

THE CLINICAL DIAGNOSIS AND BIOFLUID BASED DIAGNOSIS OF LIVER HYDATID CYSTS

I. BREZEAN¹ M. VÎLCU¹ I. PANTEA²
E. CATRINA¹ D. FERECHE³

Abstract: *There are three stages in the development of hydatid cysts: initial, tumoral and the stage of complications. In the initial and pseudotumoral stages, the diagnosis depends on topographic localisation. In the complications stage, diagnosis is established on the basis of the most frequent clinical manifestations of the gall bladder, of peritoneal syndromes, of complications involving the lungs and pleura, of venous compression syndromes or the presence of rash. The biofluid-based diagnosis of liver hydatid cysts includes parasite identification (parasitological diagnosis) and immunological investigations indicating host-vs-parasite conflict (immunological diagnosis). Liver hydatid cysts exhibit several particular features depending on their location, size, and relation to adjacent organs.*

Key words: *Liver hydatid cysts, clinical and biofluid-based diagnosis.*

The clinical diagnosis of liver hydatid cysts depends on size, location, place and degree of outward proliferation of the cyst, as well as on any complications in its development.

Three stages may be involved in the clinical evolution of a hydatid cyst:

1. **The initial stage** is asymptomatic and characteristic of small-sized cysts.
2. **The pseudotumoral stage** is due to the increased volume of the cysts, which become palpable.
3. **The complications stage:** the onset of various specific complications be they allergic, infectious or mechanical.

In the initial stage, it is hard to establish a definite clinical diagnosis, but it becomes definite in the pseudotumoral and complications stages, as outlined below:

a) In **the pseudotumoral stage**, the cysts become palpable due to their increased volume and protrusion from the parenchyma. Depending on their location, they may present differently as:

– **Cysts with inferior development** can be felt on palpation during breathing as subhepatic masses adhering to the liver. **Cysts with posterior development** may present as retroperitoneal renal masses (detectable by palpation in the lower back area)

¹ Clinica “I. Juvara” Clinic, “Dr. I. Cantacuzino” Hospital, Bucharest.

² *Transilvania* University of Braşov, Faculty of Medicine.

³ “Carol Davila” Medical University of Bucharest.

- **Cysts with anterior development** may cause visible (“watch-glass”) deformation in the right hypochondrium and the epigastrium. On palpation, the pseudotumor is elastic, regular, painless and dull on percussion. Before the advent of ultrasound, the clinical indication of a cyst used to be the vibration perceived on simultaneous palpation and percussion of the cyst, resulting in the so-called “hydatid thrill“ or on auscultation combined with percussion, resulting in the “hydatid sound”. These clinical manoeuvres are no longer performed today.
- **Hydatid cysts** developing in the central or posterior segments of the liver may cause isolated hepatomegaly.
- b) In **the complications stage**: clinical manifestations of the gall bladder are by far the most frequent. When hydatid cysts are located in the liver, the biliary fistulas from the pericyst cause allergic, mechanical and infectious complications.
- **Biliary colic and dyspeptic disorders** are due to the allergic oedema caused by the hydatid liquid in the endothelium of the gallbladder, sphincter of Oddi and the mucosa of the duodenum and jejunum (“hydatid dyspepsia” as described by Dévé). The presence of hydatid liquid in the bile ducts and intestine is secondary to the cyst rupturing in the biliary fistulas [2], [3], [4], [6], [11].
- **Migration syndrome** caused by the cyst rupturing into the bile ducts, particularly by cysts developing in the central and paramedian segments of the liver. Migration of the parasitic matter (proliger fragments, daughter vesicles) into the bile ducts may cause intense biliary colic, cholestatic jaundice, frequently accompanied by fever and chills indicating associated cholangitis. Obstructive biliary syndrome may sometimes be present as acute cholecystitis with a common bile duct cause and hydatid origin. In rare cases, parasitic matter may pass from the main bile duct into the digestive tract, from which it may be eliminated via feces (hydatidocholy, Dévé’s hydatidentery), or vomit (hydatimesis). In about 8-10% of large-sized cysts rupture occurs in the bile ducts [4], [11].
- **Hepatic abscess of hydatid origin**, a consequence of biliocystic fistula and infection of the cyst with germs from the digestive tract, presenting as painful hepatomegaly, fever, chills, altered general state.
- **Gall bladder calculi** are associated with hydatid cysts in 8-18% of cases, according to various authors, and are caused by various mechanisms.
- **Hydatid lithiasis** occurring after the rupture of the cyst into the bile ducts and the migration of hydatid matter in the bile ducts. Parasitic matter forms precipitation nuclei for bile salts. This mechanism involves the passage of the parasitic content into the bile ducts in the absence of a noisy migration syndrome (jaundice, cholangitis).
- **Parahydatid lithiasis** may occur due to stasis in the gall bladder, caused either by allergic oedema and adenopathy with compression of the pedicle of the (cystic lymph node), either by direct compression of the cyst on the bladder and subsequent changes in its position (shift to horizontal, middle, upward movement, downward movement, “sinking” into the liver) [11].
- **Common lithiasis** is a lesion coexisting with the cyst, and no causal relation can be established between the two. The last three categories were described by A. Cendan, I. Juvara et al.
- **Posthydatid lithiasis** may occur after the surgical treatment of the cyst and may be caused by stasis and infection in the cavity that remains after the removal of the parasite.

- **Peritoneal syndromes** may develop either after fissures or after the rupture of the cysts inside the peritoneal cavity.

- *Diffuse secondary peritoneal echinococcosis*, as a consequence of either abdominal trauma or a biopsy. The violent elimination of the cysts' content into the peritoneum results in anaphylactic shock with signs of peritonitis. The protoscolices contained in the cyst spread to the serous membrane of the peritoneum and develop into numerous secondary hydatid cysts.
- *Cystic hydatid peritonitis* occurs after the traumatic rupture of a hydatid cyst and the formation of a cystic intervisceral collection containing migrated hydatid matter.
- *Cystic hydatid choleperitonitis* occurs when the cyst causing cystic hydatid peritonitis is compounded by biliary fistula.

- **Lung and pleural complications.**

Lung and pleural symptoms may be non-specific, caused by cysts developing on the diaphragmatic aspect of the liver and presenting as non-productive cough and referred pain to the shoulder. Clinical examination may reveal a lack of vocal vibration, dullness and cranial convexity, absence of vesicular murmur. These symptoms may precede the development of bilio-bronchial or bilio-pleural cystic fistulas, which are rare but severe complications. Biliocystic fistulas are the first stage of these complications, followed by the erosion of the diaphragm and establishment of communication either with the pleura (bilio-pleural fistula), or with the lung (bilio-bronchial fistula) [6]. The bilio-pleural fistula may further open into the lung, forming a bilio-pleural-bronchial fistula [6]. Bilio-pleural-bronchial communication presents as hydatid vomica (hydatid phthisis) and bilious vomica (biliary phthisis). The

rupture of the cyst in the pericardium is a possible, yet very rare complication [6].

- **Venous compression syndromes** may be caused by the compression of:

- the inferior vena cava,
- the suprahepatic veins, as one of the causes of Budd Chiari syndrome,
- the portal vein, causing intrahepatic or prehepatic portal hypertension.

- **A hive-like rash** resulting from the host's reaction to contact with certain components of the hydatid fluid flowing through the biliocystic fistulas into the digestive tract [4], [5].

The differential diagnosis of hydatid cysts is established in the context of clinical signs and syndromes occurring during their evolution (tumor-like mass in the right hypochondrium, isolated hepatomegaly, obstructive jaundice, cholangitis, portal hypertension etc.).

The biological diagnosis of liver hydatid cysts includes parasite identification via a parasitological examination and the identification of the agent via indirect immunological methods.

1. Parasitological diagnosis

• *Microscopic parasitological diagnosis* is performed by direct examination of pathological fluids showing protoscolices and hooks, or indirectly by the Siebnick Passini reaction. Microscopic examination can lead to the identification of the parasite on cyst fragments due to the characteristic structure of the cuticle (concentrically laminated cuticle) and the proligera can be identified by PAS stain [1], [10].

• *Molecular parasitological diagnosis* by PCR (polymerase chain reaction) allows for the DNA identification of species and subspecies of *Echinococcus*, even when the examined sample contains a single parasite egg. Molecular parasitological diagnosis is useful in establishing the parasitic nature of samples collected from dogs (feces, scotch tape test, bowel

fragments) [1], [10] and of fluid and fragments collected by cyst biopsy.

2. Immunological diagnosis shows the relation between the host and the parasite in its larval stage, based on the immune (cellular, humoral) response of the host or by identifying specific antigens in the host's serum [1], [9], [10].

• *Cell-mediated immunity assays* show the qualitative and quantitative changes in the leukocytes involved in cell-mediated immune response, or the cutaneous effects of these changes (intra-dermal reaction) following the administration of hydatid antigens. Some of the cell-mediated immunity assays are the Casoni intra-dermal reaction, the basophil degranulation test, the lymphoblast transformation test (LTT), the eosinophilia provocation test [1].

• *Humoral immunity assays* show the existence of antiparasitic antibodies in the patients' serum on in vitro contact with various antigens. There are several ways of testing for humoral immunity specific to hydatid cysts: indirect hemoagglutination assay (IHA), enzyme-linked immunosorbent assay (ELISA-IgG), indirect fluorescent antibody test (IFAT), latex agglutination (LA), bentonite flocculation (BFT), immune-electrophoresis (IEF), contra-immunoelectrophoresis (CIF), enzyme-linked immunoelectrotransfer blot (EITB), radio-immunoassay (RIA), double diffusion (DD), radioallergosorbent test (RAST), radio-immunosorbent test (RIST), hydatid antigen dot immunobinding assay (HA-DIA) etc.

ELISA IgG (enzyme-linked immunosorbent assay) is currently the most widely used and has a specificity of 89%. The assay is used both in establishing diagnosis and in monitoring the effectiveness of the treatment, in epidemiological investigation and screening for echinococcosis [10]. In

older patients, the specificity of the assay increases in the case of liver hydatid disease compared to other site locations.

Serum electrophoresis shows an increase in gamma-globulins, and immunoelectrophoresis shows increased levels of IgG and IgE in patients with viable (fertile) liver hydatid cysts.

• *Tests for the detection of circulating hydatid antigens* and their immune complexes are less frequently used compared to the identification of specific antigens, as it is less sensitive. The detection of circulating antigens may be used in post-therapeutic monitoring and is a better indicator of parasite viability. Serum hydatid antigens are identified by the enzyme-linked immunosorbent assay (ELISA) or the coagglutination assay (Co-A); in pathological fluids (hydatid vomica, hydatid fluid collected by puncture), they can be identified by ELISA, HA-DIA, Co-A etc.

Immunology assays must be interpreted only by corroboration with epidemiological, clinical and imaging data, although their specificity is high.

3. Particular features depending on the location of liver hydatid cysts

In most cases, liver hydatid cysts are solitary (75-80% of cases) and develop mainly in the right-hand side area of the liver (80%) [5], [7]. Throughout its development, the cyst grows larger and tends to protrude to the surface of the liver (eccentric or centrifugal development) irrespective of its initial location [5], [7]. In the case of young, univesicular cysts (occurring mainly in children), at the protrusion site the cysts grows convex as a thin, translucent membrane allowing for the structure of the liver parenchyma to be seen. In the case of old, multivesicular cysts, complicated by biliary fistulas (occurring mainly in adults), the structure

is white to pale yellow, thick, specific to old, multivesicular cysts, complicated by biliary fistulas. In some cases, the protrusion site is covered in adhesions connecting it to adjacent organs or structures. One specific peculiarity of liver cysts is the change in the liver parenchyma, in its vascular structures and particularly in the bile ducts, but also the relations between the cyst and the organs and structures in the vicinity of the liver. The increased volume of the cyst may cause the compression of the small vessels in the parenchyma, the formation of small-sized clots and vascular sclerosis, as well as changes in the position of the major vessels of the liver [8]. As far as the relation between the cyst and the bile ducts is concerned, the mechanical conflict between the cyst and the intrahepatic bile ducts eventually leads to the formation of biliary fistulas in the pericyst. Fissures in the cyst membrane may allow some of the hydatid fluid to flow into the bile ducts, followed by a decrease in intracystic pressure and the flow of bile into the cyst, due to the reversal of pressure gradients (“hydatid pump”) [4].

Consequently, the presence of bile inside the cyst allows the access of germs from the digestive tract, causes the pericyst to thicken and seems to cause endovesiculation (the formation of daughter vesicles and multivesicular cysts) [2], [3], [4],[8]. In most cysts (90%) fissuring of the cyst in small-sized bile ducts is a frequent occurrence [4], [7], [11]. The cyst wall may rupture in a large-sized biliary fistula located on an intrahepatic bile ducts of suitable diameter and may be followed by the migration of hydatid matter (proliger fragments, daughter vesicles) into the bile ducts. Such migration of hydatid matter in the main bile duct may trigger obstructive and inflammatory complications. Biliary fistulas in the pericyst may be tangential or

terminal, involving all or some of the bile ducts. Cyst protrusion from the liver parenchyma leads to contact between the cyst and the organs and structures in the vicinity of the liver (stomach, duodenum, colon, kidneys, hepatic pedicle, diaphragm, lung, vena cava, peritoneum etc.) with frequent adhesions due to inflammation. These adhesions may sometimes be useful in the intraoperative detection of deep-lying cysts, especially in the posterior region of the liver, which may not be visible on inspection.

The cyst may also compress various organs adjacent to the liver, which it may rupture or create fistulas into. Compression may lead to conspicuous clinical signs: jaundice, gall bladder lithiasis, portal hypertension, Budd-Chiari syndrome, partial digestive obstruction, etc. One particular type of total protrusion of the liver hydatid cyst is detachment from the liver parenchyma and migration into the peritoneal cavity. This requires that the cyst be initially located superficially in the liver parenchyma, close to the anterior liver margin [9], [12].

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