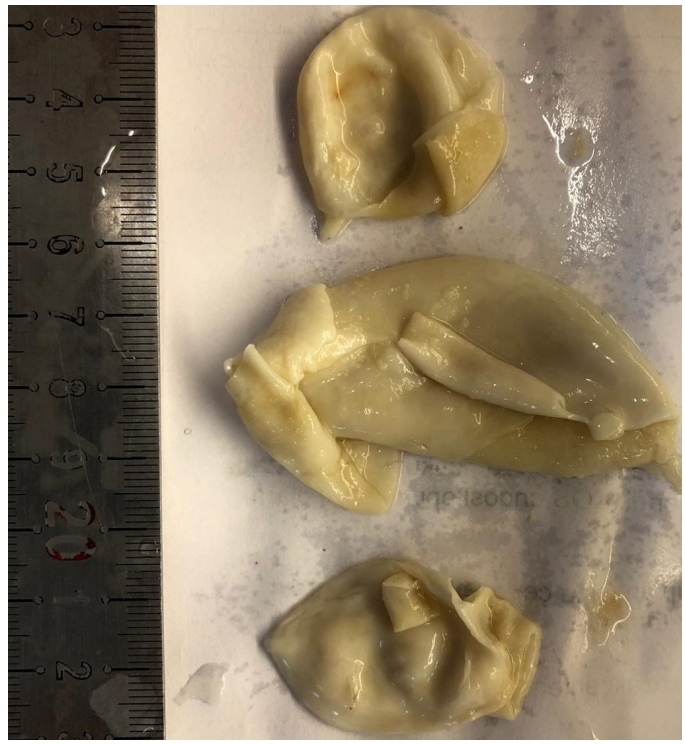

Figure 3. Macroscopic view of the cyst: 1 mm wall thickness, gray and white colored lamellar membrane

Serology may be positive depending on the vitality and location of the cyst. Serological assays for *E. multilocularis* infection are more sensitive and specific than for *E. granulosus* infection. In *E. multilocularis*, serology is likely to be positive when it involves the liver[4,44].

Positive IHA test is significant, but negative result does not exclude the disease. Again, there is no correlation between these tests and the number and size of the cysts. Antibody positivity is higher in liver cysts than in lung cysts. Serology is positive in 85-95% of liver cysts and 65% of lung cysts, depending on the test used and the condition of the cyst. While serology is positive in bone cysts, it is generally negative in brain, eye and spleen cysts[45,46]. Sensitivity (90-100%) is higher in multi-organ involvement (3.50). In the diagnosis of *E. granulosus*, antibody detection is more sensitive than antigen detection[47]. Titers of 1/160 and above are considered significant for IHA[48,49].

The ELISA (IgG) test has the best sensitivity and specificity among serological methods. Specific IgG ELISA has the highest negative predictive value (93%)[46]. Testing specific antibodies such as specific IgG1 or IgG4 instead of total IgG increases specificity[50]. The most sensitive isotypes for monitoring the success of treatment are IgG1 and IgG4 antibodies. Clinical recurrence is often associated with increased serological titers[51].

Serological assays are less likely to be positive in calcified or non-viable cysts. The sensitivity and specificity of serology is greater in *E. multilocularis*. The sensitivity and specificity of serological tests in *E. multilocularis* is 95-100%[52].

Depending on the location, size, integrity, and viability of the cyst, serological tests may be false-negative. False positivity is possible in the presence of some helminth infections (*Taenia saginata, Taenia solium*, neurocysticercosis), cancer and immune disorders[4,53].

A specific Em18 immunoblot and Em 18-ELISA test that can distinguish *E. multilocularis* is often used[54]. Serology usually stays positive for a very long time. Sometimes serology becomes negative years after complete surgical resection. Serological tests may remain positive for 12-18 months after surgery. In case of recurrence, serology becomes positive again. Follow-up of serological tests is useful to monitor for recurrence following surgical resection[47,54].

Imaging

Echinococcosis can be diagnosed with ultrasonography (USG), CT, magnetic resonance imaging (MRI). Ultrasonography is the most widely used because it is both inexpensive and easily accessible. Its sensitivity is 90-95%. Internal dissociation can be seen in the presence of daughter cysts. Ultrasonography provides active or inactive classification[55]. It is recommended to be used together with serological tests to increase its diagnostic value. The World Health Organization (WHO) Informal Working Group on Echinococcosis classification is used for diagnosis with USG. Ultrasonographic classification of echinococcosis is shown in Figure 4. In Table 2, USG features are indicated[56].

More detailed information about cysts can be obtained with CT and MRI. They The can be useful for determining the location and number of cysts, the presence or absence of daughter cysts, and the presence of ruptured or calcified cysts. Magnetic resonance imaging is costly. Its advantage over CT is not much[57]. The sensitivity of CT (95-100%) is higher than that of USG. Computed tomography is more valuable than USG in detecting the number, location and size of the cysts and detecting extrahepatic cysts. Computed tomography can also be used to monitor therapy and detect recurrences[58]. Computed tomography and MRI are more valuable in the diagnosis of lesions in other regions such as the brain[59].

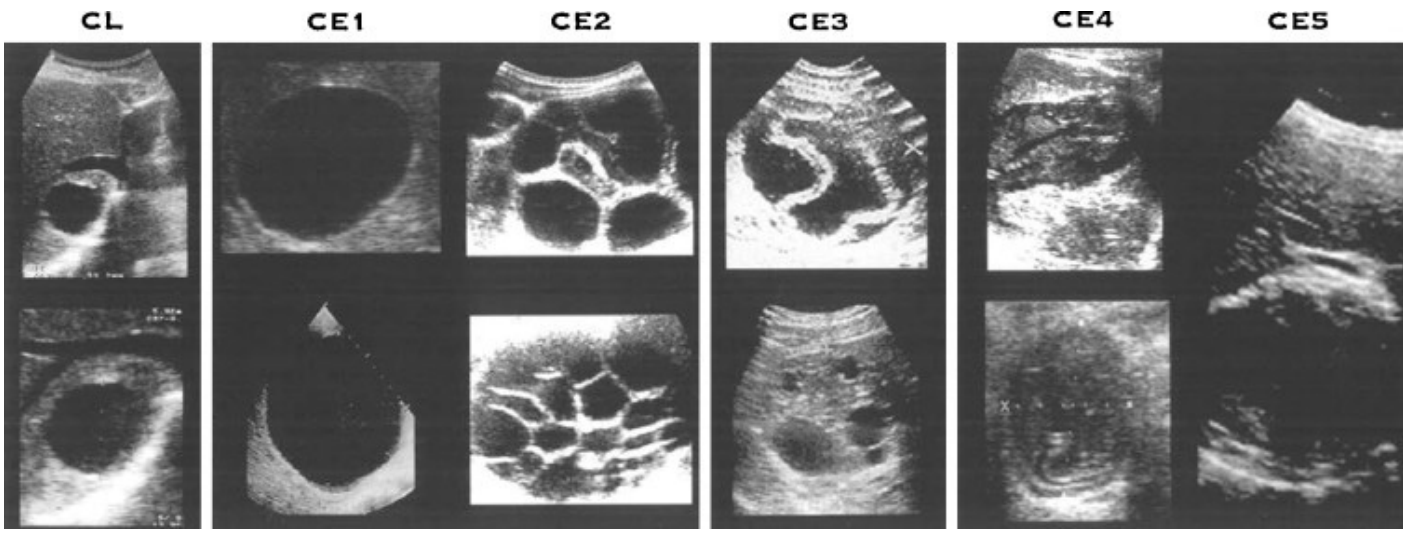

Figure 4. World Health Organization echinococcosis classification

Table 2. The World Health Organization's Classification

WHO classification	Ultrasonographic features
CL	Non-specific cystic lesion, uniform, anechoic appearance
CE 1	Cystic appearance with uniform anechoic content, the cyst wall is visible, the lesion may be round or light. Subtle echogenic ripple with repositioning (snowflake sign)
CE 2	Multivesicular, multiseptated cyst, cyst walls are visible. Daughter cysts present, honeycomb pattern
CE 3a	Unilocular cyst containing liquid with a floating membrane inside, water-lily sign
CE 3b	Cysts with daughter vesicles in solid matrix
CE 4	Cyst with heterogeneous degenerative content, no daughter vesicle
CE 5	The cyst is characterized by an arched calcified wall, producing a cone-shaped shadow; degree of calcification varies from partial to complete

CL: Cystic lesion, CE: Cystic echinococcus (stage), WHO: World Health Organization

Differential Diagnosis

Differential diagnosis should be made with simple benign cyst, tumor, hemangioma, hepatocellular carcinoma, abscess, and cavitary tuberculosis lesion. The differential diagnosis of alveolar echinococcosis should include malignancies such as hepatocellular carcinoma and liver metastases[60].

Treatment

Treatment for cystic echinococcosis includes medical therapy, surgery and percutaneous therapy[60]. Benzimidazole compounds albendazole and mebendazole are recommended for treatment. The first choice in treatment is albendazole. It is especially recommended to be consumed with fatty foods. Albendazole is used twice a day (2x400 mg), mebendazole is used three times a day (3x40-50 mg/kg). It is common to use it for four weeks and take a break for two weeks. Recent publications have shown that continuous application is equivalent or even more effective, with no increased side effects. As the duration of use increases, the amount of viable cysts decreases[4,12]. It was shown in a meta-analysis that the combined treatment of albendazole and praziquantel was more successful. Praziquantel increases the blood level of albendazole four times[61].

Perioperative medical therapy deactivates protoscolex and prevents recurrences. It also softens the cyst and makes it easier to remove the cyst. World Health Organization recommends that albendazole be started 4-30 days before surgery and continued for at least one month afterwards[62].

Treatment management according to the WHO classification: Albendazole is used for stage CE1 and CE3a cysts and cysts smaller than 5 cm. Albendazole is recommended simultaneously with percutaneous aspiration, injection and reaspiration (PAIR) for stage CE1 and CE3a cysts and cysts larger than 5 cm. The risk of recurrence is high with PAIR in stage CE2 and CE3b cysts. Stages CE2 and CE3b cysts require surgery. Albendazole is recommended with surgical application. Medication with a modified catheterization method or surgery may be recommended. Surgery is preferred in the management of complicated cysts. Surgery (WHO Stages CE2 and CE3a) is also recommended for the treatment of masses containing many daughter cysts that are not suitable for PAIR. In addition, surgery is also performed in patients where the cyst diameter is greater than 10 cm and in non-hepatic (lung, bone, brain, kidney, etc.) involvement[56,63]. Stage CE4 and CE5 cysts are inactive cysts and they are just followed up. In patients in whom surgery is not suitable and in cyst ruptures, albendazole is used for at least one month[62,63].

Surgery is the gold standard treatment. In a study examining the surgical procedures of 88 patients, open surgery was recommended for stage CE1 and CE3 cysts and large cysts. It has been emphasized that minimally invasive techniques (PAIR and Modified Catheterisation Technique) are gaining importance today. Shorter hospital stays and fewer complications have been reported with minimally invasive methods[12]. In the study of Tartar et al.[45] in which they examined 78 patients, it was emphasized that open surgery and medical treatment reduced the recurrence rate. In a study to compare treatments, 72 patients were divided into two groups. The first group underwent only surgery and the other group received medical treatment before and after surgery. It was shown that the use of albendazole in the second group reduced cyst viability and recurrence[3].

Scolicidal agents can be used intraoperatively or in the PAIR procedure. Betadine (povidone-iodine), 20% hypertonic saline, 20% Savlon (1.5/0.15% cetrimide-chlorhexidine) and 95% ethyl alcohol are known as effective scolicidal agents[64].

Prevention

The most effective method for prevention is education. There is no vaccine for this disease. Preventing or controlling disease in humans relies on control or elimination of disease in dogs. Close contact with dogs should be avoided. Fresh vegetables or fruits should be washed very well. Extreme care must be exercised

during animal slaughter. Dogs should be prevented from consuming infected sheep internal organs. Stray dogs should be restricted. The frequency of owned animals should be increased. Infected dogs should be administered praziquantel. Vaccination of sheep and cattle with E95 vaccine can develop protective immunity. With vaccination, the rate of cysts is reduced by 90-99%. Initially, two vaccinations, one month apart, followed by annual vaccinations are recommended. An effective vaccine against *E. multilocularis* has not been developed. Screening of high-risk groups in humans may be effective in early diagnosis[4,42,65].

Conclusion

In conclusion, echinococcosis is a parasitic disease. *E. granulosus* and *E. multilocularis* are the most common pathogens in humans. Humans ingest parasite eggs by direct contact with water, vegetables, soil, or host animals. Treatment of the infection is difficult, complex and expensive. It has medical and surgical treatment. Extreme care must be exercised during animal slaughter. Dogs should be prevented from consuming infected sheep internal organs. Anti-parasitic medication should be used in domestic dogs. Sheep and cattle should be vaccinated. Echinococcosis is a preventable and treatable public health problem. Slaughterhouse hygiene and public education play a key role in preventing this disease. Large quality epidemiological studies and surveillance programs should be conducted.

Ethics

Peer-review: Externally and internally peer-reviewed.

Financial Disclosure: The author declared that this study received no financial support.

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