Human cystic echinococcosis: epidemiologic, zoonotic, clinical, diagnostic and therapeutic aspects

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ARTICLE INFO

Article history:
Received 20 October 2011
Received in revised form 15 January 2012
Accepted 15 March 2012
Available online 20 April 2012

Keywords:
Human cystic echinococcosis
Zoonotic disease
Epidemiology
Echinococcus granulosus
Hydatid cyst
Surgery
Chemotherapy

ABSTRACT

This review represents an updated scenario on the transmission cycle, epidemiology, clinical features and pathogenicity, diagnosis and treatment, and prevention and control measures of a cestode parasite Echinococcus granulosus (E. granulosus) infection causing cystic echinococcosis (CE) in humans. Human CE is a serious life-threatening neglected zoonotic disease that occurs in both developing and developed countries, and is recognized as a major public health problem. The life cycle of E. granulosus involves a definitive host (dogs and other canids) for the adult E. granulosus that resides in the intestine, and an intermediate host (sheep and other herbivores) for the tissue-invasing metacestode (larval) stage. Humans are only incidentally infected; since the completion of the life cycle of E. granulosus depends on carnivores feeding on herbivores bearing hydatid cysts with viable protoscoleces, humans represent usually the dead end for the parasite. On ingestion of E. granulosus eggs, hydatid cysts are formed mostly in liver and lungs, and occasionally in other organs of human body, which are considered as uncommon sites of localization of hydatid cysts. The diagnosis of extrahepatic echinococcal disease is more accurate today because of the availability of new imaging techniques, and the current treatments include surgery and percutaneous drainage, and chemotherapy (albendazole and mebendazole). But, the wild animals that involve in sylvatic cycle may overlap and interact with the domestic sheep–dog cycle, and thus complicating the control efforts. The updated facts and phenomena regarding human and animal CE presented herein are due to the web search of SCI and non-SCI journals.

1. Introduction

Echinococcosis, also called hydatid disease or hydatidosis, is a zoonosis, and in humans it occurs as a result of infection by the larval (metacestode) stages of taeniid cestodes of the genus Echinococcus. It is characterized by long-term growth of metacestode (larval) stages (hydatid cysts) in internal organs (mainly the liver and lungs) of intermediate host animals, viz., sheep and goats. Accidentally, eggs are also ingested by humans but do not play a role in the natural cycle. Six species of Echinococcus have been recognized; four are of public health concern, which are Echinococcus granulosus (E. granulosus) causing cystic echinococcosis (CE), Echinococcus multilocularis causing alveolar echinococcosis, and Echinococcus vogeli and Echinococcus oligarthus causing polycystic echinococcosis; two new species have recently been identified: Echinococcus shiquicus in small mammals from the Tibetan plateau[1] and Echinococcus felidis in African lions[2,3], but their zoonotic transmission potential is unknown. The E. granulosus infections have been further classified as domestic and sylvatic; in the domestic form, sheep serves as the most common intermediate host while in the sylvatic form the usual intermediate hosts are caribou or moose. Human cystic echinococcosis is the most common presentation and probably accounts for > 95% of the estimated 2–3 million cases in the globe[4]. Despite some progress in the control of echinococcosis, this zoonosis continues to be a major public health problem in several countries, while in many other countries the disease constitutes an emerging and re-emerging[5]. Current analyses revealed that human CE is re-emerging problem with a remarkable economic impact in developed countries, viz., Spain[6], and the disease continues to be a substantial cause of morbidity and mortality in several parts of the globe. The major sources of morbidity are pressure effects from cyst size, location in a sensitive organ (brain, reproductive tract, bone), or cyst rupture with subsequent anaphylaxis or dissemination of the infection.
The most common affected organs, however, are the liver and the lungs where 90% of the echinococcal cysts develop; excluding liver and lungs, all the other organs of the human body are considered as uncommon sites of localization of the hydatid disease. In this review, various aspects of human CE are discussed, based upon the current publications, in SCI and non-SCI journals, and in scientific websites, by different authors from different parts of the globe.

2. Etiologic identity

The adult *E. granulosus* (3–6 mm long) resides in the small intestine of the definitive hosts, dogs or other canids[5,7]. The adult worm consists of scolex bearing a rostellum with double row of numerous hooks, four prominent suckers and a short neck region, and the strobila consist of 3 proglottids; usually one immature, one mature and one gravid proglottid make up the strobila.

The *E. granulosus* exists as a complex of different strains that differ in a wide variety of criteria having impact on the epidemiology and control of CE. The most important strain associated with the human CE appears to be the common sheep G1 strain, and is the most cosmopolitan form[5,8]. The current molecular characterization of human and animal *E. granulosus* isolates, however, demonstrated the involvement of the camel G6 strain in causing infection to humans[9,10].

3. Epidemiology

The greatest prevalence of the disease is in regions of the temperate countries, and this is an endemic disease in some parts of the world, such as South America, North Africa, Asia and Australia[11–13]. In the endemic parts, the rate of incidence of human CE has been recorded as >50 per 10⁵ person–years, and 5%–10% prevalence rate as in parts of Peru, Argentina, east Africa, central Asia, and China[4]; confirmed evidence for the emergence or re-emergence of human CE is there in parts of China, central Asia, Eastern Europe, and Israel[14]. The incidence of human hydatid cysts has been recorded as 18–20 per 10⁵ in Turkey, one of the endemic countries of the disease[5]. In Europe, human CE occurs in every country or region, where the annual incidence of hospital cases vary between <1 and >8 per 10⁵ population; in the northern part of Italy, the average annual CE incidence was recorded as 9.4–5.6/10⁵ inhabitants during 2003–2005[16]. However, Moro et al[17] reported that the actual prevalence of infection may greatly be underestimated by information from different official sources of the same geographical region; Figure 1 represents such phenomenon in Junin and in the coastal city of Chinchca. As has been documented in literatures, human CE may occur in the subjects in between 1 and 75 year of ages[14]. Epidemiologically, CE occurs mostly in poor communities raising sheep and other livestock, and involving dogs in guarding as well as herding animals. *E. granulosus* is mainly transmitted in a cycle between dog definitive hosts and livestock (mainly sheep); the human behaviour also helps to perpetuate the domestic cycle of *E. granulosus*[4]. The CE is endemic in India; the foci of the disease exist in this country with highest prevalence in Andhra Pradesh and Tamil Nadu[18]. Pednekar et al[19] reported, based upon the morphological and molecular studied, that *Echinococcus* of buffalo origin is phenotypically and genetically similar to the sheep (G1) and Tasmanian sheep (G2) strains of *Echinococcus* supporting its recognition as one species, viz., *E. granulosus* sensu stricto. In India, the annual incidence of human CE per 10⁵ persons varies from 1 to 200; it has been reported that human CE cases were with various clinical manifestations and immense morbidity[20].

![Figure 1. Human cystic echinococcosis cases per 10⁵ from different sources of a particular geographic region.](image)

4. Transmission cycle

The life cycles of *E. granulosus* can be classified as domestic, involving the domestic dog as the main definitive host and various species of domestic ungulates as intermediate hosts, or as sylvatic, involving wild carnivores (Foxes, wolves) and Cervidae (elk; *Alces alces*, reindeer; *Rangifer tarandus*, and red deer; *Cervus elaphus*) as hosts; the sylvatic cycle is reported in limited regions of the world such as North America and Eurasia[21]. In many areas of endemic infection, domestic and sylvatic life cycles coexist or overlap[7].

4.1. Natural cycle

The *E. granulosus* life cycle involves carnivores such as dogs (as well as wild canids like wolves and foxes) as definitive hosts in which the adult *E. granulosus* develops and resides in the small intestine; under natural conditions, herbivores mainly sheep (also goat, swine, cattle, horses and camels) serve as a suitable intermediate host where echinococcal cysts (larval stages) develop in various organs and tissues[5,14]. Humans function as accidental intermediate hosts, and they are usually the ‘dead end’ for the parasitic infection cycle; the consequences of human infection will be discussed later in this article.

Adult *E. granulosus* worms have been detected in various carnivores such as stray and farm dogs, red foxes, golden jackals and wolves[22–24]. Dogs play a critical role in transition the hydatidosis; the rate of infection with *E. granulosus* in stray dogs in Iran shows a prevalence of 5% – 49%[25]. The role of wild definitive hosts in the
epidemiology of *E. granulosus* is known[6]: prevalence of echinococcosis in wolves was found 14% in Spain, and the wolves parasitized with *E. granulosus* have also been found in Belarus, Italy, Finland, and Bulgaria (prevalence rate 11.5%–36%); all positive wolves harboured gravid *E. granulosus* from the sheep G1 strain. The wild definitive hosts may contribute in the transmission of animal (and human) CE in domestic cycles (Figure 2), since the G1 genotype has been found among wild animals.

**Figure 2.** Interaction between sylvatic cycle and domestic cycle of *E. granulosus* (indicated by bi-directional arrow) (A) In sylvatic cycle the definitive hosts acquire infection by scavenging herbivores acting as the intermediate hosts, (B) domestic cycle is maintained between dogs and sheep, with man as accidental intermediate host (not shown here).

### 4.2. Acquisition of infection by animals

Most forms of human CE are transmitted in domestic cycles involving dogs and livestock; the most known is the dog–sheep cycle. In a typical dog–sheep cycle, *E. granulosus* gravid proglottids or free eggs, which are passed in the faeces of infected dogs, are ingested by sheep (while grazing in the field contaminated with dog faeces), in which hydatid cysts (metacestode larval stages) develop[14]. The definitive host becomes infected by ingesting the cyst-containing organs of the infected intermediate host. Dogs usually acquire infection by ingestion of offal (liver and lungs) containing hydatid cysts with viable protoscoleces. Camels, which have an important role in transmission cycle of human CE, usually harbor G6 genotype of *E. granulosus*[21] that has also been reported from humans[26].

### 4.3. *E. granulosus* development

After ingestion by a suitable intermediate host (herbivore: sheep), the egg hatches in the small intestine and releases a hooked larva called oncosphere. The embryo, by means of its six hooks, penetrates the intestinal wall and migrates via the blood stream into major filtering organs, such as liver and lungs. In these organs, after localization, the oncosphere loses the hooks and develops into metacestode (larval echinococcal cyst or hydatid cyst) that enlarges gradually, producing many protoscoleces (future tapeworm heads) and daughter cysts that fill the cyst interior. The cycle is completed if the metacestode with fertile protoscoleces are eaten (along with the cyst–containing organs of the slaughtered parasitized sheep) by a suitable carnivore[27]. The different forms of the hydatid cysts may be of fertile, sterile and calcified types; occurrence such cysts in different organs among various intermediate host animals are represented in Figure 3. After ingestion, the protoscoleces evaginate, attach to the intestinal mucosa, and develop into adult stages in 32 to 80 days. Sexual maturity of adult *E. granulosus* occurs in the small intestine after 4–5 weeks of ingestion of offal containing viable protoscoleces. Eggs or gravid proglottids are shed in the faeces, and thus a new cycle begins.

**Figure 3.** Characteristic of livestock hydatid cysts.

### 4.4. Prevalence of hydatidosis among herbivores

The incidence of human CE is closely related to the prevalence of the disease in domestic herbivores, and currently there are reports on higher prevalence of bovine and ovine cystic hydatidosis[28]. The prevalence of infection with hydatid cyst in sheep, goats, cattle and buffaloes was recorded high in various endemic regions for *E. granulosus*[25,29]; involvement of herbivores as the intermediate hosts (bearing cystic hydatidosis) for the parasite is shown in Figure 4. Among the intermediate hosts, the most commonly infected organs are the lungs and liver[22,28,29]; the incidence of hydatid cysts in sheep, goat, cattle and camel and the organ involvement are shown in
5. Human infection (zoonotic aspect) of hydatidosis

5.1. Mode of infection

Humans become exposed to the eggs of the tapeworm after close contact with an infected dog or its contaminated environment[4]. The infected dogs pass in their feces E. granulosus eggs that adhere to hairs on the dog, and humans become exposed to the eggs after close contact with the dog (or its contaminated environment), and (humans) infected following accidental ingestion of E. granulosus eggs, or children in the course of playful and intimate contact with the infected dogs. Indirect transfer of E. granulosus eggs in contaminated water and uncooked food can also cause human infection. Certain human activities (e.g., the widespread rural practice of feeding dogs the viscera of home–butchered sheep) facilitate transmission of the sheep strain and consequently increase the risk of human infection[32].

5.2. Development of cyst

In humans, as in the herbivorous intermediate hosts, hydatid cysts of E. granulosus develop mainly the liver and lungs as unilocular fluid–filled bladders, but the cysts may develop in almost any internal organ or tissue (heart, bone, muscle, nervous system) by haematogenous dissemination, or in the abdominal cavity[4,15]. It has been documented that most primary infections in humans result a single hydatid cyst; however, 20%-40% cases are reported to have multiple cysts or multiple organ involvement, which in the same patient may indicate ingestion of many eggs of E. granulosus[20]. Salem et al[27] described human hydatid cysts due to E. granulosus infection as fertile, sterile and calcified; Figure 7 depicts the occurrence of different forms of the cysts in human liver and lungs. The protoscoleces are already formed in the fertile cysts, but a proportion of cysts does not produce protoscoleces and remain sterile.
65%), followed by the lungs (25%); the cyst occurs less frequently in the spleen and kidneys (3%), and heart, bone and brain (1%–2%). The cerebral hydatid cysts (comprising 1%–2%)[36,37] are classified as primary and secondary: primary cysts result from direct infestation of brain by the larva without any demonstrable involvement of other organs like liver and lungs[38]. Primary cysts are fertile containing brood capsules and scolices and their rupture may result in recurrent intracranial hydatid cyst; secondary cysts result from rupture of hydatid cyst in brain, and are infective with negligible risk of recurrence after their rupture[39]. The hydatid cysts, which develop in bones in < 1% cases, were found as the most debilitating manifestation of E. granulosus infection to humans[40]. The proportion of hydatid cysts that occurs in muscle has been reported as 3%–5%; cysts in the left gluteus medius measure 4.8–5.6 cm in diameter, while the cyst developed in the gastrocnemius muscle was of 10 cm as has been detected by US and CT[41]. Larval infection (hydatid disease; hydatidosis) is characterised by long–term growth of metacestode (hydatid) cysts in humans. The diameters of cysts that generally increase are variable, 1–5 cm each year. Most E. granulosus cysts are 1–15 cm in diameter when they are discovered, but some may eventually reach 20 cm[7]. The cyst in a 50–year–old woman was of 18 cm, with daughter and granddaughter cysts, weighing about 1 kg, and three other cases with cyst size 10–18 cm (2 cases) and 20 cm (1 case) were females; human CE in pregnancy revealed that hydatid cysts may grow bigger due to decreased cell-mediated immunity and humoral effects of placental steroids, as has been seen in a study that the largest cyst (20 cm) was in the pregnant woman[20].

6. Clinical manifestation and pathogenesis

On ingestion of E. granulosus eggs by human (an accidental intermediate host), the embryos escape, penetrate the intestinal mucosa, enter the portal circulation, and are trapped in the liver; a small number escape the hepatic filter, enter the systemic circulation, and are scattered to different cyst locations for immunodiagnosis of human CE, including pain in abdomen, mass per abdomen, loss of appetite and obstructive jaundice. The serological tests are helpful in making a human CE diagnosis. The current gold standard serodiagnosis is based on the detection of IgG antibodies to cyst–fluid derived native or recombinant antigen B subunits, either in ELISA or immunoblots[4]. A novel 32 kDa EpC1 antigen, which is located in the germinal layer of the hydatid cyst and the early protoscolex of E. granulosus, demonstrated antibodies in 92.2% of preoperative human cases of CE compared with 84.5% cases detected using native antigen B[4]. Rahimi et al.[20] assessed the performance of antigen B (AgB) isolated from different E. granulosus intermediate hosts and from different cyst locations for immunodiagnosis of human CE, and reported that these increased the diagnostic sensitivity and specificity of the assay (Figure 8). Al–Sakee[47] showed that E. granulosus induces both cellular and humoral immune responses, and the number of peripheral blood CD8 T cells was significantly increased in cystic echinococcosis patients; this may help diagnosis of the disease.

7. Diagnosis

The useful diagnostic methods for human CE include ultrasonography (US), computerized tomography (CT) and magnetic resonance imaging (MRI)[41]. The CT confirms the diagnosis by detecting the presence of daughter cysts and calcification in the cyst–wall; CT sensitivity ranges 90%–97%[44]. The CT demonstrates the features of the hydatid cyst; US and CT also contribute to pre–surgical diagnosis. The imaging with CT (as well as MRI) is central to the diagnosis of cerebral hydatid cysts[37]. Contrast enhanced CT scan of thorax is the diagnostic modality of choice for pulmonary hydatid cyst, and the “air bubble” sign (a relatively newly recognized radiological sign) has been reported to be very sensitive (85.7%) and specific (96.6%) in establishing diagnosis of ruptured, infected hydatid cyst[45,46]. The detection method of some extra hepato–pulmonary hydatid cysts along with their size and number and the actual localization, as has been reported by authors from different parts of the globe, are represented in Table 1. The extra–hepatic hydatid cyst disease usually remains asymptomatic unless the cyst grows and produces symptoms due to pressure, rupture to the pleural or peritoneal cavity, secondary infection, or an allergic reaction. Before the slow growing echinococcal cysts enlarge sufficiently to cause symptoms, 5–20 years elapse; abdominal pain, hepatomegaly are the most common symptoms for patients with liver echinococcosis[42]. Because the larvae of this organism usually develop as discrete single cysts, it is the least severe and most treatable form; nevertheless, large or multiple cysts may cause irreversible damage to organs, and the rupture or puncture of the cyst can seed multiple organs with larvae or cause anaphylactic reactions. Cystic hydatidosis of the bone is often asymptomatic for a long duration and is usually detected only after a sudden fracture, secondary infection or neurovascular lesion caused by compression. Hemachander et al.[20] documented presenting complaints of CE cases including pain in abdomen, mass per abdomen, loss of appetite and obstructive jaundice. The pre–operative complications include rupture of a cyst into a bronchus, bacterial infection of the cyst and obstructive jaundice, and the major complications after surgical resection with hepatic disease include single cases of pleural effusion, wound infection, biliary leak, and intra–abdominal bleeding resulting in a hepatic lobectomy[43]. Headache and vomiting due to raised intracranial tension are the most common presenting features of cerebral hydatid cysts; other manifestations include seizures, visual disturbances and ataxia[37,38].
demonstrated efficacy is useful in the management of and number of viable protoscolices [52], and as has been documented the percutaneous treatment in combination with albendazole has been found more effective than surgical cystectomy in terms of hospital stay (4.2 and 12.7 d, respectively) and complication rate (32% and 84%, respectively). The most widely used medications include mebendazole, albendazole, and praziquantel, but modifying the therapeutic approach by offering new pharmacological targets should be explored and evaluated[53,54].

9. Prevention and control

The human CE warrants more attention from clinicians, but their coordination with veterinarians and policy makers is also required to implement a more effective approach to control disease transmission Rojo-Vazquez et al[6]. Infection can be prevented through good personal hygiene to prevent hand-to-mouth transmission of E. granulosus eggs from dogs to humans, avoidance of ingestion of sheep viscera by dogs, by tailoring educational programmes, and by providing anthelmithic treatment to the definitive and intermediate animal hosts.

The current options for the control and prevention of hydatidosis include an effective livestock vaccine, potential dog vaccines against the worm E. granulosus, tailoring educational programmes, development of improved diagnostic tools for animal (definitive and intermediate) hosts and human beings, and more effective antiparasitic treatments like oxfendazole[4]. The biological cycle can be attacked at various points: regular dog deworming, controlled sheep slaughtering, vaccination of the intermediate (sheep) animal host, and in future vaccination of the definitive (dog) animal host[55–62]. However, since the wild animals involve in sylvatic cycle, which overlaps and interacts with the domestic sheep–dog cycle, this complicates the control efforts[6,14].

10. Concluding remarks

The infection of immature or mature intestinal stages of E. granulosus is not cause of morbidity to the definitive hosts, whereas the invasion of various organs (mainly liver and lungs) of humans and animal intermediate hosts by metacestodes can cause severe and fatal cystic hydatid disease. The disease is an important zoonosis, and is a serious public health and economic problem throughout the world.
It has been reported that the prevalence of hydatidosis in urban centres in India has been showing a consistently decreasing trend over the past few decades, which is possibly due to economic development and improved government legislation of abattoirs[19]. A diagnosis of hepatic and extra-hepatic echinococcal disease is more accurate today because of the new imaging techniques (MRI, CT, US) available.

Study reinforces the importance of preoperative diagnosis with CT in preventing rupture of cyst and thus achieving optimal outcome as in case of cerebral hydatid cyst. En bloc resection without inducing rupture as well as spreading the daughter cyst is recommended treatment strategy, and accepted to be curative for intramuscular hydatid disease[63,64].

The variation in *E. granulosus* may affect biology, host specificity and pathology, sensitivity to chemotherapeutics, and hence design and development of vaccines against *E. granulosus*, therefore, characterizing the exact etiological agent in different areas is imperative in order to determine the transmission patterns and control programs. Control programs based on combinations of animal vaccination, dehelminization of dogs, and education programs should be implemented to achieve effective prevention of disease transmission[65].

**Conflict of interest statement**

The authors declare no conflict of interest.

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