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Ultrasound findings in autoimmune hepatitis

Yi Dong, Andrej Potthoff, Christoph Klinger, Ana Paula Barreiros, Dariusz Pietrawski, Christoph F Dietrich

Yi Dong, Department of Ultrasound, Zhongshan Hospital, Fudan University, Shanghai 200032, China

Andrej Potthoff, Department of Gastroenterology, Hepatology and Endocrinology, Medizinische Hochschule Hannover, Hannover D-30625, Germany

Christoph Klinger, Department of Internal Medicine 1, Klinikum Ludwigsburg, Ludwigsburg D-71634, Germany

Ana Paula Barreiros, German Organ Transplantation Foundation, Region Mitte, Mainz D-55131, Germany

Dariusz Pietrawski, Christoph F Dietrich, Department of Internal Medicine 2, Caritas-Krankenhaus Bad Mergentheim, Bad Mergentheim D-97980, Germany

ORCID number: Yi Dong (0000-0002-0212-1477); Andrej Potthoff (0000-0002-2985-7281); Christoph Klinger (0000-0001-7680-8477); Ana Paula Barreiros (0000-0003-2529-6779); Dariusz Pietrawski (0000-0003-2399-2252); Christoph F Dietrich (0000-0001-6015-6347).

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Correspondence to: Christoph F Dietrich, MD, PhD, MBA, Professor, Department of Internal Medicine 2, Caritas-Krankenhaus Bad Mergentheim, Uhlandstr. 7, Bad Mergentheim D-97980, Germany. christoph.dietrich@ckbm.de

Telephone: +49-793158-2201/2200
Fax: +49-793158-2290

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Abstract

Ultrasound findings in autoimmune hepatitis (AIH) have not been reported systematically so far. The use of reliable and accurate noninvasive methods for determining fibrosis stage is important in evaluation of treatment efficacy and fibrosis regression in AIH. Imaging plays an important role in detection of complications and ruling out other possible causes of chronic liver diseases. Ultrasound elastography cut-off values in AIH patients are not the same as those in patients with chronic viral hepatitis or non-alcoholic fatty liver disease. AIH is characterized by wide fluctuations in inflammatory activity. Here we report on current knowledge of ultrasound findings in AIH.

Key words: Autoimmune hepatitis; Fibrosis stage; Ultrasound; Elastography; Chronic liver diseases

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Core tip: Accurate noninvasive imaging to determine fibrosis stages is of importance in the evaluation of treatment efficacy and fibrosis regression in autoimmune hepatitis (AIH). The cut-off values in AIH patients are not the same as those in patients with chronic viral hepatitis or non-alcoholic fatty liver disease.

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INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic immune mediated liver disease of unknown etiology^[1,2]. About one-third of the patients already have developed advanced fibrosis and liver cirrhosis at the time of diagnosis. AIH mainly affects women and is usually characterized by chronic inflammation of the liver, hypergammaglobulinemia with increased immunoglobulin G (IgG) levels and circulating autoantibodies associated with human leukocyte antigens DR3 or DR4, typical liver histology with interface hepatitis^[3], and a favorable response to immunosuppressive treatment^[1,2,4]. Once other liver diseases such as viral hepatitis have been excluded, the diagnosis of AIH can be made by serological and histological findings. AIH can range from a mild or severe course to fulminant hepatic failure. Despite corticosteroid therapy, hepatic fibrosis develops in 25% of patients with AIH^[5]. To find reliable and accurate noninvasive imaging methods for determining fibrosis stages is of importance in the evaluation of treatment efficacy and fibrosis regression in AIH^[6]. Here we report on ultrasound findings in AIH.

CLASSIFICATION OF AIH

AIH has a global distribution. It is considered as a rare disease affecting all ages and ethnic groups with a female predominance (F:M ratio 3.6:1). The incidence of AIH is around 1 per 100000 persons per year^[7]. In 1992, the International AIH Group (IAIHG) reported diagnostic criteria^[8], which were remarkably simplified in 2008^[9]. AIH is classified into two major types: AIH type 1 (AIH-1) and AIH type 2 (AIH-2). Antinuclear antibodies (ANA) and/or smooth muscle autoantibodies (SMA) could be detected in AIH-1. Also perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) could be detected in 60%-90% of AIH-1 patients^[4,5,9,10]. AIH-2 is characterized by the detection of anti-liver/kidney microsomal antibody type 1 or anti-LKM type 3^[4,10] and/or antibodies against liver cytosol type 1 antigen^[1,4]. AIH-1 accounts for about 75%-80% of all patients, however, AIH-2 is more frequently seen in children and young patients, which might present with acute onset and severe histological changes at time of diagnosis. Poor treatment prognosis, recurrence after treatment and need for lifelong treatment are more common in AIH-2^[4,11]. AIH-1 patients might also show antibodies against soluble liver/liver-pancreas-antigen SLA/LP^[12,13].

PATHOGENESIS

According to the dominant pathogenetic hypothesis,

AIH develops in genetically susceptible individuals by several triggers. The liver is attacked through mechanisms of "molecular mimicry", and is promoted by down regulation of regulatory T-cells^[3,4].

AIH may develop after the use of some drugs and biological agents or after viral infections and other events, including *de novo* after orthotopic liver transplantation^[14-16]. AIH may first develop during pregnancy and after delivery.

CLINICAL MANIFESTATIONS

Clinically AIH is characterized by fluctuation of disease activity. Its clinical symptoms range from no obvious manifestations to severe and acute hepatitis^[4,17]. Clinical manifestations range from merely elevated transaminases to liver cirrhosis and/or fulminant liver failure requiring liver transplantation^[18]. Acute AIH presents in approximately 25% patients with similar symptoms as patients suffering from acute toxic or viral hepatitis^[19]. At time of diagnosis, about one third of patients have established cirrhosis^[3]. A specific and common clinical characteristic of AIH is its association with other autoimmune diseases including first degree relatives^[20]. Concurrent extrahepatic autoimmune conditions mostly affect the thyroid gland (10%-23%)^[13]. Clinical presentation of AIH might be similar to primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). These diseases may coexist leading to overlap or variant syndromes^[21,22].

DIAGNOSIS

Due to the absence of specific diagnostic features and diversity of clinical manifestations, serological and histological features, AIH diagnosis may be a challenge^[3]. According to the International Autoimmune Hepatitis Group (IAIHG), the clinical diagnosis of AIH is based on biochemical, immunological, and histological features. Viral hepatitis should be excluded^[9]. The simplified diagnostic criteria of IAIHG for AIH is based mainly on four parameters, including autoantibodies detection, serum IgG levels, absence of viral hepatitis markers and liver histology^[9]. Histological changes including interface hepatitis, and hepatic rosette formation and emperipolesis^[9]. Autoantibodies detection is regarded as the hallmark for a timely diagnosis although not pathognomonic^[3].

LABORATORY ASSESSMENTS AND LIVER BIOPSY

Liver biochemistry is not characteristic in most of AIH patients, with elevated bilirubin and transaminases. In most patients, polyclonal hypergammaglobulinemia with particular elevated level of serum IgG is observed. However, it should be mentioned that 15%-25% of patients (especially children, elderly and acute cases) have normal IgG levels. Therefore, AIH diagnosis

should not be excluded depending on a normal IgG testing^[3]. The standard laboratory assessments include elevated LFTs, hypergammaglobulinemia, and the detection of autoantibodies (ANA, anti-SMA, and anti-LKM).

Liver biopsy is strongly recommended to confirm AIH^[13], first to make the diagnosis and second to determine the stage of disease. The diagnostic histological features of AIH include moderate to severe interface hepatitis without biliary lesions or well-defined granulomas. However, it must be noted that pathognomonic histological characteristics for AIH are missing. Regular assessment of hepatic fibrosis is important in patients with AIH because progressive fibrosis ultimately leads to cirrhosis and liver failure^[23]. It has been recommended that clinical decisions about duration of treatment or immunosuppressive therapy should be based on clinical remission and histological features^[2].

NON-INVASIVE MARKERS OF LIVER FIBROSIS

Laboratory methods can differentiate liver cirrhosis from non-cirrhosis, but their accuracy in distinguishing changes of AIH in histological stages is uncertain. Biochemical markers can reflect the therapeutic response during treatment, but they cannot reflect the severity of liver fibrosis^[5]. Many non-invasive markers for assessing liver fibrosis and cirrhosis have been applied in clinical practice^[24,25]. However, their ability to detect early stages of liver fibrosis and cirrhosis in AIH patients is still uncertain^[26]. All calculated non-invasive markers are not specific. However, it has been considered feasible to predict the degree of liver fibrosis in patients with AIH using laboratory parameters. Platelet count as well as AAR could be used to predict the presence of advanced fibrosis^[27,28].

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of AIH includes chronic viral hepatitis (B and C), primary sclerosing cholangitis, alpha-1 antitrypsin deficiency, primary biliary cirrhosis, hemochromatosis, Wilson's disease and drug-induced hepatitis (e.g., minocycline, nitrofurantoin, isoniazid, methylidopa). However, to differentiate AIH from drug-induced liver injury (DILI) might be a challenge in cholestatic and severe clinical presentations, in particular when circulating liver autoantibodies are detectable in serum^[2]. Elevated IgG serum-levels and the histological presence of plasma cells can be found as well in a significant proportion of DILI patients^[29].

Treatment

In order to prevent progressive liver fibrosis/cirrhosis, treatment aims on complete biochemical (defined by

normalization of aminotransferases and IgG level) and histological remission^[13,30]. Most patients respond well to immunosuppressive therapy, which usually results in an excellent prognosis^[1,31,32]. Steroids are used as initial therapy leading to a treatment response in 80% of patients with AIH^[33-35]. In adults, Azathioprine is effective as maintenance therapy^[5,10,30]. Treatment should be continued until normalization of laboratory tests and liver histology^[36]. Incomplete response and treatment failure occur in 14%^[37] and 7% of patients^[38], respectively^[36,39,40]. Treatment failure is characterized by a missing decrease of aminotransferase levels and, in some patients, rapid progression to cirrhosis. Consequently, alternative therapeutic regimens have to be considered^[5,41,42]. In cases of treatment failure, overlap with other etiologies should be considered. In those patients with liver failure, liver transplantation might be indicated and carries a 10-year survival rate exceeding 70%^[1]. Future anti-fibrotic therapies and monitoring fibrosis progression are essential in patients with AIH.

ULTRASOUND IMAGING

B-mode ultrasound and contrast-enhanced ultrasound

No characteristic conventional ultrasound imaging features of AIH have been described. For initial diagnosis of AIH, ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) are valuable methods to detect liver cirrhosis and its complications. Imaging of AIH play a role in the detection of complications^[21]. Enlarged perihepatic lymph nodes are a typical ultrasound feature, similar to virus hepatitis C^[43-46] (Figure 1), PBC^[47,48], PSC^[49], sarcoidosis^[50,51] and other inflammatory liver diseases^[50] in adults and children^[46,50] (Figures 1 and 2). These enlarged inflammatory perihepatic lymph nodes show typical contrast behavior and elastographic architecture^[52-59] (Figure 3).

About 1%-9% of AIH patients with liver cirrhosis develop HCC. Therefore, ultrasound follow-up examinations are recommended every six months^[60]. Characteristically, involvement of the biliary tract is absent or minimal in AIH. Magnetic resonance cholangiography (MRC) is recommended in all children and adult patients with elevated markers of cholestasis in order to detect concurrent overlap syndromes, particularly PSC.

Ultrasound elastography

Non-invasive liver ultrasound elastography methods are useful for detection and staging of liver fibrosis initially as well as during clinical follow-up. Transient elastography (TE) has been introduced first to assess liver stiffness in patients with chronic liver diseases^[61,62]. Other newer ultrasound-elastography methods include point shear-wave elastography (pSWE) and two-dimensional shear-wave elastography (2D-SWE)^[63]. These tools are integrated in standard ultrasound devices.

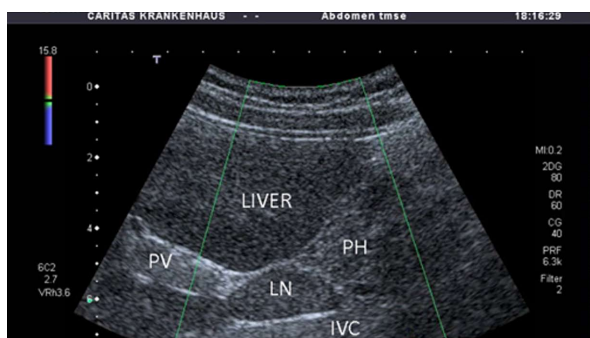


Figure 1 Enlarged perihepatic lymph nodes dorsal in the hepatoduodenal ligament between the portal vein and inferior vena cava is a typical sonographic sign of autoimmune hepatitis. PV: Portal vein; PH: Pancreatic head; IVC: Inferior vena cava.

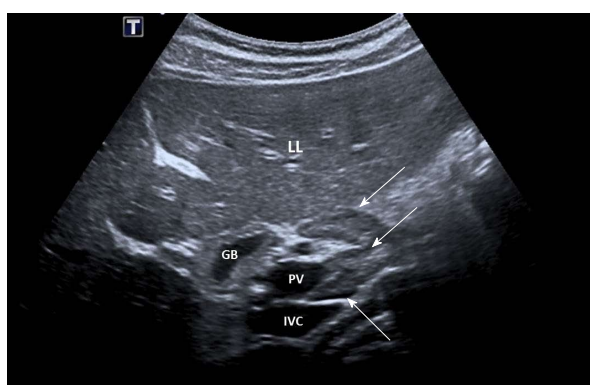


Figure 2 Enlarged perihepatic lymph nodes ventral and dorsal in the hepatoduodenal ligament between the portal vein and inferior vena cava (white arrows). LL: Liver; GB: Gallbladder; PV: Portal vein; IVC: Inferior vena cava.

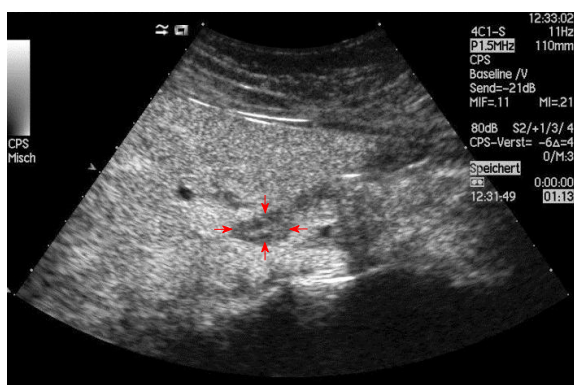


Figure 3 Enlarged perihepatic lymph nodes dorsal in the hepatoduodenal ligament is a typical sonographic sign of autoimmune hepatitis. Contrast enhanced ultrasound shows normal lymph node architecture (in between arrows).

Ultrasound elastography methods are proved to be accurate and reliable in the diagnosis of advanced fibrosis and cirrhosis, however, the diagnostic performances may be compromised by inflammation, congestion, biliary obstruction and obesity^[63]. Magnetic resonance elastography (MRE) has excellent performance parameters for all histological stages in diverse

liver diseases^[64], which represents to be a reliable alternative to SWE. MRE is less influenced by body habitus and inflammatory activity in the evaluation of fibrosis in AIH^[65-67] but its availability is limited and the investigation is more expensive.

Transient elastography

The cut-off values in AIH patients are not the same as those in patients with chronic viral hepatitis. A recent study which enrolled 108 AIH patients who underwent liver biopsies, AUROC value of liver stiffness measurement (LSM) was 0.885 for stage F2 ($n = 24$), 0.897 for stage F3 ($n = 30$), and 0.878 for stage F4 ($n = 24$). The optimal LSM cut-off value was 6.27 kPa for stage F2, 8.18 kPa for F3, and 12.67 kPa for F4^[68]. LSM was superior to other non-invasive markers in differentiating the stages of fibrosis in AIH patients^[68]. Liver stiffness measured by TE correlated significantly with the stage of liver fibrosis in a study which compared accuracy of TE and liver biopsy in AIH patients. TE correlated better than non-invasive laboratory markers^[69,70]. This study demonstrated similar cut-off values, with LSM cut-off values of 6.45 kPa for F2, 8.75 kPa for F3, and 12.5 kPa for F4^[70].

A previous study^[70] evaluated the accuracy of LSM, APRI, and FIB-4 in 100 AIH patients. TE outperformed the other non-invasive markers. LSM was proven to be closely associated with fibrosis stages ($r = 0.752$, $P < 0.01$). Patients with more advanced fibrosis stages are associated with higher LSM values. Of importance, serum ALT levels had minor effect on LSM values and hepatic inflammatory activity had no significant effect on LSM determination.

TE proved also to be more accurate than APRI score in study published by Halasz *et al*^[71] including 22 cases of AIH.

Wang *et al*^[69] conducted a retrospective study with 36 histologically confirmed AIH patients (19 treated and 17 untreated). They reported that TE was accurate for distinguishing hepatic fibrosis in AIH between stages F0-F2 and F3-F4.

While comparing to other etiologies, the higher LSM values for different Ishak stages in AIH patients are in line with the results in the literature^[69,72-74]. In a pediatric study of Behairy *et al*^[6], a total of 90 children (HCV $n = 50$, AIH $n = 20$, Wilson's disease $n = 20$) were included and underwent LSM using TE. AIH patients had both higher values of LSM and (necro) inflammation scores compared to patients with HCV and Wilson's disease. Inflammatory activity accompanying with increased serum aminotransferase levels, can increase liver stiffness may be misinterpreted as fibrosis^[75,76]. Therefore, the higher grade of (necro-) inflammatory activity in AIH patients compared to other etiologies could be a possible explanation^[2,3].

Long-term treatment with mono corticosteroids or in combination with azathioprine is proposed when the AIH diagnosis is established. The effect of treatment on the diagnostic performance of LSM has been studied

as well. Hartl *et al.*^[77] reported that performance of TE in the detection of cirrhosis is better for AIH patients who received longer treatment compared to treatment-naïve patients and patients with shorter duration of treatment. Using the cut-off of 16 kPa, the diagnostic accuracy for cirrhosis was excellent in patients ($n = 36$) under immunosuppressive treatment for 6 months or longer^[77]. A non-invasive inflammatory score has been proposed to discriminate patients with and without significant hepatic inflammation^[78]. Those scores are easy to calculate, however, they would be only suitable to patients without co-morbidities and not for patients with low inflammatory activity^[79]. Weight gain is a common consequence of corticosteroid treatment^[80,81].

Acoustic radiation force impulse imaging

Acoustic radiation force impulse imaging (ARFI) can help to distinguish liver fibrosis patients with autoimmune liver diseases from healthy subjects^[82,83]. In AIH patients after at least 2 years of biochemical remission, ARFI allowed to differentiate significant ($F \geq 2$) from non-significant liver fibrosis ($F < 2$) (2.28 ± 0.68 m/s vs 1.20 ± 0.24 m/s, $P = 0.002$)^[23]. Although large studies on ARFI elastography in AIH patients are still lacking preliminary data indicate that ARFI is a promising non-invasive method for detection and staging of fibrosis also in AIH patients.

2D-SWE

SuperSonic shear wave imaging (SuperSonic Imagine, Aix-en-Provence, France) had higher values in liver fibrosis with AIH of stages S2-S4^[84] similar to the results with ARFI^[82]. The shear moduli were 9.41 ± 2.5 kPa in S0 stage; 10.42 ± 5.1 kPa in S1 stage; 13.25 ± 5.6 kPa in S2 stage; 19.03 ± 7.8 kPa in S3 stage and 24.99 ± 9.5 kPa in S4 stage^[84].

Real-time elastography

In an animal based study, Hao *et al.*^[85] investigated the inflammation effect on fibrosis staging by measuring quantitative elasticity parameters in AIH rats (HiVision Preirus, Hitachi Medical Systems Co, Ltd, Tokyo, Japan). The grade of inflammation will influence the accuracy of Real-time elastography (RTE) measurements. The liver fibrosis index had the highest correlation with inflammation grading ($r = 0.766$; $P < 0.05$).

LIMITATIONS

Currently, ultrasound findings in AIH have been limited use so far. No characteristic ultrasound imaging features of AIH have been described in the literature. There is a need for studies to determine the better use of ultrasound in AIH patients.

CONCLUSION

In conclusion, AIH is characterized by wide fluctuations

in inflammatory activity. Thus, stage of fibrosis can be overestimated by transient elastography^[86] due to concomitant hepatic necroinflammatory activity. It can be also concluded that LSM using TE reflects the stages of liver fibrosis and correlates better than non-invasive laboratory markers in patients with treated AIH^[77,87,88]. Other non-invasive ultrasound based techniques as ARFI, 2D-SWE or Real Time Elastography are not well investigated in the population of AIH patients yet. Further studies are needed. However, current non-invasive markers/methods for the evaluation of liver fibrosis in AIH could not replace liver biopsy, especially in differentiating mild from severe stages of fibrosis^[87].

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