

CLINICAL FEATURES OF LIVER HYDATIDOSIS: A LITERATURE REVIEW

G. Lotito¹, I. Negoi^{1,2}, M. Beuran^{1,2}

¹The University of Medicine and Pharmacy “Carol Davila”, Bucharest, Romania

²Department of General Surgery, Emergency Hospital, Bucharest, Romania

Corresponding author: Gianmarco Lotito

Phone no: 0040215992308

E-mail: gianmarco.lotito@gmail.com

Abstract

Hydatidosis is a disease affecting most commonly liver and lungs and belongs to the list of the top 17 neglected tropical diseases. Hydatid disease is caused by the infection that, in humans, is due to the larval stage of the Echinococcus granulosus, more specifically by the complex of subtypes that give it the name, Echinococcus multilocularis or Echinococcus Vogeli. These complexes generate cystic hydatid disease characterized by unilocular cystic lesions. The disease spreads mostly in geographical areas with a large amount of livestock, and it is closely associated with dogs. The mechanic action produced on the tissues by the progressive growth of the cyst – even if with certain limitations – relates to the entity of the symptomatology. If the echinococcal cysts become slowly enlarged, they remain asymptomatic until their expanding size - or the effect provoked by their enlargement in an involved organ - generates symptoms. The diagnosis is based on refined imagistics (liver ultrasonography, Magnetic Resonance Imaging or Computed Tomography) and serology. The prognosis is favorable in cases of unique cyst in a location where it is easily removed by surgical intervention or if it positively responds to pharmacological treatment or to percutaneous techniques.

Keywords: *hydatidosis, Echinococcus, liver, cyst*

Introduction

Hydatidosis belongs to the list of the top 17 neglected tropical diseases (NTDs) [1]. The cysts resulting from the infection have their favorite target organs in the liver and the lungs. The symptomatology depends on the mechanic action produced on the tissues by the progressive growth of the cyst. Thus, it can remain asymptomatic or generates symptoms if they are expanded [2].

The golden standard for the diagnosis and the differentiation of the cysts is the Gharbi's classification. Gharbi (1981), in his report on 121 hydatid cysts of the liver seen in Tunisia,

classified them into five distinct types numbered from I to V, according to the echographic appearance of liver hydatids [3].

The prognosis is favorable in cases of unique cyst development in a location where it is easily removed by surgical intervention or if it positively responds to pharmacological treatment or to “PAIR”. However, possible complications can lead to the worsening of the prognosis [4].

Materials and Methods

We have reviewed the relevant articles into the PubMed/Medline and Google Scholar databases. We have used the following keywords: ‘hydatid’ OR ‘echinococcosis’ AND ‘liver’ OR ‘hepatic’.

Our study took into consideration publications and researches from the last 20 years.

The main purpose of the current study is to detail the epidemiological and clinical features of liver hydatid cystic disease.

Results

Epidemiology

The hydatid disease is caused by the infection that, in humans, is due to the larval stage of the *Echinococcus granulosus* – more specifically by the complex of subtypes that give it the name -, *Echinococcus multilocularis* or *Echinococcus Vogeli*. These complexes generate cystic hydatid disease characterized by unilocular cystic lesions [1-5].

The disease spreads mostly in geographical areas with a large amount of livestock - the disease is told to be “following the sheep as its shadow” - and is closely associated with dogs [6].

Molecular studies proved that *E. granulosus* strains might belong to more than one species; they were taken from sheep, buffalo (the most common), horses (unknown transmission) and camels, pig, cervid (rarely, by *E. Canadensis*) [7]. Therefore, these parasites can be found over all continents with prevalence in China, Central Asia, the Middle East, the Mediterranean region - in Italy 4 new cases/100.000 inhabitants are registered every year [2]- Eastern Africa and parts of South America. *E. multilocularis* – the main cause of multilocular alveolar lesions and locally invasive – can be found in Alpine and sub-Arctic regions (including Canada, the United States, Central and Northern Europe, China and Central Asia) while the *E. Vogeli* - responsible of the polycystic hydatid cyst - is found in Central and South America. In Italy, the central and southern regions (Basilicata, Abruzzo and Tuscany) and the main islands are the largest

affected areas with most of the sheep and goat livestock on the island, infected - Sicily (6.5-36.5%) and Sardinia (70.6-92.8) [8].

In Romania, hydatid disease has an increasing incidence of 5-6 cases every 100.000 inhabitants/year with a predominance in rural areas and pulmonary involvement in 30-40% of the total cases [9].

The risk of infection for humans is increasing annually due to the accretion of fox population numbers and to their “progressive urbanization”. This thesis is supported by the reports of infected foxes in areas considered until that moment to be unharmed and in the urban areas – for example Zurich where the number of foxes increased 4-fold from 1980 [10].

Morphology

In a normal life cycle of *Echinococcus* species, the adult tapeworm is 3-6 mm long with a piriform scolex - harbouring a projected rostellum armed with 2 rows of hooks and 4 suckers – and 3 to 5 proglottides, the last one being larger, mature and containing up to 5000 eggs and having the genital pore on alternative sides [11].

It lives for about 5-20 months in the dogs jejunum and it is characterized only by three of the so called “proglottides”: one immature, a mature and a gravid one. This last segment uses to break releasing eggs, morphologically similar to the ones observed in *Taenia* and are extremely hardy. The cysts enlarge slowly over years [5]. From a macroscopic point of view, the hydatid cyst is composed - from the external to the internal aspect – by two parts: (a) The pericystium represents the cyst wall, made by the liver as the result of the defensive reaction against it. Two membranes form the cyst wall: the “chynitous membrane” which is the more external and the “proligerous membrane” which is needed by the cyst to reproduce. The pericyst plays an important role in the development and survival of the hydatid cyst [12]; (b) The hydatid liquid (HCF) is the contents of the cyst and it is a clear or clear yellow liquid with some antigenic properties. It provides needed nutrition for the larval growth, playing an essential role in the lifecycle of *Echinococcus* [13].

Pathogenesis

Just like the other elements of the family of the “cestodes”, the echinococcal species are characterized by having either intermediate or definitive host. The second are canines that pass the eggs in their faeces and - following their ingestion via food, water or even dust in the setting of alveolar echinococcosis [14] - some cysts develop in the intermediate hosts such as sheep, cattle, humans, goats, camels, horses usually being infected with *E. granulosus* and mice and rodents infected with *E. multilocularis*.

The eggs present in the dog’s faeces – in the form of metacestodes – are small vesicles (60 to 70 µm in diameter) [15] consisting of 2 shells - the inner one thicker while the inside oncosphere contains 3 pairs of hooklets. They become infective when discharged. The ingested eggs leak some esacantes larvae that – in a maximum time of two hours – cross the intestinal wall, penetrating the venules or the lymphatic vessels of the intestinal villi. Either by the blood or the lymphatic circulation, they reach the liver and the lungs – where most of them stop – or they continue to other locations such as: the brain, the peritoneum, the muscles, the kidneys, the spleen or under the skin where they turn into hydatids in about 10 days [2].

The direct contact with the dog represents another route of transmission of the infection - even if less frequent. In this case, the eggs present in the perineal zone or on the dog’s fur can contaminate people living in close relation with the animal, especially children via the route of hand-to-mouth contact [16].

Prophylaxis

Prohibition of domiciliary slaughter without veterinary control, an adequate discharge in the slaughterhouse of the infected animal bowels - to impede stray dogs to have access to them – beside the general hygienic recommendations (wash the hands, not consume any food and water potentially contaminated etc. etc.) and the hygiene laws policy represent the most important prophylaxis [17].

Another fundamental strategy is to reduce the stray canine phenomena (really common in an endemic place like Romania) and an appropriate healthcare control on livestock and dogs potentially exposed to the infection.

Indeed, it is remarkable how the parasitic eggs, expelled in the dogs faeces, keep their active attitude in the environment for up to two years - or even longer [2].

Furthermore, the “Universidad Nacional Mayor de San Marcos”, in Peru, demonstrated how Oxfendazole at 60 mg, the combination Oxfendazole/Praziquantel and Albendazole/Praziquantel are all successful schemas that can be added to control measures in animals, deserving further studies for the treatment of animal CE [18].

In the attempt to provide a more appropriate tool for the surveillance of human CE spreading, the European Register of Cystic Echinococcosis (ERCE) was started in October 2014 in the context of the HERACLES project. Within HERACLES, the implementation of an international register of human CE was identified as essential to improve the public awareness and the clinical management of CE [19].

Clinical Manifestations

The mechanic action produced on the tissues by the progressive growth of the cyst – even if with certain limitations – relates to the entity of the symptomatology. If the echinococcal cysts become slowly enlarged they remain asymptomatic until their expanding size - or the effect provoked by their enlargement in an involved organ - generates symptoms. Liver hydatid cysts may require a long period of time – up to years – to become enlarged enough so as to cause symptoms and they can be discovered several years later by an accidental finding on routine x-ray or ultrasound [5]. The symptomatic patients usually experience abdominal pain or a palpable mass in the right upper quadrant, sensation of weight on the right hypochondrium, hepatomegaly - appreciated on palpation and on percussion that will result in the finding of “hydatid fremitus” - irregular fever or slightly elevated body temperature.

Complications

The cyst enlargement can compress a bile duct or can result in a cyst fluid leakage into the biliary tree - leading to a misdiagnosis with recurrent cholelithiasis - meanwhile the actual biliary obstruction can manifest as recidivistic jaundice and dyspeptic disturbances. In case of

portal vessels compression, ascites can be a complication [2].

The maximum leakage of hydatid fluid leads to the severe clinical picture of anaphylaxis – happening more rarely in hypersensitive patients - in the first place; if the cystic wall goes through a fissuration process – consisting in the spreading out of small quantities of its liquid content - we will observe toxic-allergic manifestations such pruritus, urticarial, asthmatic crisis, cough and eosinophilia [20].

Diagnosis

The paraclinical studies are fundamental not only for detecting the cyst but also in evaluating them to establish a correct strategy of treatment.

US and CT are the investigation of choice [21]; initially WHO classification was based just on US studies.

CT exam is fundamental for the surgeon to verify the position of the echinococcal cyst in the liver and so to execute the surgical intervention in the best way possible [22]. Additionally, it gives us information about the vitality of the cyst - showing its density - the presence of daughter cysts and of possible small metastases located outside of the liver. The typical sign of the presence of the echinococcal cyst is the calcification in the cyst wall. If the cysts are older, they may contain a layer composed of “hydatid sand” – rich in accumulated protoscolices – detectable at different densities depending on the imaging method used. However, the most pathognomonic finding concerns the evidence

of daughter cysts within the large cyst - not always demonstrable.

Echography is capable to detect the cyst’s aspect; it can show the presence of interior daughter cysts and can distinguish the cause of the obstruction of the biliary ducts in patients presenting symptoms of jaundice [5].

Gharbi (1981), in his report on 121 hydatid cysts of the liver seen in Tunisia, classified them into five distinct types numbered from I to V, according to the ecographic aspects [3]. Furthermore, a study published in 2016 included 45 Indian sick bovines (37 buffaloes and 8 cattle) - suffering from lung and liver cysts – stated that radiography and mainly US imaging should be combined as screening tools to rule out echinococcosis [23].

Laboratory diagnosis - known as serodiagnostic - can be useful in the detection of hydatid cysts but it is characterized by several false negative results that do not exclude the echinococcal infection diagnosis.

However, hydatid cysts in the liver elicit positive antibody responses in 90% of cases whereas up to 50% of individuals with pulmonary hydatid cyst are seronegative.

The detection of antibodies to specific echinococcal antigens by immunoblotting has the highest degree of specificity [5].

The increased diagnostic sensitivity and reliability of the Ag5 ELISA method make this antigen a promising candidate for the serodiagnosis of CE (24) as well as Cassoni’s intradermic skin reaction which showed a sensitivity of 70% [25].

Differential diagnosis

Features	If hydatid	If amoebic	If congenital	If tumor
Number of cysts	Single (possible daughter cysts)	Single (sometime few)	Variable	Single + loculations
Features of the cystic wall	Homogeneous + Thick Possible presence of calcifications	Same to hydatid's aspect	Uniform + thin	Variables with septations
Contents of the cyst	Clear and gelatinous Typical finding Of "hydatid sand"	Red-brown appearance Aspect resembling "anchovy paste"	Clear content	Green- brownish

Table 1 - Differential diagnosis in liver echinococcosis

To differentiate the hydatid cyst of the liver from simple cysts, a tool has been incorporated into the exam: the diffusion-

weighted imaging (DWI). A study comprised of 82 cysts (43 simple cysts and 39 hydatid cysts) on which DWI was made using a breath-hold

single-shot echo-planar spin-echo sequence and calculating the diffusion coefficients. On trace DWI, most hydatid cysts (95%) were hyperintense while most simple cysts (93%) were isointense within the liver.

Quantitatively, both the signal intensity and the cyst-to-liver intensity ratio of hydatid cysts were significantly higher than those in simple cysts. The calculations predicted a sensitivity of 77%, a specificity of 86% and a positive predictive value of 83% for the cyst to liver signal intensity ratio.

Thus, DWI may be helpful in the differential diagnosis of hydatid and simple cysts of the liver [26].

Prognosis

It is favorable in cases of unique cyst development in a location where it is easily removed by surgical intervention or if it positively responds to pharmacological treatment or to "PAIR". However, possible complications can lead to the worsening of the prognosis [4].

Conclusions

Although hepatic hydatidosis is a benign pathology, its evolution can lead to severe complications and a low quality of life for the patient either before or after surgery. A better knowledge of the pathology behind the local evolution of the disease can influence the therapeutic approach. Prohibition of domiciliary slaughter without veterinary control, an adequate discharge in the slaughterhouse of the infected animal bowels, beside the general hygienic recommendations and the hygiene laws, as well as the reduction of the stray canine phenomena and an appropriate healthcare control on livestock and dogs, seems to be the best way to eradicate the disease.

References

- [1]Molyneux DH. The London Declaration on Neglected Tropical Diseases: 5 years on [Internet]. Liverpool; 2017. Available from: <https://academic.oup.com/trstmh/article/doi/10.1093/trstmh/trw082/2937752/The-London-Declaration-on-Neglected-Tropical>
- [2]Cancrini G. Parassitologia medica illustrata. 2nd editio. Editore L, editor. 2012. 171-178 (chapter 2.15 "Cestodi tessutali") p.
- [3]Palmer PES, Reeder MM. The Imaging of Tropical Diseases [Internet]. 2000th ed. Palmer PES, Reeder MM, editors. Springer; 2000. 220 volume 1. Available from: <https://books.google.ro/books?id=W9hMKQ2AKLEC&pg=PA221&lpg=PA221&dq=gharbi+classification&source=bl&ots=0ySGkNO-XP&sig=hqeIe5Rv8BRQGQuS56tvkklubmE&hl=it&sa=X&ved=0ahUKEwjmlc7WoYjSAhVGGhQKHZV7BNkQ6AEIUTA0#v=onepage&q=gharbi+classification&f=false>
- [4]Pedrosa I, Saíz A, Arrazola J, Ferreirós J, Pedrosa CS. Hydatid Disease: Radiologic and Pathologic Features and Complications [Internet]. Madrid,Spain; 2000. Available from: <http://pubs.rsna.org/doi/full/10.1148/radiographics.2003.g00ma06795>
- [5]Kasper DL, Hauser LS, Jameson JL, Fauci AS, Longo DL, Loscalzo J. Harrison's principles of internal medicine. 19th ed. Kasper DL, Hauser LS, Jameson JL, Fauci AS, Longo DL, Loscalzo J, editors. Mc Graw Hill Education; 2015. 1432-1433 (chapter 8, "Protozoal infections" p.
- [6]Sindou M. Practical Handbook of Neurosurgery From Leading Neurosurgeons. 2009th ed. Sindou M, editor. Springer Verlag New York; 2009. 469 p.
- [7]Casulli A. Genetic diversity of Echinococcus granulosus complex in Europe. In: Istituto Superiore di Sanita' European Union Reference Laboratory for Parasites. Rome-Italy; 2012. p. 1-19.
- [8]Garippa G, Varcasia A, Scala A. Cystic echinococcosis in Italy from the 1950s to present [Internet]. Sassari,Italy; 2004. Available from: http://eprints.uniss.it/2675/1/Garippa_G_Articolo_2004_Cystic.pdf
- [9]Chatelain E, Hardy K, Guigay J, Tramond B, Pons F, L'her P, et al. Traitement thoracoscopique d'un cas d'hydatidose pulmonaire. 2000;
- [10]Schweiger A, Ammann RW, Candinas D, Clavien P-A, Eckert J, Gottstein B, et al. Human Alveolar Echinococcosis after Fox Population Increase, Switzerland [Internet]. Zurich, Switzerland; 2007. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2792858/>
- [11]Brunetti E, Felice C. Echinococcosis Hydatid cyst [Internet]. Medscape. Pavia,Italy; 2015. Available from: <http://emedicine.medscape.com/article/216432-overview>
- [12]Golzari SE, Sokouti M. Pericyst: The outermost layer of hydatid cyst [Internet]. Tabriz, Iran; 2014.

- Available from:
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3921523/>
- [13]Juyi L, Yan J, Xiufang W, Zhaoqing Z, Junliang L, Mingxing Z, et al. Analysis of the chemical components of hydatid fluid from *Echinococcus granulosus* [Internet]. *Revista da Sociedade Brasileira de Medicina Tropical*. Yinchuan, Ningxia Hui Autonomous Region, China; 2013. Available from:
http://www.scielo.br/scielo.php?script=sci_arttext&id=S0037-86822013000500605#aff1
- [14]Kern P, Ammon A, Kron M, Sinn G, Sander S, Petersen LR, et al. Risk Factors for Alveolar *Echinococcosis* in Humans [Internet]. Ulm, Germany; 2004. Available from:
https://wwwnc.cdc.gov/eid/article/10/12/03-0773_article
- [15]Eckert J, Deplazes P. Biological, Epidemiological, and Clinical Aspects of *Echinococcosis*, a Zoonosis of Increasing Concern [Internet]. Zurich, Switzerland; 2004. Available from:
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC321468/>
- [16]Rabinowitz P, Conti LA. *Human-Animal Medicine*. 1st ed. Rabinowitz P, Conti LA, editors. Saunders; 2009. 154 p.
- [17]CDC. Prevention and control of *Echinococcosis* [Internet]. Atlanta, USA; 2012. Available from:
<https://www.cdc.gov/parasites/echinococcosis/prevention.html>
- [18]Gavidia CM, Gonzalez AE, Barron EA, Ninaquispe B, Llamas M, Verastegui MR, et al. Evaluation of Oxfendazole, Praziquantel and Albendazole against Cystic *Echinococcosis*: A Randomized Clinical Trial in Naturally Infected Sheep [Internet]. Lima, Peru; 2010. Available from:
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2826409/>
- [19]Rossi P, Tamarozzi F, Galati F, Pozio E, Akhan O, Cretu CM, et al. The first meeting of the European Register of Cystic *Echinococcosis* (ERCE). Rome-Italy; 2016.
- [20]Brunetti E, Kern P, Vuitton DA. Expert consensus for the diagnosis and treatment of cystic and alveolar *echinococcosis* in humans [Internet]. Ulm, Germany; Pavia, Italy; 2010. Available from:
<http://www.sciencedirect.com/science/article/pii/S001706X09003581>
- [21]Williams NS, Bulstrode CJK, O’Connell PR. Bailey & Love’s *SHORT PRACTICE of SURGERY*. 25th ed. Williams NS, Bulstrode CJK, O’Connell PR, editors. Edward Arnold; 2008. 57-58 (chapter 1.5 “surgery in tropics”) p.
- [22]Dai J, Xu K, Feng X, Jin Z. *Radiology of Parasitic Diseases, A Practical Approach*. 1st ed. Li H, editor. Beijing, China: Springer; 2017. 111 (chapter 8: Helminthiasis).
- [23]A K, NS S, J M, BB S, V S, NK S. Comparison of radiography and ultrasonography in the detection of lung and liver cysts in cattle and buffaloes. [Internet]. Punjab, India; 2016. Available from:
<https://www.ncbi.nlm.nih.gov/pubmed/27847421>
- [24]D P, MF A, G B, AM R, V T, M M, et al. Diagnostic Accuracy of Antigen 5-Based ELISAs for Human Cystic *Echinococcosis* [Internet]. Alghero, Italy; 2016. Available from:
<https://www.ncbi.nlm.nih.gov/pubmed/27023205>
- [25]Dandan IS, Soweid AM, Abiad F. *Hydatid Cysts Workup* [Internet]. Beirut, Lebanon; 2016. Available from:
<http://emedicine.medscape.com/article/178648-workup>
- [26]Inan N, Arslan A, Akansel G, Anik Y, Sarisoy HT, Ciftci E, et al. Diffusion-Weighted Imaging in the Differential Diagnosis of Simple and Hydatid Cysts of the Liver [Internet]. Kocaeli, Turkey; 2007. Available from:
<http://www.ajronline.org/doi/full/10.2214/AJR.07.2251>
- [27]Mihăilă DE, Nițu MC, Potecă TD. Histopathological Aspects Described in Patients with Hepatic Hydatidosis [Internet]. Bucharest, Romania; 2016. Available from:
<https://www.degruyter.com/view/j/rjim.2016.54.issue-1/rjim-2016-0005/rjim-2016-0005.xml>