Review Article

Management of Echinococcosis

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Abstract

Cystic echinococcosis is a zoonosis caused by larval forms of the tapeworm Echinococcus granulosus and transmitted by dogs. In humans, the disease is characterized by slowly growing cyst commonly occurring in liver and lungs. Clinical features of hepatic hydatid cyst are mainly right upper quadrant pain, feeling of lump and enlarged tender liver. The cyst may be complicated by infection or rupture and may lead to anaphylactic reaction. Ultrasonography supported by serology is the main diagnostic modality. Treatment of univesicular cyst is predominantly medical or percutaneous. Percutaneous treatment (PAIR) is safe and effective and complications are infrequent. For multivesicular and complicated cyst surgery remains the mainstay of treatment.

INTRODUCTION

Human echinococcosis is a zoonotic infection transmitted by dogs in livestock raising areas. It is caused by larval forms (metacestodes) of the tapeworm of the genus Echinococcus found in the small intestine of carnivores. Human infection is acquired from ingestion of the parasite eggs from infected animals. Echinococcus granulosus causes cystic echinococcosis in humans. This relatively benign parasitic disease is characterized by slowly growing cysts most commonly in the liver (accounting for 50-70% of cases), followed by the lungs (20-30%), and less frequently the spleen, kidneys, heart, bones, central nervous system, and other organs. Developing countries with poor hygiene, where sheep and cattle are raised are high-risk areas of acquiring this disease.

Foci of hydatid disease also exist in India where the highest prevalence is reported in Andhra Pradesh and Tamil Nadu than in other parts of the country. The extent of its prevalence in animals is not known. A recent study in Delhi showed that approximately 10% of sheep slaughtered in Delhi slaughter houses were infected with the larval forms of the parasite. The prevalence of the disease is reported to be high in food animals in India.

Infection with the larvae of the fox tapeworm Echinococcus multilocularis occurs less frequently than E. granulosus. Liver is the primary site of infestation in 90% of the patients. Daughter cysts arise from the germinal membrane by budding on the outer side of the original cyst. This result in the invasion of the surrounding parenchyma by scolices and the disease behaves like a malignant disease.

ETIOLOGY AND PATHOGENESIS

Adult tapeworm lives in the upper small bowel of the domestic dogs, a definitive host. Other definitive hosts are wolves, jackals, domestic cats, and reindeer etc. Sheep, cattle, pigs and humans contain larval stage and are intermediate hosts. They are infected feco orally by Echinococcus eggs shed in the environment with feces of infected dogs. Eggs hatch in intestinal mucosa and transform into oncospheres which penetrate bowel wall, enter portal venous blood, and are carried to the liver. The embryos become encysted and grow at the rate of about 1 cm/yr. The hydatid cyst is composed of a fibrous and inflammatory outer layer of host origin, a laminated cuticle and a germinal membrane where protoscoleces grow and secrete clear fluid. From germinal layer, daughter cysts may be formed by invaginations. The life cycle is completed when the definitive host is infected by viable cyst containing organs of intermediate host. In the intestine of the dog, protoscoleces develop into adult tapeworms. Man is a dead end host and becomes feco-orally infected by echinococcal eggs.

DIAGNOSIS

The diagnosis is based on –
1. History and clinical examination
2. Imaging
3. Serology

Microscopic examination of the cyst content confirms the diagnosis.

CLINICAL FEATURES

Due to slow growth of the cyst, most patients have no symptoms. Large cysts (usually more than 10 cm in
diameter) may cause right upper quadrant pain, which is the most characteristic symptom. Pain may be intermittent or continuous and gradually increasing over a long period of time. Urticaria, asthma like symptoms and fever may occur as a response to the *Echinococcus* antigen in cyst fluid. Most common physical signs are raised right hemi diaphragm, a tender enlarged liver or a palpable liver mass.

**Complications**: Cyst may rupture into the biliary system (leading to cholangitis with or without obstructive jaundice and marked eosinophilia), into the peritoneum (leading to anaphylaxis and/or peritoneal dissemination) or into the pleura or lung (causing pleural hydatidosis or bronchial fistula). In one series, anaphylaxis complicated 10% of all peritoneal ruptures. The rupture may either be spontaneous or more usually after blunt trauma.

Rupture of echinococcal cyst can be of three types:

1. **Contained rupture** - only endocyst is torn and cyst contents are confined within pericyst. The size of cyst does not decrease on imaging.
2. **Communicating rupture** - there is tearing of endocyst and cyst contents escape via biliary radicals or bronchioles that have been incorporated in pericyst. On imaging, cyst becomes smaller with undulating membrane.
3. **Direct rupture** - both endocyst and pericyst rupture causing spillage of contents into peritoneum or pleural space and dissemination of disease.

Cysts may become infected following bacteremia or via communicating bile ducts, especially when endoscopic retrograde cholangiopancreatography (ERCP) has been performed. These patients present with high fever, sepsis syndrome and a tender liver. Pressure or mass effect on the bile ducts, portal veins, hepatic veins and inferior venacava can cause cholestasis, portal hypertension and the Budd-Chiari Syndrome, respectively.

Laboratory tests are often completely normal. Eosinophilia may be present in 40% of patients or there may be slightly elevated alkaline phosphatase or gamma glutamyl transferase.

### IMAGING

Ultrasonography is the preferred diagnostic tool for hepatic hydatid cysts. It has advantages of easy availability, cost effectiveness, and ability to classify and estimation of cyst viability. Gharbi classified hepatic hydatid cysts in to 5 types depending upon the viability:

- **Type 1** – Univesicular hypodense cyst containing "hydatid sand" (Fig. 1).
- **Type 2** – Univesicular hypodense cyst with double or undulating membrane
- **Type 3** – “Mother and daughter” cyst which is highly specific for hydatidosis

Type 4 – Detachment of the germinal layer which produces classical “Water Lilly” sign, echogenic content with solidifications or a pseudotumor aspect (Fig. 2).

Type 5 – Cyst wall calcification.

Type 1, 2 and 3 are viable cysts at postoperative parasitological examinations and type 4 and 5 are non-viable cysts.

CT scan is useful to visualize the relation of the hydatid cyst to the surrounding liver tissue, bile ducts, portal and hepatic veins and its segmental location.

**Serology**: Enzyme linked Immuno Sorbent Assay (ELISA) is used as a screening test and immuno electrophoresis (IE) as confirmatory test. An antibody titers >1:160 is usually considered positive. Diagnosis is established if both ELISA and IE are positive. Serology may be negative in 10-15% of cases, especially in well-
encapsulated cysts. Sensitivity of serological tests for liver cysts is 80-90% and specificity is 88-96%. For pulmonary cysts sensitivity is only 50 to 60%. IgG₄ response is more pronounced than that of IgG₁.⁸

**TREATMENT**

The ultimate goal of treatment is elimination of the germinal layer. Currently, three treatment options are available (1) Surgical (2) Medical (3) Percutaneous.

**Surgery**

Principles of hydatid surgery are (a) total removal of all infective cyst parts (b) avoidance of intra-abdominal spillage of cyst contents.

Mainly two types of surgeries are performed
(i) Radical
(ii) Evacuation of cyst content

Radical surgical resection includes liver resection, pericystectomy and cystectomy and has the advantage of prevention of intraabdominal spillage. The cyst is entirely removed and its opening is avoided.

Liver resection is most extensive technique. Pericystectomy involves a non-anatomical resection of the entire hydatid cyst including endocyst and pericyst. It is technically more difficult than cystectomy in which only laminar layer, germinal layer and cyst content are removed and pericyst is not resected.⁹ Surgical evacuation of cyst content is performed when radical surgery is not possible. Peroperative use of scolicidals prevents intraabdominal seedling of protoscoleces. “Frozen seal” method introduced by Saidi, in which cyst content and cyst wall are evacuated through a specially designed cone, frozen to liver surface overlying the hydatid cyst, is also helpful in avoiding intra abdominal spillage.¹⁰

Postoperative complication rates range form 8-16%, relapse rate 10-30% and in-hospital mortality is 4%.

Laparoscopic pericystectomy or drainage of anteriorly located cysts has been performed by various investigators.¹¹ This method is less traumatic and requires shorter hospital stay with faster recovery. During long-term follow-up, high success rates (77-100%), low complication (0-17%) and recurrence rates (0-9%) have been reported. However, its main use is for anteriorly located cysts.

**Medical treatment**

Benzimidazole car bamates (mebendazole and albendazole) kill the parasite by impairing its glucose uptake and have proved effective against the larval stages of *E. granulosus*.

In a prospective randomized trial, patients with single hydatid cyst were treated with mebendazole for a period of 3-6 months and followed up for 22 months (12-170). The success rate was 74% in all patients. The efficacy of albendazole (82%) was superior to that of mebendazole (56%). Relapse rate was 25% in both treatment groups. Most relapses (78%) occurred within two years while the rest of the relapses occurred between 2-8 years following treatment.¹²

Multivesicular cysts, hepatic cysts and cysts in older patients respond less well to treatment than univesicular cysts, pulmonary cysts and cysts in younger patients (<30 yrs of age).

Albendazole is also used preoperatively or before percutaneous drainage to reduce viability of the cyst. In study by Gil-Grande et al, both 1 month and 3 month preoperative course of albendazole significantly reduced cyst viability to 28% and 6% respectively.¹³ In placebo treated patients, 50% of the cysts were viable at surgery. Perioperative prophylaxis with albendazole is also advisable.

Most characteristic signs of involution following benzimidazole treatment are (1) decreased cyst size (2) detachment and collapse of inner membrane sometimes showing “Water Lily” sign (3) increased echodensity of cyst content (4) cyst wall calcification.

Albendazole absorption is dependent on gastric pH; H₂ receptor antagonist may decrease its absorption by 50%. The drug is degraded by cytochrome P-450 enzymes located in the villi of small intestine. Intraluminal degradation can be prevented by grape fruit juices.

Albendazole absorption can be significantly improved by combining with a fatty meal (4-9 fold), with praziquental (3 fold) or by administration of higher doses (10 mg/dl).¹⁴ Adverse effects are seen in 5-12% of patients and include headache, nausea, vomiting, anorexia, abdominal pain, reversible hair loss and itching. The drug is contraindicated in first trimester of pregnancy. The relative bioavailability of albendazole formulation that use arachis oil polysorbate 80 or hydroxypropyl – betacyclodextrin, as an excipient, is increased up to 4.3-9.7 fold compared to conventional preparation.¹⁵

In general there are four different goals of medical treatment.
(i) Definite cure – for univesicular cyst (type 1 and 2) 3-6 month treatment has success rate of 82% and relapse rate of above 25%, most of which occurs within 2 years. Life long follow-up is advised.
(ii) Reduction of viability and cyst size can be achieved in multivesicular cysts (type 3), however, germinal layer is rather resistant to treatment and definite cure occurs infrequently.
(iii) Preoperative reduction of viability of univesicular cysts before planning elective surgery or percutaneous drainage.
(iv) Perioperative or peri interventional prophylaxis – optimally should be started at least 3 days before the surgical percutaneous treatment and should be
continued for 3-8 weeks post-treatment in uncomplicated cases and for 3-6 months in complicated cases.

Percutaneous treatment

It is minimally invasive and very effective in the treatment of hepatic hydatidosis. The technique is called PAIR (Puncture – Aspiration – Injection – Re-aspiration).16 Usually albendazole prophylaxis is started 1 week before PAIR and continued for 3-4 weeks thereafter. Cyst is punctured under ultrasonographic guidance. Cyst fluid is subtotally aspirated; hypertonic saline (20%) or 95% alcohol is injected. Scolecidals are re-aspirated after 10 minutes. Following intracystic injection of scolecidals, both germinal layer and protoscolecies become instantaneously non-viable. Success of PAIR is defined as detachment of endocyst, rupture of daughter cysts, and non-viable protoscolecies at microscopy of cyst fluid. Ultrasonography may show heterogeneous reflection of cyst contents at 3 months, obliteration and pseudo tumor aspect at 5 month or loss of echogenicity and disappearance of cyst at 9 months.

PAIR is a safe technique with high success rate of 90-100% and low relapse rate (0-4%) in various studies. WHO Informal Working Group on Echinococcosis has reported the results of 765 hydatid cysts treated in multiple centres. The report has shown success rate of 99.7%, failure rate 0.26%, relapse rate 1.57%, and complication rate 14.8%. Anaphylactic shock and spillage occurred in 0.52% each.17

Ormeci et al has described simplified PAIR method using a mixture of 95% alcohol and 1% polidocanol. Polidocanol enhances the sclerosing effect of alcohol. The treatment is performed as an out-patient procedure without albendazole prophylaxis. After ultrasound guided puncture, cyst fluid is allowed to drain freely until it ceases and simply replaced by a mixture of absolute alcohol and polidocanol. The needle is left inside the cyst for 5 minutes and then withdrawn without aspiration. The advantages of this technique are that it is performed on out-patient basis, daughter cysts need not to be punctured separately and albendazole prophylaxis is not required.18

Contra indication to PAIR: Cystobiliary fistula (scolicidal may cause sclerosing cholangitis), cysts at risky locations, inaccessible cysts, multiple septal divisions, echogenic lesions, and inactive or calcified cysts.

Indications: Anechoic lesion ≥ 5 cm in diameter with no cyst biliary communication, patient refusing surgery, unfit for surgery or has relapsed after surgery, pregnant patients, children > 3 years of age and multiple cysts ≥ 5 cm in different liver segments.

For multivesicular cysts with or without cystobiliary fistula and containing non-drainable material, another percutaneous technique called PEVAC has been described. In this the cyst contents are evacuated with the help of large bore Amplatz sheath (14-18f) and suction catheter without using any scolicidal agent. If cystobiliary communication is detected, endoscopic sphincterotomy and stent placement is done.19

Radiofrequency thermal ablation

This is an experimental approach in which energy is applied through the needle electrodes and high temperature (up to 100°C) is achieved inside the cyst. Cyst material is aspirated after procedure. The results of this technique are preliminary and efficacy has to be proven.20

Comparison of various treatment options: Khuroo et al compared albendazole monotherapy (ABZ; 10mg/kg/day; 8 wks) with PAIR combined with albendazole (PAIR-ABZ) and with PAIR without it (PAIR). At 6-9 months follow up, all 10 cysts treated with PAIR and 12 cysts treated with PAIR-ABZ showed significant reduction in size in comparison to 2 cysts (out of 11) treated with ABZ only (P < 0.01). Maximum reduction was observed in PAIR+ABZ group (P<0.05).21

PAIR and surgery were equally effective in reducing cyst size at 17 months with follow-up study done by same author.22 In the PAIR group 88% of cyst disappeared and in the surgery group 72%. The advantage of PAIR included significantly shorter hospital stay and complication rate.

In a recent meta-analysis, the clinical outcome for 769 patients with hepatic cystic echinococcosis treated with PAIR plus albendazole was compared with 952 matched historical control subjects undergoing surgical intervention. Clinical and parasitological cure was greater in patients receiving PAIR plus chemotherapy (96% vs. 90%). Disease recurrence (1.6% vs. 6.3%), major complications (8% vs. 25%), and death (0.1 % vs. 0.7%) occurred more frequently among surgical control subjects.23

Conclusion

Patients with univesicular cyst (type 1 and 2), albendazole monotherapy is the first choice. PAIR is indicated if albendazole fails. For multivesicular cysts, the choice is either surgery or other percutaneous treatment (PEVAC or simplified PAIR). Surgery is the first choice when there is cyst biliary fistula, significant extra-hepatic extension with high risk of perforation, complicated cysts (ruptured or infected) and when expertise to percutaneous treatment is not available.

References