International Journal of Biology Research
www.biologyjournal.in
ISSN: 2455-6548
Received: 30-07-2023, Accepted: 15-08-2023, Published: 31-08-2023
Volume 8, Issue 2, 2023, Page No. 17-22

Echinococcosis: A review

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Abstract
Echinococcosis is a parasitic disease caused by tapeworms of the genus *Echinococcus*, the herbivores represent the intermediate host for this parasite such as sheep, cows, buffaloes, camels, horses, and other animals) in addition humans act as accidental intermediate hosts, while the carnivores of the canidae family are definitive hosts, humans become infected by eating parasite eggs in contaminated food, water, or soil, or after direct contact with infected hosts.
The infection is diagnosed by many methods, including ultrasonography, computed tomography and magnetic resonance Imaging Treatment of echinococcosis is often surgical because chemotherapy takes a long time, but in some cases, it is difficult to remove the cyst from some organs of the body, especially the brain.

Keywords: Echinococcosis, parasitic, humans, surgical

Introduction

Echinococcus granulosus is one of the most important Zoonotic parasites and It's considered the main cause of Echinococcosis, which has many names, including Echinococcosis, cystic echinococcosis, hydatidosis, and unilocular hydatidosis, It is one of the serious epidemiological diseases that it harms people both medically and economically in most parts of the world (Naguleswaran *et al*., 2006) [28], and spreads in many countries, including Iraq, Libya, Sudan, Egypt, Lebanon, Syria, Algeria, Palestine, and others, as well as northern, eastern, and southern Africa, the Caspian Sea, western and southern Europe, and some countries of South America that are highly endemic to this disease (Wen *et al*., 1993).
It was observed that the incidence of this disease in rural areas is high, and the reason is due to the large number of farm animals and the presence of carnivores, which helps to complete the life cycle of this parasite that needs an intermediate host such as humans, sheep, cows, buffaloes, camels, horses, and other animals) and the define host (dogs, wolves, hyenas, leopards, and other ferocious animals), and the infection rate increases during childhood as a result of children playing with dogs (Marquarst *et al*., 2000) [25].
The seriousness of this disease lies in two reasons. The first is the inability to know the infection in the early stages of its occurrence, because the disease does not show pathological symptoms until after the size of the cyst increases, which leads to pressure on the tissues adjacent to it, and when the cyst rupture, it spreads in all parts of the body except for hair and nails. The second reason is the loss of the means of treatment for this disease (Grosso *et al*. 2012) [15].

Historical review

Hydatid cysts were first described by Hippocrates in (460-379) BC. when he noticed that the liver of a deceased patient contained cysts filled with water and suggested that the rupture of this cyst could be the cause of the patient's death (Thompson and MC Manus, 2002) [41, 42], Al-Razi also referred to this in his book Al-Hawi in Medicine (Cox 2002) [3].

Francesco Redi is the first to describe the nature of parasitic disease and refute the idea of Spontaneous generation in 1684 AD, and in 1695 Hartmann described the adult worms that were found in the intestine of dogs, Tome Hunter's description in 1773 Hydatid cyst is as a spherical structure that has a cavity filled with a clear white liquid that causes the disease, Batsch described the worms in the intestine of dogs and called it Hydagena Granulosus, and the term *Echinococcus* was launched by Rudolphi in 1808 AD, which is a greek word consist of two section Echino mean Hedgehog and Coccus that means berry because it appeared in the form of granules on the surface of the inner cyst while Hydatid term it is a Greek word, meaning water vesicle, in 1852 AD, Von Siebold revealed adult worms in the intestine of dogs after several weeks of feeding on hydatid cyst that were taken from cattle (Thompson and MC Manus,2002) [41, 42].

Taxonomy of Echinococcus

According to Rahman *et al.*, (2015) classify parasite into:
Kingdom: Animalia
Phylum: Platyhelminthes
Superclass: Eucestoda
Class: Cestoidea
Subclass: Cestoda
Order: Cyclophyllidea (Bein; Braun, 1900)
Family: Taeniidae (Ludwig, 1886)
Genus: *Echinococcus* (Rud, 1801)
Species: *granulosus* (Batsch, 1786)

Type of *Echinococcus* species

The species belonging to the genus ***Echinococcus*** were classified according to the characteristics set by Xiao *et al*., (2006) [47], as in the following table:

Table 1: The most important species of *Echinococcus* in different hosts.

	E. granulosus	***E. multilocularis***	***E. oligarthra***	***E. vogeli***	***E. shiquicus***
Distribution	Cosmopolitan	Holoarctic region	Neotropical region	Neotropical region	Tibet plateau
Definitive host	Wild and domestic carnivores	Foxes/dogs	Wild felids	Bush dog	Tibetan fox
Intermediate host	Ungulates	Microtine rodents	Neotropical rodents	Neotropical rodents	Plateau pika
Adult					
Body length (mm)	2.0–11.0	1.2–4.5	2.2–2.9	3.9–5.5	1.3-1.7
No. segments	2–7	2–6	3	3	2–3
Length of large hooks (μm)	25.0–49.0	24.9–34.0	43.0–60.0	49.0–57.0	20.0–23.0
Length of small hooks (μm)	17.0–31.0	20.4–31.0	28.0–45.0	30.0–47.0	16.0–17.0
No. testes	25–80	16–35	15–46	50–67	12–20
a. Mature segment	Near to middle	Anterior to middle	Anterior to middle	Posterior to middle	Near to upper edge
b. Gravid segment	Posterior to middle	Anterior to middle	Near to middle	Posterior to middle	Anterior to middle
Gravid uterus	Branching laterally	Sac-like	Sac-like	Tubular	Sac-like
Metacestode	Unilocular cysts in viscera	Multilocular cysts in viscera	Unicystic cysts in muscles	Polycystic cysts in viscera	Unilocular cysts in viscera

Description of *Echinococcus granulosus*

This parasite is a small tapeworm that passes through three stages during its life cycle were: egg, hydatid cyst, and adult stage:

Eggs

The eggs of *Echinococcus granulosus* are identical and indistinguishable from those of Taenia spp. Fortunately, the diagnostic methods depend on the larval stage of these worms, The eggs are oval in shape, and their diameter ranges from (30-36) microns, it contains an embryo called the Oncosphere or the Hexacanth embryo because it bears three pairs of spines (Zeibig, 2012) [48].

Hydatid Cyst

It is the larval stage of *Echinococcus granulosus* found in the tissues of the intermediate host (Zeibig, 2012) [48], has a spherical or semi-spherical shape and takes the shape of the affected organ, and its size varies with age, the rate of growth of the hydatid cyst depends on the softness of the organ and the elasticity of the surrounding tissues (Halezeroglu *et al.*, 2012) [16, 17].

lung cysts grow faster than liver cysts, due to the softness of the lungs more than the liver in addition, negative pleural pressure may increase speed of cyst growth (Dincer *et al*., 2006) [6]

Whereas children's hydatid cysts grow at a faster rate and become larger than those in adults due to their highly elastic lung tissue in children (Halezeroglu *et al*., 1997) [16, 17].

The hydatid cyst grows at a variable rate, as the diameter of the cyst doubles at (16-20) weeks, and It also show different growth rates in the same patient (Romig *et al*., 1986) [33].

Hydatid cyst consists of several layers, starting from the outside, as follows

A. The adventitious layer (capsule)

It consists of strong fibrous connective tissue that is formed as a result of the host's reactions to infection, as it acts as a barrier that prevents the passage of parasite secretions that affect the host's immune system (Ekim and Ekim, 2017) [9].

B. Laminated Layer

It is a white, chitinous, strong layer with a thickness of approximately (1-3) mm, Its thickness increases with age and maintains its consistency even after the death of the parasite. This layer is secreted by the parasite and protects it from the immune responses of the host (Müller *et al*., 2007) [27], it works to enter nutrients into the hydatid cyst and prevents the entry of other materials, in addition works to support germinal layer

This layer is considered the main reason for reducing the effect of drugs used in the treatment of hydatid cysts, It consists of proteins linked to sugars, such as glucose, galactose, and galactosamine (Siracusano *et al.*, 2009) [39].

C. Germinal layer

It is a living layer whose cells contain nuclei, which protect the components of the hydatid sac, support it, and produce hydatid fluid (Ekim and Ekim, 2017) [9], it contributes significantly to the growth of the hydatid cyst through the penetration of some substances that the parasite needs for its growth, preserve its life, and controlling osmotic pressure (Eckert and Deplazes, 2004) [7, 8].

This layer contains several types of cells, including tegument cells, which are multinucleated and characterized by their rapid growth, muscle cells, glycogen storage cells, in addition undifferentiated cells that are responsible for the formation of brood capsules (Zeibig, 2012) [48].

The contents of the hydatid cyst are

A. Brood capsules

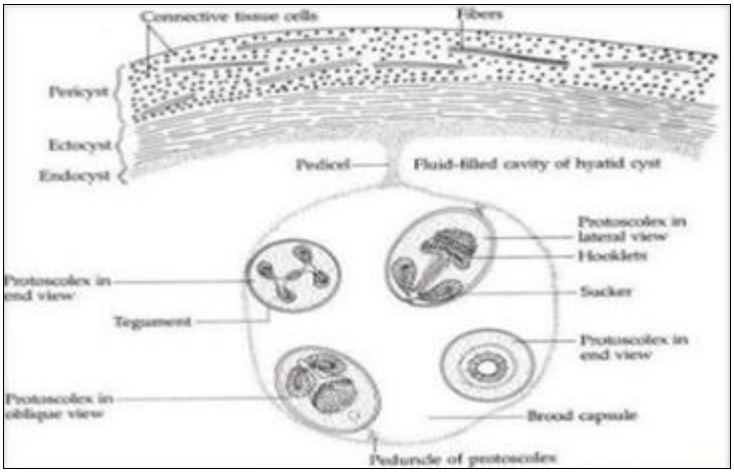
arise from the inner germ layer by endogenous budding processes and appear as masses or small buds that form towards the cyst cavity, The capsules are connected to the germinal layer by a short stalk, and as a result of repeating the budding process, protoscolices are formed inside the capsules, the number of which is about (10-30) scolex per capsule, cysts that produce brood capsules are called fertile cysts, while cysts that do not form capsules are called sterile cysts (Higuita *et al*., 2016)

B. Daughter cysts

These cysts are formed in three ways either formed from the cells of the germinal layer or from the brood capsules or protoscolices, these cysts are similar in structure to the parental cyst and it can produce protoscolices and even new daughter cysts, daughter cysts gradually detach from the germinal layer and float in the paternal cyst fluid (Mehlhorn, 2008).

C. Hydatid cyst fluid (Hydatid sand)

Is a colorless or yellowish liquid with a pH of **(**6.7–7.2**)**,It represents the main source of parasite antigens that are used in diagnostic serological tests for this disease (Izadi and Ajami, 2006) [20], the size and shape of the hydatid cyst fluid are determined by the location and the organ in which it grows. The wall of the hydatid cyst is characterized by permeability and selectivity as it allows the entry of nutrients and prevents the exit of essential substances (Safioleas *et al*., 2005) [34], as picture (1).



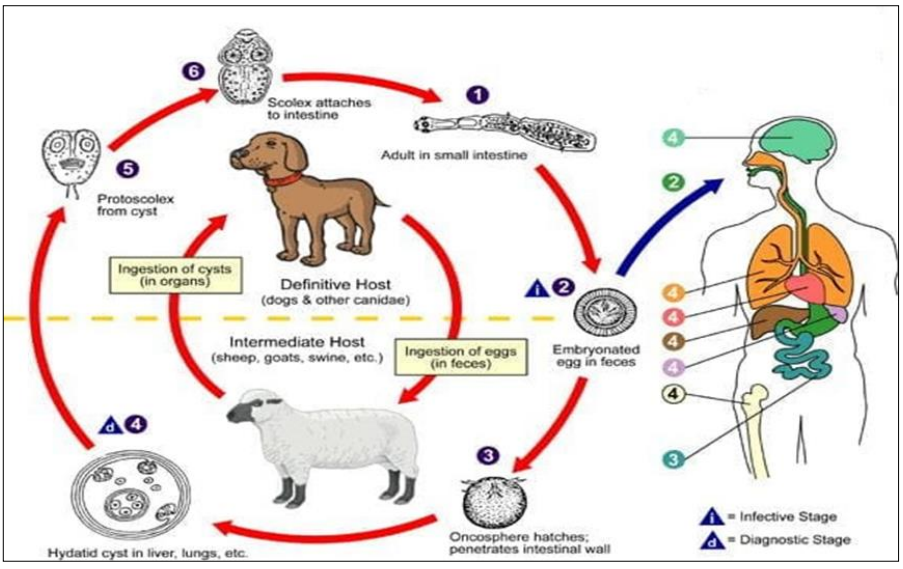
Pic 1: Hydatid cyst (Siracusano *et al.*, 2009).

Adult worm

The total length of the adult worm ranges between (9-11) mm, and it consists of **(**3-5**)** segments. The worm's body is divided into three sections, the scolex, its diameter is about (0.3) mm. and has a Rostellum surrounded by two rows of hooks, ranging in number from (28-40) hooks in addition to four Suckers cup-shaped, The scolex is followed by the neck, which is a narrow area responsible for the formation of the body segments, then the body segments, which are divided into three types: the immature segment, which follows the neck and it is short, then the mature segment, which is elongated and contains the male and female genital organs, it contains (45-65) pear-shaped testes spread across the anterior side of the segment, while the female genital organs are represented by the ovary, which consists of two irregular lobes located at the back of the segment, then last segment which is called the gravid segment contains a uterus filled with fertilized spherical eggs, their number ranges **(**300-500**)** eggs, and it is resistant to unfavorable conditions (Brožová *et al*, 2017) [2].

Life Cycle

Carnivores of the Canidae family are definitive hosts for the *Echinococcus granulosus* worm, These worms develop in the small intestine of the definitive host, and the gravid segments containing the eggs are separated from the parasite's body to pass with the feces of the definitive host to the external environment, eggs containing the hexacanth embryo, which are characterized by the ability to survive for a long period of time when conditions are appropriate, in addition to the presence of protective membranes that surround them, which helps them to withstand a wide range of temperatures and humidity, so their susceptibility to infection lasts for several months (Higuita *et al*., 2016) [18], intermediate hosts such as humans accidental intermediate, camels, sheep, cattle, buffaloes, and pigs become infected as a result of eating food or drink water contaminated with parasite eggs, also children may be infected as a result of contact with dog hair attached to parasite eggs, inside the body of the intermediate host, the outer membrane of these eggs is ruptured by the action of digestive juices, and the embryos are released from it, which adhere to and penetrate the mucous lining of the small intestine, with the help of substances secreted by large penetrating glands located in the front of the embryo, these substances also protect the embryos from digestive enzymes and the immune response of the host, in addition help it penetrate the vessels, the spherical embryo then enters through the lymphatic and mesenteric vessels and is carried with the bloodstream to settle in the target organ, the liver and lungs being the most common organs for the growth and development of hydatid cyst, other organs can be infected, but to a lesser extent including the spleen, kidneys, brain, bones, and heart (Díaz *et al*., 2011) [5], then the hydatid cyst is formed, which represents the larval stage of the parasite, after that, a primary rupture occurs in the cyst to form a new cyst in new organs, which is called a secondary hydatid cyst (Eckert *et al*., 2001) [7, 8], when the definitive host eats infected organs of an intermediate host, the parasite will reach the small intestine, the protoscolices grow into adult worms within (4-7) weeks and each worm produces thousands of eggs to repeat the cycle again (Higuita *et al*., 2016) [18], as picture (2).



Pic 2: Life cycle of *Echinococcus granulosus* (Sastry Apurba Sankar and Jaypee, 2014)

Pathological effects of Echinococcosis

Echinococcosis in humans is characterized by a long growth period and the incubation period varies from months to years in addition many cyst infections remain asymptomatic until an advanced age, which may lead to complications depending on the location of the cyst (Pakala *et al*., 2016) [31].

clinical symptoms depend on the size of the hydatid cyst, its location, type, number, immunity of the intermediate host, the overlap between the developing cysts and adjacent tissues and organs, and the patient's health status (Shaw *et al.*, 2006) [38].

The pathological effect of hydatid cysts appears as a result of the pressure of the cyst and its effect on the affected organ, as the growth of the cyst inside the affected organ causes an inflammatory reaction that leads to the formation of the adventitial capsule around the cyst, and over time, destruction and atrophy of the tissue occurs, and in advanced cases of infection it may lead to a disruption of the function of the affected organ (Gottstein, 2003) [13, 14].

The rupture of the cyst or the occurrence of leakage of its contents through the tissue facilitates the spread of the cysts due to the liberation and spread of the protoscolices, and thus leads to the occurrence of a second infection called secondary hydatidosis (Cummings *et al*., 2009) [4].

The liver represents the first organ most susceptible to hydatid cysts, with infection rate is 75%, followed by the lungs, with an infection rate of 20%, infection can also appear by 5% in other parts of the body such as the kidneys, spleen, bones, heart, brain, or any other parts of the body except for three areas were: teeth, hair and nails (Tigan *et al*., 2014) [43].

Infection to the liver leads to hepatomegaly with or without a palpable mass during clinical examination in the right upper quadrant, pain above the stomach on the right side, fever, and nausea, some complications may occur due to obstruction or invasion of the bile ducts or hepatic vessels, such as obstructive jaundice, cholangitis, liver abscesses and liver cirrhosis (Marrone *et al.*, 2012) [26].

The presence of hydatid cysts in the lungs leads to chest pain, Cough, Fever, Shortness of breath, Hemoptysis and pleurisy, as well as allergic reactions, in the kidneys, it causes haematuria, the disease affects the abdominal cavity, heart, muscles, nervous system, or other sites (Craig *et al*., 2007), and the cysts that affect the heart are very dangerous because they can rupture and cause the spread of the protoscolices and pressure on the heart Cardiac tamponade (Schantz *et al*., 2006) [36].

The first sign of cerebral infection is raised intracranial pressure or epilepsy (Faheem *et al*.,2013) [11]. while the infection of the bone, is usually asymptomatic, spontaneous fractures may occur and can destroy the cyst, in addition, the cyst can break the bone structure, and the infection in the bone tissue is associated with cysts that are not surrounded by the outer membranes, so their growth will not be determined, which will be at the expense of the erosion of the cancellous tissue in the pelvic bones and the long bones, and thus the bone erodes and becomes fragile and easy to break this is called Osseous hydatid cysts (Bekçi, 2012) [1].

The presence of a single cyst within the organ is a common condition when infected with hydatid disease, but there are cases in which the organ has multiple cysts that may reach more than 10 cysts /organ (Torgerson & Heath, 2003) [44], or the host gets infected with more than one cyst distributed among the different organs, in such cases, the pathological symptoms may be noticeable due to the severity of the infection (Eckert *et al*., 2001) [7, 8].

Diagnosis of Echinococcosis

Early diagnosis of a developing hydatid cyst in patients is very important for initiating treatment and minimizing it morbidity and mortality, There are many diagnostic techniques various that include:

Clinical Diagnosis of Echinococcosis

Clinical diagnosis is based on knowledge of the clinical symptoms and special epidemiological data of the disease in the area concerned (WHO, 2003) [46].

Imaging techniques

There are many imaging methods for diagnosing hydatid cysts in humans, and they depend on the type of organ and the stage of cyst growth, the importance of these methods is in determining the appropriate treatment method (Rasheed *et al*., 2013) [32] including:

A. X-ray

It is used to diagnose the presence of hydatid cysts in the lung, bones, and muscles, and to be a complementary method with computed tomography (CT scan) before any surgical intervention, as well as in the case of calcified cysts (Fortia *et al*., 2006) [12].

B. Anigography

This technique is used in some cases before surgery to detect invasion of the hepatic arteries and portal vein occlusion (Khuroo, 2002) [22].

C. Cholangiography

This technique is used when there are lesions inside the liver with jaundice and bile duct obstruction. It can also be used to evaluate communication between the bile ducts (Taglicozzo, 2002) [40].

D. Ultrasonography (US)

One of the most important diagnostic techniques is characterized by high sensitivity (Mandal & Manda1, 2012), it is used in the diagnosis of asymptomatic hydatid cysts in any part of the abdomen and muscles in addition to ability to clarify the structure of cysts and the presence of daughter cysts within the Hydatid cyst, it is also used to evaluate the response of cysts to treatment and to record their growth rate (Llica *et al*., 2007) [23].

E. Computed Tomography (CT scan)

This technique is used to detect hydatid cysts in any organ of the body and determine their location with high sensitivity of (90-97)%, especially small and daughter cysts outside the liver which are difficult to identify using ultrasound, It is also used to detect calcifications in the cyst wall cyst infections and prevalence protoscolecies in the peritoneum, as well as its ability to distinguish hydatid cysts from amoebic and pyogenic cysts in the liver (Mandal & Manda1, 2012) [24].

F. agnetic Resonance Imaging (MRI)

This technique is used before the operation to remove the cyst, and after the operation to ensure that there are no cysts, in the detection of recurrence of the hydatid cyst, also the detection of extrahepatic lesions and determining their locations and internal and external structure with high accuracy, especially heart infection, in addition to its ability to determine the change in the venous system inside and outside the liver, as it is used to distinguish simple cysts from hydatid cysts in the liver, as well as the use of this technique in the diagnosis of cerebral hydatid cysts and in the detection of multiple cysts and the detection of the cyst capsule (Inan *et al*., 2007) [19].

Molecular Diagnosis Test

Polymerase Chain Reaction (PCR) is used for the purpose of distinguishing between the species of the genus *Echinococcus* by using materials from the larval stage (the hydatid cyst) inside the intermediate host, then DNA is extracted to differentiate between species belonging to this genus, also used for the purpose of determining the DNA of *E. granulosus* and *E.multilocularis* in the stool sample from the definitive host (Thompson & McManus 2002) [41, 42].

Immunological Diagnosis of Echinococcosis

This method depends on finding antibodies in the sera of infected patients, and this is done by a number of tests such as the indirect

haemagglutination test, the indirect immune fluorescent antibodies test, the Latex agglutination test, the complement fixation test, the cassoni test, and enzyme-linked immunosorbent assay (Shamsier, 2011) [37]

Serological tests have been used in recent years to diagnose echinococcosis, and the sensitivity in some of these tests reaches more than 95% and it is important in detection, control and early diagnosis (Thompson, 2001) [41, 42].

Gottstein *et al.* (1993) [13, 14] indicated that after operation to remove hydatid cysts in humans, an immunoassay is performed using the ELISA technique to detect the antibody the IgG – subclass, if the test result is negative, this indicates the success of the operation, while the patients maintain a high level of the IgG-subclass, this indicates the failure of the operation.

The sensitivity and specificity of these tests depend on the stage of infection, the affected organ, the antigens, and the technique used for diagnosis, inadditon the sensitivity of the serological examination of liver cysts reach (80-90%), while for lung cysts it reaches (50-60%) (Erkan *et al*., 2004) [10].

Treatment of Echinococcosis

The treatment of echinococcosis aims primarily at removing the parasite that causes the disease completely and avoiding the recurrence or recurrence of the infection again, Therefore, it is necessary to choose the appropriate or most effective treatment in treating the infection, The treatment depends on the number of cysts, the size and location of the cyst (Nunnari *et al*., 2012) [29]

One of the ways to treat this disease in humans are:

1. Surgical treatment

Surgical treatment is the best way to control the spread of the disease, it is very suitable in simple cases in which the number of cysts is limited and within a specific organ, and in this way, complete recovery is achieved, It is the location, size, and development of the cyst that determines the surgical operation and also patient needs chemotherapy before and after the operation to prevent cysts from forming again (Khuroo, 2002) [22].

2. Chemotherapy

Numerous studies have shown that chemotherapy with medical drugs has a significant effect in completely removing hydatid cysts, especially small cysts, and that the side effects of these drugs are moderate and rarely strong and chemotherapy is used due to the presence of cysts in areas that are difficult to deal with or reach during surgery, in addition to the use of chemotherapy before and after surgery to reduce the size of the cysts and the risk of their recurrence (Eckert & Deplates, 2004) [7, 8].

The chemotherapy method needs a long time when there are cysts in the main organs such as the bones, brain and eye, while chemotherapy should be avoided in the case of large cysts, beehive-like cysts, superficial cysts prone to rupture, ineffective cysts, calcified cysts, severe chronic liver disease, bone marrow failure, and early pregnancy (Kapan *et al*., 2008) [21].

of the drugs used to treat the disease are Albendazole, Mebendale flubendazole, oxfendazole, Thiabendazole, and Oxbendazole Oxbendazole, Prazikental (Olliaro *et al*., 2011) [30].

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