PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/118395

Please be advised that this information was generated on 2020-03-07 and may be subject to change.
Evaluation of hepatic cystic lesions

Marten A Lantinga, Tom JG Gevers, Joost PH Drenth

Marten A Lantinga, Tom JG Gevers, Joost PH Drenth, Department of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, 6500 HB Nijmegen, The Netherlands

Author contributions: All authors contributed equally to this work.

Correspondence to: Joost PH Drenth, MD, PhD, Professor of Gastroenterology and Hepatology, Department of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, PO Box 9101, Code 455, 6500 HB Nijmegen, The Netherlands. joostphdrenth@cs.com

Telephone: +31-24-3614760 Fax: +31-24-3540103

Received: January 20, 2013 Revised: March 5, 2013 Accepted: March 22, 2013 Published online: June 21, 2013

Abstract

Hepatic cysts are increasingly found as a mere coincidence on abdominal imaging techniques, such as ultrasonography (USG), computed tomography (CT) and magnetic resonance imaging (MRI). These cysts often present a diagnostic challenge. Therefore, we performed a review of the recent literature and developed an evidence-based diagnostic algorithm to guide clinicians in characterising these lesions. Simple cysts are the most common cystic liver disease, and diagnosis is based on typical USG characteristics. Serodiagnostic tests and microbubble contrast-enhanced ultrasound (CEUS) are invaluable in differentiating complicated cysts, echinococcosis and cystadenoma/cystadenocarcinoma when ultrasonography (USG), computed tomography and magnetic resonance imaging show ambiguous findings. As a result, serodiagnostic tests and CEUS reduce the need for invasive procedures. USG screening of the liver and both kidneys combined with extensive family history taking remains the cornerstone of diagnostic decision making in PLD. In conclusion, an amalgamation of these recent advances results in a diagnostic algorithm that facilitates evidence-based clinical decision making.

Lantinga MA, Gevers TJG, Drenth JPH. Evaluation of hepatic cystic lesions. World J Gastroenterol 2013; 19(23): 3543-3554 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i23/3543.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i23.3543

INTRODUCTION

Hepatic cystic lesions represent a comprehensive heterogeneous cluster with regard to pathogenesis, clinical presentation, diagnostic findings and therapeutic management (Table 1). Hepatic cystic lesions predominantly remain asymptomatic and are found as a mere coinci-
dence on abdominal imaging techniques, such as ultrasoundography (USG), computed tomography (CT) and magnetic resonance imaging (MRI). The use of these techniques has greatly increased over the last years, and as a corollary, there has been an increase in incidental findings of asymptomatic hepatic cystic lesions. In most cases, hepatic cystic lesions will follow a benign course. However, it is essential to differentiate benign cysts from potentially harmful cysts, such as echinococcosis, cystadenoma and cystadenocarcinoma, which require specific treatment. Currently, clinicians must also be aware of changes in the epidemiology of certain hepatic cystic lesions. Echinococcosis has spread to previously non-endemic Western European countries. For this reason, the early and accurate diagnosis of cysts is crucial. To facilitate the diagnostic process, we provide an overview of the wide spectrum of mono- and polycystic liver diseases based on literature published over the last five years.

**LITERATURE SEARCH**

We searched the electronic database PubMed using the following search terms: “liver” and “cyst” and “diagnosis”. We limited our search to articles that were written in English, published between November 2007 and November 2012 and available in full text. A total of 992 articles were identified. For the purpose of this review, we included articles with a main focus on the evaluation of hepatic cystic lesions in humans. Screening the titles and abstracts identified 252 articles meeting these inclusion criteria (Figure 1). Additionally, we searched the reference lists from all eligible reviews for additional leads.

**SIMPLE CYSTS**

**Pathogenesis**

Simple cysts arise congenitally from aberrant bile duct cells and contain a clear, bile-like fluid. Because bile duct epithelium covers the simple cyst inner lining, it is hypothesised that simple cysts arise during embryogenesis when intrahepatic ductules fail to connect with extrahepatic ducts.

**Clinical features**

The prevalence of simple cysts ranges from 2.5% to 18% and increases with age. More than half of individuals older than 60 years are likely to have one or more simple cysts. Cysts are small in most patients but can grow to over 30 cm in selected cases. In a small fraction of patients, symptoms, such as abdominal pain, early satiety, nausea and vomiting, arise as a result of a mass effect. Physical examination may reveal a palpable abdominal mass or hepatomegaly. Complications such as haemorrhage, rupture and biliary obstruction are uncommon but are more likely in larger cysts. Intracystic haemorrhage is a rare complication of simple cysts and usually presents with severe abdominal pain, although asymptomatic presentations are also observed.

**Laboratory findings**

Laboratory findings are predominantly normal, but a minority of patients have raised serum γ-glutamyltransferase (γGT). Several studies have shown that serum and cyst fluid levels of carcinoembryonic antigen (CEA) and cancer antigen 19-9 (CA 19-9) may be elevated. CA 19-9 is expressed in the simple cyst inner epithelial lining and leads to elevated cyst fluid and serum CA 19-9 levels. CA 19-9 is not helpful in the differential diagnosis of intracystic haemorrhage.

**Diagnostic features**

Most simple cysts are diagnosed incidentally on USG (Figure 2A), CT (Figure 2B) or MRI. The diagnosis of a simple cyst is based on the following USG criteria: anechoic (i.e., fluid filled cavity), no septations, sharp smooth borders, strong posterior wall echoes (indicating a well-defined fluid/tissue interface), spherical or oval shaped and a relative accentuation of echoes beyond the cyst compared to echoes at a similar depth transmitted through normal adjacent hepatic tissue (Table 2). CT shows a sharply defined homogeneous hypodense lesion with smooth borders and strong posterior wall echoes (indicating a well-defined fluid/tissue interface), spherical or oval shaped and a relative accentuation of echoes beyond the cyst compared to echoes at a similar depth transmitted through normal adjacent hepatic tissue. MRI depicts it as a high signal intensity on T1- and T2-weighted sequences, whereas the T2-weighted sequence shows extremely high signal intensity, which does not enhance after contrast injection. USG has a reported sensitivity and specificity of approximately 90% for diagnosing a simple cyst, and recent advances in CT and MRI technology might result in even higher sensitivity rates.

In case of an intracystic haemorrhage, USG typically shows a hyperechogenic echo pattern combined with internal echoes that mimic septations or solid portions (Figure 3). In contrast, CT visualises intracystic haemorrhage as a high-density area, whereas MRI depicts it as a high signal intensity on T1- and T2-weighted sequences. Neither CT nor MRI has additional diagnostic value compared to USG in the diagnosis of cystic bleeding. The recent development of microbubble contrast-enhanced ultrasound (CEUS) enables us to visualise vascular flow within septa or solid components of cysts, which is absent in simple cysts with intracystic

**Table 1 Differential diagnosis of cystic lesions in the liver**

| Disease                        | Monocytic disease                                                                 | Simple cyst                                                                 | Echinococcosis                                                                 | Cystic echinococcosis | Alveolar echinococcosis | Cystadenoma                                                                 | Cystadenocarcinoma | Polycystic disease                                                                 | Autosomal dominant polycystic kidney disease | Autosomal dominant polycystic liver disease |
|--------------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-----------------------|------------------------|-----------------------------------------------------------------------------|-------------------|-----------------------------------------------------------------------------------|---------------------------------------------|---------------------------------------------|
| **Table 1 Differential diagnosis of cystic lesions in the liver** |                                                                                     |                                                                              |                                                                               |                       |                        |                                                                             |                   |                                                                                  |                                             |                                             |
Echinococcosis is a zoonosis caused by larval stages of taeniid cestodes (tapeworms) belonging to the Echinococcus species. Two of the six known species cause solitary cystic lesions in humans: (1) Echinococcus granulosus (E. granulosus), responsible for cystic echinococcosis (CE); and (2) Echinococcus multilocularis (E. multilocularis), responsible for alveolar echinococcosis (AE)\(^\text{[6]}\).

Echinococcosis-related deaths are uncommon in developed countries. For example, there were 41 echinococcosis-associated deaths in the United States over an 18-year study period\(^\text{[37]}\). However, echinococcosis is considered to be an emerging disease in Europe\(^\text{[38,39]}\). Thus, CE and AE are diseases with a considerable global disease impact, as indicated by a substantial loss in disability-adjusted life years\(^\text{[38,40]}\).

**Cystic echinococcosis**

**Pathogenesis:** Humans become infected by acting as intermediate hosts of E. granulosus after ingestion of Echinococcus eggs, which are excreted by infected carnivores (dogs and other canids)\(^\text{[9]}\). Infection is typically observed in areas containing large numbers of the intermediate hosts of the parasite (sheep and goats) that are in close contact with the final host (herding dogs)\(^\text{[41,43]}\).

**Clinical features:** Although CE has a worldwide geographic distribution, the highest prevalence of CE is haemorrhage\(^\text{[34]}\). Therefore, CEUS can accurately characterise these cysts when USG, CT and MRI show ambiguous findings\(^\text{[28-31]}\).

**Therapy**

The management of most simple cysts relies on a “wait-and-see” policy, and no further treatment is required in these cases. If there are symptoms, aspiration-sclerotherapy is the preferred treatment\(^\text{[32,33]}\). Laparoscopic or open surgical fenestration techniques are similarly or even more effective in reducing symptoms\(^\text{[34,35]}\) but have a significantly higher morbidity and mortality rate\(^\text{[36]}\).
Table 2  Ultrasonography features for the diagnosis of monocytic diseases of the liver

| Border          | Simple cyst | Cystic echinococcosis | Alveolar echinococcosis | Cystadenoma and cystadenocarcinoma |
|-----------------|-------------|-----------------------|-------------------------|-----------------------------------|
| Shape           | Sharp and smooth | Laminated            | Irregular               | Irregular                         |
| Echo pattern    | Spherical or oval | Round or oval        | Hyperechogenic outer ring and hyperechogenic centre | Round or oval |
| Appearance      | Anechoic    | Anechoic or atypical² | Multivesicular          | Hypoechogenic with hyperechogenic septations |
| Wall            | No septa    | Multiseptated         | Dorsal shadowing (calcified areas) | Wall enhancement |
| Posterior acoustic feature | Strong posterior wall echoes | Relative² acentuation of echoes | Dorsal shadowing (calcified areas) | Dorsal shadowing (calcified areas) |

¹Fluid-filled cavity; ²Snowflake-like inclusions or floating laminated membranes; ³Compared to echoes at a similar depth transmitted through normal adjacent hepatic tissue.

Figure 3  Complicated simple cyst on abdominal ultrasonography. Ultrasonography (USG) demonstrating a cystic lesion with a hyperechogenic echo pattern combined with internal echoes that mimic septations or solid portions (arrow) in a patient presenting with severe abdominal pain with a known history of multiple simple cysts (asterisks). Because of the known history of simple cysts, the lesion was diagnosed as a complicated simple cyst (i.e., intracystic haemorrhage).

found in the temperate zones, including the Mediterranean, Central Asia, Australia and some parts of America⁴⁴.

Because cyst growth in the liver is slow (ranging from 1-5 millimetres in diameter per year), CE can remain asymptomatic for a long time. In approximately 90% of cases, the primary presentation is a spherical, fluid-filled vesicle with an inner cellular layer and an outer laminated layer located in the liver, lungs or both⁴⁰. Symptoms occur when cysts exert mass effects within the organ or surrounding tissues or rupture, often presenting as a sudden onset of abdominal pain. Secondary cholangitis (rupture into the biliary tree), biliary obstruction and intraperitoneal rupture followed by anaphylaxis are common complications of CE and require hospitalisation⁴⁹. Worldwide mortality rate estimates vary between 2.2%-5.0%⁴⁵,⁴⁶, although the exact mortality rate of CE in developed countries remains unknown.

Diagnostic features: The diagnosis of CE is based on the following criteria: endemic region history, clinical findings (e.g., abdominal pain, fever, chest pain, and dyspnea), pathognomonic USG features and positive immuno diagnostic tests⁴⁷. USG shows a round or oval-shaped, anechoic or atypical (i.e., snowflake-like inclusions or floating laminated membranes) echo pattern with multiple septa confined by a laminated border (Table 2)⁴⁷. USG has a reported specificity of 90% and is used in combination with CT when surgical treatment is considered. MRI has not been proven to be cost-effective and has no added value⁴⁸. The currently used serodiagnostic tests to reveal E. granulosus antibodies have a sensitivity of 93.5% and specificity of 89.7%⁴⁹.

Therapy: The treatment of CE, including surgery (open or laparoscopic), percutaneous treatments [e.g., puncture aspiration injection re-aspiration (PAIR) method] and chemotherapy⁵⁰, is indicated to reduce symptoms and prevent complications⁵¹. PAIR is the treatment of choice for CE, as a recent review showed that PAIR resulted in parasitological clearance (i.e., negative serodiagnostic tests) in 95.8% of cases⁵².

Alveolar echinococcosis

Pathogenesis: AE is endemic in the Northern hemisphere (e.g., North America, Asia, China, Japan and Europe). AE occurs when E. multilocularis eggs, found in the excrement of foxes, are ingested. The spread from endemic areas to previously non-endemic Western European countries is most likely due to an increasing fox population and spillover from these wild carnivores to domestic hosts⁵³.

Clinical features: The ingested eggs develop into an alveolar structure composed of numerous small vesicles that vary in diameter from smaller than 1 mm to 3 cm. Each vesicle has the same wall structure as CE. These vesicles grow slowly and are able to reach a maximum diameter of 15-20 cm, similar to simple cysts⁵⁴. Worldwide, mortality rate estimates vary between 2.2%-5.0%⁴⁵,⁴⁶. In approximately 99% of cases, the infection is initially confined to a solitary alveolar lesion in the liver⁵⁵. After the primary infection, AE usually has an asymptomatic phase of 5-15 years prior to the development of symptoms. Symptoms are related to mass effect or are nonspecific, such as weight loss or fatigue⁵⁶. In contrast to the encapsulated growth pattern of CE, AE eventually leads to liver failure.
due to an infiltrative neoplastic growth with potential metastasis to adjacent and distant (e.g., lungs, spleen, bone, and brain) organs[6,60].

**Diagnostic features:** Typical USG aspects are observed in 70% of cases and include irregular shape and border, hyperechogenic outer ring and hypoechochogenic centre, multivesicular appearance and dorsal shadowing due to calcified areas (Table 2)[67]. Atypical USG aspects include small hyperechogenic nodules (amorphous AE), large lesions with massive necrosis (pseudo-cyst) and small calcified lesions (lent AE)[68]. In contrast to CE, MRI is superior to CT in detecting AE lesion margins[69,70]. Similar to CE, high diagnostic sensitivity (90%-100%) and specificity (95%-100%) are attained with serodiagnostic tests, and in 80%-95% of cases, AE can be differentiated from CE with the help of serologically obtained purified Echinococcus antigens[69].

**Therapy:** The approach to the management of AE resembles that of a hepatic malignancy. The cornerstone of treatment for AE includes radical surgery followed by a 2-year period of chemotherapy[68]. A recent study concluded that AE can be cured in 42% of cases by complete surgical removal of the parasitic mass. Early diagnosis could even improve this rate further[60].

**CYSTADENOMA AND CYSTADENOCARCINOMA**

**Pathogenesis**

Cystadenoma and cystadenocarcinoma are biliary cyst tumours that originate from the biliary epithelium[64]. Analogous to simple cysts, cystadenoma is considered to be a congenital disorder[60]. The exact mechanism of carcinogenesis in cystadenoma remains unknown. Several studies have suggested that cystadenocarcinoma develops from the ectopic remnants of primitive foregut sequestered within the liver[69]. In contrast, the malignant transformation of cystadenoma into cystadenocarcinoma is considered to be an alternative mechanism of carcinogenesis, as some cystadenocarcinomas may co-exist with cystadenoma[60]. This hypothesis is supported by the observation that the presence of cystadenoma increases the chance of developing cystadenocarcinoma[68].

**Clinical features**

Less than 5% of all cystic lesions of the liver are cystic neoplasms[6,61]. The clinical presentation of cystadenoma and cystadenocarcinoma is asymptomatic or tends to mimic symptoms of simple cysts or echinococcosis[66,67]. Studies have reported a predominance in women, with a mean age of onset varying from 40-60 years[64,65]. Cystadenomas appear to be slow growing, but exact growth rates are unknown. One case series evaluated 75 patients and recorded a variability in cyst size from 1.5-35 cm[68]. One study involving 63 cases diagnosed with cystadenocarcinoma demonstrated infiltrative growth in neighbour-

**Laboratory findings**

In general, liver function tests are normal. A review of 13 cases found that serum concentrations of γGT and alkaline phosphatase (AP) were elevated in 3 cases[69]. One study reported a rise in serum levels of CEA in 3 of 22 cystadenocarcinoma cases (14%) and a rise in the serum concentration of CA 19-9 in 4 of 11 cases (36%)[69]. Similar results have been reported in cases with cystadenoma: one study showed elevated serum concentrations of CEA or CA 19-9 in 2 of 3 cases[64]. Consequently, laboratory studies are not helpful in differentiating cystadenoma and cystadenocarcinoma from complicated cysts or echinococcosis.

**Diagnostic features**

The USG characteristics of cystic neoplasms for both cystadenoma and cystadenocarcinoma are the following: a round or oval shape, irregular border, hyperechogenic echo pattern with hyperechogenic septations or solid structures (i.e., papillary projections), wall enhancement and dorsal shadowing due to calcified areas (Table 2)[2]. Because of these typical cystic neoplastic features, which are absent in simple cysts, USG is a useful technique to easily discriminate between cystic neoplasms and simple cysts[35]. Like USG, CT and MRI show markedly similar characteristics for cystadenoma and cystadenocarcinoma: internal septations, thickened and irregular wall, papillary projections, calcifications and wall enhancements[64]. Cystadenomas predominantly have thinner septa and more regular walls[64], whereas solid structures, intracystic haemorrhage and vascularised septations on contrast-enhanced CT are more suspicious for cystadenocarcinoma[64]. However, in most cases, differentiation between cystadenoma and cystadenocarcinoma is not possible[60]. The same problem arises in differentiating echinococcosis and complicated cysts from cystadenoma and cystadenocarcinoma because in many cases, intracystic haemorrhage, calcifications and septations are present in these lesions[68].

Recent advances in technology have made diffusion-weighted magnetic resonance imaging (DWI) a promising MRI technique for liver lesion detection and characterisation[71]. DWI depicts the rate of diffusion of water molecules between tissues, given as the apparent diffusion coefficient (ADC)[72]. Generally, high ADC values are measured in cystic and necrotic tissue, which allow a relatively free diffusion of water, whereas low ADC values are an indication of cell-rich tissue (e.g., tumour tissue)[22,73,74]. However, because of an overlap of ADC values, differentiating cystic neoplasms, echinococcosis and complicated cysts is not possible with DWI[75]. Therefore, additional immunodiagnostic tests are needed to rule out echinococcosis. Fine needle aspiration (FNA) could be of additional help to exclude complicated cysts[76]; however, due to the risk of malignancy, FNA is generally...
not performed. In contrast, CEUS can be helpful in differentiating cystadenoma and cystadenocarcinoma from complicated cysts when USG, CT or MRI is inconclusive. CEUS characterises the vascular flow within septa in cystadenoma and cystadenocarcinoma, which is absent in complicated cysts.\textsuperscript{[20-31]} Nonetheless, surgical resection remains the golden standard for diagnosing cystadenoma and cystadenocarcinoma when CEUS is not available.

**Therapy**

The primary treatment of cystadenoma and cystadenocarcinoma is hepatic resection. A study in which 66 cases of cystadenocarcinoma were subjected to hepatic resection described a 3-year survival rate of 74%\textsuperscript{[9].}

**PCLD AND ADPKD**

**Polycystic liver disease**

Polycystic liver disease (PLD) is arbitrarily defined as the presence of > 20 liver cysts\textsuperscript{[7].} Autosomal dominant polycystic liver disease (PCLD) and autosomal dominant polycystic kidney disease (ADPKD) are two distinct genetic disorders associated with the development of polycystic livers.\textsuperscript{[78]} Liver function, as judged by parameters of liver synthesis, is not affected in PLD, as functional hepatic tissue remains unaffected\textsuperscript{[77,79].}

**Pathogenesis**

During embryogenesis, the intrahepatic bile ducts are formed from a cylindrical layer of cells (i.e., ductal plate) surrounding each portal vein. Incorrect involution of the ductal plate results in ductal plate malformation (DPM)\textsuperscript{[80,81].} DPM consists of excess embryonic bile duct structures in a ductal plate configuration that does not communicate with the normally developed intrahepatic bile ducts. The progressive dilatation of these excess intrahepatic structures during life results in multiple liver cysts\textsuperscript{[9].} Similar to simple cysts, these cysts contain a clear, bile-like fluid and an inner lining of cholangiocytes\textsuperscript{[83].}

**Genetics**

PCLD was historically considered a phenotypic variant of ADPKD\textsuperscript{[84].} However, the presence of PLD in the absence of renal cysts led to the belief that PCLD should be regarded as a separate entity\textsuperscript{[85].} The discovery of a familial form of PLD\textsuperscript{[86,87]}, genetically distinct from the heterozygous mutation in genes PKD1 and PKD2 identified in ADPKD\textsuperscript{[88]}, ultimately led to the identification of heterozygous mutations in genes encoding SEC63 and PRKCSH\textsuperscript{[88-90].} Mutation analysis identified a heterozygous mutation in PRKCSH (15%) and SEC63 (5%) in approximately 20% of studied PCLD cases\textsuperscript{[91].} In contrast, a PKD1 mutation was found in 85% of cases of ADPKD, and a PKD2 mutation was found in the remaining cases\textsuperscript{[92].}

PRKCSH and SEC63 encode hepatocystin and SEC63 proteins, respectively. Hepatocystin acts in the folding process of proteins, while SEC63 acts as part of the endoplasmic reticulum translocon\textsuperscript{[93].} Unfortunately, the exact mechanism of cystogenesis in PCLD remains unclear. Polycystin 1 and 2, encoded by PKD1 and PKD2, respectively, are important for adequate functioning of the primary cilium\textsuperscript{[94].} Its therefore suggested that primary cilia play a central pathogenic role in the mechanism of hepatic cystogenesis in ADPKD\textsuperscript{[78].}

**Clinical features**

The extra polarisation of 137 identified PCLD cases in a specific adherence region (the Netherlands) led to an estimated PCLD prevalence of 1 per 158000\textsuperscript{[77].} This number is most likely an underestimation of the true prevalence because only symptomatic patients referred to tertiary centres were included in this study, and PCLD often remains asymptomatic\textsuperscript{[95].} ADPKD is the most common monogenetic disorder, with a world-wide estimated prevalence of 0.10%-0.25%\textsuperscript{[96]}, and it is responsible for approximately 8%-10% of cases with end-stage renal disease\textsuperscript{[97].} Although ADPKD is primarily characterised by the presence of renal cysts\textsuperscript{[98]}, liver cysts are considered the most prevalent extra-renal manifestation of ADPKD\textsuperscript{[99,100].} Indeed, one study involving 230 ADPKD cases found an overall prevalence of 83%\textsuperscript{[101].} However, the exact prevalence of PLD in ADPKD is still unknown. PCLD is predominantly confined to the liver, but a few renal cysts can also be present, which leads to difficulties in the accurate differentiation between PCLD and ADPKD\textsuperscript{[102].} Although renal cysts in ADPKD ultimately lead to renal failure, renal function remains unaffected in the presence of PCLD-associated renal cysts\textsuperscript{[103].}

PCLD is predominantly discovered during the fourth or fifth decade of life and is more severe in females\textsuperscript{[97,98,103,104].} PCLD tends to lead to a higher number and greater volume of liver cysts\textsuperscript{[99].} The number of pregnancies, increased age and severity of renal disease are considered additional risk factors for liver cyst growth in ADPKD\textsuperscript{[105].} PLD is mainly asymptomatic, but mechanical complaints can arise in a subset of patients\textsuperscript{[79,106].} Complications such as intracystic haemorrhage and infection are rare and typically occur in large cysts\textsuperscript{[106].}

**Laboratory findings**

PLD causes increased yGT and AP levels in both PCLD and ADPKD patients\textsuperscript{[77].} Occasionally, increased serum aspartate aminotransferase (AST) is also found in ADPKD\textsuperscript{[107-109].} Renal function remains intact in PCLD, whereas ADPKD patients show a rise in serum creatinine due to impaired renal function\textsuperscript{[102].}

**Diagnostic features**

PLD is detected with the use of USG, CT or MRI. USG, which is accurate, non-invasive and low cost, is the preferred imaging modality for both PCLD and ADPKD\textsuperscript{[108,109].} Currently, there are no generally accepted USG criteria for PCLD. One study suggested that the diagnosis can be made in case of a positive family history of PCLD and the presence of > 4 liver cysts\textsuperscript{[78].} However,
The main objective of therapy is to reduce liver cyst volume to diminish mass effect-related symptoms\cite{115}. Hence, the only indication for reducing cyst volume is when a PLD patient reports symptoms that can be linked to the polycystic liver\cite{118}.

Surgical procedures, such as aspiration-sclerotherapy and fenestration, are indicated when PLD consists of large cysts confined to a limited part of the liver. In more extensive disease, segmental hepatic resection or even liver transplantation is imperative to relieve symptoms\cite{117}. Future medical therapies include somatostatin analogues, as several clinical trials with lanreotide and octreotide achieved polycystic liver volume reduction in PCLD and ADPKD\cite{118, 223}.

### CONCLUSION

Cystic lesions of the liver encompass a wide spectrum of disorders. As a result of the frequent use of abdominal imaging techniques in recent years, the incidence of so-called coincidental cysts has increased. Simple cysts are the most prevalent and have a tendency to follow a benign course. However, complicated cysts, echinococcosis and cystic neoplasms (e.g., cystadenoma and cystadenocarcinoma), which cause a diagnostic enigma, demand accurate diagnosis in the early stage because specific treatment could be required. Furthermore, the presence of multiple hepatic cystic lesions must raise the suspicion of PCLD or ADPKD and requires further screening.

USG remains the most accurate, non-invasive and cost-effective imaging modality for diagnosing simple cysts. Despite recent advances (e.g., contrast-enhanced CT and DWI), distinguishing complicated cysts from echinococcosis and cystic neoplasms remains impossible with USG, CT or MRI alone. Because of an ever-increasing spread of *Echinococcus* to previously non-endemic regions and its initial quiescent phase after primary infection, it is necessary to exclude echinococcosis. Serodiagnostic tests have high sensitivity and specificity to reveal *Echinococcus* antibodies. Subsequently, CEUS can be used to accurately and reliably exclude cystic neoplasms by demonstrating the absence of any enhancement within the hepatic cystic lesion. Therefore, when CEUS is available, it reduces the need for surgical resection.

The detection of multiple liver cysts requires USG screening of both kidneys and extensive family history taking regarding the occurrence of ADPKD or PCLD. When PCLD or ADPKD criteria are not met, multiple simple cysts are most likely responsible for the hepatic cystic lesions. PCLD or ADPKD could eventually be diagnosed through USG follow-up.

To summarise, we developed a diagnostic algorithm by integrating recent advances with conventional diagnostic tools (Figure 4). Our diagnostic algorithm facilitates evidence-based clinical decision making when clinicians are confronted with coincidental hepatic cystic lesions on USG. Further development of USG- and MRI-based techniques, such as CEUS and DWI, will probably lead to further improvement of hepatic cystic lesion characterisation.

---

Table 3 Ultrasonography criteria for the diagnosis of autosomal dominant polycystic kidney disease

| Family history positive\(^1\) | Unknown genotype |
|-------------------------------|------------------|
| Age (yr)                      |                  |
| $\geq 15$ and $\leq 39$       | $\geq 3$ unilateral renal cysts |
| $\geq 40$ and $\leq 59$       | $\geq 2$ bilateral renal cysts |
| $\geq 60$                      | $\geq 4$ bilateral renal cysts |

\(^1\)Exclude autosomal dominant polycystic kidney disease when $< 2$ unilateral renal cysts and $\geq 40$ years of age.

---

Lantinga MA et al. Evaluation of hepatic cystic lesions
Lantinga MA et al. Evaluation of hepatic cystic lesions

Figure 4 Diagnostic algorithm. Diagnosis of hepatic cystic lesions after detection on ultrasonography. E. granulosus: Echinococcus granulosus; E. multilocularis: Echinococcus multilocularis; CEUS: Contrast-enhanced ultrasound; PCLD: Polycystic liver disease; ADPKD: Autosomal dominant polycystic kidney disease.

ACKNOWLEDGMENTS
The authors wish to thank Melissa Chrispijn from the Department of Gastroenterology and Hepatology Radboud University Nijmegen Medical Center, the Netherlands, for her expert advice.

REFERENCES
1 Cowles RA, Mulholland MW. Solitary hepatic cysts. J Am Coll Surg 2000; 191: 311-321 [PMID: 10989905 DOI: 10.1016/S1072-7515(00)00345-8]
2 Del Poggio P, Buonocore M. Cystic tumors of the liver: a practical approach. World J Gastroenterol 2008; 14: 3616-3620 [PMID: 18599127 DOI: 10.3748/wjg.14.3616]
3 Bahirwani R, Reddy KR. Review article: the evaluation of solitary liver masses, Aliment Pharmacol Ther 2008; 28: 953-965 [PMID: 18643922 DOI: 10.1111/j.1365-2036.2008.08305.x]
4 Choi BY, Nguyen MH. The diagnosis and management of benign hepatic tumors. J Clin Gastroenterol 2005; 39: 401-412 [PMID: 15815209 DOI: 10.1097/01.mcg.0000192268.63037.a2]
5 Läuffer JM, Baer HU, Maurer CA, Stoupis C, Zimmerman A, Büchler MW. Biliary cystadenocarcinoma of the liver: the need for complete resection. Eur J Cancer 1998; 34: 1845-1851 [PMID: 10023304 DOI: 10.1016/S0959-8049(08)00166-X]
6 Nunnari G, Pinzone MR, Gruttadauria S, Celesia BM, Madeddu G, Malaguarnera G, Pavone P, Cappellani A, Copardo B. Hepatic echinococcosis: clinical and therapeutic aspects. World J Gastroenterol 2012; 18: 1448-1458 [PMID: 22590076 DOI: 10.3748/wjg.v18.i13.1448]
7 Eckert J, Deplazes P. Alveolar echinococcosis in humans: the current situation in Central Europe and the need for countermeasures. Parasitol Today 1999; 15: 315-319 [PMID: 10407377 DOI: 10.1016/S0969-4789(99)01476-3]
8 Romig T, Dinkel A, Mackenstedt U. The present situation of echinococcosis in Europe. Parasitol Int 2006; 55 Suppl: SI87-SI91 [PMID: 16352465 DOI: 10.1016/j.parint.2005.11.028]
9 Sanfelippo PM, Beahrs OH, Weiland LH. Cystic disease of the liver. Ann Surg 1974; 179: 922-925 [PMID: 4833513 DOI: 10.1097/00000658-197406000-00018]
10 Jones WL, Mountain JC, Warren KW. Symptomatic non-parasitic cysts of the liver. Br J Surg 1974; 61: 118-123 [PMID: 4816238 DOI: 10.1010/bj.1800610211]
11 Gaines PA, Sampson MA. The prevalence and characterization of simple hepatic cysts by ultrasound examination. Br J Radiol 1989; 62: 335-337 [PMID: 2653548 DOI: 10.1259/0007-1286-62-736-735]
12 Carrim ZI, Murchison JT. The prevalence of simple renal and hepatic cysts detected by spiral computed tomography. Clin Radiol 2003; 58: 626-629 [PMID: 12887956 DOI: 10.1016/S0009-9266(03)00165-X]
13 Hanazaki K, Wakabayashi M, Mori H, Sodeyama H, Yoshizawa K, Yokoyama S, Sode Y, Kawamura N, Miyazaki T. Hemorrhage into a simple liver cyst: diagnostic implications of a recent case. J Gastroenterol Hepatol 1997; 12: 848-851 [PMID: 9430029 DOI: 10.1071/BJ9904689]
14 Salemis NS, Georgoulis E, Gourgriotis S, Tsohataridis E. Spontaneous rupture of a giant non parasitic hepatic cyst presenting as an acute surgical abdomen. Ann Hepatol 2007; 6: 190-193 [PMID: 17786149]
15 Zhang YL, Yuan L, Shen F, Wang Y. Hemorrhagic hepatic cysts mimicking biliary cystadenoma. World J Gastroenterol 2009; 15: 4601-4605 [PMID: 19777623 DOI: 10.3748/wjg.v15.i46.4601]
16 Kitajima Y, Okayama Y, Hirai M, Hayashi K, Imai H, Okamoto T, Aoki S, Aki S, Gotoh K, Obara H, Nomura T, Joh T, Yokoyama Y, Itoh M. Intracystic hemorrhage of a simple liver cyst mimicking a biliary cystadenocarcinoma. J Gastroenterol Hepatol 2003; 18: 190-193 [PMID: 12640536 DOI: 10.1078/0910-3825(2003)18:190-193]
17 Waanders E, van Keimpema L, Brouwer JT, van Oijen MG, Aerts R, Sweep FC, Nevens F, Drentj JP. Carbohydrate antigen 19-9 is extremely elevated in polycystic liver disease.
June 21, 2013 | Volume 19 | Issue 23 | WJG | www.wjgnet.com

Lantinga MA et al. Evaluation of hepatic cystic lesions

haptic cysts. Am J Surg 2001; 181: 404-410 [PMID: 11448430 DOI: 10.1016/S0002-9610(01)00611-0]

Gigt LF, Legrand M, Hubers C, de Canniere L, Wibin E, De Wee B, Drault ML, Bertrand C, Devriendt H, Droisart R, Tu-gilimana M, Hautier P, Verecken L. Laparoscopic treatment of nonparasitic liver cysts: adequate selection of patients and surgical technique. World J Surg 1996; 20: 556-561 [DOI: 10.1007/BF026990086]

Bristow BN, Lee S, Shafir S, Sorvillo F. Human echinococcosis mortality in the United States, 1990-2007. PLoS Negl Trop Dis 2012; 6: e1524 [PMID: 22347516 DOI: 10.1371/journal.pntd.0000722]

Budke CM, Deplazes P, Torpgron P. Global socioeconomic impact of cystic echinococcosis. Emerg Infect Dis 2006; 12: 296-303 [PMID: 16494758 DOI: 10.3201/eid1205.050499]

Dakak A. Echinococcosis/zydatisis: a severe threat in Mediterranean countries. Vet Parasitol 2010; 174: 2-11 [PMID: 20888664 DOI: 10.1016/j.vetpar.2010.08.009]

Torgerson PR, Keller K, Magnotta M, Ragland N. The global burden of alveolar echinococcosis. PLoS Negl Trop Dis 2010; 4: e722 [PMID: 20582510 DOI: 10.1371/journal.pntd.0000722]

Eckert J, Connaths FJ, Tackmann K. Echinococcosis: an emerging or re-emerging zoonosis? Int J Parasitol 2000; 30: 1283-1294 [PMID: 11113255 DOI: 10.1016/S0020-7519(00)01303-2]

Grosso G, Grottundaria S, Biondi A, Marventano S, Mistretta A. Worldwide epidemiology of liver hydatidosis including the Mediterranean area. World J Gastroenterol 2012; 18: 1425-1437 [PMID: 22590704 DOI: 10.3748/wjg.v18.i13.1425]

Todorov T, Benov V. Human echinococcosis in Bulgaria: a comparative epidemiological analysis. Bull World Health Organ 1999; 77: 110-118 [PMID: 10887308]

Mandal S, Mandal MD. Human cystic echinococcosis: epidemiological, zoonotic, clinical, diagnostic and therapeutic aspects. Asian Pac J Trop Med 2012; 5: 253-260 [PMID: 22449514 DOI: 10.11659/Spj.000035-2]

McManus DP, Zhang W, Li J, Bartley PB. Echinococcosis. Lancet 2003; 362: 1295-1304 [PMID: 14575976 DOI: 10.1016/S0140-6736(02)12839-0]

Craig PS, Larrieu E. Control of cystic echinococcosis/hydatidosis: 1863-2002. Adv Parasitol 2006; 61: 443-508 [PMID: 16735171 DOI: 10.1016/S0065-2779(05)50011-1]

Eckert J. WHO/OIE manual on echinococcosis in humans and animals: a public health problem of global concern. Paris: World Organisation for Animal Health, 2001: 20-72

Sayek I, Onat D. Diagnosis and treatment of uncomplicated hydatid cyst of the liver. J World J Surg 2001; 25: 21-27 [PMID: 11213525 DOI: 10.1007/s00268-0020-0040]

Sbhi Y, Rimqui A, Rodriguez-Cabezas MN, Orduña A, Rodríguez-Torres A, Osuna A. Comparative sensitivity of six serological tests and diagnostic value of ELISA using purified antigen in hidatidosis. J Clin Lab Anal 2001; 15: 14-18 [PMID: 11170228 DOI: 10.1002/jcla.10231]

Brunetti E, Junghanss T. Update on cystic hydatid disease. Curr Opin Infect Dis 2009; 22: 497-502 [PMID: 19633552 DOI: 10.1097/QCO.0b013e328320301]

Buttenschoen K, Carli Buttenschoen D. Echinococcus granulosus infection: the challenge of surgical treatment. Langenbecks Arch Surg 2003; 388: 218-230 [PMID: 12845535 DOI: 10.1007/s00423-003-0975-z]

Smego RA, Sebancgo P. Treatment options for hepatic cystic echinococcosis. Int J Infect Dis 2005; 9: 69-76 [PMID: 15708321 DOI: 10.1016/j.ijid.2004.08.001]

Eckert J, Deplazes P. Biological, epidemiological, and clinical aspects of echinococcosis, a zoonosis of increasing concern. Clin Microbiol Rev 2004; 17: 107-135 [PMID: 14726458 DOI: 10.1182/cmr.17.1.107-135.2004]

Kern P. Clinical features and treatment of alveolar echinoco-
embryology of extra- and intrahepatic bile ducts, the ductal plate. Acta Cytol 1985; 29(5): 1031-1036 [PMID: 3795495 DOI: 10.1016/j.actacytol.1985.09.011]

56 Hanman J, Arslan H, Kotan C, Erikten O, Kayan M, Deveci A. MRI findings of hepatic alveolar echinococcosis. Clin Imaging 2003; 27: 411-416 [PMID: 12855751 DOI: 10.1016/S0899-7017(03)00006-8]

57 Mentzelopoulos SP, Touloumis Z, Bakoyiannis A, Tassopoulos N, Parasekva A, Athanassiou K, Safioleas M, Dervenis C. Intrahepatic biliary cyst and cystadenoma: a case for complete resection. Acta Endocrinol (Copenh) 2012; 16: 505-512 [PMID: 22709822 DOI: 10.1016/j.actaendo.2012.05.012]

58 Nishizawa K, Itoh N, Kuriyama T, Tsuchiya T, Itoh K, Shimizu H, Nonaka M. A new classification of intrahepatic bile duct neoplasms. Hepatobiliary & Pancreatic Diseases International 2004; 3: 171-175 [PMID: 15133510 DOI: 10.1016/j.hbp.2004.06.002]
Lantinga MA et al. Evaluation of hepatic cystic lesions

89

Drenth JP, te Morsche RH, Smink R, Bonifaciou J, Jansen JB. Germline mutations in PRKCSH are associated with autosomal dominant polycystic liver disease. Nat Genet 2003; 33: 345-347 [PMID: 12570599 DOI: 10.1038/ng10104]

90

Li A, Davila S, Furu L, Qian Q, Tian X, Kamath PS, King BF, Torres VE, Somlo S. Mutations in PRKCSH cause isolated autosomal dominant polycystic liver disease. Am J Hum Genet 2003; 72: 691-703 [PMID: 12529853 DOI: 10.1086/368295]

91

Waanders E, Venselaar H, te Morsche RH, de Koning DB, Hoogerhyde MD, Manco-Johnson ML, Duley IT, Everson GT. Risk factors for the development of hepatic cysts in autosomal dominant polycystic kidney disease. Hepatology 1999; 33: 1033-1037 [PMID: 10362580 DOI: 10.1002/hep.18400110169]

92

Tores VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. Lancet 2007; 369: 1287-1301 [PMID: 17434410 DOI: 10.1016/S0140-6736(07)66801-6]

93

Que F, Nagorney DM, Gross JB, Torres VE. Liver resection and cyst fenestration in the treatment of severe polycystic liver disease. Gastroenterology 1995; 108: 487-494 [PMID: 7835591 DOI: 10.1016/0016-5085(95)00787-0]

94

Belitti FA, Edelstein CL. Unified ultrasonographic diagnostic criteria for polycystic kidney disease. J Am Soc Nephrol 2009; 20: 6-8 [PMID: 19073819 DOI: 10.1681/ASN.2008111164]

95

Nicoula C, Torra R, Badenas C, Vilana R, Bianchi L, Gilbert R, Darnell A, Bru C. Autosomal dominant polycystic kidney disease types 1 and 2: assessment of US sensitivity for diagnosis. Radiology 1999; 213: 273-276 [PMID: 10540671]

96

Pei Y, Obaji J, Dupuis A, Paterson AD, Magistrini R, Diets E, Parfrey P, Cramer B, Cote E, Torra R, San Millan JL, Gibson R, Breuning M, Peters D, Ravine D. Unified criteria for ultrasonographic diagnosis of ADPKD. J Am Soc Nephrol 2009; 20: 205-212 [PMID: 1994943 DOI: 10.1681/ASN.2008060507]

97

Ravine D, Gibson RN, Walker RG, Sheffield LJ, Kincad-Smith P, Danks DM. Evaluation of ultrasonographic diagnostic criteria for autosomal dominant polycystic kidney disease. J Pediatr 1994; 343: 824-827 [PMID: 7908078 DOI: 10.1016/S0140-6736(94)92026-5]

98

Ecder T, Schrier RW. Cardiovascular abnormalities in autosomal-dominant polycystic kidney disease. Nat Rev Nephrol 2009; 5: 221-228 [PMID: 19322187 DOI: 10.1038/nrne

99

Niolli RW. Optimal care of autosomal dominant polycystic kidney disease patients. Nephrol (Carlton) 2006; 11: 124-130 [PMID: 16669974 DOI: 10.1111/j.1440-1799.2006.05355.x]

100

Gevers TJ, te Koning DB, van Dijk AP, Drenth JP. Low prevalence of cardiac valve abnormalities in patients with autosomal dominant polycystic liver disease. Liver Int 2012; 32: 690-692 [PMID: 22099398 DOI: 10.1111/j.1478-3231.2011.02683.x]

101

Drenth JP, Chrispin J, Nagorney DM, Kamath PS, Torres VE. Medical and surgical treatment options for polycystic liver disease. Hepatology 2010; 52: 2223-2230 [PMID: 21051111]

102

Temmerman F, Missiaen L, Bammens B, Lalenen W, Cassi- man D, Verslype C, van Pelt J, Nevens F. Systematic review: the pathophysiology and management of polycystic liver disease. Aliment Pharmacol Ther 2011; 34: 702-713 [PMID: 21790682 DOI: 10.1111/j.1365-2036.2011.04783.x]

103

Russell RT, Pinson CW. Surgical management of polycystic liver disease. World J Gastroenterol 2007; 13: 5052-5059 [PMID: 17876869]

104

Gevers TJ, Drenth JP. Somatostatin analogues for treatment of polycystic liver disease. Curr Opin Gastroenterol 2011; 27: 294-300 [PMID: 21912889 DOI: 10.1097/MOG.0b013e3283434331]

105

van Keimpema L, Nevens F, Vanslimbroekx R, van Ooij MG, Hoffman AL, Dekker HM, de Man RA, Drenth JP. Lanreotide reduces the volume of polycystic liver. a randomized, double-blind, placebo-controlled trial. Gastroenterology 2009; 137: 1661-8.e1-2 [PMID: 19646443 DOI: 10.1053/j.gastro.2009.07.052]

106

Caroli A, Antiga L, Cafaro M, Fasolini G, Remuzzi A, Remuzzi G. Ruggenenti P. Reducing polycystic liver volume in ADPKD: effects of somatostatin analogue octreotide. Clin J Am Soc Nephrol 2010; 5: 783-789 [PMID: 20855956 DOI: 10.2358/jasn.2009070744]
Lantinga MA et al. Evaluation of hepatic cystic lesions

10.2215/CJN.05380709
121 Hogan MC, Masyuk TV, Page LJ, Kubly VJ, Bergstralh EJ, Li X, Kim B, King BF, Glockner J, Holmes DR, Rossetti S, Harris PC, LaRusso NF, Torres VE. Randomized clinical trial of long-acting somatostatin for autosomal dominant polycystic kidney and liver disease. *J Am Soc Nephrol* 2010; 21: 1052-1061 [PMID: 20431041 DOI: 10.1681/ASN.2009121291]

122 Hogan MC, Masyuk TV, Page L, Holmes DR, Li X, Bergstralh EJ, Irazabal MV, Kim B, King BF, Glockner JF, Larusso NF, Torres VE. Somatostatin analog therapy for severe polycystic liver disease: results after 2 years. *Nephrol Dial Transplant* 2012; 27: 3532-3539 [PMID: 22773240 DOI: 10.1093/ndt/gfs152]

123 Chrispijn M, Drenth JP. Everolimus and long acting octreotide as a volume reducing treatment of polycystic livers (ELATE): study protocol for a randomized controlled trial. *Trials* 2011; 12: 246 [PMID: 22104015 DOI: 10.1186/1745-6215-12-246]

P- Reviewers de Oliveira C, Ramsay M, Silva ACS
S- Editor Wen LL
L- Editor A
E- Editor Zhang DN