

The liver involvement of the hydatid disease : a systematic review designed for the hepato-gastroenterologist

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Abstract

Hydatidosis is not uncommon in Western Europe, mainly due to the presence of immigrants from endemic countries, and hepato-gastroenterologist must then be able to manage this infectious disease. The hepatic hydatidosis is due to development in the liver of the larvae of *Echinococcus granulosus* that causes liver cysts. It can grow in size throughout the years and can give rise to complications, mainly pain, super-infection or cyst rupture. Recent progresses in imaging modalities play an important role in diagnosis, classification and evaluation of response to treatment of the cysts. Imaging techniques led to both Gharbi's and WHO's classifications. Those can provide markers of cyst activity and can help to determine the best therapeutic strategy. By combining two immunodiagnostic techniques, the diagnostic accuracy of laboratory tests is excellent. During the last decade, treatment has improved : the main therapeutic modality in the past was surgery, until the discovery of PAIR procedure (Puncture, Aspiration, Injection, Re-aspiration). Albendazole also plays an important role in the treatment of hydatid cysts either alone or as a pre-procedure or post procedure prophylaxis. This review will cover the major aspects of the disease emphasizing the recent diagnostic and therapeutic advances. (*Acta gastroenterol. belg.*, 2013, 76, 210-218).

1. Introduction

Predominant disease in developing countries, the hepatic hydatidosis can affect up to 5% of the population in highly endemic areas. The prevalence of asymptomatic hydatid disease is between 3% and 9.3% in highly endemic areas such as rural villages in the central Peruvian highlands (1). It is the most common cystic lesion after benign liver cysts. The hepatic hydatidosis is due to development in the liver, of the larvae of *Echinococcus granulosus*. The disease is common in areas of sheep farming where this infection can then be endemic : that is the case of North Africa and many countries in South America. Geographic distribution differs by country and region depending on the presence of sheep and goat (that represent the intermediate host of the parasite) and their contact dog (the definitive host). The latter mostly provides the transmission of infection to humans.

This work aims to highlight the recent guidelines in managing this parasitic disease in the real life, dedicated to the clinicians. This review will cover the major aspects of the disease, focusing on the special interest for hepato-gastroenterologists : a general overview and the most pertinent data on symptoms, diagnosis and new treatments.

2. Parasitology

Echinococcal disease develops when a person gets infected with the evolved form of the egg (the oncospheres) of a tapeworm belonging to the genus *Echinococcus*. *Echinococcus* includes four species : *E. granulosus*, *E. vogeli*, *E. oligarthus* and *E. multilocularis*. Only 2 are associated with human disease : the *Echinococcus granulosus* (cystic disease) and *multilocularis* (alveolar hydatidosis) (2). Stricto sensu, the hydatid disease is mainly due to the human development of the larval form *E. granulosus*.

Hydatidosis (or hydatid disease) is a complex zoonosis affecting many animal species. There are 3 hosts in the life cycle. A definitive host (mostly dogs), an intermediate host (e.g. sheep) and an incidental host (humans). The intermediate host is a herbivore, foremost sheep grazing along the ground. The camels, and reindeers are specific to certain regions (3). Hydatidosis affects man who accidentally becomes an intermediate host in the cycle of this helminthiasis. The adult tapeworm (2-7 mm long) may live in the small intestine of the definitive host. It consists of scolex with suckers, hooks and 3 proglottic segments. Each worm can produce thousands of eggs which are passing through the feces to the environment. The oncosphere (evolved form of the egg) can spread through the blood by the portal venous system and then passes through the liver where it usually stops. After egg ingestion by humans, the oncospheres hatch from the eggs, penetrate the small intestine and enter the blood and lymphatic tissue (passage of the oncospheres in the lymphatic system could exist and explain the unusual location such as lung cysts without concomitant liver damage). Then it will reach the liver and other visceral organs. A few days later, a fluid filled cyst will start to develop with several layers, consisting of an external membrane and an internal germinal layer, to become a metacestode. The hydatid cyst wall is composed of two membranes, an internal (or proliferous), which gives rise to daughter vesicles and an external acellular laminated

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layer, very resistant to pressure within the cyst. The cyst is surrounded by a fibrous shell which limits its extension (peri-cyst). The daughter cysts develop from the inner germinal layer. New larvae, called proctoscolices then develops from this capsule. The cysts expand over a period of years.

The infection is passed by the fecal-oral route, contamination of vegetables, water or contact between dogs and humans. There is no human to human transmission (4).

Human infection results from cohabitation between humans and dogs infected with *Echinococcus granulosus*, and the free access to the viscera of slaughtered animals. Epidemiological surveys, based on serology and autopsy, were conducted to determine the level of carriage in dogs in different countries. The rate of infection of the dog is 8% in Israel, 14% in Jordan, 22% in Tunisia (3). Man contracts the disease through ingestion of eggs in two ways (5). Through a direct contact with the feces of the dog : the dog licks its anus, defiles the fur when making its toilet, and contaminates the man by licking his face or by being stroked. Man can also be infected indirectly by drinking water or by collecting fruits and vegetables contaminated by the eggs. The eggs are highly resistant to weather conditions and can remain viable for months. Its survival depends on soil moisture conditions and temperature : low humidity and high temperature decrease the viability (6).

3. Epidemiology

The hydatid disease is most common in shepherds but also children who play with dogs or pets. Human prevalence is particularly high as the dogs have access or are deliberately fed the viscera of slaughtered animals (5). The hydatid disease is more prevalent in young adults, the average age of diagnosis is 40 years (1).

Because of its epidemiology, echinococcosis occurs more frequently in countries of sheep farming. South and Central America, Middle east, some sub-Saharan African countries, China and the Soviet Union are the most prevalent countries (2,7,8).

Even though, Echinococcosis is a cosmopolitan zoonosis. Hydatidosis is still a major public health problem in these regions of the world. In Europe, the Mediterranean countries are the most exposed (Greece, Italy, Spain, Portugal). Hydatidosis is not uncommon in France (more than 800 cases are diagnosed yearly in this country) but the vast majority of cases are due to the presence of many immigrants from countries where hydatid disease is endemic (9).

4. Clinical manifestations

Clinical aspects and circumstances of the discovery of the disease are highly variable. The disease is predominant in the liver and lung. Even if the disease is frequently benign, the mortality is not negligible and morbidity is

still high. The initial stage of infection is always asymptomatic. Cysts may increase in size from 1 to 5 cm per year. The liver is the most frequently infected (50-70%). Lungs are involved in 25 % of cases in addition to the rest of organs including : brain, kidney, bone, heart and pancreas. The cyst is unique in 65% of patients, double in 15 to 20%, and multiple in 10% to 35% of cases. There is either a primary inoculation or secondary contamination due to the rupture of the cyst and the dissemination of the daughter vesicles (10).

Symptoms of right upper quadrant pain, nausea, vomiting, or fever can occur depending on the size of liver cyst and potential compression of adjacent organs (see "complications"). The high frequency of asymptomatic hepatic location reflects the good tolerance of liver involvement in this infection. The cyst is often clinically silent, latent for many years, and well encapsulated. At diagnosis, the hepatic cyst could possibly be calcified (30 to 60% of cases). A thin calcification can be found in active cysts whereas a complete calcification is signing the parasitic death.

When evolving, the cyst can compress the surrounding tissue without any clinical significance or with a progressive sensation of tightness or heaviness of the right upper quadrant, dyspepsia, postprandial fullness. When the cyst is very large, abdominal palpation typically shows hepatomegaly, a painless swelling deforming the abdominal wall.

5. Complications

Complications occur in between 20 and 40% of cases of hospitalized patients with hepatic hydatid cysts. Three varieties of complications are described : mechanical, systemic, septic (11,12).

Mechanical complications can be divided in *adjacent compressions* and *ruptures*. Compression of surrounding organs can lead to cholangitis or veins compressions (hepatic, portal, vena cava) resulting in portal hypertension and, in few cases, in rare Budd-Chiari syndrome.

The cyst may also lead to rupture which may be communicating or contained. The rupture may be contained, when the endocyst is fissuring without any liquid flow. In the opposite, the rupture is communicating when a fistula develops between the cyst and the biliary tract (resulting in cholangitis), pancreatic ducts (leading to pancreatitis), adjacent veins, the digestive lumen or the lungs. The diagnosis of cyst rupture is not easy because the symptoms are nonspecific and polymorphic. Abdominal pain seems constant (92-100%). In a series of 83 cases (13), the clinical manifestations are dominated by the hepatomegaly (75%), fever (34%), jaundice (8%), pruritus (7%). Biliary fistulae are the most common complications of liver hydatid disease (40-60% of the complications, see figure 1). Liver cysts may rupture into the peritoneum (resulting in secondary peritonitis) or into the pleural space (resulting in pulmonary or pleural hydatidosis). After intraperitoneal rupture of a hepatic hydatid cyst, the mortality rate

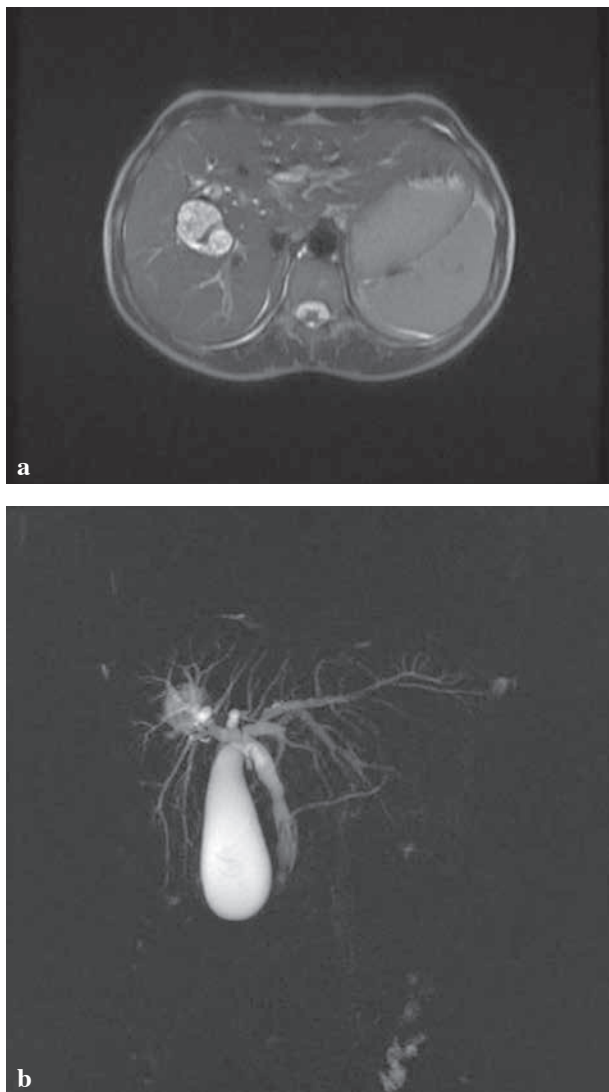


Fig. 1. — Magnetic resonance pictures showing a hydatid cyst with biliary communication. The patient (25 years old woman) was admitted with the triad of biliary colic, jaundice, and urticaria. **a.** Frontal T2 weighted MR picture showing a 46 mm × 39 mm cyst of the right lobe ; **b.** MR Cholangiography showing a biliary communicating cyst and a dilated (12 mm) main bile duct containing a heterogeneous material.

increases up to 6% and morbidity rates range between 20% and 35%. These rates are even higher for older patients with poor performance status and comorbidities. The estimated frequency of bronchial fistula in the context of lung cysts is 2 to 11% (14).

When a cyst ruptures, it can give rise to mechanical complication but also to systemic reactions.

These complications are rare (1%). The patient will complain of fever, chills, tachycardia, and dyspnea due to anaphylaxis. This is due to the release of antigenic material and secondary immune reactions (15). It can either appear abruptly, in a context of a traumatic rupture of the cyst, or less often spontaneous. It can also occur more chronically when the liquid content of the cyst is slowly spilling into the bloodstream. The clinical presentation is

more commonly benign, associated with pruritus, urticaria, lymphedema, bronchospasm. These events can be serious, causing death within hours by anaphylactic shock as a result of a IgE-dependent type I hypersensitivity phenomenon (16).

Liver abscesses may be due to the infection of the contents of the cyst. It is either secondary to a fissure of the cyst or secondary to a hematogenous spread of the infection. In a recent study, clinical and microbiological characteristics of super-infected hydatid cysts were described. In this cohort, 7.3% of 503 patients had a super-infected cyst. Finally, 55.5% of super-infected cysts were type CE2 (WHO classification). This result supports the theory that larval viability does not preclude cystic super-infection (17). There is no clear information on the viability of the parasitic cyst in case of bacterial superinfection. Manterola *et al.* found that liquid examinations revealed the non-viability of scolex in this type of cysts (18). Moreover, traditionally, this condition has been treated by simple drainage. But the same team also reports that cystostomy and drainage is usually associated with unsatisfactory postoperative evolution with residual cavity formation. This finding supports the theory that superinfection is not able to definitively kill the parasite. Manterola *et al.* advised a more aggressive procedure to achieve a cure in superinfected cysts (19). The procedure consisted of surgical drainage, parasite material extirpation and pericystic membrane resection with surrounding healthy liver parenchyma.

6. Elements of the diagnostic work-up

It is a combination of serology and imaging modalities. On routine lab work-up, there might be eosinophilia and perturbed liver function tests. But all these laboratory abnormalities are non-specific for hydatid liver disease. Imaging techniques are commonly used to detect cysts and define their characteristics in order to differentiate whether they are active or inactive, in order to decide on the best therapeutic modality.

Imaging is commonly used to visualize the hydatid cyst and its components. These techniques are accurate and, when they are used together, can often make a definitive diagnosis. They are also able to assess complications (20). The appearance of the cyst on imaging depends on its maturation.

6.1.1. Abdominal RX

It is performed in the standing position. It can highlight a diaphragmatic elevation and/or calcifications of the cyst.

6.1.2. Sonography (21)

Ultrasound (US) is the first-line examination. It has a sensitivity of 90-95% in detecting the cyst. The most common presentation is a smooth, anechoic round cyst. When there are a lot of membranes or daughter cysts, there will be the appearance of mixed echoes or internal

Table 1. — The Gharbi's and the WHO classifications and their corresponding activities

Gharbi classification	WHO classification	Activity of the cyst
	CL (cyst wall invisible)	
Type I (pure fluid)	CE1 (cyst wall visible)	Active
Type II (split wall, floating membrane)	CE3a (floating membrane)	Active
Type III (daughter cysts, with or without degenerated solid material)	CE2 (multivesicular, "rosette")	Transition
	CE3b (multiple floating membranes)	Transition
Type IV (Heterogeneous pattern)	CE4 (heterogeneous)	Transition-Inactive
Type V (calcified wall)	CE5 (calcifications)	Inactive

septa on US, which could be confused with abscess or neoplasm. To date, the classification of Gharbi is the most used who described five ultrasound stages (10, 22,23). The ultrasound may allow the classification as active, transitional or inactive (see table 1).

The WHO classification differs from Gharbi's by classifying cysts into initial undifferentiated cystic lesions (CL) and evolved cysts (CE). The presence of fluid collection with a split wall (detached laminated membrane) defines the type II in the Gharbi's classification and the CE3a in the WHO'S classification. Moreover, it is dividing CE3 into CE3a (detached endocyst) and CE3b (predominantly solid with daughter vesicles), which had an impact on the choice of the treatment modalities (24).

6.1.3. Computed Tomography (10)

It has a higher sensitivity than US reaching up to 95%. It helps to determine size, number and location of the cysts. It shows extra-hepatic cysts better than US. It can monitor response to treatment and detect recurrences. It is better than US in determination of calcifications, complications such as rupture, peritonitis and provides a better study of the anatomy (15).

It should be performed with intravenous injection of contrast medium. The typical image (type I in the Gharbi's classification) shows a fluid density close to zero Hounsfield Unit when it is homogeneous. On CT, hydatid cysts are hypodense compared to the normal liver. They are well limited and generally surrounded by a thick wall, visible on different sections before and after injection. Thin calcifications are visible in 50% of the cases. The different stages (that are well described by ultrasound) are also demonstrated on CT : detachment of the membrane, daughter-vesicles, "rosettes", heterogeneous component. Membranes, floating in the hydatid fluid, are pathognomonic. In the type 4 cyst (solid mass) hyper vascularity of the inner component is never demonstrated, and when it exists, this sign eliminates the diagnosis of hydatid disease.

6.1.4. Magnetic resonance imaging (25).

It has no major advantages when compared to CT-scan except for studying intra and extra hepatic biliary

communication and for studying the venous system. The presence of bile in the inner component of the cyst can be identified by MR cholangiography (26,27). The latter is sensitive to detect such an abnormality but is not specific.

6.1.5. Classification of Gharbi when integrating the different imaging modalities (21).

The different aspects (based on the Gharbi's classification) are summarized in table 2.

6.1.6. Monitoring of the cyst using imaging modalities (15) :

The presence of a liquid-liquid level in a type II cyst (bile reflux), dilatation of the bile ducts, the presence of hydatid material in the bile ducts, or a collapse of a cyst is suggestive of biliary-cystic communication. In this setting, the T1 hyper intensity of the cyst on MRI is an accurate sign of biliary communication. The MR cholangiography examination can highlight these abnormalities (29).

Inactivity of the cysts may be predicted by collapse, disappearance of inner septa, calcification of the cystic wall, and detachment of the germinal layer from cyst wall. Detachment of the endocyst from the pericyst is probably related to decreasing intracystic pressure, degeneration related to the host response, trauma, or response to therapy (30, 31). This sign could be used as a marker of cyst activity.

6.2.1. Indirect arguments

Eosinophilia is concomitant to the invasive phase and fades quickly. It sometimes persists (in 7-15% of cases) at a moderate level. It may reappear when a fissure of the cyst is developing.

6.2.2. Direct arguments

Serological tests highlight the specific antibodies against *E. granulosus* (32). Qualitative immunodiagnostic is useful when making the primary diagnosis while quantitative titers could be useful to check the efficacy of the treatment. Antibody detection in serum is the method of choice. Serology should be performed systematically when the diagnosis is suspected, but its diagnostic

Table 2. — Different imaging modalities integrated in the Gharbi's classification

<p>Type I : A unique anechoic cyst, sometimes containing discrete sediment or a liquid-liquid level. The wall is almost always thicker than a simple benign biliary cyst. It may contain fine calcifications, detected earlier by CT. There is no enhancement of the cyst after injection, while the enhancement of the peri-cyst is rare. The two layers (internal and external) can sometimes be identified on ultrasound (28). On MRI, the pericyst is detected as a hypo intense area in all sequences, including T2-weighted.</p> <p>Type II : Mature cyst, with a decrease of the intracystic pressure. The proligerous membrane detaches from the cuticle and gives a characteristic floating membrane (water lily sign).</p> <p>Type III : Cyst with multiple daughter vesicles, intracystic dissemination.</p> <p>Type IV : Heterogeneous pseudotumoral mass with a large central matrix. The liquid component is smaller. A contrast between an active internal proliferation of the germinal membrane and a degeneration of the cyst with debris of membrane occupying the cystic cavity. Characterized by the presence of residual fluid zones rather on the periphery of the mass, the existence of a laminated aspect of the content, the lack of contrast intake, the presence of a peri-cyst (hypo intense on T2 phases using MRI).</p> <p>Type V : The cyst is completely calcified at the periphery, or even globally, corresponding to a non-fertile cyst.</p>

accuracies is imperfect, with, in case of liver involvement, about 10% of false negative and as many false positive results. Liver cysts will have a positive serology in 85 to 95 % of the cases. Tests that might be false positive were found in other helminthic infections, cancer, or immune disorders (33). False negative tests were found in children, pregnant women and rarely due to humoral immune deficiency. Negative serology does not rule out *Echinococcal* infection. There is no correlation between number and/or size of the cyst and the value (titer) of serology. On the contrary, if the cyst is calcified or inactive, serology will be less likely positive.

The crude antigen such as hydatid fluid or proctoscoler extracts is used to perform tests based on the antigen/antibody interactions.

Qualitative methods :

Immunoelectrophoresis and electrosyneresis are the most common qualitative method. These reactions aim to put in contact the purified antigen and the patient's serum. In the immunoelectrophoresis method, antigens and antibodies create different arcs of precipitation when they meet together (1 to 15). The arc-5 test reached the higher accuracy for the diagnosis : the specificity is excellent (above 90%) but the sensitivity is insufficient (less than 80%).

Quantitative methods :

These tests are commonly the indirect hemagglutination (IHA), the indirect immunofluorescence (IIF) and especially immunoassays (Enzyme Linked Immunosorbent Assay, ELISA) using a purified antigen (fraction 5) (32). These tests are based on reactions using gradually diluted sera that allow a quantification of the titer of antibodies. They have a good specificity and excellent sensitivity. By combining two techniques, one qualitative and one quantitative, the sensitivity and specificity reached 90 and 95%, respectively (34,35).

Serological surveillance allows for controlling the therapeutic efficacy. There is often an increase in antibodies levels (even if they were negative initially) 6 weeks after a surgical resection. Thereafter, a slow decrease until the negativity occurs between 1 and 5 years. This monitoring can also be applied during a medical

(non surgical) therapy. A rapid increase in the rate of antibodies can be observed for a secondary echinococcosis.

6.2.3. Fluid aspiration as a diagnostic tool

Aspiration of the cyst aiming to obtain a direct parasitological diagnostic is not routinely done in clinical practice. It is only indicated when serology and imaging are inconclusive. This method allows confirming microscopically the presence of proctoscolices, hooklets or membranes. Active cysts will have watery fluids with elevated pressure, while inactive cysts will have cloudy fluid with low pressure. The risk of spillage and anaphylaxis is minimized by giving benzimidazoles (mainly Albendazole) before performing the procedure under U/S or Ct-scan guidance (36).

Polymerase Chain Reaction (PCR) techniques on fluid aspiration is increasingly being accepted as a complementary diagnostic tool for echinococcosis. It has been developed to detect *E. multilocularis* and *E. granulosus* nucleic acids in biological samples. PCR is most frequently applied to drainage material and biopsy samples when serological methods are negative and/or discordant (37).

7. Treatment

The treatment of hydatid cysts of the liver has long been purely surgical. The recent emergence of therapeutic alternatives brings a new era in the management of this condition. In general, the treatment of this disease should be restricted to centers that have a high level of expertise in liver surgery.

Several benzimidazole (BZD) derivatives are active against hydatidosis. Mebendazole (Vermox®) was tested in the 1970s. In the early 1980s, Albendazole was found to be more efficacious, and currently, it is the only one used in clinical practice (38,39). BZDs act by interfering with glucose consumption of nematodes and cestodes. They impair the absorption of glucose through the wall of the parasite by inhibition and disruption of the assembly of tubulin to microtubules in the cytoplasm depleting their glycogen stores. Degenerative changes in the endoplasmic reticulum, the mitochondria of the germinal layer, and the subsequent release of lysosomes result in

Table 3. — Indications of the exclusive medical approach according to the WHO

Patients with inoperable disease Patients with multiple cysts in two or more organs; Multiple small liver cysts or cysts deep in liver parenchyma; Peritoneal cysts Prevention of secondary spread of Echinococcal infection following spontaneous rupture

decreased production of adenosine triphosphate (ATP), which is the energy required for the survival of the helminthes. Due to diminished energy production, the parasite is immobilized and eventually dies. Albendazole also has been shown to inhibit the enzyme fumarate reductase, which is helminthic-specific. Their action on extra-intestinal parasites requires high doses for long periods due to their poor bioavailability (40-42) : administration of 10 to 12 mg / kg in 2 divided doses for 28 days up to 3 or 4 courses of 28 days, separated by intervals of 14 days. This dose was set in 1980s, which included treatment interruption because of limited long term toxicity data available in the early days of use (24). Nowadays the recommended dose is 400 mg BID continuously without interruption for up to 3 to 6 months in order to achieve a 30% cure. Some experts recommend giving Albendazole for 1 year (38,43).

The recommendations of the WHO-*Informal Working Group on Echinococcosis (WHO-IWGE)* for an exclusive medical treatment is summarized in Table 3 (24).

These drugs show a reversible hepatotoxicity in 1 to 5% of patients. The other reported side effects are reversible leucopenia (< 1%), hair loss (< 1%), dizziness, headache, vomiting and rash. BZD derivatives are also contraindicated in pregnancy (especially during the first trimester) because of possible teratogenicity. This teratogenicity was seen only in rabbits and rats. There are no controlled studies done in humans yet. Before starting treatment with Albendazole, a woman must have a negative pregnancy test, and after the end of treatment a waiting period for at least on month is recommended before she tries to become pregnant (24). In an optimal management, the drug level of Albendazole should be monitored every 2 weeks and then every 3 months. The blood tests should be done 4 hrs after ingestion of the morning dose and blood levels should range between 650 and 3000 nmol/ml. Measurement of blood levels of Albendazole is not done routinely in clinical practice because of cost and availability often only in research centers. Ultrasound should also be done every 3 to 6 months for the first 2 years, then yearly thereafter (43).

In patients undergoing an exclusive medical treatment, 30% of cysts disappear, 30 to 50% of the treated cysts are showing signs of degeneration or have a reduction in their size and 20 to 40% of cysts remain unchanged after 12 month (44).

Praziquantel is an isoquinolone, which has been shown to have effective protoscolicidal activity, and may be more effective than Albendazole in vitro. Praziquantel (25 mg/kg orally each day) has been used alone and in

combination with Albendazole (45,46). It is usually well tolerated but occasionally causes headache, nausea or abdominal discomfort, in addition to QT prolongation. A number of reports suggest that the combination of Albendazole and Praziquantel as medical therapy or as post spillage prophylaxis is more effective than either therapy alone. For most hepatic cysts, 2 weeks Praziquantel and 3 months Albendazole should be given to kill all protoscolices, damage or kill the germinal membrane, reduce cyst pressure and make surgery easier and safer (47). If re-assessment at 3 months shows that the cyst is disappearing, Albendazole may be discontinued. Even though chemotherapy may kill the parasite, the cyst may not collapse nor be absorbed. The dead material may become secondarily infected and re-present as an abscess.

The risk of anaphylactic shock and intraperitoneal dissemination were the major reasons to consider puncture of the cyst as a high risk procedure. This has however changed over the last two decades and has been questioned since accidental puncture of the cyst never has conducted to these hypothetical clinical complications (48). The method called puncture, aspiration, injection, re-aspiration (PAIR) was first described in 1986. It was found to be more efficacious with a lower rate of recurrence and complications, compared to surgery (49-51). It is defined as puncture under radiological guidance, mainly Ct-scan, then aspiration of cystic fluid followed by injection of a protoscolicidal agent. The World Health Organization (WHO) has now approved this procedure and considered this approach as the first line option in several situations, which will be discussed later on (52-54). It allows inactivating the parasite, destroying the proliferous membrane, evacuating the contents of the cyst and achieving obliteration of the residual cavity. Indications, contraindications and risks of the PAIR procedure are summarized in Table 4 (52-54).

7.2.1. Medical treatment prior to the PAIR procedure

Drug therapy administered before and combined with percutaneous treatment is currently highly recommended (56). Medical treatment is started 14 to 20 days before the puncture and continued 2 to 24 months after it. The combination of Albendazole plus Praziquantel has been estimated the most effective for the preoperative period (57).

The overall complication rates of PAIR vary from 1.4 to 13.7%. It is also advisable to do an ERCP pre-PAIR and to perform post aspiration imaging of the cyst using contrast to rule out possible communication with the biliary tree. Recurrence varies from 0-4% with a low morbidity of 0.9% and 2.5% mortality rate.

Table 4. — **Indications, contraindications and risks related to the PAIR procedure (55)**

<p>The indications to PAIR are :</p> <ul style="list-style-type: none"> Uncomplicated simple hydatid cysts filled with clear fluid (CE1), Cysts with or without a detached membrane or daughter cysts (CE3a) ; Inoperable patients at high surgical risk ; Pregnant patients ; Patients with multiple or disseminated cysts ; Relapses after surgery <p>The contraindications to PAIR are :</p> <ul style="list-style-type: none"> Patients with inaccessible cysts Superficially located liver cysts because of risk of rupture Cysts with no drainable solid material or echogenic foci Inactive or calcified cysts Cysts that have ruptured into the abdomen Cysts with biliary communication <p>Risks related to PAIR procedure :</p> <ul style="list-style-type: none"> Secondary spillage of hydatid fluid into the peritoneum Hemorrhage Infection Chemical sclerosing cholangitis Biliary fistula

7.2.2. Puncture

It is performed under ultrasound guidance or more commonly under CT-scan. The needle has to cross a strip of healthy parenchyma. The introduction of a catheter may allow a more efficient extraction and repeated irrigations.

7.2.3. Aspiration

The immediate aspiration of 10 to 15 ml of hydatid fluid decompresses the cyst and confirms the diagnosis (51,58). This aspirated cyst fluid should then be analyzed both biochemically and microscopically. If protozoa are absent (probably a non-parasitic cyst) the procedure should be stopped. A test for bilirubin in cyst fluid should also be performed to assess a biliary communication. If bilirubin is present, the procedure must be stopped. If no bilirubin is found, the entire cystic fluid must be aspirated.

7.2.4. Injection

It can destroy the germinal membrane and the remaining vesicles. Different agents are used as scolicides : the association of 30% saline and 95% alcohol, saline alone or with silver nitrate. More recently the injection of a 10% solution of Albendazole has proved to be efficacious. The chosen scolicide is left in place from 10 to 20 minutes. The most commonly used scolicidal agent is hypertonic saline because if there is a possible communication between the hydatid cyst and the biliary tree, the alcohol will cause chemical sclerosing cholangitis.

7.2.5. Re-aspiration

It concerns the entire injected solution and is performed under ultrasound during the same procedure.

7.2.6. Effectiveness (56,57)

This method is effective with a recurrence rate between 0 and 4% (55). A reduction in the volume of the

cyst can be seen in 20 to 100% of cases and a complete disappearance in 50-88% of cases (58)

Whatever the modality of treatment, ultrasound is a reliable modality to monitor the response. A good response is defined by a detachment of inner membrane, appearance of solid or echogenic materials and, of course, by the progressive disappearance of the cyst. Relapse is considered when there is development of a new cyst, increase in volume of the cyst either by increasing liquid or disappearance of detaching membranes.

7.3. Surgical treatment

The surgical approach of hydatid liver cysts is based on several techniques, and depends on the location and number of cysts.

Surgery has been the treatment of choice for many years until the discovery of the PAIR procedure in 1986.

According to WHO, the indications of the surgical approaches are (54) :

- Large liver cysts, with a diameter superior to 10 cm, especially if associated with multiple daughter cysts) and/or superficially located single liver cysts which have a risk of rupture.
- Complicated cysts such as those accompanied by infection, compression or obstruction are also commonly treated by surgery.

On the contrary, contraindications to surgery are (54) :

- Patients with poor general condition ;
- Very young or elderly ;
- Pregnant women ;
- Cysts that are difficult to access,
- Patients with dead or totally calcified cysts.

Surgery is performed either the open surgery or by the laparoscopic approach. The preferred technique is pericystectomy, in which the entire cyst and the surrounding

fibrous tissue are removed. The exploration of the abdominal cavity aims to find possible peritoneal grafts. It is essential to prevent the spread of hydatid fluid in the abdominal cavity using hypertonic solutions injected into the cyst, then sucked before being opened. The inspection of the cyst wall aims to highlight a possible biliary communication. The solutions of formaldehyde, 2 or 7% are no longer used because of side effects (59). Surgical mortality is usually 0.5 to 4% for the first intervention, but increases with repeated procedures. Postoperative complication rates of 10 to 25% and recurrence rates of 2 to 10% are reported (58). The *complete resection* tends to remove the residual cavity, which is a source of most of the postoperative complications (abscess and biliary fistulae) and recurrence.

The *conservative method* consists in a partial resection of the protruding dome on the surface of the liver. This resection has the disadvantage of leaving a residual cavity, and, especially in case of a potential biliary communication, may lead to biliary filling of the residual cyst. These potential complications require a long-term drainage. Other than the open surgery, the laparoscopic approach can also be used but with certain indications such as anteriorly located liver cysts. However, the patient has a higher risk of spillage and allergic reactions.

8. Conclusion

Hepatic hydatidosis is a common disease in developing countries, mainly in areas of sheep farming in the Mediterranean. The liver cyst can grow in size throughout the years and predispose the patient to primary and secondary complications, mainly cyst rupture with anaphylactic shock or biliary communication. Recent progresses in imaging play an important role in diagnosis, classification and evaluation of response to treatment of the cysts. An accurate, low cost and highly sensitive method still remains the ultrasound. This technique led to both Gharbi's and WHO's classifications, and helped to determine the best therapeutic strategy. The main therapeutic modality in the past was surgery, until the discovery of the PAIR procedure that could be considered as a new paradigm. PAIR offers lower morbidity and mortality to the patient as compared with surgery. Long term follow up should be done on patients on medical treatment in order to accurately determine its efficacy. Physicians also need to keep in mind the importance of Albendazole in the treatment of Hydatid cysts either alone or as a pre-procedure or post procedure prophylaxis. More research should be done in the area where PAIR fails, in order to determine the place of surgery in this setting.

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